

THE POSSIBILITIES
OF CURE OF THE
HODGKIN'S DISEASE
PATIENT

ROUDN. TABLE LUNCHEON

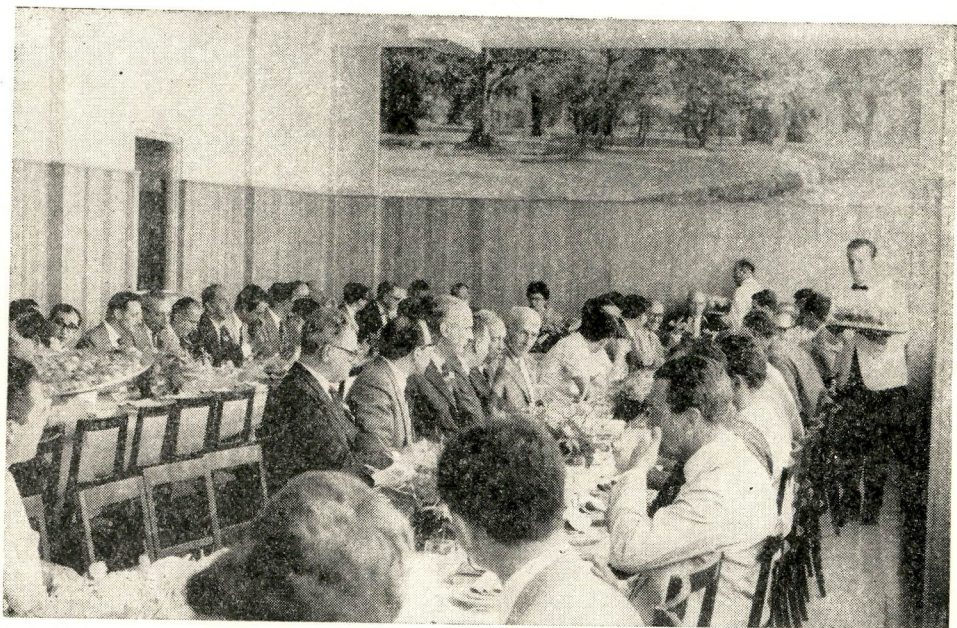
Chairman: **Dr. Joseph Burchenal**

Members: **Dr. Henry Kaplan**

Dr. John Ultmann

Dr. David A. Karnofsky

Dr. M. Vera Peters



Dr. Burchenal :

When many of us went to medical school, I think the general feeling was that HD was a generalized uniformly fatal disease of the lymphoid tissue and that there wasn't really very much one could do about it. You could give treatment, little palliative radiation therapy which was thought to make the patient feel better but there was considerable question whether it prolonged the survival time much. Since that time tremendous steps have been taken. You've heard this week a great deal about the possibilities of cure. This round table discussion will be on the possibilities of cure of the HD patient. We start off with Dr. Kaplan.

Dr. Kaplan :

I think that there are really two questions that we could discuss, may be more but the first is: "What kind of evidence do we have or could we look for that would establish that HD patients really are curable?" and secondly, using whatever evidence we have, "What estimates can one make about the prognosis for cure, not just for

survival but for cure, in the various stages of HD as our treatment techniques stand at the present time?"

I think many of you know the criteria that were stated by Easson and Russell a few years ago in their paper in the British Medical Journal. The criteria that Russell described essentially has to do with the flattening of the survival curve, so that it becomes parallel to the survival curve for a correspondingly distributed age and sex distribution in the general population. Obviously the nature of the normal curve will depend on the age and sex distribution of the type of tumor that one is discussing. The survival of normal people who are in the age bracket of cancer of the prostate will be very different from that of the expected survival of patients with an age distribution similar to that of HD, where there are many younger patients. One, therefore, would expect that in meeting the criteria of Easson and Russell the survival curve of a treated group of cases should, after some period of time, ultimately flatten out so that it becomes virtually completely flat with deaths thereafter being attributable only to those general causes of death

* Transcrição de gravação não revista pelos participantes.

that will affect any other people in the population. This is a good working definition of cure. It has one drawback that is difficult from the standpoint of working toward improving techniques of treatment, and that is it is too slow. One has to wait too many years to get the answer. It is therefore of great importance that we look for other indications of probable cure that we can observe and learn in the time interval after treatment.

I think one other index of cure might be mentioned, in passing, and then I want to discuss briefly the index of cure that we have been interested in.

I think everyone here has had occasionally the experience of observing a patient with HD who has died of some other cause, either due to acute coma or to some acute infectious process that was clinically unrelated to the original HD, and these patients have come to autopsy, careful autopsy has been done, with the previous history of HD known to the pathologist and no evidence of HD has been detectable at autopsy in such patients. There are many such instances on record now but unfortunately in any one Institution they are extremely few, and it is impossible to use such data really to prove very much beyond the unitotal value that the data have. Finally on this point, the criteria that I have been interested in has to do with the time interval from the first course of treatment to the first new evidence of disease. It is logical to assume that no patient died of HD without some clinical evidence that HD is active in that patient. Accordingly, the evidence of clinical activity should precede the time of death by, anywhere from a few weeks to several years. If the patient with HD has been treated apparently successfully and never again develops a clinical manifestation of disease, then it is going to be very difficult for him to die of HD. This is a very simple-minded logical approach and accordingly I began to look for data on this point, namely, the time interval in months between the first course of treatment and the first new manifestation of disease.

Initially I found that such data are very fragmentary. In the world's literature, there were only a handful of reports. This is sad

and surprizing when one considers how many Institutions around the world have such data in their files. One point I would like to interject here to our very dear host, Dr. Santos Silva, is that perhaps one of your young men here, at this Institution, where you have many cases in your files, could perhaps help us in this way, by searching your own records for this kind of information. What is needed is to record either in your own cases that have been treated here, and followed entirely here, or in cases that come to you from elsewhere, having been treated elsewhere, but these should be kept separately, the time interval from the first course of treatment until the first documented evidence of new disease, whether it's a lymph node or the development of fever which is later shown to be due to say bone marrow or liver involvement. I think that such data are of extreme importance and we need to get them from many parts of the world in order to know whether the little bit of data that I have been able to gather is valid and representative or not.

With that as a commentary I would like to show you just 2 slides to indicate the data that I have been able to collect to the present time from our own Institution. In addition to the material on the slides I might mention that the several case reports, approximately 6 case reports in the world's literature, in which this specific statistical information has been provided by various authors, indicates an average interval from the first treatment to the first new manifestation of approximately 12 months.

Here you see the first of 2 slides. In this slide I have tabulated the data for all patients with Stage I and II disease that we have treated on the linear accelerator, during the past 10 years or so in which there had been no previous treatment of any kind. This is again the interval to the first new manifestation of disease in months.

The cases have been shown classified by the time at risk. Obviously patients treated only during the last year could not demonstrate a new manifestation 5 years later because they haven't been followed that long. You'll notice that total count at the bottom shows that there were 109 cases avail-

lable for this analysis. Sixty-nine, or 62.12% of these patients have never, at any time, demonstrated a new manifestation of disease. Four patients have died of intercurrent disease without evidence of HD. Forty patients, or 47%, have at some later time, shown a new manifestation of disease. You'll notice that of those who have, out the 40 with new disease, 15 occurred during the first 6 months, after treatment was completed, 8 more during the next 6 months, altogether 57% of the new disease occurred during the first year. In 10 additional ones during the second year, so that altogether 82% of the new instances of disease occurred during the first 2 years. This is in a remarkably good agreement with an earlier, very crude estimation that I have made from our own data and that in the literature, which suggested that 85% of all new manifestations will occur by the end of 24 months after treatment.

Notice that in this particular study there were, of course, very few cases that had an opportunity to go longer than 5 years, only 26 were at risk, and there were none of these that showed new evidence of disease after the fifth year. In this particular group there was none after the fourth year. In any case it should be clear that the new disease is very strikingly expressed during the first 2 years, and becomes much less frequent thereafter and is extremely infrequent after the fifth year.

One could say: this is a selected group of cases and perhaps they have been selected in such a way as to reveal a biased distribution on this particular statistical manifestation. However I have now looked into another group of cases in which this criticism is not valid. These are patients who were first treated in some other Institution and they have come to us with new disease at some later date. If there are indeed many many cases of HD that are treated elsewhere perhaps who develop their new disease not during the first 2 years, but perhaps in the 5th year after treatment, or the 15th year, then surely, at random, we should see a reasonable sample of such cases in the patients that come to us since there is no obvious selection factor to bring

only the early recurrences to us for additional treatment.

In this slide you see an analysis of 60 cases in which treatment was first started at some other Institution, and the time at risk, anywhere from a few months to over 10 years, as indicated on the slide and you can see that there is only one case with a new manifestation occurring after the fifth year, in the eighth year. All of the remaining cases occurred in less than 5 years, and 90% of these were during the first 2 years.

I think that this other data, at least to me, seems to be rather convincing evidence that the time course of new evidence of disease is not randomly distributed, does not have an equal chance of occurring 5 or 10 or 15 years later, but is indeed extremely concentrated during the first 2 years, and to a lesser extent, during the first 5 years.

The data strongly suggests that if a group of 100 patients were to survive 5 years beyond the original course of treatment, one could be confident that at least 95 of those 100, and perhaps as many as 99 out of those 100, would indeed be permanently cured.

The final point I would like to make is just a brief recapitulation of what I think the prognosis might be with optimal technique in those Stages at the present time.

I stress that this has to be stated with some caution because my own data and those of Dr. Peters using the most recently devised techniques and using lymphangiography, relate still to a rather small number of cases. It will be necessary to extend such studies very considerably, not only in our own Institutions but in many other Institutions before we can be sure that the figures that have emerged up to this time are valid and representative figures. Nonetheless I would say that, optimally, it should be possible to offer permanent cure to patients in Stage-I in at least 85 to 90% of all cases. I think it should be possible to offer permanent cure to patients in Stage-II in approximately 70 to 80% of all cases, but here there will probably be a sharp distinction beginning to emerge between patients in Stage II-A and those in II-B, and I do not yet have enough data to give me

any reasonable impression of what the difference in prognosis will be, except that I am sure that there will be some difference in prognosis between the A and the B groups.

In Stage-III the statement must be made even more cautiously because, as you saw yesterday the data are extremely limited in addition to the protocol series of 19 radically treated cases that were on the slide I showed you yesterday I have approximately another 30 cases, nearly 50 cases altogether, that have been treated radically with demonstrated Stage-III disease. And of those the indications are that the overall survival free of disease for more than 2 years, and that is based on the data you just saw, one can hope that a 2 year survival cure of disease, will at least give some rough measure of potential curability. The survival free of disease for more than 2 years is approximately 60% in the entire group. My best estimate is that Stage III-A will turn out to be rather close, surprizingly close, to Stage II-A. Indeed I think that we may find that the curability of patients in Stage-III, if they have no constitutional symptoms, is better than that of patients Stage-II who do have constitutional symptoms.

The prognosis in Stage III-B is appreciably worse largely because many patients who appear to be in Stage III-B, on careful diagnostic evaluation, will, in fact, turn out later to have silent disease in the bone marrow, the liver, the lung or some other Stage IV site, which could not be detected at the time of the initial study because of the limitations of our present diagnostic techniques. So that I would predict that the optimal survival in Stage III-B, with our present techniques will probably not be much better than 30%.

In Stage-IV we still have no good estimates, but as I mentioned the other day, Stage IV is a very heterogeneous group of cases, and there are some patients with localized disease in the lung or in the subcutaneous tissue or even in the pleura, who are curable despite the presence of Stage-IV disease.

The chances are that these will comprise no more than 10 or 15% of Stage-IV, and

Stage-IV, at least in our experience, is a rather infrequent group, in HD. It is very difficult, at this time, to give any realistic estimate of curability. I simply want to make the point that even in Stage-IV there may be some cases that have chances for cure. They must be selected carefully. Certainly those with widespread bone marrow involvement are beyond the hope of cure by our present techniques.

Altogether, if one adds up the various proportions of Stages that we have found thus far, and if the proportions of Stages that we see are valid, that is, if they are representative, one might project an overall cure rate for HD. of somewhere between 50 and 70% as being possible, with the radiotherapeutic techniques that we have at our disposal at this moment.

Dr. Vera Peters :

I would like to merely confirm what Dr. Kaplan has told you so far, and add some evidence in the slides about to be projected.

The first slide demonstrates the flattening of the survival curve after 10 years even in the past experience. From 10 to 30 years, the survival curve in the overall picture is parallel to the survival curve of the normal population of equal age and sex distribution. Unfortunately I haven't demonstrated this by adding the survival curve, but I have worked it out at various times and I can say that it is fairly parallel with the experience in the central plotted line which gives the overall picture from 10 to 30 years.

The diversion after 25 years is merely because this represents a very small number of patients, I believe it was around 30 patients followed after 25 years.

Looking to the future, as suggested by Dr. Kaplan, this curve should present the same conformation but should be higher and the curve of Stages II-B and III should be slightly higher, but this remains to be seen.

The next slide gives the actual survival rate at 5, 10, 15, 20, 25 and 30 years in the past experience. Referring to the 10 year survival it is of interest that out of 358 patients we have now 100 who have survived

16 years or more, making an overall 10 year survival rate of 28%.

The next slide presents the medium survival according to the stage of the disease but using the old-staging, and will not apply exactly to the present clinical classification. In Stages I and II-A the median survival is somewhere between 10 and 12 years. Beyond that, in the later Stages the median survival is somewhere between 9 months and 2 years, if you group them according to early and late. This should be much higher and I'm not sure whether this will change but certainly the median for the later stages should rise somewhat in the future.

The next slide presents the data of actual causes of death amongst the patients who survived more than 10 years and who, in addition, had a 10 years freedom of disease interval. Some of them up to 25, 30 years. None of these patients died of HD. Actually the patients after being followed for 10, 15 or 20 or 25 years, enter the age group where cancer is more common than HD. Note that quite a few of these died of other cancers. One cancer of the cervix, 2 cancers of the bronchus, 1 carcinoma of the stomach, 4 of these died of other cancers, but none developed other lymphomas. We had in addition one other who died of extraneous disease at 8 years, who died of leukemia, I think I mentioned this one before.

This slide shows how we plotted out the effect of treatment on the 5 and 10 year survival. The top line is 124 cases who had a high tumor dose to the involvement and, in addition, received some treatment beyond the involvement to the adjoining lymphatic regions but, in our past experience this treatment was not of a high enough dose to avoid recurrent disease in a certain percentage. The lowest line is the survival curve of those who received a low tumor dose to the involvement and who did not receive any irradiation beyond the sites of involvement. The other 2 speak for themselves, the second line received a high tumor dose to the involvement but did not receive any irradiation beyond the involvement. The 3rd. line is the survival curve of those who received low doses to all the lymphatic regions, but did not receive ade-

quate treatment to any of the sites of involvement.

This is merely the evidence in the past experience of curability and the possibility that this will improve.

Dr. John Ultmann :

I would like to second the previous 2 positions that certain patients with HD are curable. I should also like to draw your attention for a moment to another way of looking at this so that we can see the whole perspective of what remains to be done. I'll do this extremely briefly.

Step 1 — I think ideally we would try and identify the etiologic agent of HD. I think that we are far from this and I don't think that the patients can wait for us to identify the agent and further more if tuberculosis, for example, is taken as a disease in which the agent has long been identified I think we will all agree that social factors, genetic factors and still other unknown factors would remain to be worked out for HD, after the agent is identified. In this regard I would only like to mention what Dr. Aisenberg has already brought up, and that is that when we have identified the agent that does cause HD we will have to face the problem of not only eradicating overt disease but preventing re-infection if there were such a thing. At the moment I think, as far as Step 1 is concerned, we are quite far removed from this ideal situation.

As far as Step 2 is concerned I believe that the most important thing in promoting curability of HD is to identify the patients with local HD. Although it is true that Dr. Peters data which she reported a number of years ago, and which we have already mentioned, that these data indicate that the patient who has the longest illness preceding appearance at the radiotherapy center may have the best prognosis because of indolent disease, it seems to me reasonable to assume that it might be useful to identify all patients early and still do better. How one can do this? I leave it to your own devices, education, alertness on the part of the physician, all th's will be helpful. In this regard the third Step in improving curability would be to alert the physician who is fortunate enough to see a patient

with one node, not to pass it up for a long period of time and just keep an eye on it, or watch it. That is, I think, a detriment to the curability of this disease.

As has already been mentioned, I believe that curability comes from the appropriate treatment, depending upon your own personal facilities, either of the local disease, with the ports that have been mentioned, or eventually of extended radiotherapy.

I think we tried to imply this morning that some progress in development of additional systemic agents will also add to the curability as defined by Dr. Kaplan, that is to say, not necessarily complete eradication of the disease but its control so that the survival of the patients approximates that of the cohort of his age group.

This was all the comment I wanted to make, Mr. Chairman, except if you permit me, since we did skip the role of surgery I thought I'd take one or two minutes to say a word on that.

You may have noticed, I don't know if the members of the audience received the first circular. This first circular had a section entitled: The role of surgery in the treatment of HD. If you look at your program now it has been modified to the role of surgery in the treatment of HD as seen by the non-surgeon. I think that is fair because all of us here at the table are non-surgeons I believe from previous experience with the Panel that we all agreed on the following: surgery as the definitive treatment of Stage I HD has no advantage, whatsoever, over aggressive radiotherapy as outlined by Drs. Kaplan and Peters.

All the patients in the literature, or almost all who have had surgery with intent to cure, have had further radiotherapy with the intent to cure a little better. Since the surgeon is incapable of knowing that he has removed that last lymph node, and since he makes it a little more difficult for the radiotherapist to do the very best job, most of us feel that the treatment of choice does not lie in this area.

Since I firmly believe that I must maintain my friendship with the surgeons, I'd like to just show you that there are plenty of things to do for the surgeon. Furthermore you'll have to have a surgical friend who

will help you make the diagnosis of the disease. The surgeon most often will help you with the lymph node biopsy. He may have to biopsy other areas and you can encourage him to do so rather than to treat without a histologic diagnosis. He will be glad to assist you with thoracotomies and laparotomies to make the diagnosis. He may have to assist you in emergencies with laminectomy and establish at the same time the diagnosis.

The second portion of the slide shows you that in the course of the treatment of a patient with HD the surgeon may have plenty to do. If you encourage him that there are things he can do he may not want to cure the patient, he may want to help you to keep the patient well. Amongst the things that he can do for most is the patient who has less than 24 hours onset spinal cord syndrome, in whom the advance of the disease is extremely rapid. The patient may be better off to have a laminectomy followed by radiotherapy than to have radiotherapy alone.

The patients may have obstruction in the gastro-intestinal tract or urinary tract, or hemorrhage from the gastro-intestinal tract in which there is some usefulness for surgery, of course. I'll come back in one minute to splenectomy. There is a role for control of pain in the patient who is severely incapacitated and may need a chordotomy or rizotomy or something in that neighborhood.

Obviously with Dr. Kaplan and Dr. Peters placing patients into categories where they will have a normal survival time as of their cohort, opens large vistas for the surgeon, namely, many unrelated conditions will occur and he can take care of this, of course, and should take care of them, and never should the internist or the surgeon assume that it is HD that is causing a new symptom. It, more likely than not, after the second or third year, is appendicitis, cholecystitis, adhesions, or what you will, or a new cancer even.

The next slide summarizes the indication for splenectomy. Occasionally when the hemolytic anemia or the thrombocytopenia, or the leukopenia can be demonstrated by the appropriate isotope studies, or by other

means, to be due to hypersplenism, it may be useful to remove the spleen.

The next slide, borrowed from Grace and Mittleman, in Buffalo, Roswell Park, indicates the experience in 5 patients, who had a red cell survival done before and after splenectomy. Before splenectomy the half-life was 11 days and after splenectomy it was normal. However I wish to remind you, if you look at their paper, that splenectomy carries a greater morbidity in HD than, let us say in Laennec cirrhosis or in post-traumatic splenectomy.

Finally I can't help but close reminding you once more that it can be quoted from the article by Grace and Mittleman that: "it is our opinion," they say, "that the role of surgery in the overall management of HD is limited to the excision for diagnostic purposes and to the management of unrelated problems which might require surgical intervention." This, I believe, is the considered judgement of most surgeons and, I think, the considered judgement of all radiotherapists and internists. (*)

Dr. David Karnofsky:

It is unfortunate that I have to be last in this group because I am not sure of the term "cure", although Dr. Kaplan has a definition for it. That does not necessarily mean that his definition is applicable to HD.

I think we like to use the word, as a matter of fact will be using the word, because I like to think that we do cure patients with HD, but nevertheless, in order to maintain a perspective on the disease and fill in the gaps that Dr. Ultmann mentioned, I think we have to avoid the use of such a definitive term. For example in tuberculosis, do we cure tuberculosis with chemotherapy? The answer is no because one may still find foci of tubercle bacilli and these may actually rise up again many years later under certain conditions. Then I think we think in terms of cure when these patients are controlled for long periods of time. Or if one gives insulin in diabetes the patient is controlled, we don't cure the disease but we come pretty close to elimi-

nating many of the immediate complications of the disease by insulin. So I would much prefer the use of the term "control" of HD. Also even in those patients that don't fall under the category of cure by virtue of the fact that they don't recur say, after they are free of disease for a 5 year interval after treatment. There are many patients with HD who do have recurrent disease. They are not cured, by any definition, yet they may work for 15 or 20 years requiring intermittent courses of treatment.

The Panel may want to go into more details exactly what it is meant by cure. A second consideration I think we have to face in discussing the term "cure". I think everyone is thinking of "cure" in relation to the effects of treatment. We have to accept the fact however that there have been patients with HD who had minimal treatment and have apparently been free of disease for many years. This is what Dr. Kaplan calls the unitotal method, but on the other hand it is still true and it indicates that there is a variation to the disease. So one can say that HD by the definition advanced, is curable even without very effective treatment. I mentioned the case yesterday of a patient who went into spontaneous regression for an unexplained reason and he apparently is cured.

I think the big question that we are trying to decide here really is: Is cure dependent on the administration of a particular form of treatment? I think yesterday I outlined the reasons for accepting intensive and extended radiotherapy as the most reasonable and effective form of treatment of HD. I agree with Drs. Kaplan and Peters that one must proceed on this basis, to treat our patients and I believe that they are correct. I'm not trying to minimize their contribution or the fact that this is the best present method of approaching the problem of HD.

I think one must keep an open mind until the data are conclusive that there is a positive correlation between the intensity and precision of therapy in suitable cases and the number of patients who live long enough, to die of unrelated causes the same as their cohorts in the population.

* Ver página ... deste Simpósio.

Dr. Joseph Burchenal:

Despite the fact that occasional spontaneous regressions occur, and sometimes people get better without perhaps what we do consider adequate therapy, you still feel that this massive intensive therapy should be used?

Dr. David Karnofsky:

I don't think there is any doubt that patients have lived longer and had longer periods free of disease, but I think it's the intellectual objection to the meaning of the term "cure", which may confuse our understanding of the disease.

Dr. Joseph Burchenal:

It's more an intellectual than a private hope?

Dr. David Karnofsky: Yes.

Dr. Henry Kaplan:

Dr. Karnofsky does not accept the definition of cure that I gave but the critical analysis that I presented as an indication of possible cure. I think it is fair to call on him for his own definition of the word "cure". As opposed to control what would you accept as a cure?

Dr. David Karnofsky:

Well I think as has been suggested already that the definition of the term of cure of HD ultimately may be dependent on the identification of the patho-physiology of the disease or the defect in the cells that are responsible for the disease and some method of demonstrating conclusively that there is no longer any evidence of this process, or the systemic disturbance, that may help the disease to exist in the individual. And this I realize is a very fanciful argument because you don't have these tools at the moment but I think there's no objection to waiting as long as your patients feel well and survive indefinitely.

Dr. John Ultmann:

I think it is wonderful to end a factual Symposium on philosophical notes. I think it's very appropriate and since you're all fatigued, you can sort of not fight back this

impulse we have to be philosophical. I will side with both Dr. Kaplan's definition and Dr. Karnofsky's. I've already mentioned personally that I agree with Dr. Karnofsky that there are many things still missing till we can speak of cure in the intellectual sense of the word. We have to understand, we have to fulfill certain postulates and so on. But on the emotional and educational side I'm afraid I must completely agree with Dr. Kaplan. I would like to reiterate this point for the following reason. Since the past few years, since Drs. Kaplan and Easson and Peters and others, have aggressively asked the medical profession the question: "Can HD be cured?" the profession has responded by examining its activities in an attempt to cure HD. That is to say, they have at last questioned the relevance of giving small doses of treatment. I think that, although intellectually I'm completely with Dr. Karnofsky, I think it would be a mistake if you went away and we broke down this wonderful concept which actually is going to bear direct benefit to the patient, namely certain patients with HD, treated a certain way can be cured. Let's cure them. Other patients, unfortunately cannot, but that's another subject.

Dr. Joseph Burchenal:

There have been certain chemotherapists who claimed that the reason chemotherapy gets such poor results is because it is used in Stage III and Stage IV disease. And that if they could only treat the early Stage I disease that they could get much better results. I believe the group in Russia have done some of this. Dr. Kaplan would you care to make any comments about the use of chemotherapy early, in place of radiation therapy?

Dr. Henry Kaplan:

At the time of the Rye Conference the only data that we could find in any one series were those that Dr. Wintrobe had at Salt Lake City and because Dr. Wintrobe was ill at that time it was not possible for him to pull out the data from his files to establish just how good this treatment really is. But to my knowledge that's the only significance there is in which reported Stage

I and II cases have been treated in this way. It's fair to say that none of those patients did have lymphangiograms, so it's probably unfair even to Dr. Wintrobe to analyze them since even he doesn't know whether they were Stage I or Stage II disease. Indeed we are in a curious situation of having to do our work over again in the post-lymphangiogram era because a great deal of the data that has been published in the past, prior to the general use of lymphangiography is no longer valid in the light of what we now know about the diagnostic inaccuracy of such data.

I will mention in this connection, for example, the paper by Shear from Memorial Hospital, on the spread of reported Stage I disease. I cannot say that it is not true but I can say that he does not know if it is true or not, because none of those cases had lymphangiograms.

Dr. Joseph Burchenal:

The reason I brought this question up is that from animal experimentation we know that the smaller the tumor the better the results with chemotherapy. I believe that the Russians' results, and I gather that Dr. Wintrobe's results also were better on Stage I and II than they were on far advanced disease. That's to be expected. The point that I would like to bring out is that these are just relatively slightly better, whereas the things that Dr. Kaplan and Dr. Peters are talking about patients where the disease goes away and does not come back, not for just a year, or 6 months or something like that. They remain free of their disease for many many years, and are presumably cured. It seems to me that chemotherapy in Stage I or II is absolutely contra-indicated, unless it might be given as an adjuvant to intensive radiation therapy, but it should in no way take the place of radiation therapy.

Dr. Vera Peters:

I just wanted to mention one other philosophical aspect of cure versus control. I think it is very important that we continue to use the word "cure" and we can always modify it by calling it apparent cures, because it gives the patient hope. The patients are young and they are very active,

they all want to know how long they could live and they want to know whether they should have families. All these things are so important to the potentially curable patient — here I am using it again — but I think we should get the cure habit in order to give the patients hope, because it has a tremendous effect on their attitude and on the way they accept their responsibilities after treatment and later.

Dr. Henry Kaplan:

I agree with Dr. Peters about the emotional importance of being able to use the word cure if there's any reasonable basis for doing so and I think we have presented the evidence that there is a reasonable basis.

I will also point out that while we are on the rebuttal from Dr. Karnofsky, that waiting for an understanding of the etiology and pathogenesis of the disease before we can invoke true cure, may be like looking for the pot of gold at the end of the rainbow. Dr. Ultmann has already mentioned that in one disease, namely tuberculosis, where we do know the cause, and we know many of the factors we have not really achieved a cure. We can easily point to a number of kinds of cancer where cure rates are now reasonably well established, where the tumors are under direct vision, that is we can see them either in the eye or on the skin and where there's freedom from the cancer for many many years, it is well documented and we can speak of cure even though we do not know the cause of either cancer of the skin or retinoblastoma. Therefore I don't see the compelling logic of having to understand the etiology of HD in order to speak of cure, if we are prepared to accept the concept of cure for any other disease for which we do not yet know the etiology.

Dr. David Karnofsky:

In self-defense I can say that I also use the word cure and I think that I've said earlier that I have no objection to the term. I think it can be a sterilizing term, not just in HD but also of our understanding of the process and I don't believe I said we have to understand the etiology to employ the term "cure". If you have some basis for

demonstrating whatever the pathogenesis or problem produced by some biochemical disturbance produced by the disease, if there is an underlying disturbance that it has been eliminated. In the case of retinoblastoma, as Dr. Kaplan points out, it is a local problem and when the tumor is destroyed apparently it does not recur. That may be true of localized HD, but there's evidence to suggest that it may not be, and this is really the area we're talking about. I will concede for practical purposes, in patient management, and in encouraging physicians to treat their patients properly, aggressively, adequately, that this Panel should agree that HD can be cured.

Dr. Henry S. Kaplan

In addition to the well-known criterion of cure formulated by Easson and Russel (1), other evidence is now available to support the view that permanent cure of Hodgkin's disease can indeed be achieved. A number of patients have died of intercurrent disease several years after treatment for Hodgkin's disease and have revealed no evidence of Hodgkin's disease at postmortem examination. If macroscopic disease were still present in clinically quiescent form in such instances, it should have been detectable at autopsy.

Secondly, I have previously called attention to the fact that new manifestations of

Hodgkin's disease are not randomly distributed in time, but tend to occur predominantly within the first two years after the initial course of treatment and decrease in frequency rapidly thereafter to become quite rare after the fifth year. A more recent analysis of our data will be presented to document this point more conclusively. Two groups of cases have been analyzed: (a) previously untreated patients with Stage I and Stage II Hodgkin's disease, who have received radical radiotherapy at Stanford Medical Center; and (b) patients previously treated elsewhere, who have come to Stanford Medical Center with new disease activity requiring treatment. In both series, it was found that between 80 and 90 per cent of the new clinical manifestations occurred within the first two years after the initial course of treatment, and only one case was encountered in which the first new manifestation of disease occurred after the fifth year. It should be clear, therefore, that a patient who has remained well for five years after an initial course of treatment has a very great chance, on the order of 95 to 99 per cent, of being permanently cured.

REFERENCE

- 1 — EASSON, E. C., and RUSSELL, M. H. The Cure of Hodgkin's Disease. *Brit. Med. J.* 5347: 1704-1707, 1963.