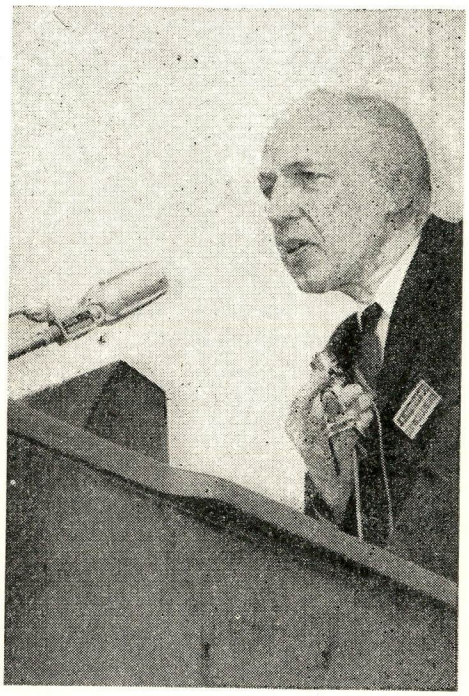
THE ROLE OF CHEMOTHERAPY IN THE TREATMENT OF HODGKIN'S DISEASE*

DR. DAVID A. KARNOFSKY



I want to take this opportunity to thank the members of the Brazilian Health Service and the National Cancer Institute for inviting me to participate in this Symposium. It's been an instructive and pleasurable experience.

The size and resources of Brazil are overwhelming and the opportunities unlimited, and on each visit here one is stirred by how much more has been done and yet what still remains to be done. The common interest in the achievements and progress of Brazil and the United States unites us as much as do the ties of our profession.

The use of drugs in the chemotherapy of lymphomas began in 1942, 25 years ago, during World War II, when Goodman, Gilman, **et al.** (1) under conditions of military secrecy administered a derivative of nitrogen mustard, tris (B-chloroethyl) (HN3), to patients with leukemias and lymphomas. A year later, in 1943, Dr. Leon Jacobson, of the University of Chicago, studied methyl bis (B-chloroethyl) amine (HN2) under the same secret precautions, since HN2 was a potential war gas, and observed therapeutic responses in Hodgkin's disease. Following the end of World War II, the first published reports appeared on the use of nitrogen mustard in the treatment of Hodgkin's disease (2, 3, 4).

Since 1947 many potential anti-cancer drugs have been tested for therapeutic activity against neoplastic disease in man, and in almost every instance the drugs have been evaluated also in patients with Hodgkin's disease.

Polyfunctional alkylating agents

The different categories of drugs that have been tried include the nitrogen mustard group, which are also referred to as the "polyfunctional alkylating agents". More than 50 functional alkylating agents have been prepared for clinical trial. Following the clinical studies with HN2 and HN3, triethylene melamine (TEM) was widely used, because it was effective by both the oral and intravenous routes (5). Chlorambucil became available in 1954 and has been used extensively by the oral route, and in 1957, cyclophosphamide (Cytoxan, Endoxan) was developed for oral and intravenous administration.

Advantages of the new derivatives are: 1) they are effective and usually well-tole-

---

* Transcrição de gravação, revisto o original pelo autor. This investigation is supported in part by the INC grants CA-08748 and CA-05826.

rated by mouth and, 2) in contrast to nitrogen mustard, they can be given intravenously without causing severe nausea and vomiting. There is little evidence that one alkylating agent has any greater specificity for Hodgkin's disease than another, or that it will produce a more selective therapeutic response at doses causing less severe injury to the bone marrow. Some clinicians believe, however, that cyclophosphamide produces less platelet depression than the other alkylating agents, at equivalent therapeutic doses, and, therefore, recommend its use when bone marrow function is impaired.

Antimetabolites and Antibiotics

Antimetabolites, including methotrexate, 6-mercaptopurine, and 5-flourouracil, have been evaluated in Hodgkin's disease, and none appears to have an important role in the treatment.

Antibiotics, such as Actinomycin D, streptonigrin, and mitomycin-C, have been used in Hodgkin's disease and, while they have produced objective evidence of benefit, they are not as effective as other available drugs.

Adreno-cortical hormones first became available for clinical use in 1949. They have been used extensively in Hodgkin's disease, and prednisone is the most widely used derivative. There is a specific indication for prednisone in acquired hemolytic anemia, but it should not be used as a primary form of treatment or as a supportive measure during the major course of the disease. They are largely employed in the patients with very far advanced disease refractory to other forms of treatment, when brief periods of symptomatic improvement may result (7).

Vinca alkaloids

These became available about 1960 and both vinblastine and vincristine have important indications in the relief of symptoms and control of systemic disease (8).

N-methylhydrazine (Procarbazine, Natulan)

This agent was developed in Switzerland, and it is the most recent addition to the group of drugs active in Hodgkin's disease (9).

The use of drugs in the management of Hodgkin's disease will be discussed under 5 headings:

1. Techniques of evaluation for therapeutic activity.
2. Properties of the presently available drugs,
3. Evidence for therapeutic activity in patients,
4. Indications in specific clinical situations, and
5. Experimental approaches to enhance chemotherapeutic activity.

1. **Techniques of evaluation for therapeutic activity:** In testing drugs for therapeutic activity, the evidence for a favorable effect in Hodgkin's disease is based on suppression of manifestations of the disease, such as a decrease in the size of enlarged lymph nodes, liver and spleen, decrease in fever and itching, increase in well-being, etc. It has not been feasible, with the drugs thus far evaluated, to measure their effect on survival time since favorable responses are usually brief and must be maintained by frequent courses of treatment. If a drug produces a prolonged or permanent disappearance of the signs and symptoms of the disease in a significant per cent of treated patients, prolongation of survival will become apparent, but this has not been the case for the drugs now in use.

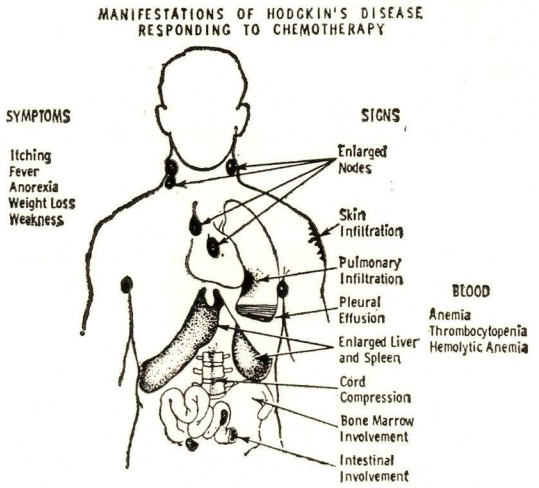


Figure 1 demonstrates some of the major manifestations of Hodgkin's disease which may be modified by chemotherapy, and are

useful in measuring the therapeutic activity of a drug. Each patient, prior to treatment, has the important abnormalities due to the disease listed, such as cutaneous manifestations, pulmonary infiltrates, effusions, hepatosplenomegaly, bone marrow involvement, anemia, thrombocytopenia, fever, weight loss, weakness, etc. After an adequate trial of treatment, the degree and duration of improvement in the listed criteria are determined, e.g., regression of enlarged nodes and decrease in fever. Besides these specific changes, we are interested in measuring the overall benefit to the patient in terms of his performance status (PS) (Table 1). If the patient had a performance status of 60 prior to treatment because of a high fever, weakness and inability to do useful work, restoration to normal activity, PS 90, represents substantial benefit. In contrast, a patient may show objective regression of lymph nodes and relief of fever without significant change in his PS, which remains at 60; the beneficial effect of the treatment in this situation may not be apparent to the patient.

TABLE 1
CRITERIA OF PERFORMANCE STATUS (PS)

	%	
ABLE TO CARRY ON NORMAL ACTIVITY; NO SPECIAL CARE IS NEEDED.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort some signs or symptoms of disease.
UNABLE TO WORK; ABLE TO LIVE AT HOME; CARES FOR MOST PERSONAL NEEDS; A VARYING AMOUNT OF ASSISTANCE IS NEEDED.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires ocasional assistance but is able to care for most of his needs.
	50	Requires considerables assistance and frequent medical care.
UNABLE TO CARE FOR SELF; REQUIRES EQUIVALENT OF INSTITUTIONAL OR HOSPITAL CARE; DISEASE MAY BE PROGRESSING RAPIDLY.	40	Disabled; requires special medical care and assistance.
	30	Severely disabled; hospitalization is indicated, although death not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

We have also developed a simple classification of **Category of Response** of the patient to a particular drug, so that we can compare the results obtained with different drugs in terms of suppression of the manifestations of the diseae (Table 2). Patients obtaining a O-A, B, or C category of response may show some drug effect, which may be of scientific interest, but the response is without significant benefit to the patient. Category I responses refer to significant degrees of improvement which are of practical value to the patient. It is necessary to treat a substantial group of patients in order to arrive at a picture of the drug's range and duration of effectiveness, and the results of treatment in each case must be related to the degree of toxicity induced by the drug.

As Dr. Ultmann noted earlier, there is a definite association between the frequency, degree and duration of improvement to

treatment and the inherent rate of progression of the disease. If the disease is rapidly progressive, the response is generally brief, whereas it is more complete and prolonged in patients with a less severe form of Hodgkin's disease. The duration of improvement may, therefore, correlate better with the activity of the disease than with the efficacy or lack of efficacy of a particular drug. Nevertheless, the effective agents noted do appear to have some degree of specificity, in that a patient refractory to one class of drug, such as an alkylating agent, may respond to a vinca alkaloid or procarbazine.

TABLE 2

CATEGORIES OF RESPONSE

CATEGORY 0 NO CLINICALLY USEFUL EFFECT ON THE COURSE OF THE DISEASE

0 — 0	Disease progresses — no objetive or subjective benefit.
0 — A*	Subjective benefit without favorable objective changes.
0 — B*	Favorable objective changes without subjective benefit.
0 — C	Subjective benefit and favorable objective changes in measurable criteria, but of less than one montn's duration; then the disease progresses.

CATEGORY I CLINICAL BENEFIT WITH FAVORABLE OBJECTIVE CHANGES IN ALL MEASURABLE CRITERIA OF THE DISEASE

I — A*	Distinct subjective benefit with favorable objective changes in all measurable criteria for one month or more.
I — B*	Objective regression of all palpable or measurable neoplastic disease for one month or more in a relatively asymptomatic patient, who is able to carry on his usual activities without undue difficulty. The observed tumor regression should be unequivocal and it is suggested that all lesions be reduced at least 50% in bulk. This category applies as long as the regression persists, and ends if any lesion old or new recurs.
I — C	Complete relief of symptoms, if any, and regression of all manifestations due to the active disease for one year or more. The relation to the frequency of therapy is not relevant, if the disease does not recur between courses of therapy.

* Categories apply as long as improvement from baselines persists. Superscript: time in months of duration of response. Example : $0 — A^4$ or $I — B^3$.

CATEGORY II INTERRUPTION OR SLOWING IN THE PROGRESSION OF THE DISEASE WITHOUT DEFINITE EVIDENCE OF SUBJECTIVE OR OBJECTIVE IMPROVEMENT. No criteria are presently available to classify this type of response. Statistcial evidence of prolongation of survival time in specific patterns of cancer may some day be applicable.

ADEQUATE THERAPY

The adequacy of the course of treatment should be defined in the patients who complete the course of treatment. In most cases therapy is given to the of toxicity in order to give the maximum opportunity for an anticancer effect. If the patient can be observed following treatment for at least two weeks for signs of benefit, this ordinarily represents an adequate trial.

If tumor regression and a satisfactory clinical response occur before signs of toxicity appear, this is also considered an adequate trial.

LEVELS OF TOXICITY

1 + —	Slight
2 + —	Moderate
3 + —	Life threatening — patient recovers
4 + —	Directly lethal or a proximate contributory cause of death

2. **Properties of the presently available drugs:** The drugs used in the treatment of Hodgkin's disease are well know, and they will be reviewed briefly:

Nitrogen mustard (Mustargen, HN2). This is the earliest and one of the most widely used polyfunctional alkylating agents. It is given intravenously, and the usual dose is 0.4 mg/Kg. of body weight. We generally give this as a single dose if the patient has normal bone marrow function and is in good general condition. If there is any question about the patient's status we may fractionate the dose, 0.2 mg/Kg. as asingle dose repeated in a few days if the blood picture is satisfactory. At therapeutic doses, the alkylating agents may produce a decrease in the leucocyte and platelet counts and hemoglobin level. If the patient receives an excessive dose, this will result in bone marrow depletion, with increased susceptibility to infection and bleeding manifestations. HN2 as well as the other alkylating agents must be used cautiously, since maximal change in the peripheral blood picture may not occur for 2 to 3 weeks after the last dose. The use of these agents, therefore, requires frequent examinations of the peripheral blood picture. HN2 is used principally in acute situation, when a rapid response is required, such as spinal cord compression, superior vena cava syndrome or respiratory distress due to Hodgkin's disease. In ambulatory patients, where maintenance therapy is feasible, alkylating agents without the acute gastro-intestinal effects of HN2 are preferred.

An alternative to HN2 is intravenous **thio-TEPA.** In comparative studies it appears to have a therapeutic action similar to HN2, and it has the advantage of causing less nausea and vomiting. The total dose is generally about twice that of HN2 by weight; we generally give 0.8 mg/Kg. as compared to 0.4 mg/Kg. of HN2. If the patient will not take an oral alkylating agent as directed, thio-TEPA intravenously, 0.2 to 0.4 mg/Kg. once a week or every other week, may be a satisfactory form of maintenance therapy.

Of the oral alkylating agents, we prefer **chlorambucil** in most situations. The usual dose is 0.1-0.2 mg/Kg. (6-12 mg) each day, and a favorable response may occur in 2 to 3 weeks or sooner. The dose must be decreased in patients with poor bone marrow function, and in all cases the blood count must be followed at weekly intervals. If the patient responds, a maintenance dose of 2-4 mg/day may be effective. This should be interrupted periodically to allow the bone marrow to recover, if meanwhile the disease is being controlled satisfactorily.

Cyclophosphamide may be given orally or intravenously. The intravenous dose, equivalent to 0.4 mg/Kg. of HN2, is 40 mg/Kg. or about 100 times as much by weight. This dose can be decreased or fractionated if there is concern about the patient's bone marrow function. Cyclophosphamide causes less nausea and vomiting than nitrogen mustard. The daily oral dose is in the range of 1-3 mg/Kg. (50-200 mg), and this can be given daily for long periods. The chief disadvantages of cyclophosphamide are the occurrence of cystitis, which may be hemorrhagic, and temporary alopecia. There is a clinical impression that cyclophosphamide is more useful than the other alkylating agents in reticulum cell sarcoma.

A second class of drugs in Hodgkin's disease is the vinca alkaloids, **vinblastine** (Velban) and **vincristine** (Oncovin). **Vinblastine** differs from vincristine only in the presence of a methyl in place of a formate group, but this produces a considerable difference in their pharmacological properties. Vinblastine is generally the preferred derivative in Hodgkin's disease. It is usually given intravenously once a week, in the dose range of 0.1 to 0.3 mg/Kg. We begin at the lower dose ,and if a satisfactory response occurs, this same dose is continued; otherwise, it may be raised each week to 0.15-0.20 mg/Kg. if the blood picture allows. A maintenance schedule can be established in the responsive patient, and 0.1 mg/Kg. given at weekly or every other week injections. The most important toxic effect of vinblastine is bone marrow depression, which may be transient, and the blood count should be obtained before each injection. Occasionally some patients develop signs of neurotoxicity, including a peripheral neuritis, ileus, constipation, as well as alopecia and stomatitis. **Vincristine** is used in patients with impaired bone

marrow function, since the neurotoxicity is generally the limiting factor in dosage. The usual dose is 0.01-0.025 mg/Kg. (0.6-2.0 mg) intravenously each week. The patient must be followed carefully for a loss of deep tendon reflexes and neurotoxicity. If a response is obtained at 0.025 mg/Kg., a maintenance level may be established in the range of 0.01-0.015 mg/Kg. each week.

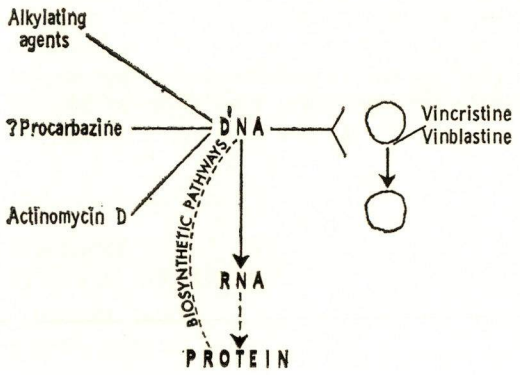
A third class of drugs is the **adreno-cortical hormones,** of which **prednisone** is the principal representative. When prednisone is used in far-advanced Hodgkin's disease, no longer responsive to alkylating agents, vinblastine or x-ray therapy, we generally begin with a large dose, in the range of 60-100 mg/day, and if significant improvement occurs, this dose can be reduce to maintenance levels, although generally large doses are necessary. In hemolytic anemias, a smaller dose may be adequate.

The newest drug for Hodgkin's disease is **procarbazine** (Natulan). This drug is still an experimental agent in the United States, and has not been approved by the Food and Drug Administration for commercial sale. Procarbazine is given orally, at a daily dose ranging from 50 to 300 mg/day. One generally begins with the smaller dose, and as the patient becomes acclimated, the dose is increased. The nausea and vomiting, which often occur at the onset of treatment, tend to disappear as treatment continues. After 2-3 weeks at a dose of 200-300 mg/day, when the blood picture begins to be adversely affected, the dose is temporarily interrupted or reduced to a maintenance level in the range of 50 mg/day. Procarbazine is active in Hodgkin's disease, but its indication in relation to the other drugs available, has not been defined.

Actinomycin D (Cosmegen) has been effective in Hodgkin's disease, but it is not as useful or as well tolerated as the other agents described, and we no longer recommend it.

It is interesting to consider the site of action of drugs which influence some of the manifestations of Hodgking's disease. Figure 2 shows the classical sequence in cellular growth and function; DNA producing RNA, including messenger RNA, which in turn directs the synthezis of specific proteins or

CELLULAR EFFECTS OF DRUGS USED IN HODGKIN'S DISEASE



enzymes. Replication of DNA precedes cell division. Of the many drugs studied in Hodgkin's disease, the effective ones appear to act on DNA, either altering its structure or interfering with its funcion. The alkylating agents and procarbazine have been shown to damage DNA, Actinomycin D interferes with the formation of DNA-dependent RNA, and the vinca alkaloids inhibit mitosis. The drugs which interfere with biosinthetic pathways in proliferating cells have been weakly active or ineffective in Hodgkin"s disease. At present there are no data on the specific cells in Hodgkin's disease susceptible to the anti-cancer drugs which results in regression of enlarged nodes, and alleviation of systemic symptoms. Are the neoplastic cells the ones that are being damaged directly or is a normal cellular reaction to the neoplastic cells being suppressed? This is a problem ready for intensive investigation.

3. **Evidence for therapeutic activity in patients:** In quantitating the therapeutic activity of an anti-cancer drug in Hodgkin's disease, it has been noted earlier that the individual patient's response varies with the clinical activity of the disease; if the patient is in good general condition, with rather indolent disease, the response to any effective agent may be complete and prolonged. If the patient has a more acute process, and if he is refractory to radiotherapy and to other chemotherapeutic agents, the response to a new form of treatment is usually poor. Reported response rates to specific agents are largely meaningless, unless the clinical status of the patients

treated is described in detail and the type of response clearly stated. With the alkylating agents, for example, one can expect a Category I response rate of 90% if the drug is used as the first treatment; late in the disease response rate may drop to 60% or less. A generalization, with many exceptions, is that the response rates to the effective agents againts Hodgkin's disease are approximately the same in patiens in similar circumstances, although patients refractory to one agent may sometimes respond temporarily to another type of drug. In Tables 3 and 4 are listed recent data on

TABLE 3

HOGDKIN'S DISEASE

CLINICAL EFFECTS OF IV VINBLASTINE

Total number of patients = 79
Number adequate = 79

Category of response	Number	Numbers of patients/duration of responses Months												
I — C	7	13	14	15	16	17	18	19	20	21	22	23	24	36
		2	1+			1						1	1+	1
		Months												
I — A	35	1	2	3	4	5	6	7	8	9	10	11	12	
I — B	6	10	7	4	2	2	2	1	1	2	2	2		
O — A, B														
C, II	23		2			2	1	1	1					
O — O	8													

This table is reproduced with the king permission of the authors MacDonald and Lacher (11).

TABLE 4

HOGDKIN'S DISEASE

Total number of patients = 79
Number adequate = 56

Category of response	Number	Numbers of patients/duration of responses Months													
I — C =	1														
I — A =	33	1	2	3	4	5	6	7	8	9	10	11	12	13	14
I — B =	1														
O — C =	6														1+
O — B =	1							1							
O — A =	4	10	11	3	4	1	2				2				
O — O —	10														
Too early to evaluate =	2														

This table is reproduced with the kind permission of the authors Brunerr and Young (9).

categories of responses with vinblastine (11) and procarbazine (9). Of 79 patients receiving an adequate course of intravenous vinblastine, 48 had a Category I response, ranging from 1 month to 36 months. Of this group, 7 had a I-C response, in that all evidence of disease disappeared for one year or longer. Seventy-one of the 79 (90%) patients showed evidence of therapeutic effects from vincristine, but in 23 the response was brief and inconclusive.

Of 53 patients receiving an adequate course of procarbazine (Table 4), 35 (62%) obtained a Category I response, and 46 of the 56 patients (82%) showed some evidence of therapeutic activity, although in 11 cases it was of no significant benefit to the patient. The duration of improvement with procarbazine was considerably shorter than with vinblastine, 1-2 months as compared to 4 months, but this may be due, in part, to case selection. We are attempting to develop better methods of presenting clinical result in order to clarify comparative therapeutic activity of chemotherapeutic agents.

4. **Their indications in specific clinical situations:** How does the physician know which drug to use in a specific clinical situation; should he give vinblastine, vincristine, chlorambucil or nitrogen mustard? There are no firm rules, because much of the basis for a decision depends on the physicion's training, experience with various agents, availability of x-ray therapy, and his analysis of the clinical problem. All that one can emphatically recommend is that the physician analyze the situation carefully, review the patient's previous treatments and the responses that occurred, and define in his own mind what he hopes to accomplish by a particular method of treatment. He should then act deliberately, and give each drug an adequate trial before turning to another form of treatment. I can briefly comment on some of our own preferences in the use of these drugs.

For acute situations, such as impending cord compression or acute respiratory distress due to superior vena cava compression, we prefere nitrogen mustard, although thio-TEPA may be an equally effective alternative. We have more confidence in the dose of nitrogen mustard that is both safe and effective. If the patient is ambulatory, and does not require a rapid course of treatment, chlorambucil is the oral alkylating agent of choice. We prefer using an alkylating agent as the first drug, and if the patient becomes resistant to it, vinblastine is the second agent. If serious bone marrow depression exists, vincristine would be used instead of vinblastine. Procarbazine is the third agent, and prednisone may be used in the advanced stages of the disease. We use one drug at a time because it is easier to follow the patient in terms of giving an adequate dose, and the therapeutic activity of this drug can be interpreted.

The major indication for chemotherapy is the patient with generalized disease and systemic symptoms, such as fever, itching, weight loss and anemia which has not been controlled by localized x-ray therapy. In the situations the use of drugs may suppress symptoms and keep the patient in good condition for long periods. We maintain a close liason with our radiotherapists, and while chemotherapy is used to try to alleviate symptoms, in many cases persistent local disease is treated with radiotherapy. If indicated, or, to put it another way, we are not alarmed by a depressed leucocyte count due to chemotherapy if local radiotherapy is required. As the disease advances, one must be prepared to accept greater risks from treatment in the hope of obtaining clinical improvement.

5. **Experimental approaches to enhance chemotherapeutic activity:** Finally, I will comment briefly on some experimental problems in the treatment of Hodgkin's disease. A distinction should be made between the use of anti-cancer drugs in a convencional and acceptable manner, and their use in a controlled study under experimental conditions. If a patient is being managed in a convencional manner, one may modify the treatment, or add other drugs in the interests of total patient care. In a controlled study, the patient is being managed under a carefully developed protocol, and treatment is continued until the study is completed. In beginning a controlled study, there must be some preliminary evidence to

suggest that the design of the study will lead to a meaningful conclusion. In Table 5 are listed several current therapeutic programs, of many in progress.

TABLE 5
HODGKING'S DISEASE
EXPERIMENTAL CHEMOTHERAPY

1. ADJUVANT	—	Alkylating agent with local x-ray Rx
2. INTENSIVE CHEMOTERAPY	—	Single drug or combination
3. COMBINATION	—	Vinblastine + Chlorambucil
4. NEW DRUGS	—	Daunomycin
		Imidazole carboxamide dimethyltriazeno
		Cycloheximide (for fever)

a. **Adjuvant chemotherapy**. En 1949 we began a program of using a course of nitrogen mustard in combination with intensive radiotherapy for localized Hodgkin's disease (12). This involved the injection of 0.4 mg/Kg. HN2 followed by a tissue dose of 3000 rads delivered to the involved area and adjacent lymph nodes. This schedule was well-tolerated, and we had the impression that nitrogen mustard contributed to the prolonged control of the disease in the irradiated area; disease reappeared outside the irradiated area in some cases, indicating that nitrogen mustard by itself not act prophylactically to eliminate areas of occult disease. This preliminary study has now been organized under a formal protocol.

b. **Intensive chemotherapy**. The National Institutes of Health and cooperating groups in the United States have initiated a far more intensive chemotherapy program, designed to try to obliterate cell foci of Hodgkin's disease. A combination of nitrogen mustard, vincristine, procarbazine and prednisone has been given in repeated courses at the maximum tolerated dose. In one schedule these drugs are administered during a two week period, and the treatment is interrupted until bone marrow recovery occurs, and the treatment cycle is repeated three times. This is an experimental study, a physician should not undertake it in an isolated patient until there is sufficient evidence available to demonstrate the efficacy of this approach. The combination is being evaluted in localized as well as in advanced Hodgkin's disease.

Another approach has been the use of continuous chemotherapy in patients in whom the disease is apparently under satisfactory control following localized radiotherapy. Patients have been placed on vinblastine, chlorambucil or on combinations of drugs for long periods in the hope of preventing a relapse. This, in my opinion, is not a reasonable use of the presently available anti-cancer drugs.

c. **Combination therapy**. Some of the anti-cancer drugs are being used in combinations, in place of a single drug. Lacher and Durant (13) have presented evidence that patients not responding satisfactorily to vinblastine or chlorambucil separately, may show grater improvement on the combination.

d. **New agents**. Several new agents are under investigation, including daunomycin (14), an Italian antibiotic, imidazole carboxamide dimethyltriazeno (ITC) and actidione (15). The latter has specifically prevented the fever of Hodgkin's disease, although it is effective only during the period of drug administration.

The approaches represent investigational areas of chemotherapy. The list will change as new approaches are developed, and the current studies are completed.

SUMMARY AND CONCLUSIONS

Chemotherapeutic agents have been used in the treatment of Hodgkin's disease for more than 25 years, and their value is clearly established. The important groups are :

1. the polyfunctional alkylating agents,
2. the vinca alkaloids,
3. procarbazine, and
4. the adrenal steroids.

These agents are principally indicated in widespread symptomatic Hodgkin's disease.

We prefer to use one agent at a time, and evaluate its effects before considering the use of another. When chemotherapy is advisable, our present preference is to start with an alkylating agent and, if the patient becomes refractory to it, a vinca alkaloid, and then procarbazine; prednisone may be useful in the late stages of the disease. Some clinicians, however, prefer vinblastine as the initial form of treatment. Some of the experimental approaches in the chemotherapy of Hodgkin's disease have been noted, including the combination of x-ray therapy and chemotherapy, combinations of active anti-cancer drugs, and trials of new agents.

REFERENCES

1 — GOODMAN, L , WINTROBE, M. M., DAMESHEK, W., GOODMAN, M. J., GILMAN, A., and MCLENNAN, M. T.: Nitrogen mustard therapy; use of methyl-bis(*B*-chloroethyh)amine hydrochloride and tris(*B*-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. JAMA *132*: 126, 1946.

2 — JACOBSON, L. O., SPURR, C.L., GUZMAN BARRON, E. S., SMITH, T., LUSHBAUGH, C., and DICK, G. F.: Nitrogen mustard therapy; studies on the effect of methyl-bis(*B*is-chloroethyl)-amine hydrochloride on neoplastic diseases and allied lisorders of the hemopoietic system. JAMA *132*: 263, 1946.

3 — WINTROBE, M. M., MCLENNAN, M. T., and HUGULEY, C. M., Jr.: Clinical experiences with nitrogen mustard therapy. In: Approaches to Tumor Chemotherapy, p. 347. Washington, D. C., Am. Assoc. Advancement Science, 1947.

4 — KARNOFSKY, D. A., BURCHENAL, J. H., ORMSBEE, R. A., CORNMAN, I., and RHOADS, C. P.: Experimental observations on the use of the nitrogen mustards in the treatment of neoplastic diseases. In: Approaches to Tumor Chemotherapy, p. 293. Washington, D. C., Am. Assoc. Advancement Science, 1947.

5 — KARNOFSKY, D. A., BURCHENAL, J. H., ARMISTEAD, G. C., Jr., SOUTHAM, C. M., BERNSTEIN, J. L., CRAVER, L. F., and RHOADS, C. P.: Triethylene melamine in the treatment of neoplastic disease; a compound with introgen-mustard-like activity suitable for oral and intravenous use. A.M.A. Arch. Int. Med. *87*: 477, 1951.

6 — Conference on Hodgkin's disease, New York, November 25-26, 1957. In: Ann. N. Y. Acad. Science *73*: 1-380, 1958.

7 — Hall, T.C.; Choi, O.S.; Abadi, A.; and Krant, M. J. — High dose corticoid therapy in Hodgkin's Disease and other Lymphomas, Annals of Internal Med. *66*: 1144-1153, 1967.

8 — KARNOFSKY, D. A.: Chemoterapy of Hodgkin's disease. Cancer *19*: 371, 1966.

9 — BRUNNER, K. W., and YOUNG, C. W.: A methylhydrazine derivative in Hodgkin's disease and other malignant tumors; therapeutic and toxic effect studied in 51 patients. Ann. Int. Med. *63*: 69, 1965.

10 — KARNOFSKY, D. A. : Meaningful clinical classificiation of therapeutic responses to anticancer drugs. Clin. Pharm. Therapeutics *2*: 709, 1961.

11 — MACDONALD, C. A., and LACHER, M. J.: Oral vinblastine sulfate in Hodgkin's disease. Clin. Pharm. Therapeutics *7*: 534, 1966.

12 — KARNOFSKY, D. A., MILLER, D. G., and PHILLIPS, R. F.: Role of chemotherapy in the management of early Hodgkin's disease. Am. J. Roentgenology, Rodium Therap. and Nuclear Med. *XC*: 968, 1963.

13 — LACHER, M. J., and DURANT, J. R.: Combined vinblastine and chlorambucil therapy of Hodgkin's disease. Ann. Int. Med. *62*: 468, 1965.

14 — TAN, C., TASAKA, H., YU, K.-P., MURPHY, M. L., and KARNOFSKY, D. A.: Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease; clinical evaluation with special reference to childhood leukemia. Cancer *20*: 333, 1967.

15 — YOUNG, C. W., and KARNOFSKY, D. A.: The necessity of protein synthesis for fever in Hodgkin's disease. Proc. Am. Assoc. Cancer Res. *8*: 75, 1967 (Abstract).

Dr. John E. Ultmann

Surgery as the definitive therapy of Stage I Hodgkin's disease has no advantage over agressive radiotherapy directed to the involved lymph nodes and to adjacent areas.

The most frequent indication for surgery in the management of Hodgkin's disease is biopsy for diagnosis. Usually, a superficial lymph node is biopsied. The surgeon should choose a large node, preferably one **not** located in the inguinal area. A portion of the lymph node may be sent to the laboratory to search for tuberculosis, toxoplasmosis or other organisms. When lymph nodes are not readily accessible for biopsy, consideration is given to thoracotomy or laparotomy. Occasionally, the diagnosis is made following laminectomy or splenectomy.

In the course of Hodgkin's disease, certain complications arise which may lead to surgical intervention. Laminectomy should be done in those patients with chord compression whose symptoms are of recent origin and progressing rapidly, and whose lesion can be localized. Laminectomy is indicated particularly in the presence of vertebral bone destruction. Relief of obstruction or hemorrhage secondary to gastro-intestinal Hodgkin's disease may require surgical intervention. More rarely, obstructive uropathy may require temporary nephrostomy. Following surgical intervention in these complications, radiotherapy is usually indicated. Splenectomy may be performed, at times, in patients with hypersplenism. The very high operative mortality, together with the short survival periods of those patients surviving operation, lead Grace and Mittelman to conclude that splenectomy in this group of patients has a very limited indication. Selection of patients with clinical problems **largely** due to hypersplenism is essential. Red cell survival and sequestration studies are very useful in selecting candidates. The improvement following splenectomy may be striking, as evidenced by red cell survival studies changing from T/2 11.2 days pre-splenectomy to T/2 27 days post-splenectomy. A rise of hemoglobin values of 4 to 6 gram % occurred in 6 of 13 cases. Granulocytes and platelets increased substantially in 6 and 8 cases, respectively, of 13 patients studied.

For control of intractable pain, neurosurgical intervention — including alcohol blocks, chordotomy and other procedures — may at times be indicated.

Grace and Mittelman have summarized recently the role of surgery in the over-all management of Hodgkin's disease, noting that it is limited to excision for diagnostic purposes and to the management of unrelated problems which might require surgical intervention.

we do treat the patients with other things and we're really not truly evaluating Indocin by itself, but in some individuals who were getting aspirin and who were actually getting steroids and had dailly fever of 103 or 104 and who could not be given an alikilating agent or Velban because of severe bone marrow toxicity, might be tied over at a lower temperature level such as 101°, that would be 38° C, rather than 40° C. We have not encountered any toxicity so far but there are a number of things to look for which I don't, at this moment want to go into. It is very well tolerated and for brief periods of 2 to 3 weeks may be just the useful thing to do till you can turn to something else.

Dr. Henry S. Kaplan:

Thank you. I think this is the point that has impressed me in a small number of cases, perhaps 4 or 5 cases. We have seen patients in whom we know that there was no response to aspirin or to steroids, in which Indocin has brought about a prompt suppression of fever. They have been quite confortable and the virtue of this is not that the disease process is specifically affected but that in some of these cases at least we have seen this interval result in a return of what appeared to be an exhausted bone marrow. So that after a total of 4 to 5 weeks on Indocin, in which patients were maintained in a state of considerable confort, it was again possible to resume specific therapy which would not otherwise have been possible. I think in that sense it may have something more to offer than much of the other non-specific therapies.

I would like to raise a question which I think again both of our speakers migh comment on. For many years, as you know, it has been said that chemotherapeutic agents have not prolonged life in the malignant lymphomas, including HD. I think that most of the early evidence strongly indicated that this was the case. However, in recent years we have witnessed as you've heard this morning, the introduction of a number of new agents, and some these agents seem to be effective after other agents have exausted their usefulness. One can again get a significant duration of remission as you've heard, a 10 month average duration with Velban, a 5 month average duration with Methylhydrazine. These drugs are used one after another and one can't help but feel ,as I have observed, our chemotherapy program, under Dr. Rosenberg, that today the older view that life is not prolonged, may no longer be true. As more and more good and effective agents are introduced, even though they still do not offer cure, I think that they are beggining to offer significant prolongat'on of life. I know that this is an unorthodox point of view and I want to introduce it for both Dr. Karnofsky and Dr. Ultmann to discuss.

Dr. John E. Ultmann:

I believe that in order to discuss this, two points ought to be made in the introduction. The first point is: that we want to be absolutely sure that we do not convey the idea that a single patient has ever been cured by chemotherapy. All we can really hope to look for is prolongation and palliation, compatible life that has been prolonged, but no cure, no cure. Again we must say this no matter what is going to come up next in our discussion.

The second point is that since the majority of patients who receive chemotherapy have had some experience with radiotherapy, and since the majority of patients whom received one chemotherapeutic agent eventually receive at least another, if not others, it is going to be virtually impossible to say for any group of patients that this agent or that agent has prolonged the life of a group of patients. All one can really do is look at this in a sweeping, panoramic point of view.

If you took our own series where there were 115 patients with Stage-III from 1951 to 1964, none of them treated with Velban or Methylhydrazine, there was a 5 year survival of 23%, which I say with pride, it's rather good when you consider that for Stage-III disease the 5 year survival in the literature has ranged, (originally Stages III and IV I should say), has ranged originally from 10% to about 20%. The first point I'd like to make is, I believe that the survival rate is a little better in our series because we've used a little less chemotherapy with the alkylating agents. We've been cautious because there's ample evidence that an occasional patient is harmed by over-enthusiastic chemotherapy. If then, to

this 23% 5 year survival you unitotally do what Dr. Kaplan suggests, that is, you add what appears to be an extension of about 8 or 10 months, actually from 4 months to 18 months of life with Velban, which about 60% of the patients could achieve in our statistical analysis, and if you then add the possibility of a 5 month survival, which ranges from 2 months to 11 months, with Methylhydrazine, again, at least as shown in our series and in some of Mathé's patients, in patients who have gone through the cycle of 2 other drugs, one at least surmizes that one could, for a typical patient, add these averages. If you do this one would think that certainly life can be extended by at least a year speaking conservatively, and possibily 1 year and ½ for the average patient.

Dr. Karnofsky:

I agree with what Dr. Ultmann has said and I just want to emphasize that life is being prolonged in patients who still have active HD, in other words, these are patients that are not being cured but have reccurrent progressive disease. The question is what is responsible for it, as Dr. Ultmann pointed out; first we have to decide whether one agent is more likely to have been responsible for prolongation of life than another. I don't think that we can attribute prolongation of life to any particular agent. We also have to consider what's happened tc the management of patients with advanced HD. I think this is one of the major progesses that have been made. In our own clinics where we know that patients who previously looked as if they might be on the verge of expiring from the disease, improve on treatment and go on and live another 2, 3 or 4 years. There are many factors that are involved. One is that we are using palliative radiotherapy more aggressively in these patients. We are habilitated, so to speak, in chemotherapy. We have availability of blood transfusions. We have many active supportive measures that have been introduced. In terms of antibiotic control for intercurrent infection which are often life threatning. The treatment of chord-compression which might in the past have been responsible for paralysis and early death, has been controlled in 75% of patients and they go on to another period.

There is a remarkable improvement in the overall attitude and management of the disease, and in which chemotherapy is playing a very important part.

Dr. Henry S. Kaplan:

Thank you very much gentlemen. I think we all appreciate very much the remarks of both Dr. Karnofsky and Dr. Ultmann. I'd like now to close this part of our program and to go on to the presentation by Dr. Robert Lukes on the pathological aspects of Burkitt's Tumor.