Br. J. Cancer (1975) **31**, Suppl. II, 456

CLINICAL TRIALS IN THE NON-HODGKIN'S LYMPHOMATA AT STANFORD UNIVERSITY EXPERIMENTAL DESIGN AND PRELIMINARY RESULTS

S. A. ROSENBERG AND H. S. KAPLAN

From the Departments of Medicine and Radiology, Stanford University School of Medicine, Stanford, California, U.S.A.

Summary.—Preliminary results of controlled clinical trials in 127 patients with non-Hodgkin's lymphomata are reported. The rationale for identifying 7 study groups is presented. Treatment programmes which are being studied vary from involved field irradiation to the most aggressive treatment tolerable.

The early results suggest that patients with both favourable and unfavourable histologies but of limited extent can be controlled with irradiation. Patients with advanced disease but with favourable histological subgroups are doing as well with a conservative drug programme as with 2 aggressive treatment regimens. These controlled studies and those of others, facilitated by the use of the Rappaport classification and laparotomy staging, give promise of clarifying and improving the management of patients with these lymphomata.

OUR EFFORTS to improve the results of therapy and study therapeutic variables by means of controlled clinical trials in the non-Hodgkin's lymphomata began in 1962. At that time we initiated identical studies for patients with Hodgkin's disease and those with lymphomata other than Hodgkin's disease. Our Hodgkin's disease trials were productive and over a period of 10 years were modified as new information became available from our own studies and those of others (Kaplan and Rosenberg, 1973). This was not the case for our trials with the non-Hodgkin's lymphomata. The diseases as we had classified and studied them were unpredictable and therapeutic trial results were inconclusive (Rosenberg and Kaplan, 1970). The studies were discontinued in 1967 and our group, joined by Dr R. F. Dorfman in Surgical Pathology, embarked upon a detailed retrospective review of our patient data. It was hoped that application of the Rappaport classification (Rappaport, Winter and Hicks, 1956; Rappaport, 1966) would clarify the unpredictable responses to therapy that we had observed. During this same period, the value of aggressive diagnostic staging techniques for an understanding and management of Hodgkin's disease was being demonstrated (Glatstein, Trueblood, Enright, *et al*, 1970; Rosenberg, 1973) and the importance of adequate bone marrow biopsy in the non-Hodgkin's lymphomata were apparent to our group (Rosenberg, 1975). Greater experience with wide field, high dose irradiation and the potential of modern combination chemotherapy led us to review our efforts to understand and to control these lymphomata (Jones, Kaplan and Rosenberg, 1972).

It is the purpose of this report to present the details and rationale of our current clinical trials, initiated in July 1971. We also present our first analyses of the results of these trials, which must be considered as very preliminary.

PATIENTS AND METHODS

The criteria for patient selection are presented in previous reports (Rosenberg, Dorfman and Kaplan, 1975). In summary, the following criteria were used: (1) Diagnostic biopsy was reviewed by the Stanford Division

of Surgical Pathology and classified according to the Rappaport Classification; (2) the patient was previously untreated; (3) the patient lived within 300 miles of the Stanford Medical Center; (4) age between 10 and 65, with option to accept patients to age 70 if they were in satisfactory general medical condition; (5) patient and referring physician agreed to the investigative nature of the diagnostic and therapeutic programmes, and patient provided appropriate informed consent; (6) the patient did not have the clinicopathological diagnosis of chronic lymphocytic leukaemia based upon previously defined, relatively arbitrary criteria (Jones *et al.*, 1973); (7) there existed no previous or concurrent medical condition which would seriously compromise the patient's ability to withstand the diagnostic and therapeutic programme planned or the interpretation of the results of the studies.

Patients underwent extensive diagnostic studies and procedures which have been detailed elsewhere (Rosenberg and Kaplan, 1970; Rosenberg, 1973). These included routine laboratory and roentgenological procedures, bipedal lymphography, bone marrow biopsy and exploratory laparotomy with splenectomy.

All patients are presented at a formal staging conference, at which the final pathological stage is agreed upon after presentation of all clinical, laboratory, roentgenological and pathological information. The Ann Arbor staging classification is utilized (Carbone *et al.*, 1971). Treatment options are selected by drawing a sealed envelope containing a designation determined by a table of random numbers supervised by Dr B. Brown of our Biostatistics Division.

In designing the trials, it was appreciated that there were at least 8 and possibly 10 histological subgroups in the Rappaport classification scheme. There were 4 major stages and multiple substage designations employing the "E" (extranodal), "S" (spleen), and "A" or "B" (absence or presence of systemic symptoms) system. We utilized the information from our recent retrospective reviews (Jones *et al.*, 1973), and combined categories to reduce the number of experimental groups. As shown in Tables I and II, 7 experimental groups were defined. The favourable nodular histological varieties (NLWD, NLPD, NM) were combined with the one favourable diffuse variety (DLWD) and the poorest nodular subgroup (NH) was combined with the remaining diffuse varieties (DLPD, DM, DH, DU). Pathological Stages I and II were felt to be of similar prognoses and were combined. Patients with limited extranodal disease, "E" designation as defined by the Ann Arbor Conference, were assigned in accordance with their lymph node extent of disease. The absence or presence of systemic symptoms (A or B) or of splenic involvement, "S", did not influence the trial group assignment, though these finding were carefully determined and recorded. The sites of Stage IV involvement were recorded but did not influence the treatment protocol assignment. If mixed or composite histological pictures were found (Goffinet *et al.*,

TABLE I.—*Non-Hodgkin's Lymphoma Trials, Histological Subgroups (Rappaport)*

	Nodular	Diffuse
Lymphocytic, well differentiated	NLWD	DLWD
Lymphocytic, poorly differentiated	NLPD	DLPD
Mixed, lymphocytic–histiocytic	NM	DM
Histiocytic	NH	DH
Undifferentiated	—	DU

TABLE II.—*Non-Hodgkin's Lymphoma Trials, Experimental Groups*

Pathological stages	Histological subgroups	Study group
I, I_E, II, II_E	NLWD, NLPD, NM, DLWD	J–1
I, I_E, II, II_E	NH, DLPD, DM, DH, DU	J–2
III, III,$_E$ III_S, III_{ES}	NLWD, NLPD, NM, DLWD	J–3
III, III,$_E$ III_S, III_{ES}	NH, DLPD	J–4
III, III,$_E$ III_S, III_{ES}	DM, DH, DU	J–5
IV	NLWD, NLPD, NM, DLWD	J–6
IV	NH, DLPD, DM, DH, DU	J–7

1973) the assignment was made to the subgroup with the poorest prognosis.

For patients with favourable histology and limited disease (J–1 study group) our retrospective studies suggested an overall excellent prognosis without a clear advantage of one form of radiotherapy over another. We felt that we should try to determine whether or not total lymphoid irradiation is more successful than treating the known disease only.

Patients who after pathological staging had limited disease, Stages I or II, but unfavourable histology were thought to require aggressive therapy in all cases. Encouraged by the tolerance of the patients and the results of our recent Hodgkin's disease trials (Rosenberg *et al.*, 1972), we decided to test the curative potential of aggressive chemotherapy following total lymphoid irradiation (J–2 study group). The choice of the chemotherapy programme presented a problem. We were not satisfied that chemotherapy studies and reports had given significant attention to the prognostic value of the Rappaport classification. We preferred to use a relatively standardized chemotherapy regimen, hopefully the same one for all cytological types. The 3-drug combination developed and reported by the group at the National Cancer Institute was selected as the most promising at the time (Bagley *et al.*, 1972). This combination, called "CVP", uses cyclophosphamide, vincristine and prednisone. We decided to add bleomycin to this regimen in half of the patients, selected at random in all of the study groups. When used as an adjuvant to radiotherapy, such chemotherapy was administered for 6 cycles, beginning approximately 60 days after completion of the radiotherapy.

Patients who had favourable histological pictures with widespread lymphoid involvement (Stages III, III_E, III_S or III_{ES}), with or without systemic symptoms, comprised the J–3 study group. The same treatment options were used in this group as for the J–2 study; total lymphoid irradiation to all patients, half selected at random to receive intensive CVP chemotherapy with or without bleomycin after the irradiation.

Those patients who had widespread lymphoid disease with unfavourable histological pictures were divided into 2 groups: those with intermediate prognoses (NH, DLPD) and those with the poorest prognoses (DM, DH, DU). In the former group, the J–4 study, total lymphoid irradiation was planned for all patients. The chemotherapy group, however, was started on drug treatment before the irradiation for 2 or 3 cycles ("split course" chemotherapy) in an effort to gain systemic control of the disease in order to delay or prevent extranodal extension of the disease from unirradiated lymphoid sites. The total of 6 cycles of chemotherapy was to be completed following completion of the total lymphoid irradiation. For those patients with the least favourable histology, the J–5 study compares the results of chemotherapy alone for 6 consecutive cycles without irradiation with those of split course chemotherapy plus total lymphoid irradiation as described for the J–4 study group.

The appropriate selection of treatment options for patients with pathological Stage IV disease presented difficult problems. Patients with favourable histological patterns could be expected to have an indolent course. There were inadequate data concerning the value of high dose total lymphoid irradiation in these patients. Yet the disease is often very radiosensitive and it was postulated that reduction of major bulky sites of disease might facilitate chemotherapy control, even cure of the disease. It seemed important, however, to have a conservatively treated group as a control because the median survival of these patients was often prolonged and experience with surgically staged patients

TABLE III.—*CAT Combination Chemotherapy*

		Day				
		1	2	3	4	5
Adriamycin	60 mg/m², i.v.	X				
Cytosine arabinoside (Ara-C)	3·0 mg/kg i.v.		X	X	X	X
6-Thioguanine (6-TG)	2·5 mg/kg po		X	X	X	X

C-TG given 12 hours after Ara-C.
Cycles repeated at 3-week intervals, blood counts permitting.

was not available to serve as a retrospective control. Therefore, a 3-arm randomization design was agreed upon (J–6 study). One group of patients would receive aggressive chemotherapy alone until a complete remission was documented by all studies, including repeat bone marrow and/or liver biopsies. Four " consolidation " cycles would follow and quarterly maintenance cycles would be administered for a period of 24 months following documentation of the complete remission. If after 12 cycles of chemotherapy a complete remission had not been documented, the potentially curative attempt with chemotherapy would be declared a failure and appropriate palliative therapy prescribed. The second arm of this study adds total lymphoid irradiation to the same chemotherapy plan, interrupting the drug programme after 2 or 3 cycles of chemotherapy if the disease is under satisfactory clinical control. The chemotherapy is then resumed, if possible, within 60 days of completion of the irradiation. The conservative arm of this study utilizes oral, daily, single drug chemotherapy in modest dose. Cyclophosphamide was the drug of choice but in some cases chlorambucil was substituted because of patient intolerance. Doses of approximately 2·0 mg/kg body weight of cyclophosphamide or 0·1 mg/kg of chlorambucil were used initially and modified in accordance with response and tolerance.

Patients with unfavourable histology and Stage IV disease presented a serious problem in trial design. In terms of prolonged disease-free survival no satisfactory chemotherapy programme was available. It was decided to test the CVP combination, with or without bleomycin alone or in the split course plan combined with total lymphoid irradiation. After approximately 2 years of experience with this drug combination, the poor results to be described below led to the development of a new, more promising drug regimen utilizing cytosine arabinoside, Adriamycin (doxorubicin) and 6-thioguanine (CAT). The dosage schedule of this regimen is shown in Table III.

Actuarial curves of survival were determined by the method of Kaplan and Meier (1958) from the date first seen at Stanford. Disease-free survival was determined from the date of completion of irradiation. The Gehan test was applied to actuarial data to determine the level of significance of observed differences (Gehan, 1965).

RESULTS

A total of 127 patients have completed the diagnostic studies and been randomized to the treatment groups as of 1 March 1974. The results of these studies as of the same date are listed in Table IV. Maximum follow up for patients from the initiation of therapy is only 32 months.

TABLE IV.—*Non-Hodgkin's Lymphoma, Stanford Clinical Trials (as of March 1974)*

Study group	Total patients	$A\bar{s}$	$A\bar{c}$	Under therapy	$D\bar{c}$	$D\bar{s}$
J_1A	4	3	1	0	0	0
J_1B	3	3	0	0	0	0
J_2A	14	9	1	2	2	0
J_2B	14	10	0	2	2	0
J_3A	6	5	0	0	0	1†
J_3B	7	2	2	3	0	0
J_4A	1	0	1	0	0	0
J_4B	2	1	0	0	1	0
J_5A	3	0	0	1	2	0
J_5B	3	1	0	1	1	0
J_6A	17	8	6	2	1	0
J_6B	16	7	0	6	2	1‡
J_6C	14	5	9	14*	0	0
J_7A	11	1	0	4	6	0
J_7B	12	5	0	4	3	0
Total	127					

* Patients are on planned continuous therapy.
† Radiation hepatitis.
‡ Disseminated varicella.
$A\bar{s}$—alive without disease. $A\bar{c}$—alive with disease.
$D\bar{s}$—dead without disease. $D\bar{c}$—dead with disease.

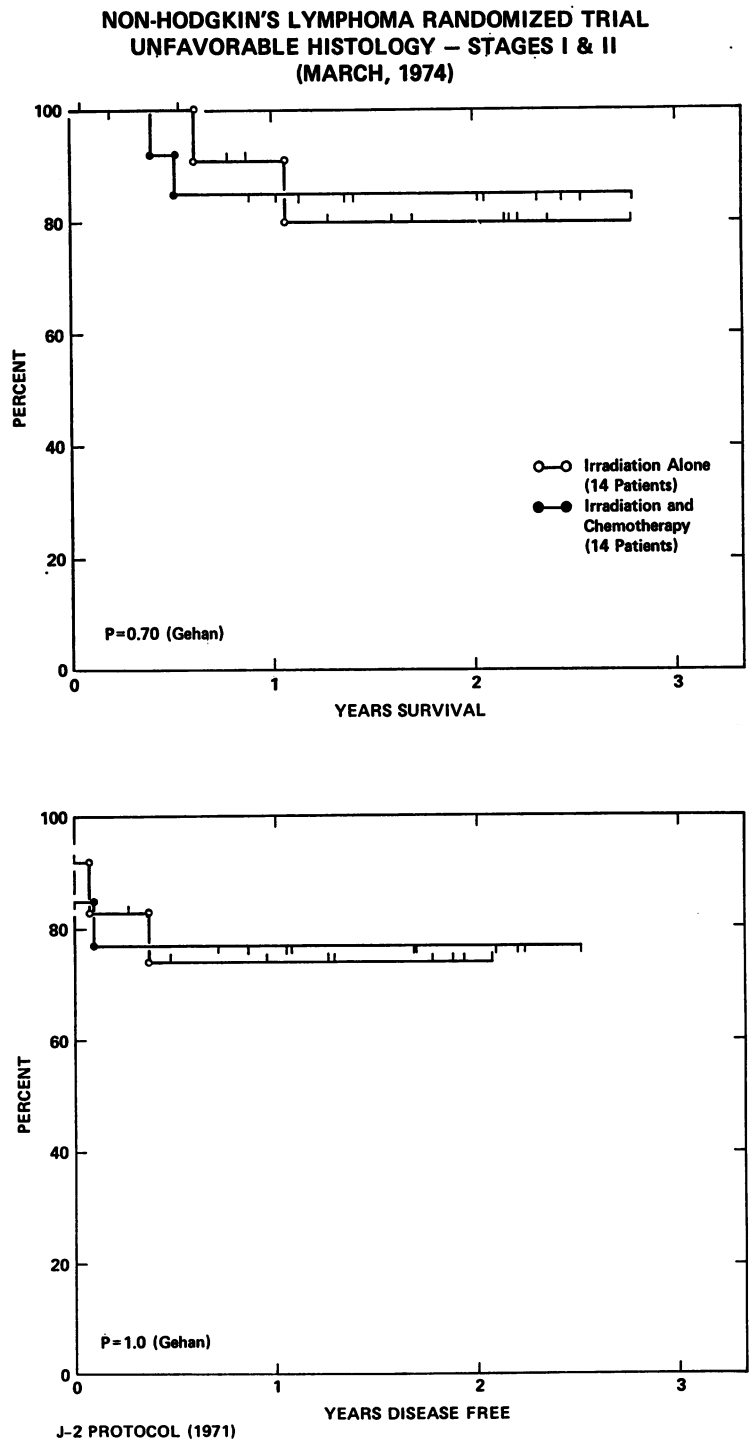

FIG. 1.—Actuarial analyses (Kaplan–Meier) of survival and disease-free survival of the J–2 study.

In some of the study groups, the numbers of patients are very small and 25 patients are still under therapy. The results must therefore be considered as preliminary and are presented and discussed only to emphasize several significant observations.

The use of extensive staging procedures reduces the numbers of patients with favourable histology and Pathological Stage I and II disease. Only 7 such patients have been seen and all are well to date, after limited or extensive irradiation. One patient treated with limited fields developed disease in an untreated site and has been treated with additional irrradiation (J–1 study).

A satisfactory number of patients are being accrued in the J–2 study. Actuarial curves of survival and disease-free survival are shown in Fig. 1. We are achieving very good control in this group of patients for the limited length of the follow up period. To date, there is no evident advantage of adding chemotherapy to the irradiation. The 5 out of 28 patients who relapsed did so during or within 3 months of their irradiation and 4 died within a year of treatment initiation. Approximately 75% are disease-free at 2 years on actuarial basis with 10 patients at risk for 2 or more years.

Very little can be said about the patients with Pathological Stage III disease (J–3, J–4, J–5 studies). With different treatment protocols for 3 histological groups, the numbers of patients are too few to allow any conclusions at this time. Though the majority of patients with non-Hodgkin's lymphoma present with Clinical Stage III disease, after bone marrow biopsy and laparotomy with splenectomy only about one in 6 (17%) have Pathological Stage III disease

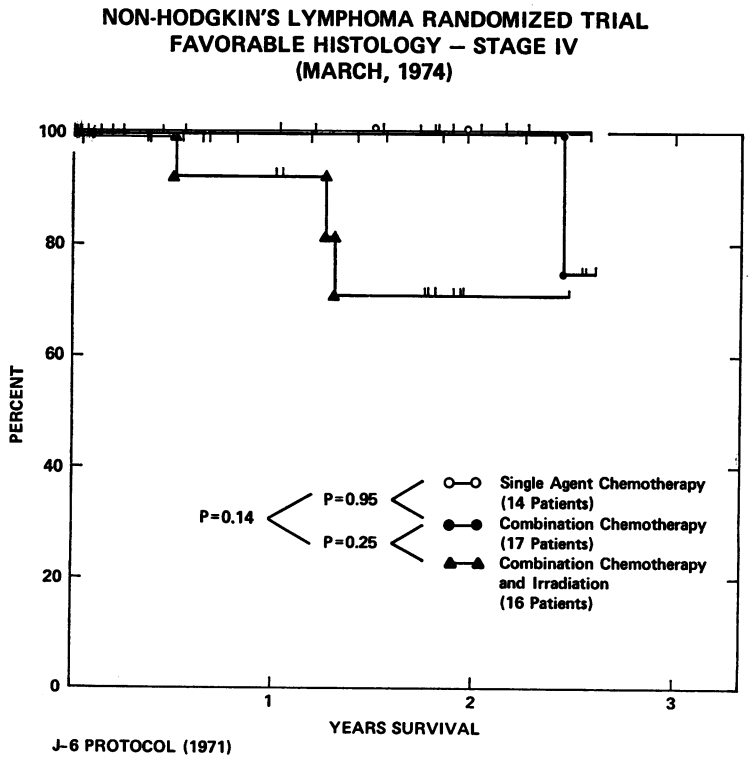

FIG. 2.—Actuarial analysis (Kaplan–Meier) of survival of the J–6 study.

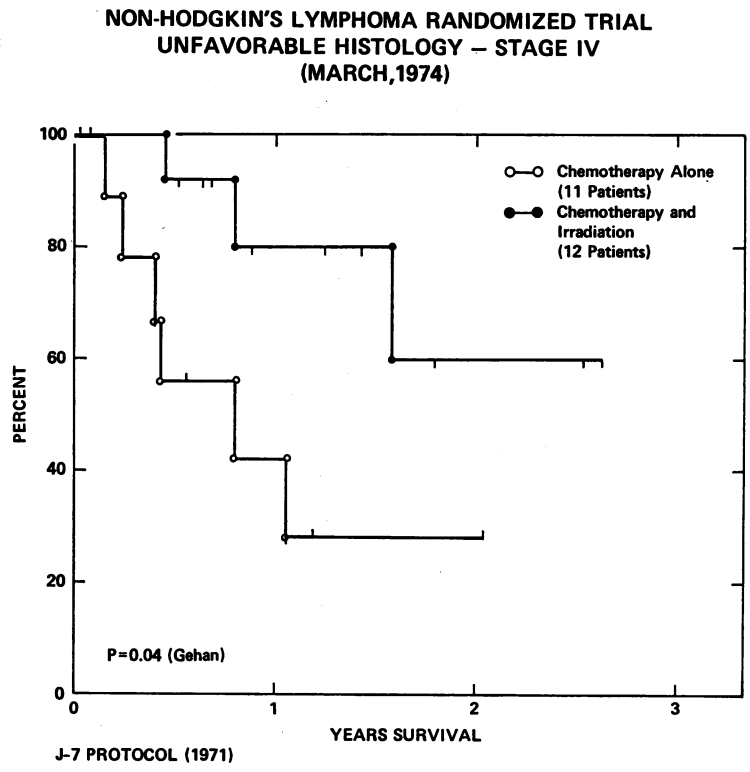

FIG. 3.—Actuarial analysis (Kaplan–Meier) of survival of the J—7 study.

(Rosenberg *et al.*, 1975). This will pose problems for investigators planning to study treatment programmes for this particular disease extent.

The J–6 study is very interesting to date (Fig. 2). The numbers of patients accrued are satisfactory, considering that this is a single institution study and a 3-way randomization was used. The favourable histology grouping is confirmed since only 4 of 47 patients have died despite the widespread (Stage IV) extent of their disease. Complete remissions of the disease have been achieved in about 50% of the patients. There are no significant differences in complete remission rates or deaths among the 3 treatment programmes: aggressive chemotherapy (J_6A), aggressive chemotherapy combined with irradiation (J_6B), or continuous single agent chemotherapy (J_6C). Some patients receiving both chemotherapy and irradiation are having prolonged treatment periods because of difficulty in tolerating the intensive chemotherapy after irradiation. Despite apparent complete clinical remission, patients may still have a positive bone marrow biopsy, in some cases after a year or more of cyclic combination chemotherapy. Yet we are observing an increasing number of patients in complete remission, including negative marrow study, after single agent chemotherapy. Three of 15 patients in the conservative drug programme have required a departure from this regimen. Two have been given more intensive cyclic chemotherapy, one after splenectomy. A third patient required limited irradiation for progressive localized skin and femoral node disease despite excellent control of all other sites.

It is too early to draw other major conclusions from the J–6 study. The median survival of these patients is expected to be at least 5 years and considerable time will be required to know the influence, if any, on survival as a result of our 3 different approaches. It is important for investigators to appreciate the good natural history these patients enjoy even without the benefit of specific therapy.

The picture is very different for patients with unfavourable histology and Stage IV extent (J–7 study). The CVP chemotherapy, with or without bleomycin, does not provide a significant complete remission rate; only one of 11 patients has achieved a complete remission with drugs alone, and 6 of 11 are already dead of their disease. The results may be somewhat better if irradiation is used between a split course of the chemotherapy (Fig. 3). Five of 12 patients are in documented complete remission, but only one of these is of the diffuse histiocytic (DH) variety.

It is too early to evaluate the CAT chemotherapy programme, though the initial response rate appears to be higher than that observed with CVP.

COMMENTS AND CONCLUSIONS

Controlled clinical trials of the diverse groups of patients with non-Hodgkin's lymphomata are proving feasible but difficult. Great attention must be paid to careful histological classification and diagnostic studies before assigning patients to appropriate treatment groups. Patients with localized disease (Pathological Stages I and II) can be approached successfully with irradiation. The studies to date do not clarify the extent of required fields or the desirability of supplementing irradiation with chemotherapy.

Patients with Pathological Stage III disease are uncommon, especially in certain of the Rappaport subgroups. Considering the sampling problem in determining bone marrow and/or liver involvement, perhaps clinical trials should combine patients with Pathological Stage III and IV extent together, regarding them all as " generalized. "

The relatively benign natural history of patients with favourable histological patterns, despite generalized disease, must be acknowledged. Our studies fail to show an early advantage of aggressive treatment approaches. However, it may require as long as 5 or 6 years to determine whether patients enjoying good early disease control on conservative programmes will have greater difficulty with their disease in subsequent years, in comparison with the aggressively treated patients.

The poor prognosis of patients with unfavourable histology and Stage IV disease is not significantly altered by CVP chemotherapy. New combinations, especially for patients with diffuse histiocytic lymphomata, must be developed. Various combinations including Adriamycin show early promise for these patients in our studies and those of others (Bonadonna *et al.*, 1969; McKelvey *et al.*, 1974). There is a suggestion from our studies that irradiation may improve the chemotherapy results for these patients.

These clinical investigative efforts require the collaborative efforts of pathologists, roentgenologists, surgeons, chemotherapists, radiotherapists and oncology nurses. Though complex and difficult, such studies, based on the sound foundation provided by the Rappaport histopathological classification and laparotomy staging, give promise of significantly improving the outlook for patients with non-Hodgkin's lymphomata.

The design and implementation of these studies have involved numerous colleagues and especially R. F. Dorfman (Pathology), R. Castellino (Diagnostic Radiology), S. E. Jones (Medicine), E. Glatstein, Z. Fuks (Radiotherapy) and B. W. Brown (Biostatistics). Supported by Grants CA-05838 and CA-08122 from the National Cancer Institute, National Institutes of Health.

REFERENCES

BAGLEY, C. M. JR, DEVITA, V. T. JR, BERARD, C. W. & CANELLOS, G. P. (1972) Advanced Lymphosarcoma: Intensive Cyclical Combination Chemotherapy with Cyclophosphamide, Vincristine, and Prednisone. *Ann. intern. Med.*, **76**, 227.

BONADONNA, G., MONFARDINI, S., DELENA, M. *et al.* (1969) Clinical Evaluation of Adriamycin, a New Antitumour Antibiotic. *Br. med. J.*, iii, 503.

CARBONE, P., KAPLAN, H. S., MUSSHOFF, K., SMITHERS, D. W. & TUBIANA, M. (1971) Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res.*, **31**, 1860.

GEHAN, E. A. (1965) A Generalized Wilcoxon Test for Comparing Arbitrarily Singly-censored Samples. *Biometrika*, **52**, 203.

GLATSTEIN, E., TRUEBLOOD, H. W., ENRIGHT, L. P., ROSENBERG, S. A. & KAPLAN, H. S. (1970) Surgical Staging of Abdominal Involvement in Unselected Patients with Hodgkin's Disease. *Radiology*, **97**, 425.

GOFFINET, D. R., CASTELLINO, R. A., KIM, H., DORFMAN, R. F., FUKS, Z., ROSENBERG, S. A., NELSEN, T. S. & KAPLAN, H. S. (1973) Staging Laparotomies in Unselected Previously Untreated Patients with Non-Hodgkin's Lymphomas. *Cancer, N.Y.*, **32**, 672.

JONES, S. E., FUKS, Z., KADIN, M. D., DORFMAN, R. F., KAPLAN, H. S., ROSENBERG, S. A. & KIM, H. (1973) Non-Hodgkin's Lymphoma. IV. Clinicopathologic Correlation in 405 Cases. *Cancer, N.Y.*, **31**, 806.

JONES, S. E., KAPLAN, H. S. & ROSENBERG, S. A. (1972) Non-Hodgkin's Lymphoma. III. Preliminary Results of Radiotherapy and a Proposal for New Clinical Trials. *Radiology*, **103**, 657.

KAPLAN, E. S. & MEIER, P. (1958) Non-parametric Estimations from Incomplete Observations. *Am. Statist. Ass. J.*, **53**, 457.

KAPLAN, H. S. & ROSENBERG, S. A. (1973) Current Status of Clinical Trials; Stanford Experience, 1962–72. *Natn. Cancer Inst. Monog.*, **36**, 363.

MCKELVEY, E. M., GOTTLIEB, J. A., COLTMAN, C. A. & WILSON, H. E. (1974) Treatment of Non-Hodgkin's Lymphoma with Hydroxyldaunomycin (Adriamycin) Combination Chemotherapy. *Proc. AACR, ASCO*, Abstr. No., 802, **15**, 184.

RAPPAPORT, H. (1966) *Tumors of the Hematopoietic System.* Washington D.C.: Armed Forces Institute of Pathology. Sec. 3, Fasc. 8, p. 91.

RAPPAPORT, H., WINTER, H. J. & HICKS, E. B. (1956) Follicular Lymphoma: A Reevaluation of Its Position in the Scheme of Malignant Lymphomas, Based on a Survey of 253 Cases. *Cancer, N.Y.*, **9**, 792.

ROSENBERG, S. A. (1973) The Clinical Evaluation and Staging of Patients With Malignant Lymphomas. *Proc. 7th Natn. Cancer Conf.* p. 369.

ROSENBERG, S. A. (1975) Bone Marrow Involvement in the Non-Hodgkin's Lymphomata. *Br. J. Cancer*, **31**, Suppl. II, 261.

ROSENBERG, S. A., DORFMAN, R. F. & KAPLAN, H. S. (1975) The Value of Sequential Bone Marrow Biopsy and Laparotomy and Splenectomy in a Series of 127 Consecutive Untreated Patients with Non-Hodgkin's Lymphoma. *Br. J. Cancer*, **31**, Suppl. II, 221.

ROSENBERG, S. A. & KAPLAN, H. S. (1970) Hodgkin's Disease and Other Malignant Lymphomas. *Calif. Med.*, **113**, 23.

ROSENBERG, S. A., MOORE, M., BULL, J., JONES, S. E. & KAPLAN, H. S. (1972) Combination Chemotherapy and Radiotherapy for Hodgkin's Disease. *Cancer, N.Y.*, **30**, 1505.