Cancer

APPRAISAL OF METHODS FOR THE STUDY OF CHEMOTHERAPY OF CANCER IN MAN: COMPARATIVE THERAPEUTIC TRIAL OF NITROGEN MUSTARD AND TRIETHYLENE THIOPHOSPHORAMIDE

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From the Eastern Cooperative Group in Solid Tumor Chemotherapy

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THE Eastern Cooperative Cancer Chemotherapy Group was formed under the sponsorship of the Cancer Chemotherapy National Service Center of the National Cancer Institute in 1955.[1] The members of the group undertook a critical examination of the methodology of clinical cancer chemotherapy trials

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and, based on this review, began a study of cancer chemotherapy in man. It was hoped that this study would permit an understanding of what was required for quantitative comparisons between the effectiveness of two anticancer drugs. These investigations were modeled in part upon the experience gained in a similar study of acute leukemia.[2] The specific purposes were:

1. To study the feasibility and usefulness of collaborative clinical research in cancer chemotherapy. Successful collaboration would (a) permit more rapid evaluation of new drugs, (b) take advantage of the experience of several investigators, (c) solve the problem of common criteria and other semantic traps, and (d) allow broader generalization from the results than would be possible from those of a single hospital.

2. To apply known principles of the therapeutic trial to clinical cancer chemotherapy. Most of the drugs now available are so toxic that one is usually balancing minor therapeutic gain against the possibility of serious therapeutic mischief. Widely varying claims are also made by different clinicians about the usefulness of any given drug, not only because of differences in criteria and semantics, but also because of different frames of reference developed in respective experiences. Direct comparative trial under similar conditions would give reliable data on the place of several drugs in the therapy of cancer.

3. To develop useful quantitative measures of antitumor effect of drugs upon human solid tumors. Quantification of the effects of drugs upon animal and human tumors is needed in order to determine the predictability value of studies in animal cancer for human cancer.

4. To compare the effectiveness of two alkylating agents, triethylene thiophosphoramide (thio-TEPA, TSPA) and methyl-bis(β-chloroethyl)amine (HN2, mechlorethamine, nitrogen mustard). HN2 is widely used and is considered by many to be "standard" therapy. Thio-TEPA was chosen as the "new agent" because when the study was planned its relative effectiveness was under debate.[3-5]

The present communication records in detail the methodology of this trial and presents the results obtained in the comparison of the two alkylating agents.

MATERIALS AND METHODS

General Plan.—The methods chosen for the therapeutic trial were the classic ones described elsewhere.[6-12] The major components of the trial were:

1. Study of four representative tumors—an adenocarcinoma (cancer of the breast), an epidermoid carcinoma (cancer of the lung), malignant melanoma, and a lymphoma (Hodgkin's disease).

2. Inclusion of no patient who was a candidate for definitive surgical or radiation therapy (all patients had an inoperable primary or metastatic tumor).

3. Comparison of effects concurrently, to avoid the serious difficulties involved in the use of historical controls.

4. Randomization of patients by tumor type between the two drug therapies. The purpose of the randomization was to give all patients an equal chance of receiving either drug without bias, conscious or unconscious, and thus provide comparability of the two groups.

5. Use of objective measurement of tumor size as an end point of drug effect.

6. Final determination of effect by all cooperating investigators, by vote without the prejudicial knowledge of which drug the patient had received.

7. Administration of specified dosages of drugs for standard time periods for all patients, so as to avoid as much as possible large differences in drug dosage.

8. Statistical analysis of data.

9. Frequent meetings of the investigators to ensure common application of the conditions agreed upon and common solution of unanticipated difficulties.

The result of the above considerations was a protocol which each investigator followed (Appendix A). It will be noted that drug was injected once daily for 4 days at the start of treatment, followed by a series of weekly injections starting 2 weeks after the first course of injections, unless hematopoietic depression (of specified severity) precluded. The individual doses were 0.1 mg./Kg. for HN2 and 0.2 mg./Kg. for thio-TEPA. The full course of treatment was 90 days.

Collation of Data.—The details of the chemotherapy data on individual patients, i.e., the completed flow sheet, measurement sheets,[13] and summary sheet (Appendices B, C_1, C_2, D, and E), were sent to the statistician. These were reproduced and distributed to all participants. The reproductions did not show which drug had been given. Evaluations were made by the participants independently prior to the group meeting. Appendix F contains the instructions for the use of these forms. At the meeting the individual patients were discussed and these votes were recorded on the evaluation sheet (Appendix G). As seen in the evaluation sheet, the estimation of drug effect was divided into these categories: (1 and 2) change in tumor size, (3) major untoward effects, (4) other beneficial effects, (5) total evaluation, (6) survival time, and (7) change in number of metastases.

Decision as to reduction in individual tumor size was made independently by each participant after observing the plots of the products of serial measurements for each lesion. In appraising the reduction of total tumor mass, the change in the number of tumors as well as change in size of measured tumors had to be considered.[14] Early in the study it was apparent that transient reduction in total tumor mass was sometimes followed by rapid recrudescence. Thus total reduction in tumor size is divided into "transient" (less than 90 days) and "prolonged" (reduction still present at end of 90-day period). "Other beneficial" effects included appreciable improvement in activity, appetite, weight, and well-being, and decrease in pain or other symptoms. Toxicity is considered under "major untoward" effects. In general, an untoward effect was considered major when it was severe enough to preclude the administration of further alkylating agent. The purpose of the "total evaluation" was to obtain an over-all judgment on whether the administration of drug resulted in a net benefit to the patient.

Definition of Responses.—Treatment was considered to give a positive response if either (1) the total measured tumor mass decreased, with no lesions increasing in size and no new lesions appearing, as recorded in item 2 of the voting sheets, or (2) the group of voting physicians considered that the treatment had been of benefit to the patient as a whole, considering subjective responses and untoward effects in addition to tumor measurements.

Measure of Duration of Response.—A positive response was defined as having begun at the time two consecutive measurements of all lesions were as small or smaller than the previous measurements, and it was considered to have ended when two consecutive measurements showed increases.

TABLE I.—REASONS FOR REJECTION OF PATIENTS FOR STUDY

TYPE OF CANCER	TOTAL PATIENTS CONSIDERED	TOTAL TREATED IN STUDY	TOTAL REJECTED	REASONS FOR REJECTION					
				TUMOR NOT MEASURABLE	PRIOR TREATMENT	OTHER TREATMENT INDICATED	NOT PROVED OR WRONG DISEASE	MORIBUND OR DIED BEFORE STUDY BEGAN	OTHER
Breast	250	76	174	40	45	36	6	15	32
Lung	325	132	193	39	23	21	64	20	26
Melanoma	58	30	28	9	3	5	2	3	6
Hodgkin's disease	86	20	66	10	27	4	16	0	9
Total	719	258	461	98	98	66	88	38	73

A portion of the log book of one institution was lost; hence, the number recorded is less than the true total for this study.

TABLE II.—COMPOSITION OF THE PATIENT SAMPLE BY HOSPITAL

TYPE OF CANCER	HOSPITALS						
	JOHNS HOPKINS	DISTRICT OF COLUMBIA GENERAL	JACKSON MEMORIAL	NATIONAL CANCER INSTITUTE	ROSWELL PARK	LEMUEL SHATTUCK	ALL GROUPS
Breast	7	23	6	17	22	1	76
Lung							
No prior x-ray	17	24	20	8	8	26*	103*
Prior x-ray	6	2	5	2	4	10	29
Melanoma	3	2	4	19	—	2	30
Hodgkin's disease	—	—	8	9	2	1	20
Total	33	51	43	55	36	40	258

*Including 15 patients subsequently given x-irradiation as primary therapy as a further comparison with HN2 and TSPA. This portion of the study will be reported separately.[18]

Drugs.—Single lots of thio-TEPA and HN2 stored at 4° C. as dry powder in ampules were used throughout the study. The potencies did not change, as shown by the equivalent hemopoietic depression seen in patients at the start and end of the study. In addition, chemical and biologic assays of thio-TEPA were identical before and after the study.

RESULTS

Patients.—Of 719 patients considered for study, 461 were rejected for the reasons shown in Table I. The composition of the group of 258 patients studied is shown in Table II.

TABLE III.—SELECTED CHARACTERISTICS OF PATIENTS AT START OF DRUG THERAPY

TYPE OF CANCER	DRUG	NUMBER OF PATIENTS*	MALE	FEMALE	MEDIAN AGE (YEARS)	MEDIAN WBC (THOUSANDS)	MEDIAN HGB (GM. %)	MEAN PERFORMANCE STATUS†	DURATION OF DISEASE FROM DIAGNOSIS TO THERAPY (MONTHS)	
									MEAN	95% CONFIDENCE LIMITS
Breast	TSPA	39	1	38	56	7.5	12.3	1.97	18.6	11.2-31.0
	HN2	35	0	35	56	5.9	11.8	1.87	16.3	10.3-25.7
Lung										
No prior x-ray	TSPA	42	40	2	58	10.2	11.9	2.19	1.5	1.2- 1.9
	HN2	45	44	1	60	10.9	11.7	1.88	1.5	1.1- 2.0
Prior x-ray	TSPA	14	14	0	56	10.5	11.2	2.00	6.5	4.2-10.1
	HN2	15	14	1	60	9.4	13.5	1.93	5.2	3.9- 6.9
Melanoma	TSPA	16	6	10	42	7.0	12.8	1.94	13.7	7.5-25.2
	HN2	14	6	8	54	7.8	12.0	1.77	6.2	3.0-12.7
Hodgkin's disease	TSPA	11	5	6	27	7.6	10.7	0.55	1.5	1.1- 2.1
	HN2	9	6	3	31	7.5	10.4	1.29	3.6	1.5- 8.4

*On whom complete data were available for all items given.
†The lower this number, the better the performance status (see Appendix F).

TABLE IV.—COMPARABILITY OF PATIENTS BY SITES OF METASTATIC INVOLVEMENT

TYPE OF CANCER	DRUG	TOTAL* PATIENTS	MEAN METASTATIC INVOLVEMENT†	PER CENT OF PATIENTS HAVING METASTATIC INVOLVEMENT‡						
				C	O	S	P	L	V	NONE OR NOT NOTED
Breast	TSPA	39	2.7	46	59	26	49	62	26	0
	HN2	35	2.9	60	66	29	43	60	29	0
Lung										
No prior x-ray	TSPA	39	1.7	5	33	21	56	41	23	13
	HN2	42	1.9	12	31	21	57	45	21	14
Prior x-ray	TSPA	13	2.3	15	46	46	38	62	31	15
	HN2	15	1.8	27	33	20	53	33	13	7
Melanoma	TSPA	16	2.6	81	31	31	50	44	19	0
	HN2	14	1.6	79	7	0	36	21	21	7
Hodgkin's disease	TSPA	11	1.4	18	0	9	18	64	27	18
	HN2	7	1.8	29	0	14	29	71	43	0

*On whom complete data were available.
†Average number of major systems or sites having metastases.
‡Since there is a probability of under-reporting of metastases, these data should not be used as a description of total metastatic spread. Any system having involvement was reported no more than once per patient no matter how many actual metastases of that system were reported. C = cutaneous, O = osseous, S = soft tissue, P = pulmonary, L = lymph nodes, V = visceral.

Comparability of Patients Receiving HN2 With Those Receiving Thio-TEPA.—As shown in Table III, there was reasonable comparability of age, performance status, initial hemoglobin, and leukocyte count. Median duration of disease before therapy was comparable for the patients receiving the two drugs, with perhaps two exceptions. In Hodgkin's disease, the thio-TEPA–treated patients

TABLE V.—TOTAL DOSAGE AND DURATION OF TREATMENT WITH DRUGS

TYPE OF CANCER	DRUG	TOTAL PATIENTS	PATIENTS WITH POSITIVE RESPONSE			PATIENTS WITHOUT POSITIVE RESPONSE		
			NUMBER	MEAN DURATION OF DRUG PERIOD (DAYS)	MEAN AMOUNT OF DRUG GIVEN (MG.)	NUMBER	MEAN DURATION OF DRUG PERIOD (DAYS)	MEAN AMOUNT OF DRUG GIVEN (MG.)
Breast	TSPA	39	3	82.3	125	36	60.4	108
	HN2	37	8	74.2	57	29	60.8	47
Lung								
No prior x-ray	TSPA	42	4	80.3	145	38	50.8	114
	HN2	46	11	71.3	61	35	46.6	49
Prior x-ray	TSPA	14	1	90.0	210	13	50.4	120
	HN2	15	0	——	——	15	52.2	50
Melanoma	TSPA	16	2	20.0	57	14	56.0	113
	HN2	14	0	——	——	14	54.6	49
Hodgkin's disease	TSPA	11	8	66.7	111	3	76.6	158
	HN2	9	9	66.7	65	0	——	——

TABLE VI.—SUMMARY OF VOTING BY NUMBER OF PATIENTS

TYPE OF CANCER	DRUG	SINGLE TUMOR DECREASE		TOTAL MEASURED TUMOR DECREASE		UNTOWARD SIDE EFFECTS		OTHER BENEFIT		TOTAL BENEFIT TO PATIENT		TOTAL PATIENTS
		YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	
Breast	TSPA	10	29	3	36	3	36	3	36	3	36	39
	HN2	12	25	7	30	4	33	6	31	8	29	37
Lung												
No prior x-ray	TSPA	9	33	4	38	0	42	3	39	4	38	42
	HN2	14	32	9	37	0	46	7	39	8	38	46
Prior x-ray	TSPA	3	11	0	14	0	14	1	13	2	12	14
	HN2	3	12	0	15	3	12	0	15	0	15	15
Melanoma	TSPA	5	11	2	14	2	14	0	16	1	15	16
	HN2	3	11	0	14	0	14	0	14	0	14	14
Hodgkin's disease	TSPA	10	1	7	4	0	11	4	7	5	6	11
	HN2	9	0	8	1	1	8	5	4	9	0	9

were started on therapy earlier in the course of their disease than those who received HN2. The opposite trend is apparent in the melanoma subgroups. In neither instance, however, do the subgroups differ at the 0.05 level of significance. The patients with Hodgkin's disease receiving thio-TEPA also had a somewhat better performance status prior to therapy. In Table IV an attempt is

made to appraise the extent of metastatic involvement by listing the number of patients having metastatic spread to various sites. While this is an arbitrary and perhaps artificial categorization, it does give an indication that the two treatment groups had approximately equally extensive disease. In Table V are

TABLE VII.—RESPONSES OF ALL PATIENTS TO HN2 AND THIO-TEPA

TYPE OF CANCER	DRUG	FAILURES*				SUCCESSES†			PER CENT SUCCESSES	GRAND TOTAL
		WITH UNTOWARD EFFECTS	WITH NO UNTOWARD EFFECTS	WITH SINGLE TUMOR RESPONSE	TOTAL	REDUCTION IN TUMOR MASS	GENERAL BENEFIT ONLY	TOTAL		
Breast	TSPA	3	26	6	35	3	1	4	10	39
	HN2	4	19	5	28	7	2	9	24	37
Lung										
No prior x-ray	TSPA	0	33	5	38	4	0	4	10	42
	HN2	0	30	4	34	9	3	12	26	46
Prior x-ray	TSPA	0	10	2	12	0	2	2	14	14
	HN2	3	9	3	15	0	0	0	0	15
Melanoma	TSPA	2	10	3	15	2	0	2	12	16
	HN2	0	11	3	14	0	0	0	0	14
Hodgkin's disease	TSPA	0	1	2	3	7	1	8	73	11
	HN2	0‡	0	0	0	8	1	9	100	9

*Increase, no change, or regression of single lesion of total measured tumor mass.
†Significant reduction in total measured tumor mass or objective improvements related to tumor regression (general benefit).
‡One patient with "untoward effects" is included as a success.

TABLE VIII.—GRADED MEASURES OF RESPONSE FOR PATIENTS SHOWING POSITIVE RESPONSE

TYPE OF CANCER	DRUG	PATIENTS SHOWING POSITIVE RESPONSE		MEAN DURATION OF RESPONSE (DAYS)		MEAN REDUCTION IN MEASURED TUMORS	
Breast	TSPA	4/39 = 10%	N.S.D.*	45 ± 11.6	N.S.D.	30 ± 19%	N.S.D.
	HN2	9/37 = 24%		36 ± 7.5		44 ± 9%	
Lung—no prior x-ray	TSPA	4/42 = 10%	N.S.D.	65 ± 19.0	N.S.D.	50 ± 10%	N.S.D.
	HN2	12/46 = 26%		50 ± 8.5		39 ± 8%	
Hodgkin's disease	TSPA	8/11 = 73%	N.S.D.	44 ± 7.3	S.D.†	36 ± 6%	S.D.
	HN2	9/9 = 100%		81 ± 5.6		70 ± 6%	

*No significant difference.
†Significant difference ($P < 0.01$).

shown the duration of drug therapy and the total amounts administered. Duration of therapy was equivalent for both groups. The patients on thio-TEPA received approximately twice as much drug as those on HN2, validating the original intent of giving double the dose of HN2, a dose ratio chosen, on the basis of preliminary human pharmacology, to achieve equivalent marrow toxicity.

Responses to Treatment.—In Table VI are shown the basic data on the voting on response. These results are summarized in Table VII. Reduction in size of a single tumor when several metastases were present was not considered as a "success."

Hodgkin's disease: In previously untreated Hodgkin's disease, there was no significant difference in the number of patients responding positively to the drugs. Of the 9 nitrogen mustard–treated patients, 8 had marked regression of tumor, while this was true in 7 of 11 treated with thio-TEPA. In Table VIII the character of these regressions is examined. The mean remission following the thio-TEPA was 44 ± 7.3 days, while that achieved on nitrogen mustard was

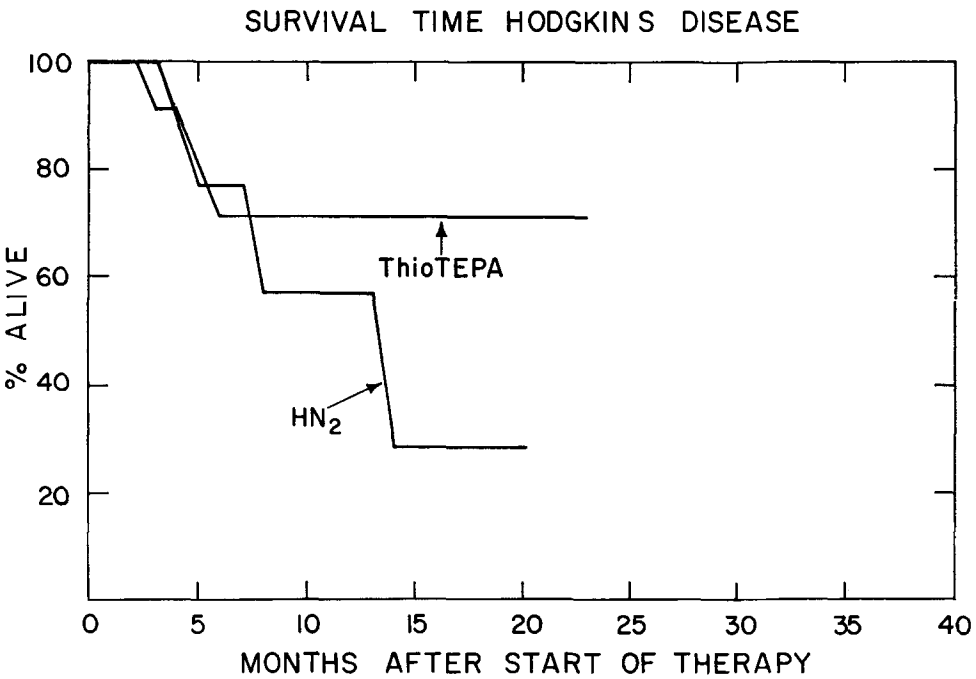

Fig. 1

81 ± 5.6 days. It should be pointed out that the study ceased at 90 days and patients were not observed beyond that for duration of remission, so that the average remission in the HN2-treated group was 81 days out of a possible 90. The mean maximum reduction in tumor size was 36 ± 6 per cent for the patients on thio-TEPA and 70 ± 6 per cent for those on HN2. Both of these differences concerning the character of the remission are significant at the 0.01 level.

Cancer of the lung without prior irradiation: More patients receiving nitrogen mustard had antitumor effect than those receiving thio-TEPA. The mean duration of tumor regression (Table VIII) was 65 ± 19.0 days in the 4 patients responding to thio-TEPA, and 50 ± 8.5 days in the 12 patients responding to HN2. Neither of these differences is significant at the 0.05 level.

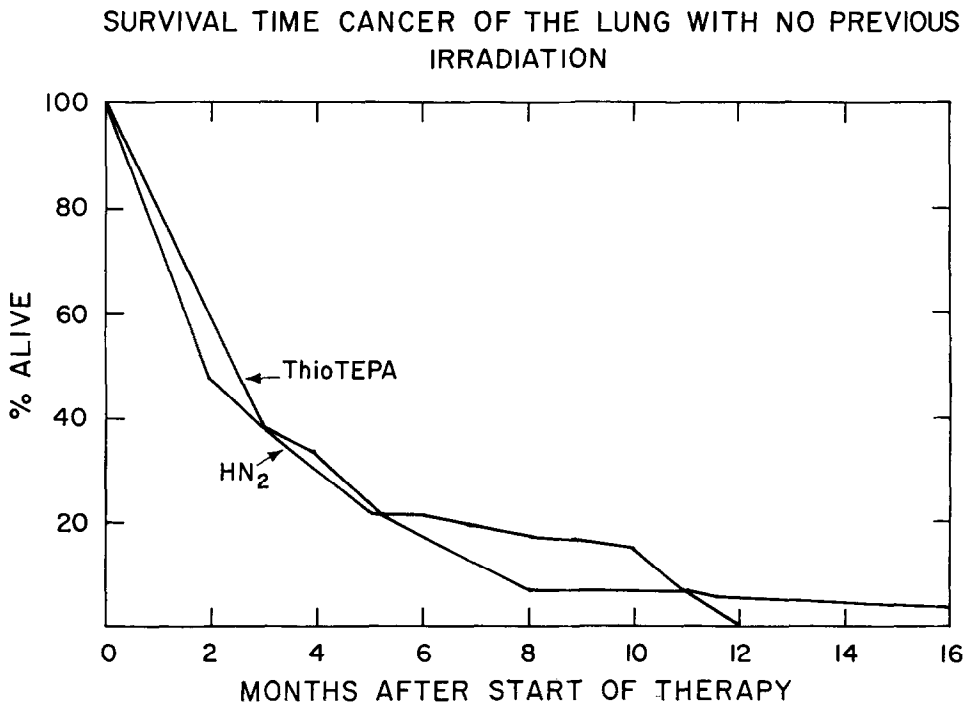
SURVIVAL TIME CANCER OF THE LUNG WITH NO PREVIOUS IRRADIATION
100
80
60
40
20
% ALIVE
ThioTEPA
HN2
0
2
4
6
8
10
12
14
16
MONTHS AFTER START OF THERAPY

Fig. 2

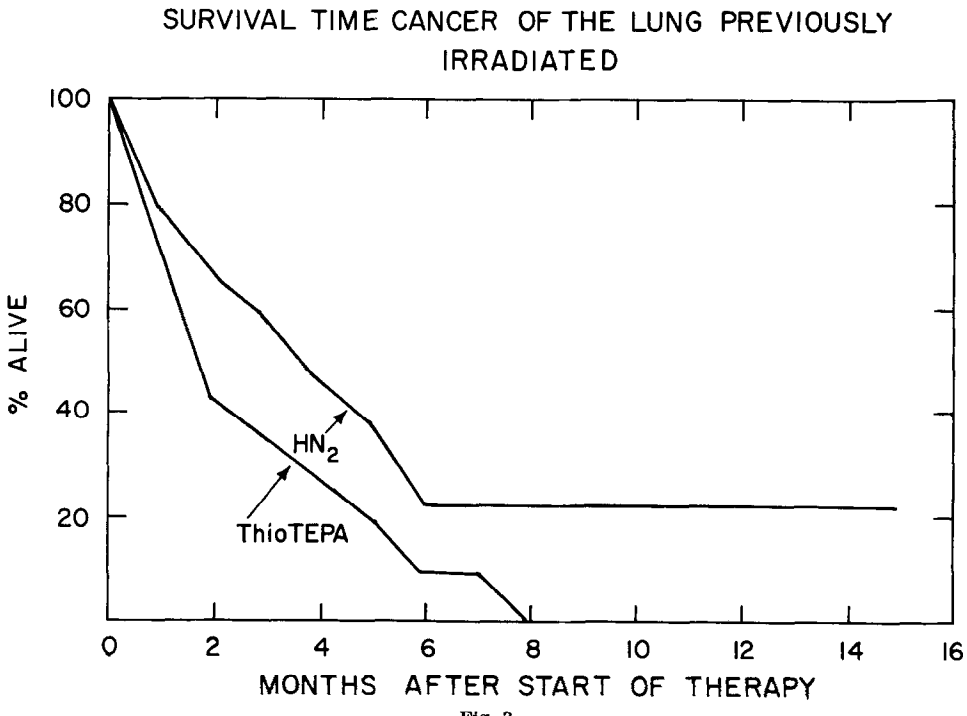
SURVIVAL TIME CANCER OF THE LUNG PREVIOUSLY IRRADIATED
100
80
60
40
20
% ALIVE
HN2
ThioTEPA
0
2
4
6
8
10
12
14
16
MONTHS AFTER START OF THERAPY

Fig. 3

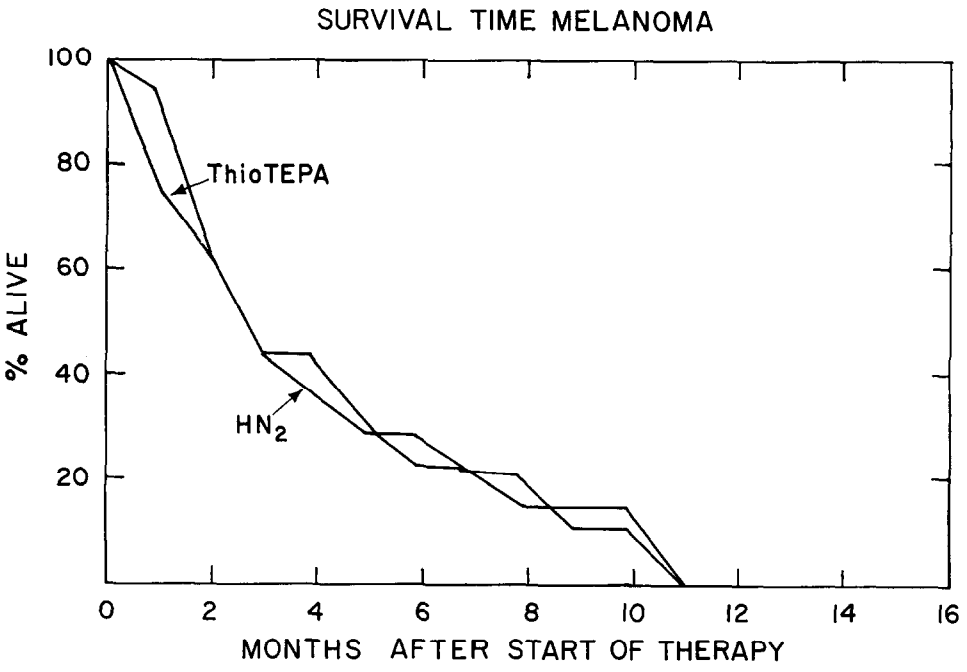
SURVIVAL TIME MELANOMA
100
80
60
40
20
% ALIVE
ThioTEPA
HN2
0
2
4
6
8
10
12
14
16
MONTHS AFTER START OF THERAPY

Fig. 4

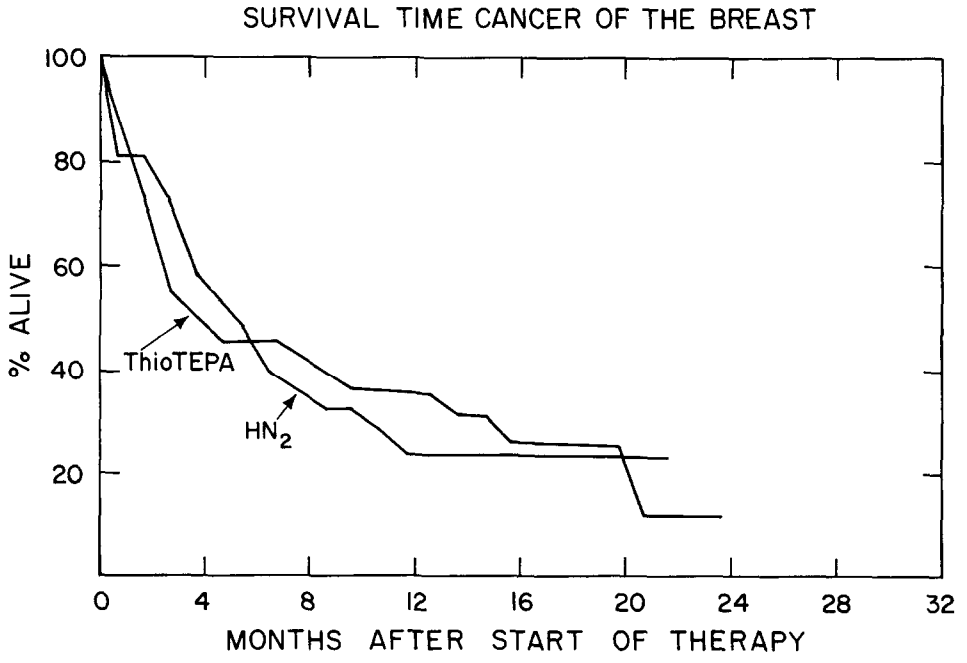
SURVIVAL TIME CANCER OF THE BREAST
100
80
60
40
20
% ALIVE
ThioTEPA
HN2
0
4
8
12
16
20
24
28
32
MONTHS AFTER START OF THERAPY

Fig. 5

Carcinoma of the lung with prior irradiation: There were very few antitumor effects and no significant differences between the two drugs. It can be noted in Table III that this group of patients was treated 6 months after diagnosis, while the patients who had received no irradiation were treated 1.5 months after diagnosis.

Malignant melanoma: There were no significant differences although 2 patients on thio-TEPA showed a transient antitumor effect. In 1 patient an effect occurred during the course of a pregnancy; in the other patient, during a rapidly degenerating course. In neither instance was the tumor regression marked.

Cancer of the breast: Both drugs were associated with antitumor effect. The mean length of regression was 45 ± 11.6 days for the 4 patients responding to thio-TEPA and 36 ± 7.5 days for the 9 patients responding to HN2 (Table VIII). The mean reduction in tumor size was 30 ± 19 per cent for thio-TEPA and 44 ± 9 per cent for HN2. The differences are not significant at the 0.05 level.

Life Table Analyses of Survival Times.—These are shown in Figs. 1 to 5 and are calculated from the time of onset of treatment.[15,16] There were no significant differences for any of the diseases between the survival of patients receiving nitrogen mustard and of those on thio-TEPA.

TABLE IX.—MAXIMUM WHITE BLOOD CELL COUNT CHANGES* (MEDIANS IN THOUSANDS)

TYPE OF CANCER	DRUG	NUMBER OF PATIENTS	COUNT		
			AT START	LOW	CHANGE
Breast	TSPA	33	7.6	3.9	3.7
	HN2	35	7.0	3.0	4.0
Lung					
No prior x-ray	TSPA	31	10.7	5.7	5.0
	HN2	38	12.4	5.7	6.7
Prior x-ray	TSPA	11	12.7	6.1	6.6
	HN2	14	10.5	5.8	4.7
Melanoma	TSPA	14	8.3	4.2	4.1
	HN2	13	7.7	2.6	5.1
Hodgkin's disease	TSPA	11	7.6	4.1	3.5
	HN2	8	8.1	2.9	5.2
All diseases	TSPA	100	9.6	4.9	4.7
	HN2	108	9.5	4.2	5.3

*Excluding patients for whom data were incomplete.

Comparative Effect of the Two Drugs on the White Blood Cell and Platelet Counts.—These are shown in Tables IX and X. Nearly equivalent responses of the white blood cell and platelet counts are seen in all instances. The differences noted in changes of the white blood cell and platelet counts in Hodgkin's disease are not significant at the 0.05 level.[17] These equal responses indicate that the dosages of drugs used gave equivalent hematologic effects.

Comparative Toxicity of Nitrogen Mustard and Thio-TEPA.—Toxic effects from drugs sufficient to warrant discontinuation of therapy are shown in Table XI. There were no striking differences between the two drugs.

TABLE X.—MAXIMUM PLATELET COUNT CHANGES* (MEDIANS IN THOUSANDS)

TYPE OF CANCER	DRUG	NUMBER OF PATIENTS	COUNT		
			AT START	LOW	CHANGE
Breast	TSPA	34	282	151	131
	HN2	34	259	104	155
Lung					
No prior x-ray	TSPA	33	331	165	166
	HN2	40	319	182	137
Prior x-ray	TSPA	13	303	132	171
	HN2	14	249	100	149
Melanoma	TSPA	14	244	140	104
	HN2	13	246	128	118
Hodgkin's disease	TSPA	11	303	146	157
	HN2	8	246	86	160
All diseases	TSPA	105	301	150	151
	HN2	109	270	125	145

*Excluding patients for whom data were incomplete.

TABLE XI.—LIST OF MAJOR UNTOWARD EFFECTS AS DETERMINED BY VOTING

TYPE OF TOXICITY	NUMBER SHOWING TOXICITY	
	PATIENTS ON HN2	PATIENTS ON THIO-TEPA
Excessive vomiting	2	0
Thrombocytopenia* and leukopenia† without sepsis or bleeding	5	2
Thrombocytopenia and leukopenia with sepsis or bleeding	0	3
Mental confusion	1	0
Total	8	5
Total patients	122	121

*Platelet count below 75,000 per cu. mm.
†Leukocyte count below 3,000 per cu. mm.

DISCUSSION

Cancer is a collective term encompassing a variety of diseases often manifesting themselves in such insidious and subtle ways upon the host as to make difficult the measurement of the effects of therapy. Because of the frequent lack of something to measure accurately, only a minority of patients with cancer can be studied to obtain precise data on the effect of drugs. A single hospital cannot

make enough observations in such highly selected patients to give adequate data within a reasonable time. To the authors, collaborative research in cancer chemotherapy seems the most feasible mechanism for the rapid and accurate clinical evaluation of the many new drugs shown to have antitumor activity in experimental systems. The present study was started in order to estimate the validity and practicability of this type of chemotherapeutic study in patients with cancer. The experiences of the group to date permit the conclusion that such a technique is feasible and with certain improvements should provide a precise method for the quantitative comparison of two or more anticancer therapies. Some general comments are in order concerning the advantages and shortcomings of this technique.

Advantages.—(1) The technique provides a larger number of suitable patients than could be seen in one hospital. (2) The effects of the drug upon the tumor can be expressed quantitatively. (3) The end point of drug effect is objective, and bias, to a large extent, has been eliminated from the judgment of effect. (4) In comparing one drug with another, the drugs can be given to groups of patients with comparable extent of disease. (5) The application of the protocol is comparable for all patients with respect to the criteria used, pharmacologic factors, and general clinical management. (6) Direct comparison of the toxic effects of drugs is possible.

Objections.—The objections which might be made against this method of studying drugs are as follows: (1) Too much time is required in planning and carrying out such studies, in having frequent meetings, and in traveling to and from these meetings. (2) Randomization procedure may not achieve comparability of patients. (3) Protocol studies do not permit the investigators the independence of action desirable in the practice of medicine.

A brief comment should be made concerning these objections. It is unquestionably true that such studies require a great deal of thought in planning and can be carried out only by frequent meetings of the investigators and discussion of their difficulties. Moreover, it is essential in such trials that such meetings be frequent in order that the criteria agreed upon be kept constant, that problems as they arise be settled by a general consensus, and that the various methods of evaluation be applied equivalently by the several investigators. Such planning is difficult, but the alternative to it requires that many of the most important factors in such trials be left to the operation of chance. The difficulties of such trials are most apparent in the first trial undertaken. When the investigators have worked together and solved the initial problems of criteria and judgment of effect, subsequent studies proceed much more rapidly.

It appears that the present study perhaps did not achieve full comparability of the groups of patients with Hodgkin's disease. There was a lack of correspondence in median duration of disease before therapy and in performance status of patients at the start of therapy. These differences indicate that the thio-TEPA–treated patients were treated somewhat earlier in the course of their disease than the patients given HN2. The reason for the lack of comparability may be the small size of the groups—11 and 9 patients, respectively—with the subsequent

greater opportunity for an unfortunate chance distribution. The comparative effectiveness of HN2 and thio-TEPA in Hodgkin's disease cannot be fully decided on the basis of these data, partly because the thio-TEPA-treated patients had somewhat earlier disease than those patients who received HN2 and may have offered a greater therapeutic challenge. It should be pointed out, however, that studies in which efforts to achieve randomization are made are preferable (even if not completely successful in achieving comparability of groups) to studies utilizing haphazardly chosen groups or historical controls.

It is also true that some physicians may find such protocol research too rigid and inflexible. Once the investigators have agreed to the conditions of the trial, such studies do limit the independence of the investigator to administer drugs of uncertain therapeutic value because of the particular suitability of the patient. This circumstance is a strong advantage rather than a disadvantage. The frequent changes invoked in many clinical investigations, while they may be a source of ego satisfaction to the physician, often result in data which do not answer the question the investigator has posed. If the physicians apply their knowledge of disease in the design of the trial and fully anticipate the possible decisions, then the application of the trial can be rigid without interfering with the right of the patient to the best medical care. In actual fact, the repeated regular examinations and laboratory observations required in such studies enforce one of the basic tenets of medical practice—namely, to examine the patient thoroughly at frequent intervals and accurately record the observations.

The data and experiences of this study have posed some questions on several important problems facing those who have the responsibility of conducting trials of antitumor drugs in patients. These are: (1) Is it necessary to restrict such studies to the small minority of patients who have easily measurable disease? (2) In trying to decide (within some confidence limits agreed upon) which drugs should be accepted as active chemotherapeutic agents and which should be rejected because of inactivity, what should be the optimal sample size for the numbers of patients studied? (3) Should such trials be conducted only with patients who have tumors highly sensitive to drug effect or with those whose tumors are relatively insensitive, or both? (4) What is the best end point for the judgment that a drug causes regression of human cancer? (5) Should several dose levels and dose regimens be explored in a given trial?

These studies are best carried out with patients with directly measurable disease and with those who have not had previous therapy. It would be possible, however, to design such trials with patients whose disease was otherwise nonmeasurable by using survival time as the end point. When one uses survival time as a measure of the effectiveness of a drug used in patients who may receive subsequent drugs, numerous assumptions are made. The first major assumption is that patients coming off the study drugs (say A and B) will receive essentially the same subsequent treatment, no matter what prior drug they received. The second important assumption is that neither A nor B leaves any residual effects which would cause differential reactions (favorable or unfavorable) with any of the subsequent treatments given. A third assumption which might be made is that

for late-cancer patients all subsequent treatment is essentially useless anyway and, therefore, will make no change in the patients' survival time. If later treatment were merely useless, this last assumption would not be dangerous. When later treatment may be worse than useless—where it may hasten death—then this becomes a dangerous assumption.

Treatment that is worse than useless may cause differences in survival time which are more apparent than real. For example, say drug A is "good," drug B "useless," and drug C "worse than useless." If a trial is begun with patients on A and B, more of the patients who have had B (and thus "failed") will go on to get C and have their deaths hastened. What differences there were between A and B will thus be exaggerated.

From the present studies, survival time seems a much less sensitive measure of the effect of drug than does regression in size of tumor, and therefore the use of survival time as the end point might result in the rejection of drugs which, although they did not influence survival time, at least were sufficiently active to cause regression of the tumor mass. It should also be clear that chemotherapy trials are nearly always undertaken in patients who have extensive and late disease. This circumstance not only complicates judgment on whether new complications are due to toxicity of the drug or progression of disease, but also leaves one with the unhappy, yet real, possibility that late disease is insensitive to drug therapy and active compounds may thus be missed.

The data of this trial give some estimates of the sample size required for comparative trials. It can be seen from the data of the Hodgkin's disease trial that if unpaired randomization is used, a sample size of 20 (10 patients for each drug) may be too small to ensure adequate comparability. A sample size of 15 for each drug, as shown in the patients with melanoma and also with cancer of the lung previously irradiated, gave some irregularities in comparability, but less than in the Hodgkin's disease group. Sample sizes of 25 to 40 for each drug, as in cancer of the breast and in nonirradiated cancer of the lung, resulted in closely comparable groups for the parameters measured. For sample sizes of 20 or more patients for each drug, it is suggested that simple randomization will achieve excellent comparability. For smaller sample sizes, either the criteria for inclusion in the study must be more tightly drawn or paired randomization may be needed to ensure equivalent distribution of the patients to the different groups. Thus, in Hodgkin's disease, one might pair for such factors as high initial leukocyte count and platelet count or for duration of disease longer than 2 months, so that equal distribution between the two drugs could be achieved for these modalities. It must be pointed out, however, that such pairing may be difficult and will be of significant value only if the criterion on which pairing is accomplished is highly correlated with therapeutic effect.

The data of this study would strongly suggest that comparative trials be conducted with patients with tumors which are partially sensitive to at least the "standard" drugs. Virtually no information other than toxicity is forthcoming when a comparative trial of two drugs is conducted against tumors which fail to respond or only occasionally respond to either, as in melanoma and cancer

of the lung with prior irradiation. In such instances far more information on drug effectiveness and toxicity would result if drug was given to one group of patients while another group received identical, good medical care plus a placebo. Limited to diseases not known to respond to chemotherapeutic agents, this latter design would not only be morally justifiable but would better fulfill the physician's obligation to reject toxic or ineffective drugs as soon as possible.

The size of experimental groups necessary to demonstrate a significant difference between two treatments is related to how small a difference the researchers consider medically important. The larger the difference, the smaller the experiment needed to show it. For example, if one were to work at the 0.05 significance level,* if treatment A produced 5 per cent positive responses and one were looking for an improved treatment B which produced 10 per cent positive responses, 513 cases would be needed in each treatment to have 90 per cent assurance that the given, single trial would uncover a significant difference. However, for the same significance level (0.05) and the same assurance (90 per cent), if A gave 5 per cent positive and B gave 25 per cent positive, 63 cases would be needed in each group.

These sample sizes are so large partly because only "yes-no" variables—either positive or negative—have been considered. If a measured or graded response is used (see Table VIII and discussion of responses in Hodgkin's disease), smaller sample sizes are needed. The yes-no (quantal) approach is the least powerful one that can be used. This study suggests that the graded response in the size of the tumor is the most sensitive index of chemotherapeutic activity. Finally, as indicated above, survival time, even when graded in life tables, is an even less sensitive index of drug activity than a quantal response on tumor regression.

The problem of studying multiple doses and dosage regimens in studies of the type described is an important one which has not been adequately studied. A priori, it would seem desirable to adopt such an approach wherever possible so as to allow for broader generalizations concerning drug comparisons.

SUMMARY

Suggestions are made for the conduct of chemotherapy trials in patients with cancer. Application of the principles involved are illustrated in a comparative study of triethylene thiophosphoramide and nitrogen mustard in cancer of the lung and breast, melanoma, and Hodgkin's disease. Neither drug was appreciably effective in cancer of the lung which had previously been irradiated or in melanoma. In cancer of the lung not previously irradiated and in cancer of the breast, 30 to 50 per cent reduction in tumor size occurred in 10 to 26 per

*"Significance level" corresponds to what has become fashionable in statistical circles to call Type I error—the error of saying that there is a difference when really there is not. Another type of error also exists—the Type II error. This is the error made when one says a difference does not exist when it really does. Thus, if one asks for 90 per cent assurance that a given experiment will yield a significant difference if it really exists (as large or larger than one postulates), then one is willing to take a 10 per cent Type II risk.

cent of the patients. In Hodgkin's disease certain factors limit the completeness of the comparison, but it is possible to draw the tentative conclusion that thio-TEPA was less active than HN2 (in the doses used) in inducing remissions. The advantages and disadvantages of this type of trial are discussed and several suggestions are made for improved experimental design.

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REFERENCES

1. Endicott, K. M.: The National Cancer Chemotherapy Program, J. CHRON. DIS. **8**:171, 1958.
2. Frei, E., III, Holland, J. F., Schneiderman, M. A., Pinkel, D., Selkirk, G., Freireich, E. J, Silver, R. T., Gold, G. L., and Regelson, W.: A Comparative Study of Two Regimens of Combination Chemotherapy in Acute Leukemia, Blood **13**:1126, 1958.
3. Wright, J. C., Golumb, F. M., and Gumport, S. L.: Summary of Results With Triethylene-Thiophosphoramide, Ann. New York Acad. Sc. **68**:937, 1958.
4. Bateman, J. C.: Palliation of Cancer in Human Patients by Maintenance Therapy With NN'N" Triethylene-Thiophosphoramide and N-(3-Oxapentamethylene), Ann. New York Acad. Sc. **68**:1057, 1958.
5. Ultman, J. E., Hyman, G. E., and Gellhorn, A.: Chlorambucil and Triethylene-Thiophosphoramide in the Treatment of Neoplastic Disease, Ann. New York Acad. Sc. **68**:1007, 1958.
6. Medical Research Council: Streptomycin Treatment of Pulmonary Tuberculosis, Brit. M. J. **2**:760, 1948.
7. Tucker, W. B.: Experiences With Controls in the Study of Chemotherapy of Tuberculosis, Transactions of the 13th Veterans Administration Conference on the Chemotherapy of Tuberculosis, 1954, p. 15.
8. Marshall, E. K., Jr., and Merrell, M.: Clinical Therapeutic Trial of a New Drug, Bull. Johns Hopkins Hosp. **85**:221, 1949.
9. Lasagna, L.: The Controlled Clinical Trial: Theory and Practice, J. CHRON. DIS. **1**:353, 1955.
10. Chalmers, T. C., Eckhardt, R. D., Reynolds, W. E., Cigarroa, J. G., Jr., Deane, N., Reifenstein, R. W., Smith, C. W., and Davidson, C. S.: The Treatment of Acute Infectious Hepatitis. Controlled Studies of the Effects of Diet, Rest and Physical Reconditioning on the Acute Course of the Disease and the Incidence of Relapses and Residual Abnormalities, J. Clin. Invest. **34**:1163, 1955.
11. Zubrod, C. G.: Experimental Design in Clinical Trials of Antitumor Drugs, Proceedings 3rd National Cancer Conference, Philadelphia, 1957, J. B. Lippincott Company.
12. Zubrod, C. G.: Procedures Recommended for the Clinical Trial of Alkylating Agents, Ann. New York Acad. Sc. **68**:1246, 1958.
13. Regelson, W., Zuckerman, P., Holland, J. F.: Co-ordinate Grid-Mapping Technique in Medicine, Cancer **10**:437, 1957.
14. Brindley, C. O., Markoff, E. and Schneiderman, M. A.: Direct Observation of Lesion Size and Number as a Method of Following the Growth of Human Tumors, Cancer **12**:139, 1959.
15. Merrell, M., and Shulman, L. E.: Determination of Prognosis in Chronic Disease, Illustrated by Systemic Lupus Erythematosus, J. CHRON. DIS. **1**:12, 1955.
16. Cutler, S. J., and Ederer, F.: Maximum Utilization of the Life Table Method in Analyzing Survival, J. CHRON. DIS. **8**:699, 1958.
17. Festinger, L.: The Significance of Difference Between Means Without Reference to the Frequency Distribution Function, Psychometrika **11**:97, 1946.
18. Chalmers, T. C., and Dederick, M.: Symposium on Chemotherapy of Cancer, Nov. 11-12, 1959, J. Nat. Cancer Inst. Supplement. To be published.

APPENDIX A

Protocol

In brief, the effects of mechlorethamine (HN2) and triethylene thiophosphoramide (thio-TEPA) will be compared in patients with easily measurable tumors of four types—malignant melanoma, Hodgkin's disease, epidermoid carcinoma of the lung, and carcinoma of the breast. It is to be emphasized that no patient will enter the study if there is a clear-cut indication for other types of therapy and that, also, should the demands of the best medical practice require deviation from the protocol, the patient will be considered as a drug failure and be given the indicated optimum therapy.

A. Selection of Patients.

Patients will be included in the study only when all the criteria listed below in 1 and 2 are present.

1. General.
   - a. Biopsy proof of cancer with reasonable certainty as to site of origin. An effort is to be made to secure and save the pertinent biopsy material for later review.
   - b. Primary or metastatic disease whose size is easily measurable with calipers, either directly or on an x-ray film.
   - c. Extent of disease is such that surgery or irradiation cannot offer patient cure or extended palliation.
   - d. No previous irradiation to the tumors to be measured. This would not exclude the study of metastases in patients where only the primary had been irradiated, nor would this exclude that group of primary bronchogenic carcinomas which have had previous irradiation. These will be randomized separately.
   - e. No previous alkylating agents.
2. Specific.
   - a. The following tumors will be studied:
     - (1) Breast.
       - (a) All premenopausal women with metastatic breast cancer should have had previous sterilization by oophorectomy or x-irradiation. An arbitrary period of at least 6 weeks of post-therapy observation will be allowed in order to appraise the effects of sterilization.
       - (b) Sterilized premenopausal women or postmenopausal women with or without previous therapy (e.g., androgens, estrogens, cortisone or its derivatives) can be included. When the patients have received such therapy, the administration of alkylating agents should not start until 3 months shall have elapsed since the beginning of hormonal therapy, and until at least 6 weeks shall have elapsed since the cessation of hormonal therapy. Patients with previous adrenalectomy or hypophysectomy are not to be included in the trial.
     - (2) Bronchogenic Carcinoma.
       - (a) Only epidermoid and undifferentiated tumors will be included. It is essential that primary lesions be clearly measurable, when they are the only tumors being observed.
       - (b) Patients who have previously received no irradiation will constitute one subgroup. These will be randomized separately from patients in group (c).
       - (c) Patients who have previously received irradiation will constitute a second group. Before starting these drugs, at least 6 weeks of observation should be made to allow recovery from the effects of irradiation.
       - (d) Patients with frank pulmonary infection should be treated first with antibiotics; only those whose infections come under control are to be included in the study.
     - (3) Malignant Melanoma.
     - (4) Hodgkin's Disease.

B. Pretreatment Studies.
Each patient is to have the following base-line studies performed prior to therapy: Complete history and physical, hemoglobin, hematocrit, white blood count, differential, platelets, urinalysis, and x-ray of chest and skeleton.

C. Studies During Treatment.
1. Once weekly: Hematocrit or hemoglobin, white blood count, platelet count and differential white count, urinalysis, and weight.
2. X-rays: Chest film once each month; otherwise, lung once every 2 weeks and bones once each month if lesions are being measured by these techniques.

D. Mechanics of Study.
Randomization among the treatment groups will be done separately for each hospital and for each tumor type. Each investigator will be provided with a series of envelopes for each of the tumor types. The investigator will previously have made an estimate of the number of patients with a given tumor type that his group will treat. If he is to treat 20 cases of carcinoma of the breast, he will receive 20+ sealed envelopes, numbered 1 to 20+ on the outside. Inside there will be a slip indicating what therapy the patient is to receive. The type of treatment will have been predetermined randomly by the biometrician. In order to collect data on the kinds of samples selected by each hospital, it is desirable to obtain as much information as possible on the nature of this sample.
1. A log book should be kept of all patients who are considered for possible chemotherapy by each group. The name of the patient should be recorded as soon as he comes up for consideration. If he is rejected for study, the most important reason for the rejection should be noted.
2. If the patient is considered suitable, as soon as this determination is made he is to be considered formally in the study and assigned a number. If for some reason therapy is discontinued before the end of 90 days, he must still be regarded as part of the trial, the subsequent events documented, and the patient included in the final tabulation of results.

E. Dosage of Drug.
Single batches of thio-TEPA and HN2 have been distributed by the Chemotherapy Center. These should be stored at approximately 4° C. The HN2 is the commercially available material in 10 mg. ampules, to be diluted to 10 c.c. in normal saline and the appropriate dose to be injected through the tubing of an infusion previously started by venipuncture. It is essential that the veniclysis be well established and definitely in the vein, since HN2 is an extremely irritating material. Thio-TEPA is furnished in ampules containing 15 mg. of the base plus an inert filler to increase the dry volume. This is then diluted with 3 c.c. of normal saline, the required dose removed and injected by the direct intravenous route. The remaining solution in the ampule is discarded. For safety's sake it is well to recall that the total volume of administered solution here rarely exceeds 3 c.c.

HN2 is to be given intravenously in the dose of 0.1 mg./Kg. of body weight daily for an initial course of 4 days. Thio-TEPA is to be given in a dose of 0.2 mg./Kg. of body weight daily also over a 4-day period by the intravenous route initially. After the original course, the patient is to be observed for a 2-week period from the time of the last dose. If the white blood cell count and the platelet count are satisfactory (see below), once weekly intravenous dosages are given—HN2, 0.1 mg./Kg; thio-TEPA, 0.2 mg./Kg. This is shown in outline form:

	Thio-TEPA	HN2
Initial course	0.2 mg./Kg. for 4 days	0.1 mg./Kg. for 4 days
Evaluation at end of 2 weeks from last dose, then continue:	0.2 mg./Kg. once a week	0.1 mg./Kg. once a week

No drug is to be given if the WBC count is below 3,000 or the platelet count below 75,000. The dose is to be reduced to one-half of the scheduled dose if the WBC count is 5,000 or below, or the platelet count below 100,000. If it is necessary to skip a dose by reason of a hematologic depression, an interval of 7 days should elapse and the patient should be re-evaluated for resumption of drug at that time. The duration of therapy will be for an arbitrary period of 90 days. All patients receiving HN2 will receive 50 mg. of chlorpromazine by mouth a few minutes before injection of HN2. Barbiturate may be given at discretion of physician either before or after the dose. Patients on thio-TEPA will not be given chlorpromazine premedication. No patient in this study should receive long-term or routine chlorpromazine administration.

The tumor masses which are to be selected for serial measurement of lesion size are only those having discrete borders and those which are easily accessible to application of the calipers or easily demonstrable on roentgenograms. Not more than five cutaneous and/or subcutaneous tumor masses, two pulmonary masses, and two osseous masses are to be measured serially. The total number of tumor masses in the three areas—(1) skin and subcutaneous tissue, (2) lung, and (3) bone—are to be followed separately. Observations on lesion size and number are made for the cutaneous and subcutaneous lesions once each week; for pulmonary lesions, on x-ray films taken every 2 weeks; and for osseous lesions (lesion size measurements only), on films taken every 4 weeks. The total number of osseous lesions is determined on x-ray skeletal surveys taken at the start and end of the study. Lesions which have been selected for serial measurement, whether palpable masses or those which can be seen only on x-ray, should be measured with calipers in two dimensions, one being the largest diameter and the other being the diameter perpendicular to the first diameter. Both of these measurements should be recorded as such on the measurement sheet. At the time of measurement, only a single measure is taken and no effort is to be made to take a mean of several measurements. All observations should be done, if possible, by a single individual for any given patient. If the observer must be changed during the course of a study, there should be a period of overlap of measurements by both old and new observer to preserve continuity, for it has been found that absolute measurements vary depending on the examiner, but that slopes of growth are fairly independent of the observer.

Any base-line measurements of palpable tumors or of pulmonary tumors must be taken within 3 days of the start of drug. Base-line measurements of x-ray size of osseous metastases must be made on x-rays taken within 10 days of starting drug. Techniques of taking x-rays should be standardized for the study in each hospital, but these need not be the same for each hospital. All groups will use the same calipers* for measuring. These are described in the Fisher catalogue—#12-130, caliper, vernier, stainless steel, range 0-12 cm.

The raw data on measurements should be forwarded to the Chemotherapy Center at the conclusion of the study of each patient. Definitions as to effect will come from a consideration of these data. All possible positive effects from chemotherapy will be reviewed by the other senior investigators in the study at suitable intervals. They will be in ignorance of which treatment was given. The total effect on patient as to toxicity of drug, improvement in well-being, pain, weight, anemia, etc., should be recorded. For this, careful consideration has been given by the group as to what information should routinely be included in progress notes and flow sheet. Also special procedures such as serum uric acid and calcium balances should be recorded when available.

RECORDS TO BE KEPT

A. Measurements of tumor size and total number (see Appendix D).
B. Grid map for front and back of figure to indicate position of tumors (see Appendix C).
C. Log book for all patients considered for the study.

*The calipers now in use are the Gehartet original helios.

D. Individual summaries of each drug trial (see Appendix E).
E. Flow sheet of symptoms, signs, and laboratory data to be filled out on each visit in the outpatient area, or weekly when the patient is in the hospital, with appropriate instruction sheet (see Appendix B).
F. Postcards to be checked and mailed to the Chemotherapy Center after each envelope is opened.

APPENDIX B

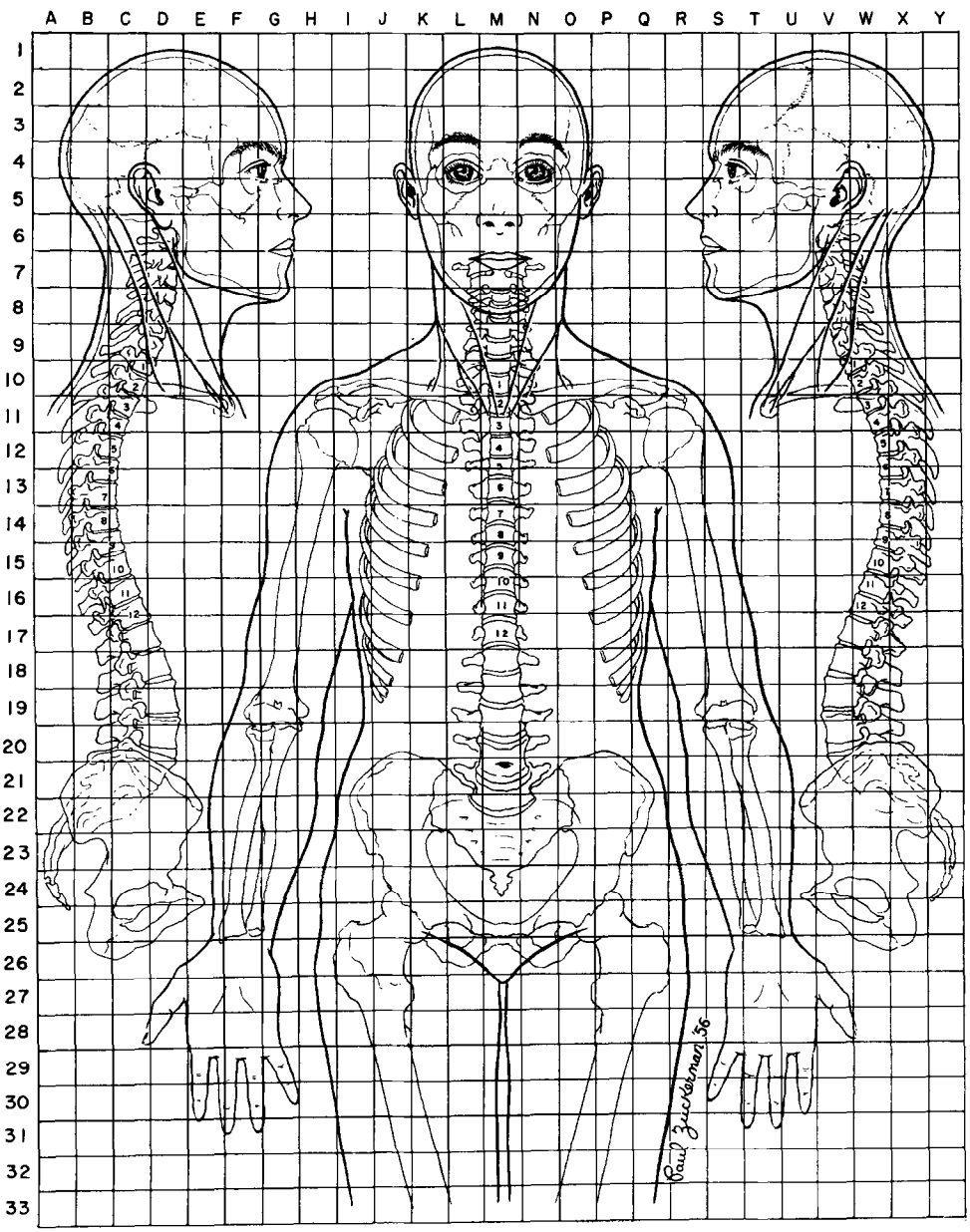
Flow Sheet

PROGRESS REPORT – SUMMARY AND IDENTIFICATION

1. Day on Drug													
2. Date													
3. Hosp. or O.P.D.													
4. Laboratory and Physical Measures													
Weight (lbs-Kgms)													
Edema													
Temperature													
Pulse													
Spleen)cm. below													
Liver) C.M.													
X-ray													
Hgb													
Hematocrit													
WBC (1000)													
Polys													
Platelets (1000)													
5. Patient Reaction Performance													
Pain													
Food Intake													
Nausea													
Vomiting													
Skin & Mos. Memb.													
CNS Signs													
G. I.													
Cardio-Vascular													
6. Orders Transfusion													
Antibiotics													
Drug Dose													
Initials													
Progress Note													
7. Patient	Ward		Case No. In Series				Institution Investigator						

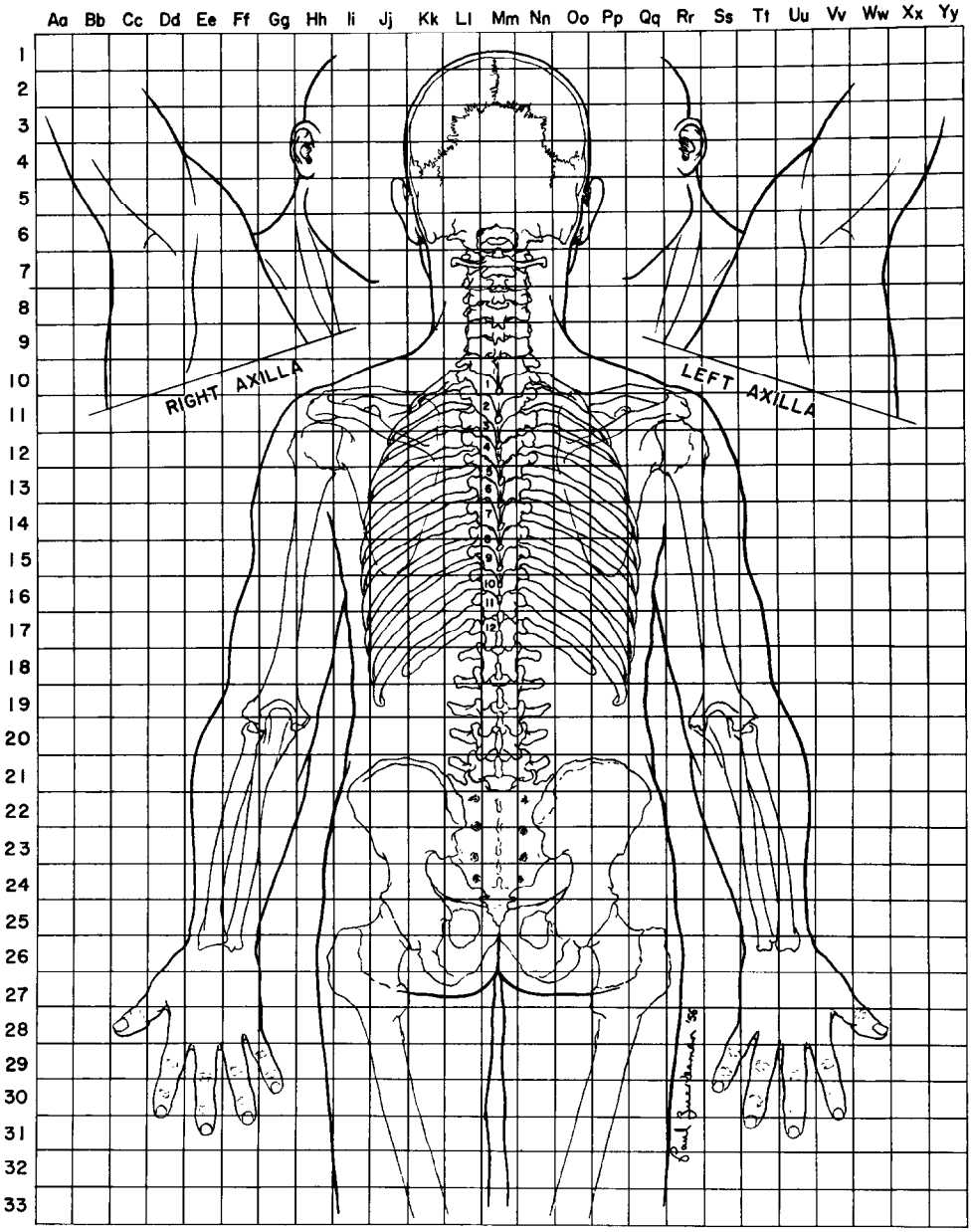
APPENDIX C_1

Grid Map



APPENDIX C_2

Grid Map



APPENDIX D

Measurement Sheet

PROGRESS REPORT – TUMOR MEASURE

Day on Drug													
Date													
Drug Dose													
8. Initials													
Location:													
9. Initials													
Location:													

Patient's Name	Ward	Case No. In Series	Institution Investigator

APPENDIX E

Summary Sheet

PROGRESS REPORT – SUMMARY AND IDENTIFICATION

10. Narrative Summary

11. Complications

12. Prior Treatment

13. Surgery Y N Copy Autopsy Y N Att: Y N	15. Dates	M	D	Y		Code
Tumor Metastases C O S P L V	Symptoms					
	Diagnosed					
	Admit to Hosp					
	On Study					
	On Drug					
	Off Study				A	D
	Off Drug				A	D
	Discharged				A	D
	Death					

14. Age	Male	Female	Race

Patient's name	Ward

16. Drug	Schedule	Route

Case No. In Series	Institution Investigator

APPENDIX F

Instructions for Completion of Data Sheets

FOR FLOW SHEET

1. *Day on Drug.*
   Put in the total number of days from the time the drug was first given to patient.

2. *Date.*

3. *Hosp. or O. P. D.*
   Indicate by *H* if patient is hospitalized or by *O* if patient is being treated as outpatient.

4. *Laboratory and Physical Measurements.*
   Weight—in kilograms or pounds, as is used in your institution; cross out the unit which is not used.
   Edema—0-none, 1-slight, 2-moderate, 3-severe.
   Temperature—in degrees centigrade.
   Pulse—b.p.m.
   Spleen, Liver } centimeters below costal margin.
   Hemoglobin
   Hematocrit
   Differential count—in per cent.
   WBC—in thousands.
   Platelets—in thousands.

5. *Patient reaction.*
   Performance—Record in this section the performance that the patient is *capable* of. For example, a patient in the hospital for metabolic studies may be fully capable of normal activities, but will remain in bed through his own choice. Such a patient should be coded 0, "normal."
   - 0 Normal activity.
   - 1 Symptoms, but nearly fully ambulatory.
   - 2 Some bed time, but needs to be in bed less than 50 per cent of normal daytime.
   - 3 Needs to be in bed greater than 50 per cent of normal daytime.
   - 4 Unable to get out of bed.

   Pain
   - 0 None
   - 1 Mild
   - 2 Moderate
   - 3 Severe

   Food Intake—Give calories of food intake if available, otherwise list patient's appetite as:
   - 3 Poor
   - 2 Fair
   - 1 Good

   Nausea
   - 0 None
   - 1 Some
   - 2 Marked

6. *Orders.*
   Transfusions—Check if given.
   Antibiotics—Check if given; note at beginning of row the specific antibiotic given; use next row if necessary.

Drug dose—Give in milligrams of specific drug used. Do not name the drug.
Initials—Initialled by person carrying out examination.
Progress note—If a progress note was written and included in the record, check here.

7. *Patient identification.*

Case No.—Give hospital record number.
Series—Give the serial number of this patient in the specific series at this institution, i.e., B-5 means fifth breast patient in this study.

FOR MEASUREMENT SHEET

Day on drug.
See previous instructions.
Date.
Drug dose.
Give in milligrams of specific drug used. Do not name the drug.

8 & 9. *Initials.*

Initials of person making measurements.
Measurements.
Report measurements in centimeters, giving major diameter and the largest diameter at right angles to the first measurement. If more lesions are measured, extra pages should be attached. Identify all lesions on the anatomic figure as "location."

FOR SUMMARY SHEETS

10. *Narrative Summary.*

Indicate your opinion as to the effect of the drug for this course of treatment under study and other related remarks.

11. *Complications.*

12. *Prior Treatment.*

Be sure to include use of steroids, hormones, any alkylating agents.

13. *Surgery, Autopsy.*

Circle *Y* for yes, *N* for no.
Copy attached—Indicate "yes" or "no" if a copy of surgical and/or autopsy protocol is included.
Metastases—Encircle appropriate letter.

C Cutaneous
P Pulmonary
O Osseous
L Lymph involvement
V Visceral (liver, spleen, etc.)
S Other soft tissue

14. *Patient Identification.*

Circle symbol for male or female.

15. *Dates.*

Record month (M), day (D), year (Y).
Check (A) or (D) to show whether patient was alive or dead at the time.
Symptoms—Date patient reports symptoms were first noticed (this may at times be only month and year, or possibly year only).
Diagnosed—Date a confirmed diagnosis was made.
On study—Date study drug was first administered.
Code—Leave blank.

APPENDIX G

Solid Tumor Cooperative Study Group Patient Evaluation Sheet

1. Case No.———————————
   Patient's Name———————————
   Date Presented———————————
2. Hospital Reporting———————————
3. Hospital Voting———————————
   Age———————
   Sex———————
4. Evaluation (check appropriate boxes)

Reduction in Tumor Size		Other Effects		Total Evaluation
1. Single Tumor	2. Total Tumor Mass	3. Major Untoward	4. Other Beneficial	5. Benefit to Patient
Y*	Y $\frac{T\dagger}{P}$	Y	Y	Y
N‡	N	N	N	N

6. Survival (in days)
   a. From symptoms:
   b. From diagnosis:
   c. From therapy:
7. Number of tumors
   a. Start———————
   b. End———————
   c. Graphed———————

*Yes.
†T = transient (less than 90 days); P = prolonged (90 days or more).
‡No.