Exhibit C
to Kalasinsky Declaration

WICA6777 VP 2/17

Request # 32468962 BILL FEB 17, 2012

Web (PDF) For: vhacoill@va.gov FEB 17 2012

Dept. Vet. Aff. -- Central Office
Library (10P2C2)
810 Vermont Avenue NW
Washington, DC 20420-0001

RUSH PDF

RUSH DOCLINE: Journal Copy EFTS Participant

Title:	Cancer chemotherapy reports. Part 1
Title Abbrev:	Cancer Chemother Rep
Citation:	1962 Feb;16():141-8
Article:	The Veterans Administration surgical Adjuvant Grou
Author:	HIGGINS G;SERLIN O;HUGHES F;DWIGHT R
NLM Unique ID:	7607105 Verify: PubMed
PubMed UI:	13907245
ISSN:	0069-0112 (Print)
Fill from:	**Any format**
Publisher:	National Cancer Institute, Bethesda Md :
Copyright:	Copyright Compliance Guidelines
Authorization:	RW
Need By:	N/A
Maximum Cost:	~~**$15.00**~~ $16.00
Patron Name:	Susan Blauert
Referral Reason:	Not owned (title)
Library Groups:	AFMLC,AMEDD,DCAHSL,DOD,FEDLINK,FreeShare,NAVY,VALNET
Phone:	1.202.461-7576
Fax:	202.273.9125
Email:	vhacoill@va.gov
Alt Delivery:	Email(PDF),Email(TIFF),Fax,Web(PDF),Web(TIFF)
Routing Reason:	Routed to CAUCLA as Refer on after NLM
Received:	Feb 17, 2012 (01:50 PM ET)
Lender:	University of California, Los Angeles/ Los Angeles/ CA USA (CAUCLA)

Bill via EFTS only to: DCUVAC

Dept. Vet. Aff. -- Central Office
Library Service (10P2C2)
810 Vermont Avenue NW
Washington, DC 20420-0001

THE VETERANS ADMINISTRATION SURGICAL ADJUVANT GROUP—INTERIM REPORT[1]

George A. Higgins, Oscar Serlin, Felix Hughes, and Richard W. Dwight

The Veterans Administration Surgical Adjuvant Cancer Chemotherapy Study Group was formed late in 1957, utilizing the clinical material of 22 participating hospitals. This study was designed to determine the effectiveness of tested alkylating agents, nitrogen mustard (HN2) and thioTEPA (TSPA), given at the time of surgical resection of major visceral cancer. Chosen for this study were cases of primary carcinoma of the lung, stomach, colon, and rectum. In addition to determining whether chemotherapy administered at, and soon after, operation as an adjunct to resectional surgery will increase the cure rate or appreciably prolong the survival time, the study has as a secondary objective a comparative study of the value of chemotherapy used in cases with minimum residual or seeded cancer cells as compared with extensive neoplastic disease. Obvious by-products of such a study are information concerning the toxicity of the agents employed as well as the accumulation of extensive statistical data concerning the various characteristics of cancer in the areas under study as well as in the operative management of these cases.

At the time of the operation, patients selected for the study were placed in "curative" or "palliative" groups under strict criteria based upon histopathologic evidence of residual disease left behind at the time of operation.

Randomization of patients into treatment and control groups was first done by the use of sealed envelopes which were opened at the end of the operation. Since the first year of the study, selection of patients has been by the double-blind method with packets containing either drug or a placebo. Statistical advice, as well as randomization of cases and collection and analysis of data, has been provided by the Follow-up Agency of the National Research Council.

HN2 was selected for study in cases of carcinoma of the lung because of isolated reports of favorable response to this drug in far-advanced cases of bronchogenic carcinoma. At the onset of the study, the drug dose was 0.1 mg./kg. given intrapleurally at the close of the operative procedure and a similar dose intravenously (i.v.) at that time. A similar dose was then given i.v. on the 1st and 2d postoperative days, a total of 0.4 mg./kg. When the study had been in progress for several months, an analysis of the 30-day mortality figures indicated a statistically valid increase in the treated as opposed to the control group. For this reason, the i.v. dose on the day of operation was discontinued, the other dose remained the same, with the stipulation that the total dosage not exceed 22.5 mg. For the stomach and colon-rectum study, thioTEPA was used in a dose of 0.2 mg./kg. given intraperitoneally at the close of the operation and 0.2 mg./kg. given i.v. at the same time. The same dosage was then given i.v. on the 1st and 2d postoperative days for a total of 0.8 mg./kg. Early analysis of the 30-day mortality figures indicated a discrepancy similar to that found in the lung study and the i.v. dosage given at the time of the operation was therefore eliminated. Thus, the total dosage administered was 0.6 mg./kg., not to exceed 45 mg.

[1] The participating doctors of the VA Adjuvant Study Group and the location of their respective VA Hospitals are: *Richard W. Dwight*, Boston, Mass.; *Philip Cooper*, Bronx, N.Y.; *Harry H. LeVeen*, Brooklyn, N.Y.; *Fred W. Preston*, Chicago, Ill. (Research); *Alfred Keirle* and *Luis Gonzalez*, Cincinnati, Ohio; *John Nickel*, *Robert E. L. Rochelle*, and *Jerry S. Wolkoff*, Cleveland, Ohio; *John P. North*, Chairman, 1957-1960, and *Robert P. Hays*, Dallas, Tex.; *William Gillesby*, Hines, Ill.; *George L. Jordan, Jr.*, and *Samuel Law*, Houston, Tex.; *Samuel Walker* and *Richard L. Lawton*, Iowa City, Iowa; *George Higgins* and *Jack Zimmerman*, Kansas City, Mo.; *Glen Young*, Long Beach, Calif.; *Felix Hughes*, Memphis, Tenn. (Kennedy); *Donald J. Ferguson* and *Edward W. Humphrey*, Minneapolis, Minn.; *John V. Smith*, Oakland, Calif.; *William S. Nichols* and *Oscar Serlin*, Philadelphia, Penna.; *Francis Jackson*, Pittsburgh, Penna.; *H. W. Harrower*, Providence, R. I.; *Luis Passalacqua* and *Jose H. Amadeo*, San Juan, P.R.; *Falls B. Hershey* and *Robert C. Donaldson*, St. Louis, Mo.; *George Higgins*, Chairman, 1960–, Washington, D.C.; and *Miles B. Smith*, Wood, Wisc. Also working with the group on this study were *Dr. Gilbert W. Beebe* and *Mr. Robert Keehn* at the statistical center and *Dr. Lyndon E. Lee, Jr.*, Coordinator, VA Central Office.

The accumulated experience of the study is shown in table 1. Of the 6228 patients screened, 2728 have been selected for study. Of these, 1416 are still being followed.

TABLE 1.—Cumulative Experience of the Veterans Administration Adjuvant Cancer Chemotherapy Study Group for October 1957–June 1961

	Screened	Selected for study	FUDR pilot study	Patients being followed
Lung	2243	1007		454
Stomach	1815	444	25	150
Colon-Rectum	2070	1277	50	812
Total	6228	2728	75	1416

Since this study was started, several substudies have been undertaken within the group and protocols for additional substudies are under consideration at the present time. In cases of carcinoma of the stomach and colon-rectum falling into the palliative or nonresectable group at operation, a pilot study with FUDR as a surgical adjuvant has been in progress since March 1961. This study was primarily aimed at determining the toxicity of this agent when used as a surgical adjuvant agent and plans are being made to use this drug in the curative group of cases. A protocol is being prepared for the use of supravoltage roentgen therapy as preoperative treatment in certain selected cases of bronchogenic carcinoma and it is contemplated that this study will begin in the near future. The group is also considering the use of a different drug to be used as an adjuvant in cases of bronchogenic carcinoma or possibly altering the dose schedule of HN2 now being used. A number of compounds are now being studied by the Veterans Administration Lung-Cancer Study Group with the prospect of finding an agent effective against bronchogenic carcinoma which can be safely used as a surgical adjuvant in "curative" cases. With the increased interest in the intra-arterial infusion method of administration of chemotherapeutic drugs, as subgroup of the Adjuvant Cancer Chemotherapy Group has been organized to explore the possibilities of this method of therapy as well as to gain experience in some of the technical problems arising with this mode of administration. As soon as sufficient experience has been gained, a protocol will be prepared so that the efficacy of this modality of treatment can be carefully evaluated.

CARCINOMA OF STOMACH
(Dr. Serlin)

Complications (Table 2)

In 43 cases treated with the full dosage of thioTEPA (0.8 mg./kg.), complications developed in 58.1%; whereas complications developed in 43.1% of 51 patients in the control group. It should be pointed out that complications of all types, both major (such as wound dehiscence, pulmonary embolism, and peritonitis) and minor (such as fever of unknown origin, ileus, and diarrhea) have been recorded. This results in an apparently high rate of complications. In the reduced-dosage schedule (0.6 mg./kg.), complications developed in 50.8% of 122 patients as compared with 47.7% of 109 patients in the control group. These figures show that reducing the dosage of thioTEPA did not materially reduce the rate of complications, nor is there any statistical difference between the rate of complication in either group.

TABLE 2.—Complications after stomach surgery

	Full dose		Reduced dose	
	Treated	Control	Treated	Control
Total patients	43	51	122	109
Without complications	17	28	58	55
With complications	25	22	62	52
Unknown	1	1	2	2
Percent with complications	58.1	43.1	50.8	47.7

Operative Mortality

All patients who died within 30 days after the operation are counted as an operative death Figure 1 shows that the operative mortality for all patients treated with surgery alone or with surgery + placebo averaged approximately 10%. The operative mortality in the full-dosage series is slightly greater than 23%, and that in the reduced-dosage series closely approximates this figure. Reducing the dosage of thioTEPA did not reduce the operative mortality and the mortality rate in patients treated with thioTEPA remains higher than the control group.

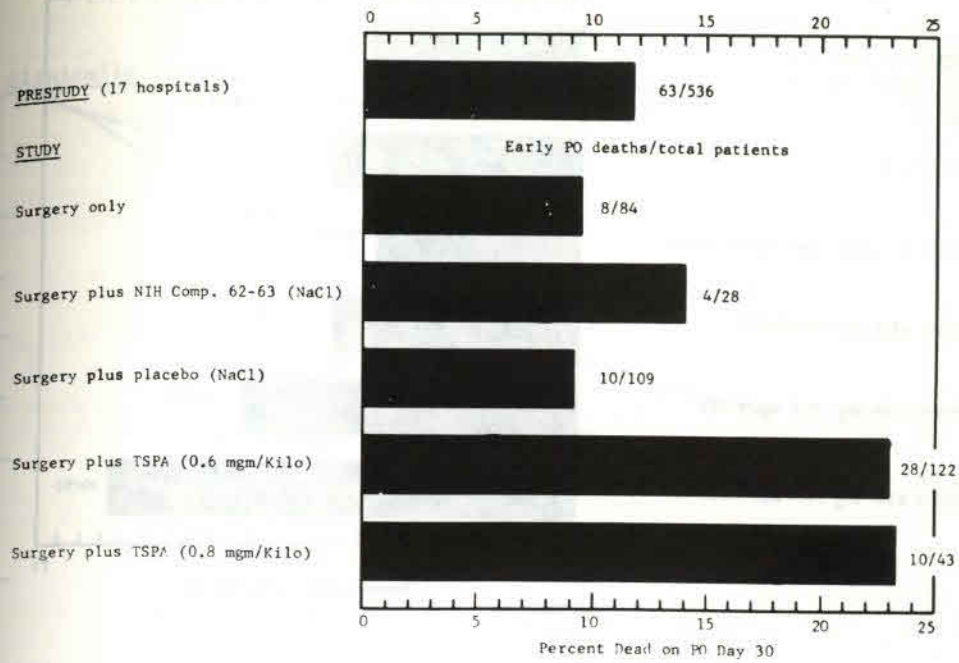

FIGURE 1.—Early postoperative (30-day) mortality-stomach surgery reports received by July 15, 1961, for surgery performed by June 15, 1961.

In an attempt to discover the cause of the increased mortality in the treated patients, we analyzed the causes of death (table 3). Suture line leak, either at the duodenal stump or at the anastomotic site, caused 11 of the 26 deaths in the low-dosage group (42%). However, this same complication of surgery caused 6 of 8 deaths in the control group (75%). The remaining causes of death in the treated group were scattered. There were 8 patients with a depression of the white blood cells or platelets, or both, and in 4 of them, infection played a part in death. Only 2 patients with a suture line leak had a blood cell depression.

It appears that it is not possible to implicate thioTEPA as a cause of suture line leak nor can we specifically say that the blood cell depression played a large part in causing death in the early mortality group.

Survival Studies

Figure 2 shows the survival figures based on those patients who survived the 30-day postoperative period. It can be seen that the lines of the control group and those of the full-dosage schedule approximate each other after 36 months. In the reduced-dosage series, there is a definite difference in that a greater number survive at the end of 24 months. While the number of patients in the reduced-dosage series is relatively small, if this trend continues, there will be a statistically significant improvement in the survival at the end of 5 years.

TABLE 3.—Cause of death (30-day mortality) on reduced dosage of thioTEPA in carcinoma of the stomach

Cause of death	Treated	Control	Total
Peritonitis or empyema due to suture line leak	11	6	17
Peritonitis or empyema without suture line leak	2		2
Sepsis (including septicemia, enterocolitis, abscesses, etc., but not peritonitis)			
Cardiovascular (including pulmonary emboli)	4	2	6
Pulmonary (pneumonia, atelectasis)	1		1
Cerebro-vascular			
Renal failure	1		1
Technical error	3		3
Cancer death in palliative cases	1		1
Miscellaneous	3		3
Total	26	8	34

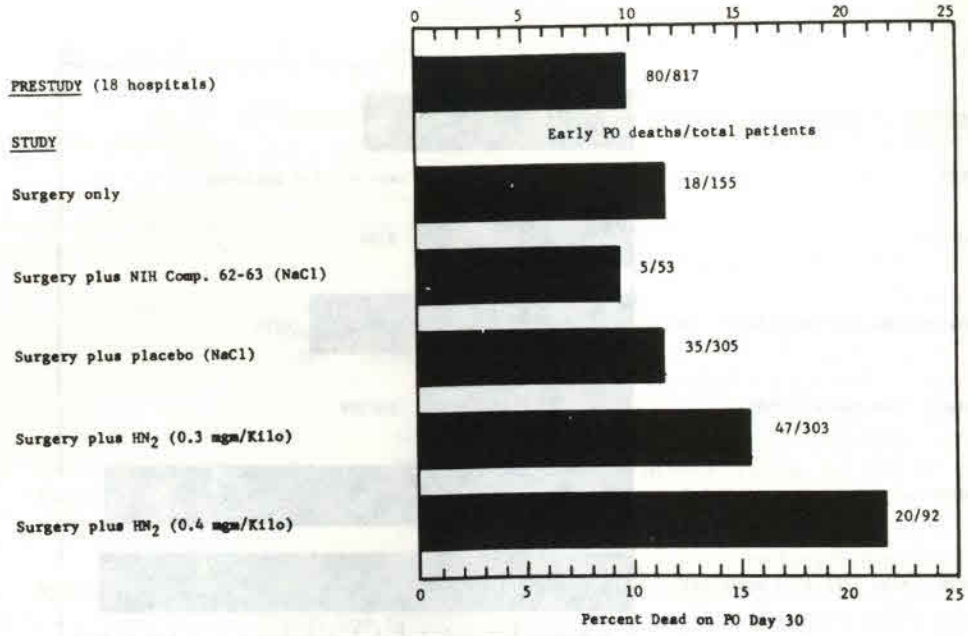

FIGURE 2.—Early postoperative (30-day) mortality-lung surgery reports received by June 15, 1961, for surgery performed by June 15, 1961.

In conclusion, it can be said that thioTEPA administered in a total dosage of either 0.6 mg./kg. or 0.8 mg./kg. at surgery and in the immediate postoperative period appears to increase the operative mortality although the exact mechanism of its action is not known. At the present time, it appears that thioTEPA in the reduced dosage (0.6 mg./kg.) at 24 months may increase the survival rate. If this trend continues, the difference will be a significant one. It should also be noted that the number of patients in this study to date is relatively small and for this reason we plan to continue the study.

CARCINOMA OF THE LUNG
(Dr. Hughes)

Our study of bronchogenic carcinoma continues to be focused on the possible effect of HN2 upon the postoperative mortality, complications, and survival of surgically treated patients.

Figure 3 shows the 30-day postoperative mortality experience as of June 15, 1961. The top three bars indicate the postoperative experience in prestudy surgery only and saline-treated patients. The 1025 operations were followed by 103 postoperative deaths, approximately 10%. The 4th and 5th bars are from the present concurrently randomized study. Patients having surgery and saline showed 11.5%, and treated cases showed 15.5% postoperative mortality. The lower bar shows the early experience (21.5%) when the adjuvant therapy consisted of four doses of HN2.

Table 4 shows the incidence of complication in these cases. The difference is not great between treated and control cases. Many minor complications are included in the data and most were successfully treated. Figure 4 shows 50% three-year survival of "curative cases" and approximately 20% three-year survival of "palliative" resections, counting the patients surving on the 30th postoperative day as 100%. In curative cases, surgery + saline was followed by survival as good as that of patients having surgery and HN2; in the palliative cases some increased survival indicates a possible HN2 benefit.

TABLE 4.—Complications after lung surgery

	Full dose		Reduced dose	
	Treated	Control	Treated	Control
Total patients	92	81	303	305
Without complications	39	45	146	162
With complications	52	34	148	138
Unknown	1	2	9	5[1]
Percent with complications	56.5	42.0	48.8	45.2

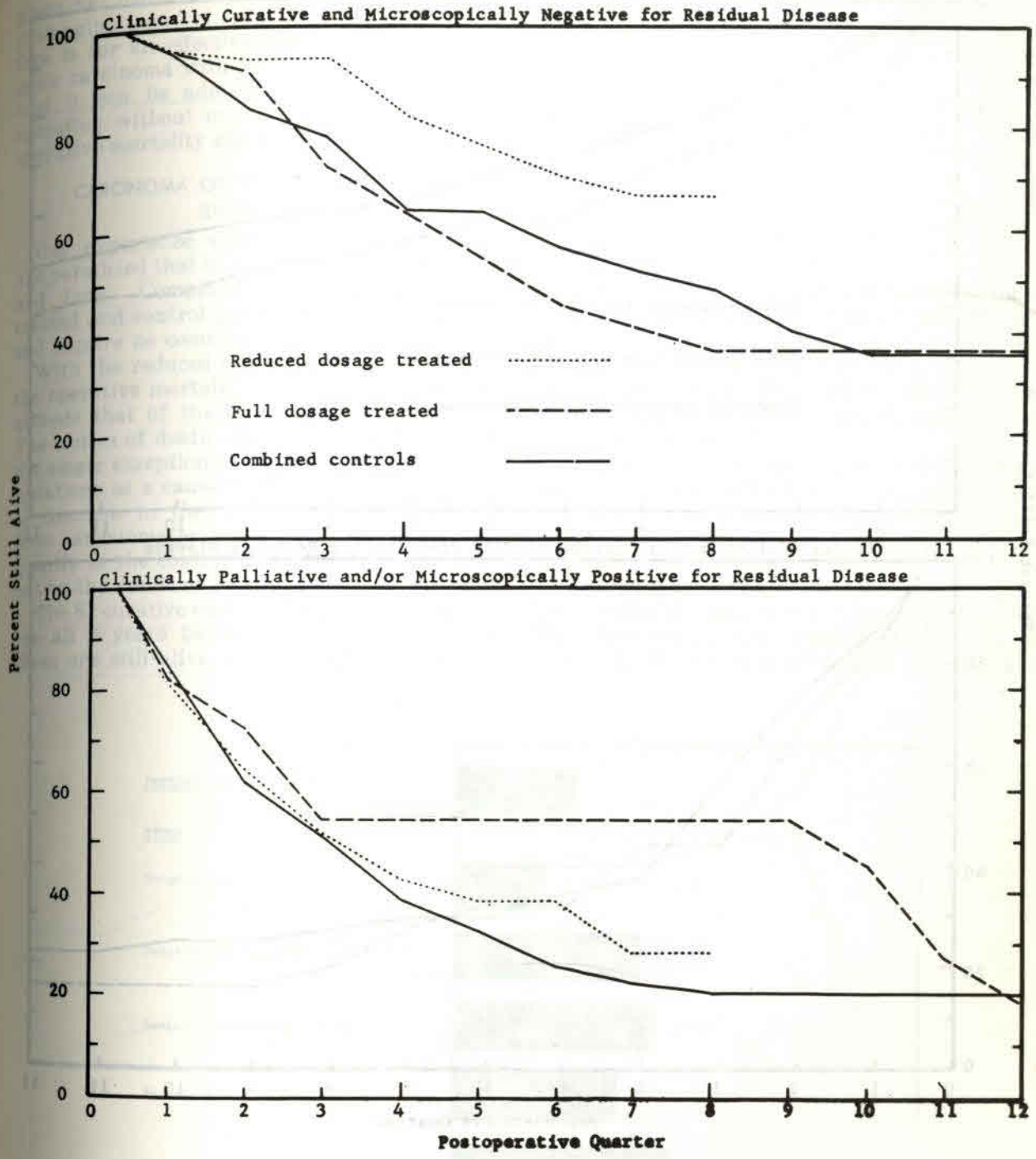

FIGURE 3.—Percent of stomach patients alive 1 month after surgery who are still alive at successive postoperative quarters; reports received by July 15, 1961.

surgery performed by

d saline showed
wed 15.5% post-
er bar shows the
hen the adjuvant
s of HN2.
e of complication
nce is not great
ol cases. Many
uded in the data
reated. Figure 4
val of "curative
% three-year sur-
ns, counting the
postoperative day
surgery + saline
good as that of
HN2; in the palli-
rvival indicates a

ung surgery

	Reduced dose	
trol	Treated	Control
81	303	305
45	146	162
34	148	138
2	9	5[1]
.0	48.8	45.2

IERAPY REPORTS

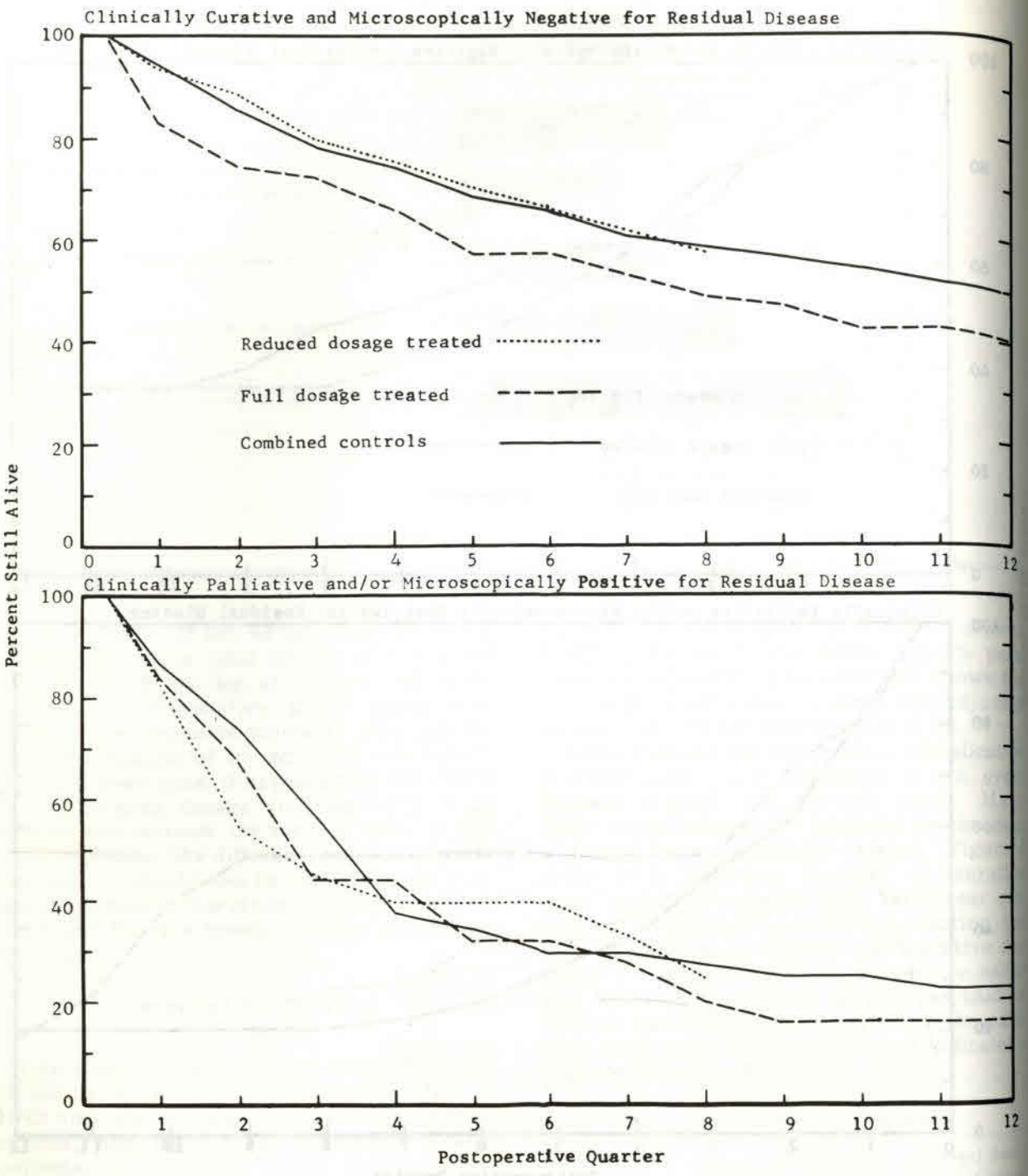

FIGURE 4.—Percent of lung patients alive month 1 after surgery who are still alive at successive postoperative quarters; reports received by July 15, 1961.

In conclusion, it appears that HN2 as now given has had little, if any, beneficial effect in prolonging survival. Our greatest need therefore is for an effective drug against bronchogenic carcinoma with a sufficiently low toxicity that it can be administered at the time of operation without unduly increasing the postoperative mortality and morbidity.

CARCINOMA OF THE COLON-RECTUM
(Dr. Dwight)

Our experience with colo-rectal carcinoma has paralleled that in carcinoma of the stomach and lung. Complications occurring in the treated and control group are given in table 5 and require no comment.

With the reduced dosage (about 800 cases), the operative mortality in the controls slightly exceeds that of the treated patients (fig. 5). The causes of death are the same in both with the single exception of the cardiovascular complications as a cause of death, which are twice as common in the treated cases. Peritonitis from anastomatic leaks occurred more frequently in the control cases and therefore cannot be the result of local use of the drug.

The 81 curative cases in the full-dosage series are all 3 years beyond surgery and 65% of them are still alive (fig. 6). There is no important difference in survival between those who received the drug and those who did not If we take the 203 curative cases in the reduced-dosage series who have passed the 2-year mark, we again find no drug effect; 84% of the treated and 86% of the controls are alive on their 2d anniversary.

There is, however, quite a marked difference between treated and untreated palliative cases in both the full-dosage and reduced-dosage series. Unfortunately, this difference has no statistical significance.

Can we draw any conclusions from our study at present? We believe not. Cancer of the colon kills less swiftly than cancer of the lung or stomach. It is still possible that we may find

TABLE 5.—Complications after colon-rectum surgery

	Full dose		Reduced dose	
	Treated	Control	Treated	Control
Total patients	60	54	433	443
Without complications	28	29	214	243
With complications	31	24	207	192
Unknown	1	1	12	8
Percent with complications	51.7	44.4	47.8	43.3

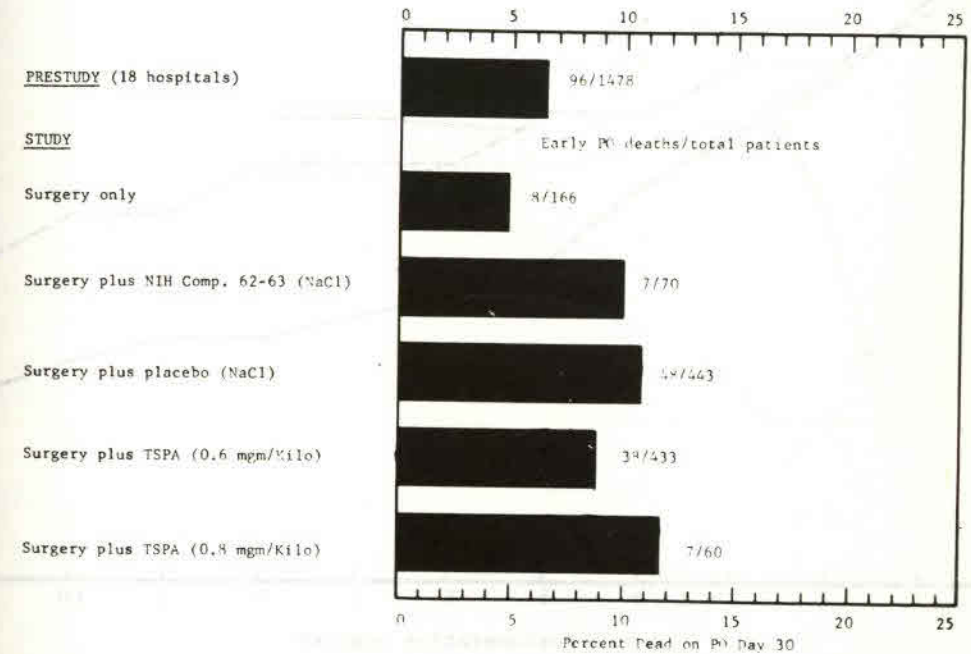

FIGURE 5.—Early postoperative (30-day) mortality-colon-rectum surgery reports received by July 15, 1961, for surgery performed by June 15, 1961.

a reduction in the number of recurrences in the treated cases during the 4th and 5th years after operation. It is more likely that we shall have to use a more effective drug and also try to discover the most effective timing in relation to surgery.

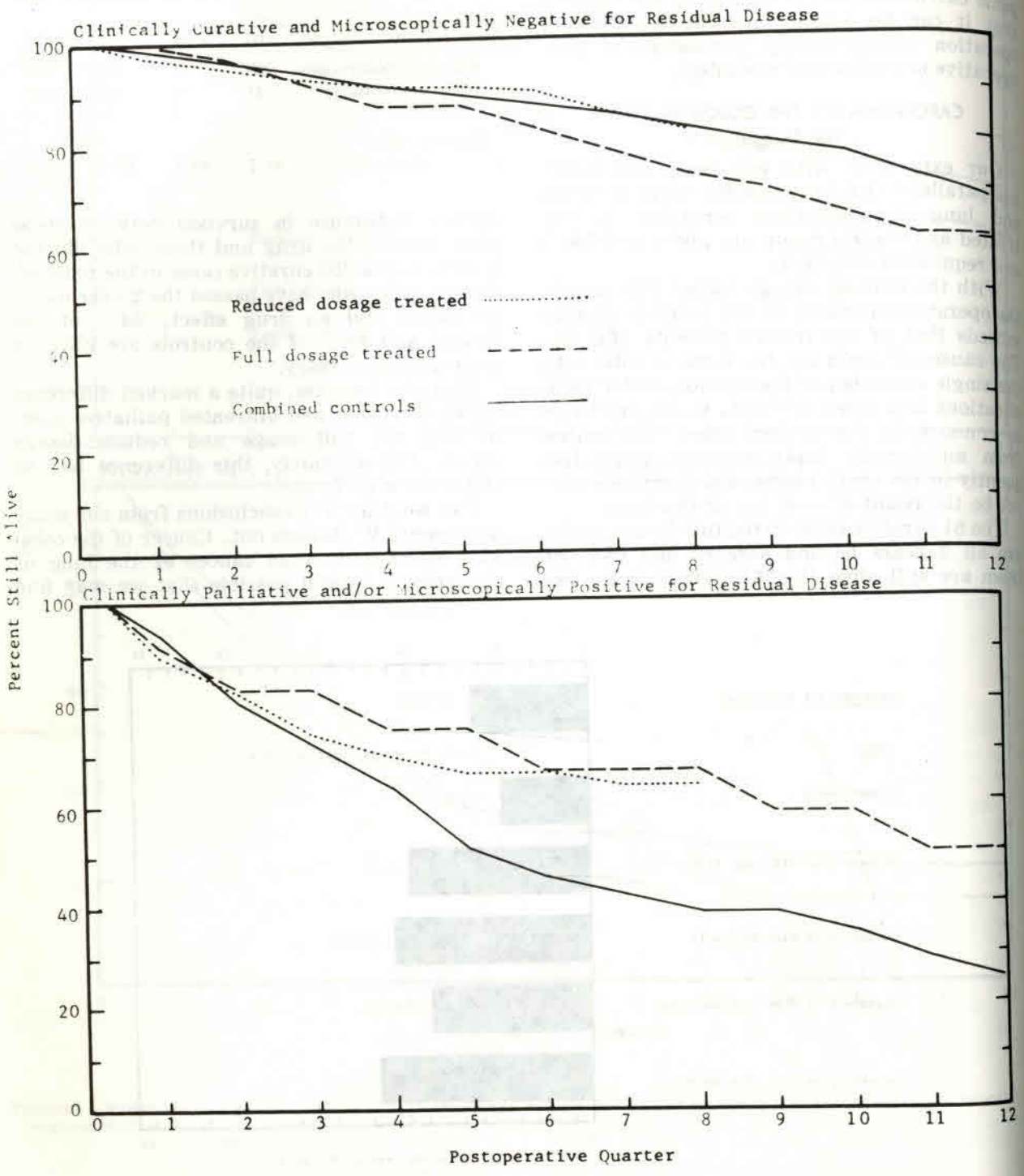

FIGURE 6.—Percent of colon-rectum patients alive at 1 month after surgery who are still alive at successive postoperative quarters; reports received by July 15, 1961.