1197R

REPOSITORY Oak Ridge Operations
COLLECTION Records Holding area ~~Documents~~ 1944-94
BOX No. A-12-9 Bldg. 2714-14
FOLDER Personnel-1, FOIA Howard Rosenberg

717256

SEP 15 1981

Mr. Howard L. Rosenberg
1401 16th Street, N.W.
Washington, D. C. 20036

Dear Mr. Rosenberg:

Please accept this letter in response to your Freedom of Information Act ("FOIA") request of August 24, 1981, which was deemed to have been received by the Oak Ridge Operations Freedom of Information Officer as of September 3, 1981. Your request will be answered using the same numbering system as the request.

Items 1) through 3) are available through the National Technical Information Service, Springfield, Virginia 22151. Since these documents are publicly available, they are not within the purview of the FOIA.

In response to item 4), the requested medical records are exempt from disclosure under the (b)(6) exemption for "personnel and medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of personal privacy." Your suggestion that "identifying names" be excised would be a useless exercise since the medical records pertain to only two people, whose identity you have surmised. Since one of the individuals to whom the records pertain has requested the records, with your apparent assistance, you may wish to gain access to the records from that person when the records are furnished in the near future.

With regard to item 5), there is no responsive document in existence. Enclosed you will find a copy of a protocol for the immunotherapy of acute leukemia dated July 11, 1967 (later in time than the referenced article). While both the enclosed protocol and the article referenced in item 4) refer to a preexisting protocol for immunotherapy of acute leukemia, no such document has been located. It appears that either the prior protocol did not exist in written form, or it was disposed of in the Government's (including its contractor, ORAU) files after issuance of the draft amendment. The medical treatment program for the subject of the articl is a part of the medical records, which are exempt from disclosure as discussed above.

PERSONNEL-1
FOIA 6897

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

DOE F 1228.10 (7-79) OFFICIAL FILE COPY

With regard to item 6), there is no responsive document. The ORAU/ORNL Committee on Human Studies had not been formed prior to the case to which you refer.

With regard to item 7), there is no responsive document. There was no "protocol," but a treatment decision, based on the facts of the particular patient, prescribed by the radiologist and authorized by the staff physician in charge of the patient.

In response to item 8), the requested documents are a part of the patient's medical records and are, therefore, exempt from disclosure under the (b)(6) exemption, discussed earlier herein.

Addressing what you perceive as our inconsistency in our FOIA responses of March 5, 1981, and July 28, 1981, with regard to "protocols," we believe the confusion resulted from semantic differences in terminology, and our interpreting your request from a greater base of knowledge than that from which the request was formulated. The result was that we answered the question we thought you had asked. By way of illustration, your February 13, 1981, request asked for: "c) Protocols issued for LETBI/METBI studies, including those issued for reviewed (sic) by the Human Use Committee. (Therapy protocols)." We responded that the activities we thought you meant by "LETBI/METBI studies" were therapy programs, individualized treatment procedures, specifically developed and prescribed by the patient's treating physicians, and did not involve "protocols," since they were not experiments. Your July 10, 1981, request, on the other hand, based on the list of research projects we furnished you in our response of March 5, requested "copies of the protocols submitted [under proposals to the ORAU/ORNL Committee on Human Studies]." We responded with copies of such protocols, which we do not consider to be what we understood you to mean by the phrase "therapy protocols," which do not exist outside the individual patients' records. Even under the protocols submitted to the Committee, individual treatment programs were specifically developed and prescribed. Patients included in the particular study, and the particular method of treatment being investigated, would be within the boundaries of the protocol. There was no attempt to keep documents from you, just a good faith misinterpretation based on different understandings of the descriptive language being used. We suggest that great reliance not be placed on the term "protocol," because it has several meanings, it may be developed before a study or after results have been obtained, and it may be written or not.

With regard to protocols submitted to the Committee prior to 1969 related to radiation therapy and immunotherapy, the Committee was established in April 1967, so there were no submissions prior to that time. You have been furnished all protocols submitted to the Committee from its inception in 1967 that dealt with radiation therapy/treatment involving total body irradiation, which

we understood to be your area of interest. Your latest request, for the first time, raises the question of "immunotherapy" studies. To keep the record straight, and avoid confusion of the sort we have experienced over "protocols," our responses have been limited to radiation therapy/treatment involving total body irradiation. We have not furnished protocols for immunotherapy or radiation therapy/treatment studies presented to the Committee not involving total body irradiation, if such protocols exist. All protocols/proposals submitted to the Committee involving total body irradiation have been submitted to you. The enclosed protocol for the immunotherapy of acute leukemia is the only known protocol submitted to the Committee on the topic. It was not furnished to you previously because it does not involve total body irradiation. While the document indicates an intent to develop a "written final plan," we found no later document on the topic.

I, as the Authorizing Official, Oak Ridge Operations, have determined that your request should be denied with regard to items 4) and 8) pursuant to exemption (b)(6). My position title is Assistant Manager for Administration.

DOE's regulations provide that a denial of records, in whole or in part, or a determination that a record does not exist, may be appealed to DOE's Office of Hearings and Appeals by writing the Director, Office of Hearings and Appeals, Department of Energy, 2000 M Street, N.W., Washington, D.C. 20461, within 30 days from your receipt of this letter. Both the envelope and letter must be clearly marked "Freedom of Information Appeal." Additional requirements of an appeal are set forth in 10 CFR Part 1004.8(b). Judicial review will be available after the appeal determination either in the district in which you reside or have a principal place of business, or in which the records are situated, or in the District of Columbia.

There is no charge associated with this response.

Sincerely,

Original Signed by
W. T. Hamstead
W. T. Hamstead
Assistant Manager
for Administration
Authorizing Official

CC-10:JLF

Enclosure:
As stated

bcc w/o enc: Wayne Range, M-4

CC-10:JLFoutch:mh:61204:9/14/81

CONCURRENCE	
RTG. SYMBOL	CC-10
INITIALS/SIG.	JLF
DATE	9/14/
RTG. SYMBOL	ORAU
INITIALS/SIG.	[illegible]
DATE	9/14/
RTG. SYMBOL	BR-13
INITIALS/SIG.	WRB
DATE	9/14/8
RTG. SYMBOL	AD-40
INITIALS/SIG.	WTH
DATE	9/15/8
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Form 3811, Jan. 1970

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Howard L. Rosenberg
1401 16th Street, N.W.
Washington, D. C. 20036

3. ARTICLE DESCRIPTION:

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	811774	

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PS Form 3800, Apr. 1976

1114177

JACK ANDERSON
1401 16th Street, N.W., Washington, D.C. 20036

August 24, 1981

Mr. Wayne Range
Department of Energy
Oak Ridge Operations
P.O. Box E
Oak Ridge, Tn. 37830

re: FOIA Request

Dear Mr. Range:

Under the provisions of the Freedom of Information Act, 5 U.S.C. 522, I am requesting access to the following records:

1) ORAU Research Report 123 of 1973.
2) ORAU Research Report of 1969.
3) ORAU Research Report of 1966.
4) All medical records of the case pertaining to an experimental immunologic approach used in the treatment of acute leukemia by Drs. C.L. Edwards et.al. This case was written up by those gentlemen under the title "Immunotherapy of Cancer and Immunocompetent Cells," and published in Experimental (1966) Hematology by ORAU. I would like the medical records of that case with the identifying names excised of course, in accordance with the Privacy Act.
5) The therapeutic protocol devised for the aforementioned case. (note #4)
6) The application for the use of humans as experimental subjects submitted to the ORAU/ORNL Committee on Human Studies prior to the aforementioned case. (note #4)
7) The protocol under which the child, [redacted] was treated with approx. 350 r of whole body radiation on Dec. 3, 1968.
8) Consent forms signed by the [redacted] child's parents prior to all experimental procedures.

81 AUG 27 AM 10:40

INFORM

In an earlier letter to me dated March 5, 1981, Dr. J.T. Hamstead, the acting assistant manager for administration, wrote that "no protocols existed for what you refer to as the 'LETBI/MeTBI' studies." Yet, in your latest response to my requests you provided some of thoseprotocols. However, none of them predate 1969, although the study of TBI in patients with hematologic disorders began more than a decade earlier I believe. Am I to understand that no written protocols or applications for the use of humans as experimental subjects in radiation therapy and immunotherapy existed prior to 1969? If they did, I would appreciate your provision of, as I requested, "all radition therapy protocols submitted for review to the ORAU/ORNL Committee on Human Studies" or in lieu of that, confirmation that protocols for the use of humans as experimental subjects were not required prior to 1969. As you can see, I am amending my request for therapy protocols to include experiments concerning immunotherapy. (See note #4 above.)

As you know, the act permits you to reduce and waive fees when the release of the information is considered as "primarily benefitting the public." Since I am requesting this information as part of an on-going inquiry into the effects of radiation on man, and into the U.S. government's

1114178

PERSONNEL
FOIA 6457

efforts to quantify those effects, and since these questions are still open to wide debate, and since a Congressional probe into the clinical programs at Oak Ridge is currently underway, I believe that this request fits that category and I therefore ask you to waive any fees as you have done in the past. My original request for a fee waiver was granted on Feb. 20, 1981 and subsequently I received another fee waiver on July 28, and since this request is a continuation of the same inquiry, I assume fees will continue to be waived.

If all or any part of this request is denied, please cite the specific exemption(s) which you think justifies your refusal to release the information, and inform me of the appeal procedures available to me under the law. I would appreciate your handling this request as expeditiously as possible. I look forward to hearing from you within 10 days, as the law stipulates.

Sincerely yours,

Howard L. Rosenberg
Staff Associate

'81 AUG 7 AM 10:10
RECEIVED

1114179

1-3: NTIS (National Technical Information Service) Springfield VA 22151

4: [redacted] case

Benson will verify

5: treatment procedures specifically developed & prescribed for indiv by treating physicians, in whatever format is included as part of patients' medical records.

6: Before Human Studies committee — Established in 1967... no applications prior to that time

Any protocols? Who prescribed [redacted]?

7. final judgment in crisis situation, prescribed by radiologist, authorized by for therapeutic purposes after chemotherapy became ineffective

~~no known formal treatment protocols.~~

Prescribed by Drs Comas & Edwards (Staff physicians) Read her in charge of patient

8. Part of medical records, privacy... her consent, or the records we will furnish her.

1114180

September 9, 1981

Mr. Howard L. Rosenberg
1401 16th Street, N.W.
Washington, D. C. 20036

Dear Mr. Rosenberg:

In response to your letter of August 28, 1981, I am aware of no statute or regulation that requires Government employees to answer "interrogatives" in a non-litigation situation. I suggest, therefore, that future requests for information be restricted to a procedure you are fully familiar with, the Freedom of Information Act.

Since your most recent FOIA request (August 24, 1981) raises the same question of protocols as your interrogatives, that matter will be addressed in the agency's formal FOIA response. I previously furnished you information on ORAU-123, the other matter raised by your letter of August 4. I find, therefore, nothing more to which I need respond.

Sincerely,
ORIGINAL SIGNED BY
James L. Foutch

James L. Foutch
Deputy Chief Counsel
for Legal Services

CC-10:JLF

CC-10:JLFoutch:mh:61204:9/9/81

CONCURRENCES

RTG. SYMBOL	INITIALS/SIG.	DATE
CC-10	JLF	9/9/81

PERSONNEL -1
FOIA
6767

DOE F 1325.10 (7-79)

1114181

OFFICIAL FILE COPY

M-4

September 4, 1981

Mr. Howard L. Rosenberg
Staff Associate
JACK ANDERSON
1401 16th Street, N.W.
Washington, DC 20036

CC-10

Dear Mr. Rosenberg:

This is in response to your letter of August 24 concerning a Freedom of Information Act request for certain records of Oak Ridge Associated Universities.

You requested a waiver of fees in connection with the request and we have determined that such a waiver is appropriate. Accordingly, your request has been deemed to have been received for action as of September 3, 1981, and it is under consideration by the Authorizing Official for Oak Ridge Operations.

We will notify you should it appear that we will be unable to respond within the 10 working days provided by Department regulations.

Sincerely,

Wayne Range
Freedom of Information Officer

bcc: Chief Counsel, CC-10
W. R. Bibb, Research Division

M-4:WRANGE:kc:60888:9-4-81

PERSONNEL - 1
FOIA 6680

1114182

JACK ANDERSON
1401 16th Street, N.W., Washington, D.C. 20036

Friday, August 28, 1981

Mr. James L. Foutch
Deputy Chief Counsel
for Legal Services
Department of Energy
Oak Ridge Operations
P.O. Box E
Oak Ridge, Tn. 37830

Dear Mr. Foutch:

I received your letter of August 25, 1981. Your assumption that because I have published a single article on the LETBI/METBI experiments I am no longer interested in responses to my interrogatives and that I have obtained all the information I require is quite simply, wrong.

Looking forward to your reply and explanations.

Sincerely,

Howard L. Rosenberg
Staff Associate

PERSONNEL -1
FOIA

1114183

6566

August 25, 1981

Mr. Howard L. Rosenberg
1401 16th Street, N.W.
Washington, D. C 20036

Dear Mr. Rosenberg:

Your letter of August 4, 1981, to David Darugh was received in this office on August 10. Because your letter referred back to a March 5, 1981, FOIA response for which I helped gather documents, Mr. Darugh forwarded your letter to me.

While my response to your letter was in preparation, an advance copy of your Mother Jones article was furnished us by a television network interview crew. Since the article dealing with the LETBI/METBI facilities has now been published, I must assume that you have obtained all the information you require on the subject and that no response to your August 4 letter is needed.

If you are still interested in ORAU-123, it is available from the National Technical Information Service, Springfield, Virginia 22151. The cost is $7.50.

Sincerely,

ORIGINAL SIGNED BY
James L. Foutch

James L. Foutch
Deputy Chief Counsel
for Legal Services

CC-10:JLF

CC-10:JLFoutch:mh:61204:8/25/81

CONCURRENCE
RTG. SYMBOL CC-10
INITIALS/SIG. JLF
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PERSONNEL — FOIA 6408

FORM P-4A

MEMORANDUM

TO Those Listed Below DATE July 11, 1967

SUBJECT PROTOCOL FOR THE IMMUNOTHERAPY OF ACUTE LEUKEMIA

COPIES TO File

After our discussion with Dr. Peter Alexander, it was felt that our protocol for the immunotherapy of acute leukemia should be amended. Enclosed is a revision of the protocol which incorporates some of these changes that were proposed.

Please feel free to make any further amendments. If there is any omissions which should be included, please note this also.

We would hope to have a "working" protocol ready in expectation for our next suitable patient. I would appreciate it if you would forward your comments to me so that a written final plan can be drawn up.

Thank you for your help.

Helen

Helen A. Vodopick, M.D.

/1

Copies To: Dr. Andrews
Dr. Congdon
Dr. Edwards
Dr. Gengozian

1114185

Andrews

AMENDED PROTOCOL FOR THORACIC DUCT CANNULATION - LYMPHOCYTE INFUSION

1. Disease -

   leukemia untreated - probably child,

   or solid tumor, incurable but to apparent limited extent.

   ABO compatible normal person to receive killed malignant cells and to donate "sensitized thoracic duct lymphocytes.

2. Collection of malignant cells - either leukemic cells obtained by bone marrow aspiration (anticoagulant 4% K_2 EDTA) or piece of solid tumor minced and washed with Tc 199. For preservation: autologous serum 50% + 20% DMSO in Tc 199; ratio 1:1 with cell suspension.

   a) Freeze by means of slow freeze liquid nitrogen (1°C/min) to preserve these cells for future use;

   b) Remove DMSO before irradiation and wash with Hank's buffered salt solution;

   c) Irradiate with 10,000 R or more just before giving.

3. Route of sensitizing dose - intralymphatic into normal recipient.

   Use Sweeney adaptor to remove large particles.

4. Thoracic duct cannulation of "sensitized" recipient -

   Time of cannulation: Day 4-7. Check for pyroninophilic cells in thoracic duct lymph and in blood smears (possibly use this to determine when cannulation should be done).

5. Before infusion of lymphocytes into recipient -

   a) leukemic - patient should be in full remission. No steroids are given during administration. Stop antileukemic drugs just before commencing lymph infusion.

      After infusions - ? continue antileukemic drugs.

   b) solid tumor - ? immunosuppressive agent to patient before sensitized lymphocytes are given.

1114186

6. Lymph collections -

   a) room temperature

   b) anticoagulant heparin, ~100 u, in 25 ml 5% dextrose/water

   c) spin blood bottles, 200 x g

   d) do not wash cells (keep lymph to minimum

   e) Collections every 3 hrs - check sizing (pick up larger pyroninophilic cells fater this way)

   f) Keep sufficient number of cells for
      1) cell count
      2) smears - Wright's and methyl green - pyronine Y stains

   g) Infuse into patient as soon as processed.

7. Rx for reaction - to control possible graft versus host reaction.

   a) steroids

   b) Imuran - when temperature rises, diarrhea, skin rash, not attributable to anything else occurs.

8. Evaluation of effect -

   a) Clinical remission or regression of tumor

   b) In vitro testing.

1114187

Note for J. L. Foutch

There are no protocols for METBI or LETBI studies, as such. Protocols for patients that involved the use of these facilities were developed for each individual patient concerned and was based solely on the individual's medical condition and needs. Indicated radiation therapy was prescribed as directed by the radiologist. Existing protocols related to or involving the METBI or LETBI and submitted to the Committee on Human Studies for review/approval have been provided to you.

The referenced ORAU-112 report cites some 194 patients that were treated in METBI (not LETBI) between 1959-1968. LETBI was constructed in 1967. The cited studies were completed or near completion when the Committee on Human Studies was established, in 1967, and consequently protocols were not required for the Committee.

ORAU-123 is available from the National Technical Information Service, Springfield, Va. 22151 @ $7.50.

REB 8/12/81

Cancer treatment research
Involving TBI, so utilized LETBI/METBI facilities.

ORAU 112

1114188

I trust the confusion is now behind us. I hope, on your part, to understand, completely the activities about which you inquired.

Dear Mr. Rosenberg:

Please accept this letter in response to your letter of August 4, 1981, to David Daugh of our Office. I am responding, rather than Mr. Daugh, because I participated in the preparation of the agency's response of March 5, 1981, which you appear to find inconsistent with the agency's response of July 28, 1981. ~~I am writing [illegible] in the hope that I can explain the two responses sufficiently so that you understand the "apples and oranges" situation which caused your confusion.~~

Item c of Attachment A to your February 13, 1981, Freedom of Information Act ("FOIA") request stated ~~[illegible]~~ the desired information as follows:

> "c. Protocols issued for LETBI/METBI studies, including those issued for reviewed (sic) by the Human Use Committee. (Therapy protocols)"

Our response, based on our understanding of what you meant by "LETBI/METBI studies," particularly in light of your parenthetical "(Therapy protocols)", was that there are no

1114189

protocols, since the LETBI/METBI activity was treatment based on the individual's needs, not experimentation. ~~[illegible]~~ The therapy program was explained further in response to items c and d.

Your July 10, 1981, requested "verbatim copies of the protocols submitted" with respect to the "listing of proposals submitted for review to the 'ORAH/ORM Committee on Human Studies.'" Our response of July 28, 1981, transmitted those protocols, ~~[illegible]~~ which involved cancer treatment research.

Perhaps, ~~[illegible]~~ addressing my specific points in your August 4 letter and trying to deal with them ~~[illegible]~~ the clearest way of clarifying the confusion is to explain the activities that involved the LETBI/METBI facilities. The METBI facility was completed in 1959; the LETBI facility was completed in 1967. Both of these facilities were utilized for individual treatment programs as explained in our March 5, 1981, response. The results of these treatment programs were utilized in stud

1114190

HOWARD LAWRENCE ROSENBERG
8709 Sundale Drive, Silver Spring, Maryland 20910
(301) 585-6408

August 4, 1981

Mr. David Darugh
Office of Chief Counsel
Oak Ridge Operations
Department of Energy
PO Box E
Oak Ridge, Tn. 37830

Dear Mr. Darugh:

Regarding my FOIA request of July 10, 1981 and your response of July 28, 1981, I have a couple of questions that I hope you can answer for me.

In an earlier letter to me dated March 5, 1981, Mr. W.T. Hamstead, the acting assistant manager for administration, wrote that "no protocols existed for what you refer to as the 'LETBI/METBI' studies." Yet, in your latest response to my requests you provided some of those protocols. For example, the project protocol entitled "Studies of Total Body Irradiation in Patients with Hematologic Disorders" clearly relates directly to LETBI and METBI. However, none of those protocols predate 1969 although the experiments in those facilities began as early as 1960.

Am I to understand that no written protocols or applications for the use of humans as experimental subjects in radiation therapy existed prior to 1969? The ORAU 112 report, which you forwarded earlier, indicated that some 194 patients were treated in LETBI and METBI by 1970. Were they all treated between 1969-1970? If not, I would appreciate your provision of, as I requested, "all radiation therapy protocols submitted for review to the ORAU/ORNL Committee on Human Studies" or in lieu of that, confirmation that protocols for the use of humans as experimental subjects were not required prior to 1969.

There are a couple of references in the materials you sent me to a report known as ORAU-123. Since this report relates to the information I'm requesting, could you forward me a copy or is it necessary for me to submit another FOIA request.

Thank you for your consideration.

Sincerely,

Howard L. Rosenberg
1401 16th St. NW
Washington, D.C. 20036

PERSONNEL — 1
FOIA 5996

111491

How Much Radiation Can An Astronaut Withstand? NASA Used Dwayne Sexton To Find Out.

INFORMED CONSENT

BY HOWARD L. ROSENBERG

The dimly lit hallway weaved left and right like a maze. Clutching Dwayne's small hand, Mary Sue Sexton fell in step behind the white-coated technician. They passed a control panel and walked through a wrought-iron gate into the chamber. The room was dark except for a brilliant halo over an empty, aluminum bed.

Dwayne climbed over the nylon net surrounding the bed and settled into the trough-shaped berth. Mary Sue exchanged reassuring smiles and a hesitant wave with her six-year-old son. Then she turned and stepped back out to wait in the hall.

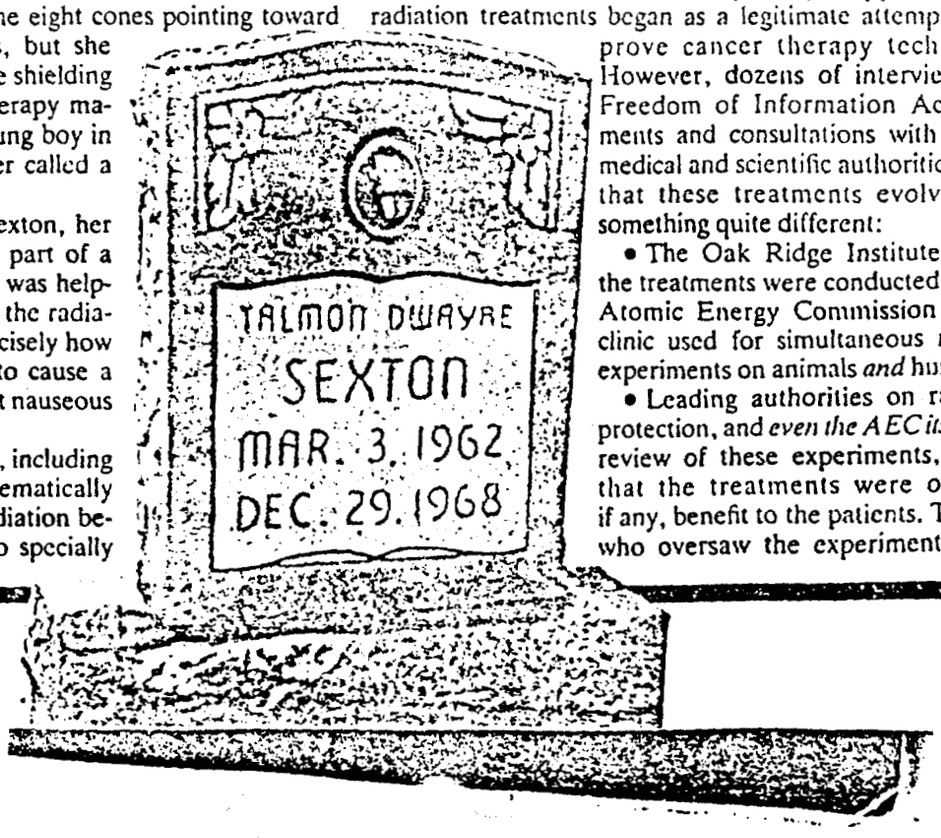
Mary Sue could not see the eight cones pointing toward Dwayne from the shadows, but she could hear a slight hum as the shielding was removed and the teletherapy machines began bathing the young boy in what one of the doctors later called a "sea of radiation."

Unknown to Mary Sue Sexton, her son Dwayne was serving as part of a government experiment: He was helping to find the parameters of the radiation sickness syndrome—precisely how large a dose it would take to cause a person to lose his appetite, get nauseous and vomit.

At least 89 cancer patients, including Dwayne Sexton, were systematically exposed to large doses of radiation between 1960 and 1974 in two specially designed chambers at the Institute of Nuclear Studies in Oak Ridge, Tennessee. Medical confidentiality has prevented identification of most of these patients. Information provided by medical personnel at the facility and a telephone canvassing of one area of Tennessee led to the unfolding story of Dwayne Sexton and how he was used to obtain data for the United States' space program. It is hoped that the publication of this account will spur other patients who went through these experiments or their families to come forward with more information about the controversial treatments.

Based on an 18-month *Mother Jones* investigation and a review of thousands of pages of documents obtained under the Freedom of Information Act (FOIA), it appears that the radiation treatments began as a legitimate attempt to improve cancer therapy techniques. However, dozens of interviews, the Freedom of Information Act documents and consultations with leading medical and scientific authorities reveal that these treatments evolved into something quite different:

- The Oak Ridge Institute, where the treatments were conducted, was an Atomic Energy Commission (AEC) clinic used for simultaneous research experiments on animals *and* humans.
- Leading authorities on radiation protection, and *even the AEC itself* in its review of these experiments, judged that the treatments were of little, if any, benefit to the patients. The man who oversaw the experiments, how-



1114192

ever, is today one of the government's chief experts on the effects of radiation.

• The government doctors administering the treatments knew of other therapy techniques—using either different types of radiation exposure or chemotherapy—that were superior. At least in Dwayne Sexton's case, the government scientists at Oak Ridge initially withheld these better-established cancer treatments.

• The clinic facilities were "substandard" according to the government itself, and the AEC eventually forced its own clinic to close down.

• Patients did not offer their *fully informed* consent to be part of some experiments. And some patients, like Dwayne Sexton, were subjected to several different types of experiments.

• Though the treatments were administered as cancer therapy, one primary purpose was to obtain data for the United States' space program on human reactions to radiation.

> *Patients did not offer their fully informed consent, and facilities were criticized as "substandard."*

HOW IT BEGAN

NASA, the National Aeronautics and Space Administration, urgently needed data on human sensitivity to radiation, and the cancer patients who came through the doors of the Oak Ridge Institute of Nuclear Studies became the human guinea pigs who provided this information.

Animals had been the first to breach the boundaries of space. Dogs and chimpanzees and monkeys were metamorphosed into avian creatures, hurtling through the stratosphere atop rockets. Down below, scientists were wrestling with unanswered questions about how human beings would stand up to the effects of radiation. Nausea and vomiting caused by radiation sickness were possibly manageable ailments on the ground. But to an astronaut wearing an oxygen mask, they could prove fatal.

Hard data on human radiosensitivity was vital to NASA. But who would volunteer to be exposed to potentially lethal doses of radiation? In Oak Ridge, Tennessee, a pathologist at the AEC's clinic, Clarence Lushbaugh, agreed to search for some of the answers NASA wanted.

ATOMIC CITY, USA

Oak Ridge is called the "Energy Capital of the World" nowadays. It used to be known as the "Atomic City." This was the town created by Uncle Sam to produce fuel for the Manhattan Project's A-bombs during World War II. Hidden in hollows amid rolling hills of black oak, massive factories for producing bomb-grade uranium rose up within a perimeter of total military security. The limestone ridges along the snaking Clinch River offered natural protection from air attack. Power from the Tennessee Valley Authority was in plentiful supply.

Today Oak Ridge's broad, main avenues are still lined with Army barracks, converted and refurbished as apartment buildings. The "downtown" area is a modern shopping center. The denizens of the "Energy Capital" are a curious mix of rural-bred hill people and scientists and technicians from around the world. One out of every 35 Oak Ridgers holds a Ph.D. degree—one of the highest per capita ratios in the nation.

Clarence Lushbaugh arrived in 1963 to head the AEC clinic's ominously titled "Applied Radiation Biology Division." A short, balding man with a combative personality, Lushbaugh likes to say he "grew up in the gutters" of Cincinnati, Ohio, where his name, Clarence, "was a fighting name—you had to protect a name like Clarence." Most of his friends now call him "Lush," but the feisty attitude of his youth has not mellowed much in 65 years. The nameplate behind Lushbaugh's desk informs visitors that he is the HSOBIC—Head-Son-Of-a-Bitch-In-Charge.

Educated at the University of Chicago, where he received his bachelor's degree, a Ph.D. in pathology and an M.D. in medicine, Lushbaugh began his career in 1949 as a pathologist in Los Alamos, New Mexico—another "atomic city." He doubled as the government town's coroner. In 1963, Lushbaugh moved to rural Tennessee and became a member of the staff of the Oak Ridge Institute.

"In Los Alamos," he explains, "we had plenty of radioisotopes and plenty of machinery, but we didn't have a whole lot of sick people because it was a rather young population." Oak Ridge offered the same access to radioisotopes plus a large group of Tennesseans who were grateful for free medical attention at the AEC clinic.

The Oak Ridge Institute had a mandate from the Atomic Energy Commission—which was then the government agency charged with promoting nuclear energy—to conduct research into the "beneficial applications of radiation." Some significant achievements did come out of Oak Ridge's clinic, including the development of a cobalt 60 (C-60) teletherapy machine, which served as a prototype for others now used in cancer therapy at hospitals across the country.

Lushbaugh was teamed with eminent hematologist Gould Andrews. Lushbaugh's star was rising. Andrews "was probably the world-renowned expert in taking care of persons with radiation injuries," Lushbaugh says modestly, "and I was the world-renowned expert at trying to figure out what went wrong at the autopsy table."

If someone was acutely irradiated in an accident, no matter when or where, Andrews was called in to give medical attention. His hunched figure was unmistakable—he was afflicted with extreme curvature of the spine. Andrews was a compas-

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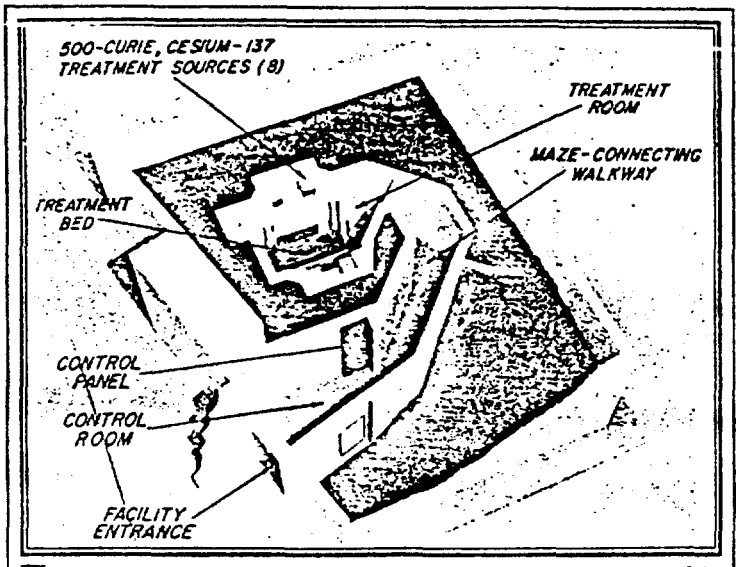
sionate and competent attendant to his patients, but whenever his medical ministrations failed, it was Lushbaugh's turn. Lushbaugh did the autopsies.

Shortly after his arrival in Oak Ridge, Lushbaugh won a NASA contract to conduct a retrospective analysis of the effects of radiation: a hunt for the point at which the syndrome symptoms appear. He looked for clues in the medical charts of cancer patients who had been treated with radiotherapy. By the end of 1964, Lushbaugh had compiled data on more than 3,000 patients at 43 different hospitals.

But the retrospective analysis had its limitations. The patients had received varying doses of radiation, and their doctors had not kept detailed notes on reactions in the systematic manner of a research scientist. A "prospective" study was needed. Oak Ridge was the ideal place for the study and Lushbaugh was the ideal choice to conduct it. By carefully monitoring patients during and after radiotherapy at the clinic, Lushbaugh and his associates could be on the lookout for syndrome symptoms and could correlate them with the exact dose of radiation received.



This is a model of the METBI facility at Oak Ridge. Here and in another chamber 89 cancer patients were treated with high levels of radiation. The project apparently began as an attempt to improve cancer therapy. Ultimately, the experiments benefited NASA.

"BENEFICIAL" USES?

In 1960, the Oak Ridge clinic had begun operating a therapy chamber known as METBI—the Medium-Exposure-Rate Total-Body Irradiator. Built in a special wing of the tiny clinic, METBI was designed for experiments testing spray irradiation as a treatment for blood cancers. It was part of the Atomic Energy Commission's effort to use its nuclear wares to find those "beneficial applications of radiation."

Prior to World War II, researchers at the Memorial Sloan-Kettering Cancer Center in New York discovered that by spraying a leukemia victim's total body with X-rays, the radiation could be used to depress the bone marrow and kill cancerous blood cells forming there. Then, during the war, scientists found that injections of radiophosphorus and several nitrogen mustards could achieve essentially the same results at only a fraction of the cost. "In essence," said one of the AEC's consulting physicians, "spray irradiation techniques were superseded by simpler and better techniques."

Lushbaugh agrees. "The hematologists began using these nitrogen mustards," he says, "and so they began hogging all these patients with leukemia. . . . Well, obviously, the radiotherapists and the whole damn field of radiologists were not going to put up with that. So they came along with a system for doing the same things as the nitrogen mustards, [the difference being that] you don't have to hold the guy down and stick needles in him."

What they came along with at Oak Ridge was METBI—and a new twist in the technique of spray irradiation. Doctors at Sloan-Kettering used an X-ray machine to spray their patients, but the Oak Ridgers thought that radiation-emitting isotopes like C-60 and cesium 137 (Ce-137) would be more flexible than a bulky machine.

Lushbaugh explains it this way: "See, with an X-ray tube, you would put the person on the floor in the fetal position, with his knees drawn up, and you'd zap him from the right side with an X-ray machine and then you'd flip him over and irradiate him from the other side." The METBI facility was a quantum improvement.

The doctors could zap their patients in a specially designed room with doses ranging from 1.8 rads per hour (1.8r) to 300 rads per hour (300r). These are extremely high doses—an ordinary chest X-ray is about one-tenth of a rad—but the exposures were and are considered therapeutic in treating some cancers. But as we will see in Dwayne Sexton's case and those of the other 88 patients in these experiments, the massive radiation doses were not only part of a treatment plan, but also a way of gathering data for the space program.

The treatment of leukemia patients in METBI began as soon as the facility was operational. Gould Andrews directed the clinical hematology staff. Lushbaugh monitored the cancer patients for signs of the syndrome. Many aspects of the syndrome were already known even then. The government's handbook for the holocaust, *The Effects of Nuclear Weapons*, reports that "for doses between 200 and 1,000 rads the probability of survival is good at the lower end of the range, but poor at the upper end. The initial symptoms are similar to those common in radiation sickness . . . the larger the dose, the sooner will these symptoms develop."

As part of the federally funded Oak Ridge Associated Universities—a consortium of 50 colleges and universities throughout the South—the AEC clinic had a ready-made network from which to draw patients. Doctors in the rural South regularly referred cancer patients to Oak Ridge. Among them were people suffering from Hodgkin's disease, chronic lymphocytic leukemia, chronic granulocytic leukemia, polycythemia rubra vera, idiopathic thrombocythemia and lymphosarcoma cell leukemia.

The Oak Ridge researchers began their study by exposing patients to 50 or 100 rads at a time in the METBI chamber at a rate of 1.5 rads per minute. According to an internal progress report written in 1970, doctors involved in the experiments apparently never really thought these large doses would benefit the patients much, but since the cancer victims would probably require radiotherapy anyway, the scientists at Oak Ridge hoped to obtain some of the syndrome data NASA wanted. "It was not our plan to evaluate the long-

Courtesy of Oak Ridge Associated Universities

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range effectiveness of these relatively large individual doses," Andrews, Lushbaugh and their colleagues explained in the report. "This would have required establishing a total treatment plan with this technique, which we were not prepared to do."

The scientists wanted to "be able to add or substitute other forms of treatment," which is not surprising, in light of the fact that the doctors virtually admitted that the METBI exposures were *not even the best method of treating the cancer patients with radiation.* "One should not infer from this study," they wrote in a candid assessment of the experiment, "that we expected these individual or infrequently given exposures to produce better clinical results . . . at present, we feel that some pattern of fractionated exposure [small doses of radiation in several treatments] probably offers a preferable approach for total-body radiotherapy."

What these large, single exposures in the METBI chamber *did* offer was the best opportunity to monitor for the radiation sickness syndrome. According to a report of the experiment provided to NASA, at least two patients at Oak Ridge received doses of 500 rads prior to a treatment called "bone marrow transplantation." Obviously, these two people were ideal subjects for the doctors involved in the NASA study to monitor for the syndrome.

Mary Sue asked the doctor, "Does Dwayne have leukemia?" He suggested a cure might be found at Oak Ridge.

ENTER, DWAYNE SEXTON

It was June of 1965 and the humid air was just hinting at the oppressive Tennessee summer ahead when three-year-old Dwayne Sexton first took sick. The auburn-haired boy just wasn't his usual self. First-born child of Talmon and Mary Sue Sexton, Dwayne had his daddy's dimpled chin, his mother's wide, brown eyes and enough energy to keep them both busy. That summer he changed. "Dwayne just wanted to sit or lay down," his mother remembers. "He was tired, run-down."

They visited the family doctor, who diagnosed Dwayne as anemic and prescribed liquid iron and vitamin B-12. The treatment didn't help much. Dwayne's normally rosy cheeks remained pale and waxy. Mary Sue insisted the doctor hospitalize him and find out what was wrong. Blood transfusions began in an attempt to counter the anemia. Finally, Mary Sue asked the doctor point-blank: "Does Dwayne have leukemia?" The physician said no, and then suggested that maybe the cause and cure of Dwayne's illness could be found at Oak Ridge. The arrangements had already been made. Mary Sue began keeping detailed notes in a journal.

On July 27, Dwayne checked into the Oak Ridge clinic for the first time. A chest X-ray was taken and bone marrow was withdrawn from his hip for a test. Mary Sue just happened by a room where one of the doctors was confiding the bad news to Talmon: Dwayne had acute lymphatic leukemia.

Two days later Mary Sue wrote in her journal: "The medical staff discussed a type of treatment they would like to try on Dwayne. It was stated it could possibly be a cure for him. We know there is no hope at all for Dwayne except for a short life for him of from six weeks or maybe up to a year and a half, and he would be so sick so much of the time."

Mary Sue and Talmon agonized over the decision. "We decided it was worth the risk we would have to take for a chance at a cure for Dwayne," she noted in the journal. "We were reassured that the experiment was promising enough to take a chance with."

The doctors told the Sextons that Dwayne's case was virtually hopeless. They mentioned that there were various possible treatments but pointed out that, at best, all the treatments might do is provide a temporary reprieve. The Oak Ridge researchers then explained that they were interested in "bone marrow transfers," Mary Sue recalls. "They said it was experimental and would kill the leukemia cells. They offered that as an alternative. We took it as a desperation move for the health of our child."

THE CONSENT FORM

Both Dwayne's parents signed a consent form drafted by the Oak Ridge doctors. It reads, in part, "We understand and agree to a special experimental procedure designed to try to help our child who has acute leukemia. This will consist of removing bone marrow from the child, subjecting the marrow to radiation designed to kill the leukemic cells and subsequently injecting these cells into the mother . . . there are some risks involved for both mother and child. The nature of these has been explained to us, and we are willing to accept them."

In fact, the signing of the form by the Sextons did not really constitute "informed consent." Dwayne's parents were apparently misled into believing that the experimental bone marrow transfer was his best and only hope for survival. However, that treatment was clearly untried, and several better alternatives for treating acute lymphatic leukemia were widely known and available. According to Dr. Peter Wiernik, director of the Baltimore (Maryland) Cancer Research Center and a former official of the National Cancer Institute, a therapy protocol consisting of several chemical agents was the "common treatment at that time."

Instead of chemotherapy, eight days after his arrival at Oak Ridge, Dwayne was wheeled into the clinic's surgical arena and sedated. Bone marrow was carefully extracted through *seventeen* punctures in his legs, hips and breastbone. The marrow was then irradiated—probably in the METBI chamber. That afternoon, the irradiated bone marrow was

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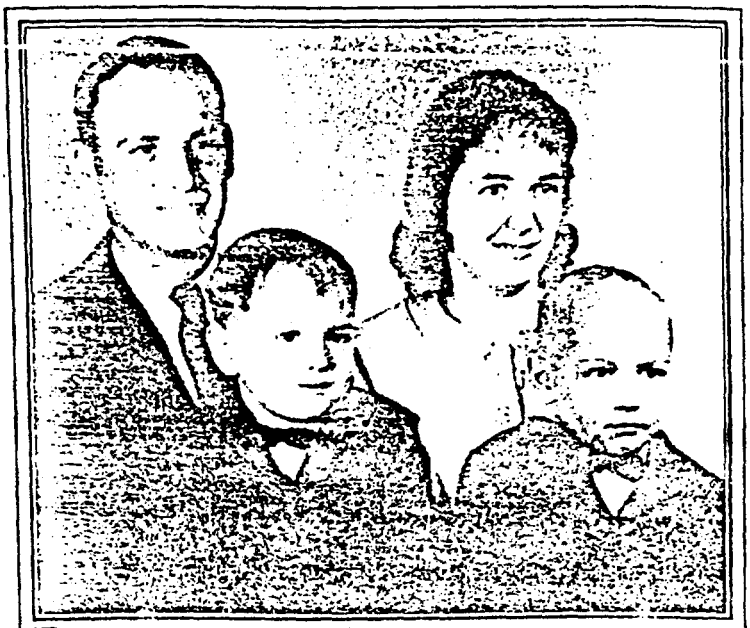
transferred into four syringes injected into each of Mary Sue's hips and arms.

For Mary Sue, the injections were merely a painful irritant, but she was stoic about her discomfort. After all, her pain might help save Dwayne's life. But her eyes welled with tears when she pulled back the sheet covering her son's unconscious body and began counting the puncture wounds in his legs and chest.

On August 16 there was more surgery. A small incision was made in Mary Sue's left thoracic duct just above the collarbone, and a tube was inserted. For five days fluid drained through the tube into a plastic vacuum bag. This "serum" was filtered and then injected into Dwayne.

The doctors had hoped that Mary Sue's healthy body would build up antibodies, which would destroy the leukemic cells injected into her. Then, the antibodies in her blood serum could be used to fight the leukemic cells produced in Dwayne's bone marrow. But by mid-November of 1965, it was clear that this experiment had failed. Dwayne Sexton's condition was worsening.

"It was a superb idea," says the Baltimore Cancer Center's Peter Wiernick. "But you just cannot do those things in humans first thing." Medical authorities contacted by *Mother Jones* agreed that it is simply unethical to inject cancer cells into a healthy human being, unless it is clearly a last resort. In Dwayne's case, it was not. Other therapies, whose worth was already proven, were readily available at the time. Today, research into cancer therapies using antibodies is still under way at several facilities, including the National Cancer Institute. Yet even now, 16 years after Dwayne's treatment, the experiments are conducted largely on laboratory animals and on human cancer cells in laboratory dishes.



This picture of the Sexton family was taken in September 1967, about a year before Dwayne, on the right, died at the Oak Ridge clinic.

After the failure of the bone marrow transfer, the Oak Ridge Institute doctors belatedly began treating Dwayne Sexton with chemotherapy.

A NEW GIMMICK

The Oak Ridge researchers were collecting syndrome data in earnest at that time, but the METBI facility had its problems and limitations. In addition, the Oak Ridgers had a new theory they wanted to test: Could they alleviate some of the side effects of the therapy by using lower doses of radiation over days or even weeks of continuous exposure?

By 1967, the AEC had financed the construction of a second facility at Oak Ridge: LETBI—the Low-Exposure-Rate Total-Body Irradiator. The difference between it and METBI was like the difference between the Ritz and a fleabag hotel. In fact, the paneled LETBI chamber was specifically designed and furnished to look like an ordinary hotel room where patients undergoing therapy could relax and feel like they were on vacation. Except the LETBI chamber had no windows.

LETBI was really two rooms, one built within the other. The outer chamber was concrete. Inside, a smaller, wooden box was centrally positioned. Between the walls were eight cobalt 60 teletherapy machines, which created a radiation field that could administer doses as low as 1.5 rads per hour.

The radiation machines were operated and monitored remotely from an instrument console located in an adjacent control room. The panel also contained closed-circuit TV monitors, a communications system linked to the chamber and a read-out for the syndrome cord—an umbilical specifically developed to study the vital functions of patients as they underwent these new radiation treatments. The 65-foot umbilical was used to search for syndrome symptoms.

By monitoring read-outs, technicians could watch for subtle changes in respiration that would indicate nausea. The syndrome study had advanced to the point where the doctors knew a patient was about to get sick and vomit before the patient did.

The patients "would really run the whole thing," Lushbaugh explains. "Just by [the patient] opening the door [to leave the chamber], the whole thing would turn off, and he'd go out and take a leak and go back in, and somebody would bring him his meals."

Lushbaugh was successful in coming up with data that helped determine how much radiation it took to induce the syndrome. But NASA still wanted to know whether milder symptoms of radiation sickness might reduce an astronaut's ability to perform routine tasks in space.

DWAYNE'S LAST CRISIS

A series of strategically placed mirrors enabled Mary Sue to watch Dwayne in the METBI chamber. He thumbed a well-worn comic book contentedly while the machines were turned on. Just four months shy of his seventh birthday, Dwayne had become all-too-familiar with the routine of hospital life. Over three and a half years, he had spent countless days at the Oak Ridge clinic. Despite the failure of the bone marrow transfer, chemical therapies had kept his leukemic cells in remission—until this new crisis.

Mary Sue silently mumbled a prayer. On Thanksgiving Eve 1968, blood had begun trickling from Dwayne's nostrils and oozing from the back of his throat. Mary Sue could not stop the hemorrhaging. The Sextons sped the 70-mile drive from their home in Robbins, Tennessee.

Now she watched anxiously as Dwayne began to fidget on the aluminum bed. The only hope for prolonging his life, the doctors said, was to depress Dwayne's bone marrow with a

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large enough dose of radiation to kill the cancer cells growing there. It was risky. The amount of radiation would also kill other cells and effectively knock out his body's immunity to bacteria. Dwayne would have to be closely guarded against deadly infection.

From METBI, Dwayne was wheeled into the nearby LETBI chamber, which the Oak Ridge doctors were using as a germ-free isolation ward. The umbilical monitor was strapped around his waist. The doctors told Mary Sue they needed to watch his vital signs carefully. They *didn't* tell her they were using the umbilical to collect data for their NASA study. Dwayne Sexton accepted this latest radiation therapy without a whimper.

"That radiation dose they gave Dwayne may have done the job," Mary Sue says now of the attempt to arrest the growth of the cancer cells, "but I think it done it a bit too much, possibly." In the following weeks, Dwayne's weight dropped by half to less than 30 pounds.

He barely had the strength to lift his head off the pillow, but he enjoyed picking through a flood of letters and Christmas cards, which poured in from relatives and friends. Mary Sue slept beside Dwayne in an empty bed, keeping a constant vigil. "Dwayne didn't care what they did to him," she says, "as long as his Mommy was there. It was like a fairy tale. He was such a brave little boy."

Dwayne knew intuitively his life was ending. "Don't cry, Mommy," he told Mary Sue as she stroked his forehead. "I'm going to be with Jesus."

Morgan believes he was "misled" about the clinic. "My hope & trust were misplaced," he says now.

OF MICE & MEN

Medical science has its own system of judging advances in treatment and therapy. Teams of doctors with expertise in the particular area of research carefully consider and evaluate their fellow doctors' projects.

On several occasions during the LETBI and METBI experiments, inspectors from the AEC visited the Oak Ridge clinic. Judging by the documentary records available, most of the so-called peer reviews by doctors who scrutinized the facility were less than laudatory. One reviewer charged "the directors weren't paying enough attention to what was going on. There had been a previous site visit a couple of years before mine, and their report was ignored."

The report of the review team dispatched to Oak Ridge in March 1974 could not be ignored. They called the clinical facilities "substandard" and recommended the facility be shut down or the program be moved elsewhere. Dr. William Bibb, now the Energy Department's director of research in Oak Ridge, argues that the clinic was closed because "it was giving exquisite care to the people it was taking care of, but it was not providing any research results at all."

On the contrary, the evidence indicates that patients were not receiving "exquisite care." The physicians' judgments of which therapy might be most beneficial to the patients may have been clouded by their desire to come up with "beneficial applications of radiation" for the AEC and syndrome data for NASA. The cancer patients who came to the clinic for help became, in effect, laboratory animals.

In a confidential report, members of the AEC review team that visited the clinic in 1974 expressed their uneasiness with the low quality of the facility and the poor patient care. They characterized the nuclear medicine program as "very pedestrian" and gave the clinical hematology division "an unfavorable rating." But more importantly, the reviewers discovered that some patients at the clinic may have had their lives jeopardized: just beneath the wooden floor of the LETBI chamber, the Oak Ridge researchers had suspended on plastic cords approximately 50 cages of laboratory mice.

Leukemia patients, especially those undergoing radiotherapy like Dwayne Sexton, are virtually defenseless against infection. In hospitals they are carefully isolated from any source of harmful bacteria. Yet, at Oak Ridge, the clinicians were experimenting by irradiating mice and men simultaneously and thus, according to the AEC report, exposing the patients to potentially deadly infection from the animal cages hung directly below the LETBI treatment chamber.

Twice a week, animal caretakers crawled between the inner and outer shells of the LETBI facility to provide fresh food and water for the mice. They carried the dirty cages "through the patient area to an elevator and down to the cage washer," noted the AEC review report. "This entire arrangement seems to be questionable because of the necessity of transporting the animals, animal wastes and equipment through areas used by patients who frequently have compromised host defense mechanisms." In other words, patients whose bodies are incapable of fighting off infection. "This area," the reviewers wrote, "would appear to be highly prone to severe infestations of vermin."

Human guinea pigs are essential to every discovery designed to prolong life, relieve suffering or improve the quality of the human condition. Sooner or later, someone has to submit to new therapies to determine whether they are effective or useless. Doctors routinely comb the professional journals of their various disciplines, searching for clues of discovery provided by their peers' successes and failures.

The 14 years of experiments by the Oak Ridge researchers provided few of those clues. Clarence Lushbaugh did produce a 224-page report on the LETBI and METBI studies for NASA, but he did not publish a single scientific paper on the

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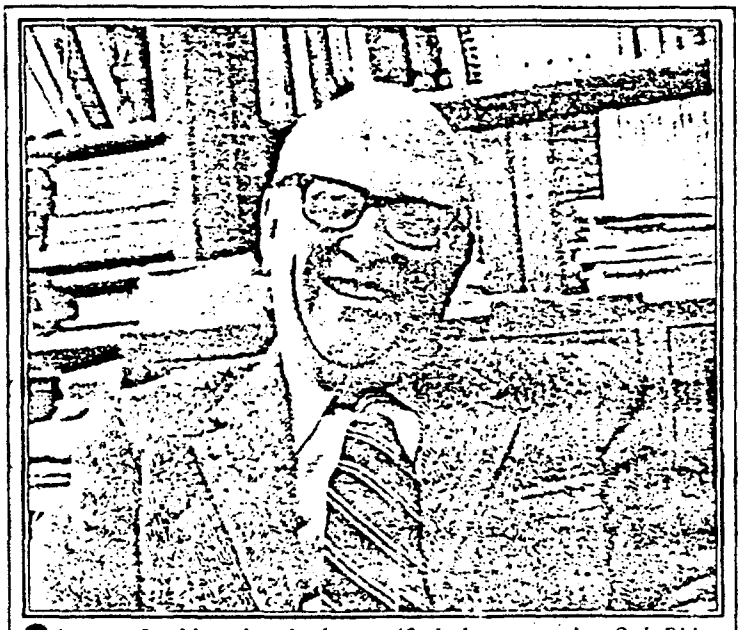
experiments in any recognized journal because "we never considered them to be of enough scientific quality." In his report's summary, Lushbaugh cautioned that the studies should "not be considered definitive." In fact, the experiments raised more questions than they answered.

WERE PATIENTS HELPED?

In their confidential report, the AEC reviewers lambasted the researchers for their work, which they labeled "dismal." The report explicitly says the METBI and LETBI programs evolved "without adequate planning, criticism or objectives." The bone marrow transplant experiments received especially harsh criticism. "In view of accepted therapeutic modalities, ethical questions were raised with respect to the protocols employed in these studies," the confidential AEC report read.

The chamber experiments didn't even result in any appreciable improvement in radiotherapy techniques. "There is little if any clinically useful data on the METBI and LETBI programs," one of the AEC reviewers wrote in his confidential report four years later. "LETBI has been used long enough to establish (if I understand Dr. Lushbaugh correctly) that a very low dose rate does not offer any advantage over the administration of the dose at a higher rate in small, daily fractions."



Clarence Lushbaugh, who has testified about exposing Oak Ridge patients to radiation, now says his role was not significant.

Was the purpose of the experiments primarily to provide data for the space program?

In the beginning, Lushbaugh and Andrews wrote in 1970, a principal objective of the experiments "was to seek information that might lead to improved radiation therapy." However, that noble search for the light of knowledge was soon corrupted. "During the course of the study," they noted in their progress report, "the urgent need arose for information on hematologic effects in man, since the National Aeronautics and Space Administration was faced with potentially high levels of radiation exposures in space exploration."

In short, the syndrome search took precedence. It is not surprising that the METBI and LETBI experiments—with respect to cancer therapy—would get a lower priority: Lushbaugh and Andrews admitted in their 1970 progress report that they did not expect "these individual or infrequently given exposures to produce better clinical results" and that a different radiation treatment "probably offers a preferable approach for total-body radiotherapy."

Despite the documentary evidence, Lushbaugh denies emphatically the suggestion that the experiments were conducted principally for NASA's benefit. He claims his monitoring program was simply "piggybacked" onto the LETBI and METBI cancer therapy treatments. The Energy Department's William Bibb also denies that the search for the syndrome motivated the experiments. "It was the AEC that financed that," Bibb says. "With or without the NASA study, that program would have gone on." Yet, Lushbaugh's 1975 report to NASA clearly states that "the radiobiologic studies" were "carried out with joint AEC and NASA support during the years 1964 to 1974." NASA's support was financially crucial, especially in the experiments' final years.

According to Allen Webb, chemist at the clinic during the experiments, "In the early 1970s, Lushbaugh had to kick asses and pull strings to get enough money to keep LETBI running. NASA provided the monies."

Lushbaugh himself estimates that during the ten years NASA sponsored his research, the space agency provided "three or four million dollars." The records available are limited to the period between 1969 and 1976 and account for payments by NASA of only $799,766 of the total amount. Lushbaugh's colleague, R.C. Ricks—who coauthored the report for NASA—says that with the exception of about $5,000 he spent for bicycle ergometry equipment, NASA paid his salary and Lushbaugh's salary, and the rest of "the funds were spent primarily for salaries for people to be at LETBI."

Clearly, the paper trail of evidence leads directly to the space agency. An attachment to NASA purchase orders (signed by AEC officials and authorizing funds for the project) notes that "the 'Prospective' Human Radiation Sensitivity studies will be continued and will be increased in number in both LETBI and METBI as more patients appropriate to this type of therapy are referred to us." Without NASA money, there would not have been enough cash to continue.

Did the LETBI and METBI radiation experiments actually benefit the patients?

The AEC's reviewers answered that question with an unequivocal and emphatic no. "There has been little thought," they wrote in a disturbing assessment of the experiments, "as to therapeutic utility or potential long-range consequences." In any medical facility, what is best for the patient should always be of paramount importance; and yet, the AEC reviewers accused the Oak Ridge researchers of ignoring whether the therapy they employed was doing any good. Unfortunately, at least 89 cancer patients—including Dwayne Sexton—passed through the LETBI and METBI chambers before the government came to that belated conclusion and itself ordered a halt to the experiments.

THE AFTERMATH

Gould Andrews left the Oak Ridge clinic after the AEC ordered the facility closed and joined the faculty of the University of Maryland. Lushbaugh asserts that it was

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Photograph by Howard Rosenberg

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INFORMED CONSENT

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Andrews who determined which patients should be irradiated in the chambers and how big a dose they should get. However, a number of those involved in the experiments remembered that a committee of the clinic's staff—including Lushbaugh—made the determinations collectively. Andrews cannot speak for himself. He died in the summer of 1980.

Dr. Karl Z. Morgan was the director of the Oak Ridge National Laboratory's Health Physics Division during the LETBI and METBI experiments. Morgan is known throughout the world as the "father of health physics," a science dedicated to the prevention of radiation damage. He is probably the leading figure on radiation protection in the United States and, as such, could hardly be called "antinuclear." Currently a professor of physics at the Georgia Institute of Technology, Morgan believes that during his tenure at the Oak Ridge national laboratory, he was sadly confused about the purpose and results of the LETBI and METBI radiation experiments.

"I naively thought that the purpose of this nearby center [the clinic] was to use ionizing radiation in the treatment of cancer in a manner that had been proven to offer justifiable hope of remission and, in some cases, a cure," Morgan says today. "I believe I was misled, and my hope and trust in this program were badly misplaced."

As it turns out, one of Morgan's lifetime friends, his childhood Sunday school teacher, was one of the 89 patients who went to the Oak Ridge clinic for help and became a subject for the radiation syndrome study. Information about the nature of this clinic has, for Morgan, a special pain.

"The evidence strongly suggests," Morgan continues carefully, "that the purpose of this program was not what we were led to believe." Though Morgan trained dozens of medical doctors himself in methods of using radiation for human benefit, he says he is "appalled, overcome with consternation and filled with a deep sense of indignation" by the news that the cancer patients treated at the Oak Ridge clinic really became guinea pigs for the space program. "It causes one to wonder," Morgan concludes, "whether the members of the medical profession who were responsible could have been sincere the day they took the Hippocratic oath."

Clarence Lushbaugh still has his offices at the clinic itself, but now he is the director of the Oak Ridge Associated Universities' Medical and Health Sciences Division and brags that "only God can retire me." Just months after the review team concluded its damaging report on the clinic, Lushbaugh was awarded another ongoing contract, this one by the Energy Department to conduct an epidemiological analysis of possible health risks to nuclear workers at the Energy Department's Oak Ridge plants.

Lushbaugh's new research project could be another potential bombshell if it confirms the results of a previous study of nuclear workers. That study, by University of Pittsburgh professor Thomas Mancuso, revealed—after 12 years of work—that nuclear workers at the Energy Department's Hanford, Washington, atomic works suffered a significant increase in the incidence of certain types of cancer at radiation exposure levels *well below* "safe" limits.

While Lushbaugh has no experience in conducting epidemiological analyses, as in this new study, he does have experience in coming up with the sort of data the government likes. In his final report to NASA on the LETBI and METBI experiments, Lushbaugh explained that one of his objectives in undertaking the project was that "these unbiased clinical observations were sorely needed to defend existing environmental and occupational radiation exposure constraints from attack by well-meaning, but impractical, theorists."

In the past, when the government faced troubles because nuclear workers or atom bomb test victims were suing Uncle Sam for injuries they sustained, Lushbaugh was counted on to offer "expert testimony" against them. That was exactly what took place in U.S. District Court in Las Vegas, Nevada, on May 16, 1977.

Seven years earlier an underground nuclear bomb test at the nearby Nevada Test Site went awry. Scientists had miscalculated the power of the so-called Baneberry bomb, and a mushroom cloud broke through the earth's crust and rose some 10,000 feet into the sky. The cloud began drifting toward an AEC base camp. Setting aside their own safety, 13 guards frantically evacuated the camp. Three of the 13 later died of leukemia, apparently because of their exposure to unsafe amounts of radiation. Two of the widows sued the federal government. Clarence Lushbaugh testified against one of the women.

Lushbaugh now denies he had any significant role in the actual operation of METBI and LETBI. Yet, to prove his own expertise on radiation effects during his testimony at the Baneberry widow's trial, Lushbaugh described the LETBI and METBI experiments. He testified that "we ourselves exposed persons to various total-body doses of radiation, and this was an ongoing study that I worked in and subsequently I became the leader of it, and we radiated persons with various kinds of leukemias in a specially designed room where they actually lived in a sea of radiation with their daily dose."

Dwayne Sexton died at the Oak Ridge clinic on December 29, 1968, a month after his last therapy session in METBI. A limited autopsy was performed. The cause of death was determined to be acute strep and staph infection.

It seems we only miss you more
As each passing day goes by
Yes, our hearts have all been broken
Yet we try hard not to cry

You were such a bright spot in our lives
Since the first day you came
There's an empty place in our home
That will never be the same

—from a poem dedicated to Dwayne, by Mary Sue Sexton, written three months after his death

In the entire history of the United States Manned Spaceflight Program, not a single astronaut ever received a high-enough dose of radiation to suffer from the syndrome. Dwayne Sexton did.

Howard L. Rosenberg is the author of Atomic Soldiers *(Beacon Press, 1980). He also describes himself as "a writer and rider" on the staff of Jack Anderson's "Washington Merry-Go-Round." Supplementary research for this article was contributed by the Environmental Policy Center.*

1114199

The Oak Ridger

33RD YEAR—NO. 152—482-1021 OAK RIDGE, TENNESSEE, WEDNESDAY, AUGUST 19, 1981 20 CENTS

Soggy Aug.

August is getting rather soggy. Mostly cloudy with a 40 percent chance of rain and a few thundershowers this afternoon, tonight and Thursday. High today, upper 70s; low tonight, mid 60s; high Thursday, near 80.

ORAU answering magazine charge

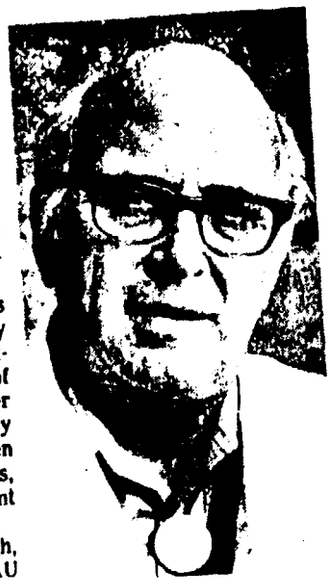
By CATHERINE FOSTER

A national magazine will be charging Thursday that Oak Ridge Associated Universities, as part of its research into the treatment of cancer, experimented with a number of cancer victims in order to gather data for the National Aeronautics and Space Administration.

The story, in Mother Jones magazine, charges specifically that six-year-old Dwayne Sexton, who died Dec. 29, 1968 of leukemia, died because cancer researchers at ORAU were busy gathering data for NASA, even though, the magazine charges, better methods of treatment were available.

But Dr. Clarence Lushbaugh, a cancer researcher at ORAU then and now, denies the charges, saying that cancer victims were treated in an effort to help them live a little longer, and that research was done to help other victims of the disease, not to help NASA.

Persons involved in writing and researching the story were not talking today, saving their information for a "Today" show broadcast on NBC Thursday morning, and for a Thursday morning press conference in Washington.



LUSHBAUGH

But the story charges that Dwayne died as a result of being irradiated at the same time that animals used in experiments were treated.

ORAU, of course, was widely known for operating a small medical hospital at its medical division's facilities on East Vance Road where many persons afflicted with cancer, often in its terminal stages, came for treatment. A number of these patients died at the facility there over the years of treatment and study and the results of the studies there were widely publicized as part of ORAU's research mission.

A copy of the article, scheduled for release Friday, was obtained early this afternoon by The Oak Ridger. The article charges that those researchers at ORAU administering the treatments knew of other therapy techniques that were superior, but did not use them because they wanted to do studies. It also charges that treatment facilities here were "substandard."

Dr. Lushbaugh strongly denies this, saying that all treatment given had "the interest of the patient" first, with research interests secondary, and that facilities are of excellent quality.

The article also charges that Dwayne's parents, and others, were not given full information about the treatment and the patients' options in seeking other forms of treatment.

Dr. Lushbaugh denies this, too, saying that procedures were explained in detail to all persons seeking treatment at ORAU, and at its predecessor Oak Ridge Institute for Nuclear Studies.

Dr. Lushbaugh did agree to the writer's characterization of him as "a short, balding man with a combative personality," however, he said today during an impromptu press conference that included The Oak Ridger and representatives of CBS News.

Dr. Lushbaugh made his statements at midday today at the Department of Energy offices here and was providing a taped interview with CBS News at his ORAU office later this afternoon. CBS News reporter Bruce Hall was conducting the interview, to be broadcast as part of their coverage of the Mother Jones announcement.

The boy's mother, Mary Lou Sexton, who lived in Robbins, in Scott County, at the time of the

(Continued on Page 6 No. 8)

Back-to-school news; board meets Thurs.

Back-to-School features are included in today's Oak Ridger on pages nine through 12, 17 and in the special Downtown section.

Anderson and Roane county school systems are highlighted in the Downtown section. A story on new teachers to the local school system is on page nine. A listing of Oak Ridge High School 1981 graduates' future plans is on page ten.

Features on new trends in education can be found on page 11 and in the special downtown section.

A complete listing of Oak Ridge bus routes will be published Aug. 26.

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increase for this year, a 3 percent increase the following year, and a wage reopener the final year of the contract, in addition to other non-economic issues in the contract.

Null said that it is common practice that wage increase percentages are fairly consistent at all four of the Nuclear Division facilities. He said that he is confident that the Paducah workers will be receiving the same wage increases as the ATLC received, adding that when ORGDP's contract comes up for renogitation in October, the OCAW Local 3-288 will receive similar wage increases.

The talks in Paducah began this morning without the federal mediator, who was unable to attend because of a death in his family.

Cobert could not disclose the particulars of the negiotiations, but said that the fact that they are talking is a good sign.

day.

The vessel was one of three French-built gunboats being transferred from France to Iran. The other two were not attacked and were reported Tuesday in Oran, Algeria, on their way to Iran.

French Defense Minister Charles Hernu said Tuesday night the government would not provision the comandeered vessel and suggested that the hijackers take it back into international waters. However, he said it would be against tradition for the navy to force it to leave.

Reminding France of the Iranian government's anger when it granted ex-President Abolhassan Bani-Sadr asylum after his escape from Iran, Foreign Minister Mir Hossein Musavi said: "This adventurist act has once again put France to the test."

"Granting asylum to pirates is

Decline in economy greater than thought

WASHINGTON (AP) — The nation's economy fell further than was first thought during the April-June quarter, declining at an annual rate of 2.4 percent after racing ahead at a rate of 8.6 percent in the first quarter, the government reported today.

The drop in inflation-adjusted gross national product had been estimated at 1.9 percent in the Commerce Department's original report one month ago.

The department's new report said corporate profits also dropped sharply in the second quarter as the overall economy weakened.

Before-tax profits fell 12.5 percent to a seasonally adjusted annual rate of $224.9 billion and after-tax profits dropped 11.3 percent to a rate of $150.1 billion in the quarter. Both rose 3 percent in the January-March period, the report said.

Corporate profits from current production — a category which does not include inventory profits — declined 7.9 percent to an annual rate of $187 billion in the second quarter after rising 10.7 percent in the first three months of the year.

As the Commerce Department reported one month ago, major reasons for the GNP decline were a decrease in inflation-adjusted final sales by American businesses and a big drop in net exports, a category that had helped push GNP upward in the first quarter.

A number of economists are predicting that inflation-adjusted GNP will also be down in the current July-September quarter, thus fulfilling one commonly accepted definition of an economic recession — two consecutive quarters of negative GNP.

Hearing set on TVA coal gasification plant

GUNTERSVILLE, Ala. (AP) — A public hearing is planned Sept. 17 on the Tennessee Valley Authority's application to begin work on facilities associated with a $1.6 billion coal gasification plant, the Army Corps of Engineers announced.

The proposed plant would process 10,000 tons of coal a day into methanol and methane. The liquid methanol could be used as an automobile fuel, while the methane — natural gas — could be burned as a fuel.

TVA needs the permit and approval by its three-member board of directors before beginning a year of preparation at the Murphy Hill site on the Tennessee River, 12 miles northeast of Guntersville.

The federal agency then would turn the project over to a consortium of private companies which would build the plant.

An environmental impact statement for the project has been prepared by TVA. Copies will be available at the Corps of Engineers hearing, which will be at 7 p.m. CDT in the Guntersville High School auditorium.

Col. Lee W. Tucker, district engineer of the Corps of Engineers in Nashville, Tenn., said the public is invited to comment on the proposed facilities. He said information gathered at the hearing would be considered in evaluating the proposal.

TVA is applying for a Department of the Army application to construct water-related facilities associated with the coal gasification plant. Plans call for a water intake, discharge system, coal receiving dock and sulfur loading dock, barge slip, barge access channel and access roads.

TVA has $125 million in congressional appropriated money that will be put into site preparation, said Bob Brookshire, assistant to TVA's program manager for coal gasification.

Charles Lindbergh landed at Le Bourget field outside Paris on May 21, 1927, to end his historic solo flight across the Atlantic Ocean. Lindbergh's nonstop trip, which began at New York's Roosevelt Field, took 33½ hours.

• Number 8

ORAU

— From Page One

child's death, is scheduled to appear both on the "Today" broadcast and at the press conference. The Oak Ridger was not able to determine Mrs. Robbins' current address.

The writer of the article, Howard Rosenburg, who works for investigative reporter Jack Anderson, was in Oak Ridge doing interviews for the story in January, he said today.

Rosenburg refused to release any details about the article, saying, "You have to understand the spot I'm in. The press conference is tomorrow, and I'll be glad to tell you anything after that."

Others expected to be both on "Today" and at the press conference are Karl Z. Morgan, formerly head of the health physics division of Oak Ridge National Laboratory, now a teacher of health physics at Georgia Institute of Technology, and Peter Weirnick, director of the Baltimore Cancer Research Center.

Morgan told Mother Jones that he was "sadly confused" about the purpose and results of the ORAU effort.

"I naively thought that the purpose of this nearby center was to use ionizing radiation in the treatment of cancer in a manner that had been proven to offer justifiable hope of remission and, in some cases, a cure," Morgan told Mother Jones. "I believe I was misled and my hope and trust in this program were badly misplaced."

He is also quoted as saying, "It causes one to wonder whether the members of the medical profession who were responsible could have been sincere the day they took the Hippocratic oath."

Attempts to reach Mother Jones editor Richard Reynolds in Washington were unsuccessful.

John Haffey, ORAU spokesman, said this morning that he had "no detailed knowledge of the story" and no comment.

Bonson

ORAU-112

HEMATOLOGIC AND THERAPEUTIC EFFECTS OF TOTAL-BODY IRRADIATION (50 R TO 100 R) IN PATIENTS WITH MALIGNANT LYMPHOMA, CHRONIC LYMPHOCYTIC AND GRANULOCYTIC LEUKEMIAS, AND POLYCYTHEMIA VERA

December 1970

Medical Division
Oak Ridge Associated Universities, Incorporated
Oak Ridge, Tennessee

UNITED STATES ATOMIC ENERGY COMMISSION • DIVISION OF TECHNICAL INFORMATION

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ORAU-112
BIOLOGY AND MEDICINE
(TID-4500)

HEMATOLOGIC AND THERAPEUTIC EFFECTS OF TOTAL-BODY IRRADIATION (50 R–100 R) IN PATIENTS WITH MALIGNANT LYMPHOMA, CHRONIC LYMPHOCYTIC AND GRANULOCYTIC LEUKEMIAS, AND POLYCYTHEMIA VERA*

G. A. Andrews, F. V. Comas, C. L. Edwards, R. M. Kniseley,
C. C. Lushbaugh, and Helen Vodopick

* *From the Medical Division, Oak Ridge Associated Universities, under contract with the U. S. Atomic Energy Commission.*

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Hematologic and Therapeutic Effects of Total-Body Irradiation (50 R - 100 R) in Patients with Malignant Lymphoma, Chronic Lymphocytic and Granulocytic Leukemias, and Polycythemia Vera*

G. A. Andrews, F. V. Comas, C. L. Edwards, R. M. Kniseley, C. C. Lushbaugh, and Helen Vodopick

Introduction

Since 1957 the staff of the Medical Division of Oak Ridge Associated Universities has been studying the hematologic and clinical courses of patients receiving total-body irradiation. In an early experiment the radiation therapy was done in connection with attempts to graft bone marrow (1). We also have studied intensively the hematologic courses of victims of accidental exposure to radiation (2-7). The present report covers the therapeutic and hematologic results of a ten-year study — 1959 through 1968 — of single exposures of 50 R and 100 R given at approximately 1.5 R/min in a specially designed facility for total-body radiation therapy. Some of the data from this series have been published previously in brief form (8).

This study was initiated with two principal objectives; the first was to seek information that might lead to improved radiation therapy for disseminated malignant disease, especially leukemia and lymphoma, by determining the best criteria for selection of patients, radiation dose, and dose rate. For many years radiotherapists have been able to control progression of certain hematologic disorders by giving "spray X-irradiation" and have obtained similar effects using internally administered radiation, in particular phosphorus-32 (9). Fractionation and dose protraction quite logically have been used to reduce the incidence of undesirable side effects and are believed also to decrease the damage to normal tissues more than to malignant ones. However, differences in fractionation, energy of the beams, and uniformity of exposures to different parts of the body make it difficult to evaluate and compare the effects of various radiation-exposure patterns used in such therapy.

The second objective was to acquire radiobiologic information. The radiobiologic aspects of total-body irradiation on man have been studied clinically

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* From the Medical Division, Oak Ridge Associated Universities, under contract with the U. S. Atomic Energy Commission.

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since Walsh (10) first described radiation sickness in 1897. The dose-response relationships, however, are still poorly known and present estimates are based largely on conjectures and extrapolations from animal experiments, or from experience with accident victims, atom bomb casualties, and patients treated by irradiation. Because patients in the past ordinarily have been treated with divided doses, it has been difficult to compare biologic effects in the many clinical series with each other, or with the effects seen after radiation accidents.

We decided to obtain baseline data by giving individual doses of 50 or 100 R and then observing the patients long enough to evaluate effects. These single doses of radiation, somewhat higher than individual doses in a fractionated regimen, would provide a response that could be measured with a clear temporal relation to the date of irradiation. In contrast, an effect gradually induced by two or more variably spaced small doses would be more difficult to analyze and compare among groups of patients. Single exposures also would permit us to compare the hematologic responses with those of accident victims who usually receive single rapid exposures. Careful definitions of the effects of 50 R and 100 R, as attempted in this paper, are a necessary basis for later evaluating the effect of fractionation.

It was not our plan to evaluate the long-range effectiveness of these relatively large individual doses of total-body irradiation as a repetitive and sole therapy. This would have required establishing a total treatment plan with this technique, which we were not prepared to do. The larger doses provide a less continuous control, a possible disadvantage emphasized by Osgood. We wanted to be able to add or substitute other forms of treatment when specific clinical considerations seemed to indicate them. One should not infer from this study that we expected these individual or infrequently given exposures to produce better clinical results than fractionated total-body or portal irradiation. At present we feel that some pattern of fractionated exposure, such as that of R. E. Johnson (11), probably offers a preferable approach for total-body radiotherapy. The data reported here, by defining the range of clinical and hematologic effects that single exposures of 50 and 100 R can be expected to produce in these diseases, should provide a yardstick for comparisons in future total-body irradiation trials using different exposure patterns.

Such information, even though obtained in the abnormal conditions of disease, is helpful for assessing levels of accidental gamma and neutron irradiation injury and guiding therapeutic efforts. During the course of the study the urgent need arose for information on hematologic effects in man, since the National Aeronautics and Space Administration was faced with potentially high levels of radiation exposures in space exploration. The principal answers we sought were the pattern of responses for leukocytes, red blood cells, and platelets in chronic lymphocytic leukemia, lymphoma, chronic granulocytic leukemia, and polycythemia rubra vera. What differences occurred in response to 50-R and 100-R exposures? Did normal blood cells differ in radiosensitivity from their counterparts in proliferative disorders? For example, do platelets have a different radiosensitivity in chronic lymphocytic leukemia or lymphoma compared with polycythemia rubra vera? Or, do "normal" lymphocytes of polycythemia rubra vera have the same sensitivity as lymphocytes of chronic lymphocytic leukemia? We also wanted to observe

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the degree and length of clinical improvement as manifested by relief of general symptoms, and regression of masses, lymph nodes, liver, and spleen. In addition, we wanted to determine the incidence and analyze the nature of the unpleasant symptoms of acute radiation exposure which are included in another study (12).

This report completes one phase of our total-body irradiation study program. In brief this study will: 1) provide baselines for the study of fractionation effects, 2) be simpler to analyze than more complex regimens, 3) provide information relevant to radiation injury in "normal" humans. It will not: 1) demonstrate that 50 or 100 R is better than the currently accepted fractionation modes, or 2) analyze the long-range therapeutic effectiveness of these doses.

Materials and Methods

Patients - A total of 89 treatments were given. This report covers information on 29 exposures to 50 R, and 55 to 100 R. The remaining five were dropped from the protocols because of an urgent need for additional or different therapy before the study was finished, or because of the patient's inability to meet the appointments for follow-up outpatient visits during the study period. The number exposed and their disease categories are listed in Table 1, along with the abbreviations used in the text.

All patients with these diseases admitted to the Medical Division hospital during this period were considered for this therapeutic program. The diagnoses were established by clinical history, physical examination, and microscopic study of surgical biopsies, bone marrow, and peripheral blood samples. The urgency for treatment was assessed, and those patients whose condition required some other kind of therapy, or no therapy at all, were omitted. If the clinical status was changing rapidly and we anticipated that other additional treatment might be needed during the postirradiation observation period, these patients were also excluded. If no clearly superior therapy was available for a particular patient and the total-body radiation treatment was regarded as an acceptable way of management, the patient was offered this form of treatment, following an explanation of the research protocol. Informed consent was obtained in accordance with ethical practice to protect the rights of the individual as a research subject. We recognize some bias in the selection of one of the two doses. In a concern for the patient's safety early in the study we evaluated only the results of 50-R exposures before using the higher dose. Later, some of the patients selected for the 100-R exposure were those with more pronounced symptoms, or in lymphoma, had tumor masses that were judged to need the more vigorous treatment. On reviewing histories and clinical status,* however, we believe that these biases are not sufficiently great to prevent us from comparing a 50-R group with a 100-R group. Other forms of treatment for the disease were discontinued before the irradiation, except that

* Summaries of clinical histories and status changes of the individual patients have been collated and included in the Appendix of this report.

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in a few patients who required it, maintenance steroid therapy was kept up (see Tables D and E in Appendix). Of the patients with chronic lymphocytic leukemia, blood transfusions were given during the six-week posttreatment period (Table 2) to three exposed to 50 R and four patients exposed to 100 R. No other treatments were given during this time.

Table 1

Patients Exposed to Total-Body Radiation in Each of the Disease Categories

	50 R			100 R		
	1st R_x	2nd R_x	Total R_x	1st R_x	2nd R_x	Total
Chronic Lymphocytic Leukemia (CLL)	12	3	15	16	4	20
Malignant Lymphoma	5	0	5	17	5	22
Hodgkin's Disease	1	0	1	1	0	1
Chronic Granulocytic Leukemia (CGL)	6	2	8	4	0	4
Polycythemia Rubra Vera (PRV)	0	0	0	7*	1	8
Total	24		29	[illegible]		55

*One patient had primary hemorrhagic thrombocythemia rather than PRV.

Hodgkin's disease was originally included in the study but was eliminated early because we believed that a larger dose is needed to control the malignant process than we could safely give to the whole body at one time. The most effective modern therapy for this disease is irradiation of lymphatic tissues, sometimes involving large fields, but allowing some hematopoietic tissue to remain unirradiated. The lesions of this disease are generally less radiosensitive and less intimately involved in hematopoietic tissue than those that can be helped by total-body irradiation.

Study Protocol - A uniform study protocol was devised to collect laboratory data on specified days during the six-week study period (Table 3). The six-week period of data collection was adopted as the most reasonable compromise between clinical research objectives and patient's needs; a longer period would

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Table 2

The Requirement for Blood Transfusions in Patients with Chronic Lymphocytic Leukemia Before and After Radiotherapy with 50 R and 100 R TBI

		Transfusions during 6 weeks pretreatment		Transfusions during 6 weeks posttreatment	
Radiation Dose	No. Patients	No. Patients	No. Trans.	No. Patients	No. Trans.
50 R	13	3	18	3	15
100 R	8	3	15	4	31

have been clinically more desirable, and most of the patients continued under our care and had further observations. Because of the enormous spread of initial blood values, all results were normalized by using the immediate pretreatment values for each patient as 100%. In most instances, this value consisted of the average of day minus three and day zero (pretreatment) counts; in a few only day zero values were available. Table 4 gives the ranges and geometric means of the pretreatment data from which the normalized curves were derived.

Table 3

Protocol for Blood and Bone-Marrow Sampling Times Used in 50 R and 100 R TBI Study for All Patients

Radiation Day	-7	-3	0	+1	+2	+3	+4	+7	+14	+21	+28	+35	+42
Bone Marrow		x					x				x		
WBC, RBC, Platelets Blood Film, Hgb., Hct.	x	x	x	x	x		x	x	x	x	x	x	x
Uric Acid		x	x	x			x	x	x	x	x		

1114210

Table 4

Range of Pretreatment Blood Values Among Patients in Each Category

(Average of Day -3 and Day 0)

Diagnostic Group	No. of Exposures	Leukocytes $mm^3 \times 10^3$			Absolute Lymphocytes/$mm^3 \times 10^3$			Platelets/$mm^3 \times 10^3$			Hemoglobin gm/100 ml		
		Range		Geom. Mean	Range		Geom. Mean	Range		Geom. Mean	Range		Geom. Mean
		High	Low		High	Low		High	Low		High	Low	
Polycythemia Vera 100 R	8	41.6	10.0	25.3	4.2	1.2	2.1	1,619	289	806.1	15.9	11.6	13.6
Chronic Lymphocytic Leukemia - 50 R	15	304.0	9.8	83.5	294.9	9.4	76.9	337	40	131.9	16.8	8.3	12.5
Chronic Lymphocytic Leukemia - 100 R	20	396.2	6.2	69.8	388.6	4.3	61.4	412	13	113.1	14.8	6.9	11.4
Chronic Granulocytic Leukemia - 50 R	8	463.9	52.1	114.5	9.8	1.4	3.5	1,061	211	446.5	14.2	9.0	11.3
Chronic Granulocytic Leukemia - 100 R	4	246.3	103.8	148.5	4.2	0.9	2.1	1,326	392	707.5	12.0	9.0	10.4
Malignant Lymphoma 50 R	5	14.2	6.5	9.6	9.9	1.6	4.5	238	50	134.1	16.2	9.7	13.5
Malignant Lymphoma 100 R	22	28.3	2.3	7.7	26.9	1.1	3.4	444	45	205.0	15.8	8.5	12.4
Hodgkins - 50 R	1			10.0			2.9			310			11.0
Hodgkins - 100 R	2	11.5	9.0		10.3	2.0		521.2	481.2		10.2	8.2	

1114211

Bone-marrow aspirations were performed according to the protocol described; we have decided not to present the findings in the present report.

Laboratory Methods

The hematologic studies were performed on venous blood samples using well established laboratory methods. The hemoglobin value was determined by the cyanmethemoglobin method and hematocrit percent by the Wintrobe method. Leukocytes and erythrocytes were counted electronically. Platelets were enumerated by the method of Brecher and Cronkite using phase microscopy (13). When platelet counts were low, dilutions of 1:20 were used rather than 1:100. The number of small squares counted in the chamber was increased to 10, 25, or 50 until more than 100 platelets were counted, or all platelets in 50 squares counted. In determining absolute lymphocyte values for patients with PRV, we performed differential counts on 400 leukocytes for greater statistical confidence.

The Radiation Facility and Dosimetry

The irradiation room, designated the medium-exposure-rate total-body irradiator (METBI), was completed in 1959; it is an eight-foot cube, concrete shielded, with a 385-curie source of cesium-137 in each of the eight corners. A maze connects the treatment room to its control room where a nurse or operator is in visual contact with the patient by a series of mirrors. The patient lies on an aluminum bed suspended in the center of a homogenous 2 x 2 x 6 foot radiation field. The beams from the eight sources are shaped so that the exposure rate is uniform to within ± 5% within the treatment volume. The exposure rate can be varied by a series of attenuating filters and values from 0.64 to 1.52 R/min have been used; but most treatments were given at 1.50 R/min. This facility has been described in detail by Brucer (14) and a detailed description of the radiation field has been published (15).

We made two independent dosimetry studies to determine the dose received by patients. We filled three compartmentalized phantoms with Fricke chemical dosimeter and determined spectrophotometrically the average dose to each of the 13 compartments. In addition, we measured the midplane isodose lines by an ionization probe; details are given by Hayes et al (16). In the second study,* with a tissue-equivalent plastic phantom containing an implanted skeleton and density-adjusted lung spaces, we measured the dose to various organs using LiF thermoluminescent dosimeters in the volumes representative of these organs. Except for the bone marrow, the average rad response of the dosimeters in an organ was defined as the average organ dose. We calculated the marrow dose as a weighted average since this tissue, located at variable depths beneath the

---

* W. L. Beck and T. R. Stokes performed the thermoluminescent dosimetric measurements as part of our continuing total-body irradiation program.

1114212

Table 5

Variations in Average Dose to Body Compartments According to Body Size

Compartment	Average Compartment Dose in Rads Per 100 R		
	Adult*	Adolescent*	Child*
Head	78	81	79
Neck	76	83	84
Chest	63	66	70
Abdomen	66	69	71
Pelvis	65	70	71
Arms	76	78	75
Thighs	75	78	82
Legs	86	88	87
Feet	76	78	81
Whole Body	70	74	75

*Hayes Water Phantoms

surface, is not placed uniformly in a single, well defined site. The assumed marrow distribution used for the dose estimates was that suggested by R. E. Ellis (17) for a normal man. It is well known that its volume and location varies widely in patients with the diseases studied here.

The average tissue dose to the total torso of a standardized normal adult was estimated by each of the dosimetry studies to be 65 rads/100-R exposure by the compartmentalized phantom study and 68 rads/100 R by the heterogeneous phantom. The minimal bone-marrow dose occurs in the pelvic region and is only 53 rads/100 R. Variations in dose due to difference in body size and configuration are shown in Table 5. Table 6 lists the absorbed dose in various organs.

OBSERVATIONS

Chronic Lymphocytic Leukemia

During the first six weeks after therapy in 35 patient treatments with either 50 R or 100 R, palpable lymph nodes shrank in 20 and remained unchanged in 12.

1114213

Table 6

Anatomical Organ Doses in Cesium-137 Total-Body Irradiation Facility

Organ	Total Organ Dose (Rads/100 R)		
	Average	Ranges	
Bone Marrow	64	53-86	(137)*
Cerebellum	77	74-81	(9)
Cerebrum	75	70-79	(21)
Heart	66	58-70	(16)
Intestines	67	54-76	(107)
Kidneys	66	62-70	(6)
Lenses of Eyes	87	85-90	(2)
Liver	67	61-78	(42)
Lungs	67	58-77	(185)
Skin (above sternum)	73	72-75	(2)
Skin (front waist)	74	72-75	(2)
Spleen	69	64-73	(7)
Stomach	64	59-69	(34)
Thyroid	76	75-77	(2)

*Figures in parentheses indicate the number of bodily locations where dose was measured with LiF dosimeters.

Of the palpable spleens, ten were smaller after treatment, seven remained unchanged, but palpable, and seven enlarged during the same interval. There was no clear pattern of change in liver size.

Twelve patients gained weight, 13 lost, and eight had no change. (The others are unrecorded.) The general feeling of well-being improved to some degree in 21, remained unchanged in 12, and decreased in two. We could not demonstrate with any of these clinical responses that the effect of 100 R was greater than that of 50 R, although the small numbers of patients is a deterrent to comparisons.

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Figure 1 shows the WBC responses of individual patients to 50 R and Fig. 2 those to 100 R. Radiosensitivity differed considerably from patient to patient. In both groups of patients (50- and 100-R exposures) there was a subgroup of "resistant" patients whose response was significantly less pronounced. There was no trend of climbing toward pretreatment values by day 42 in either dose or sensitivity subgroup.

Figure 3 shows the changes in mean blood lymphocyte numbers following 50-R and 100-R exposures in the resistant and sensitive patients. We saw no statistically significant differences in the degree of lymphocyte depression caused by these two doses. Although the most rapid fall occurred in the first week, a nadir was not reached until three or four weeks after exposure.

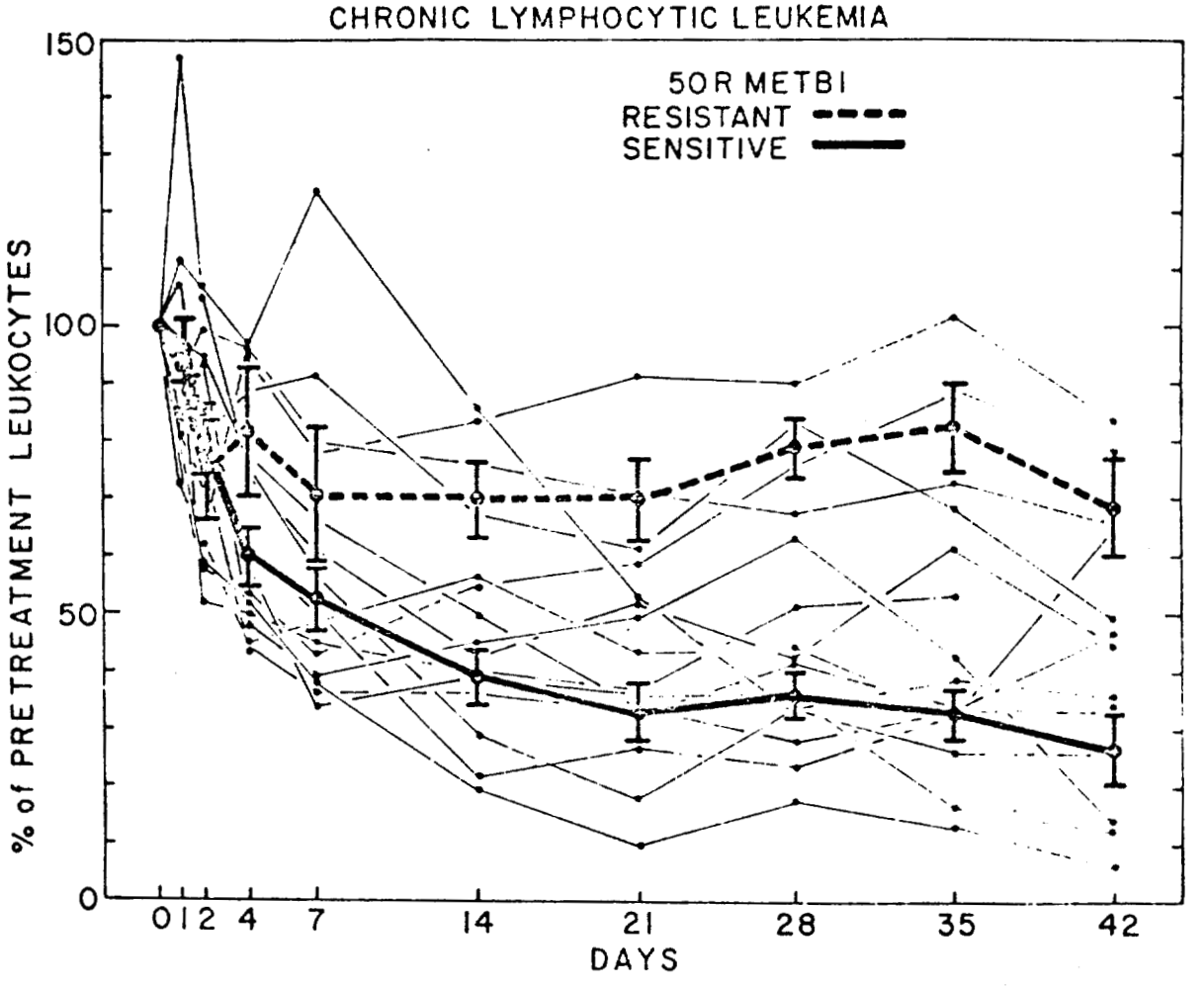

Fig. 1. Changes in the white blood levels in 15 patients with chronic lymphocytic leukemia after 50 R. The leukocyte counts have been normalized to the individual patient's pretreatment values. Two geometric means with their standard errors are shown; one (solid line) is that for the leukocyte levels in the 11 more responsive patients and the other (dotted line) is that for the four patients whose course seems more resistant. The two computed means (after seven days) are statistically different at the 95% confidence level.

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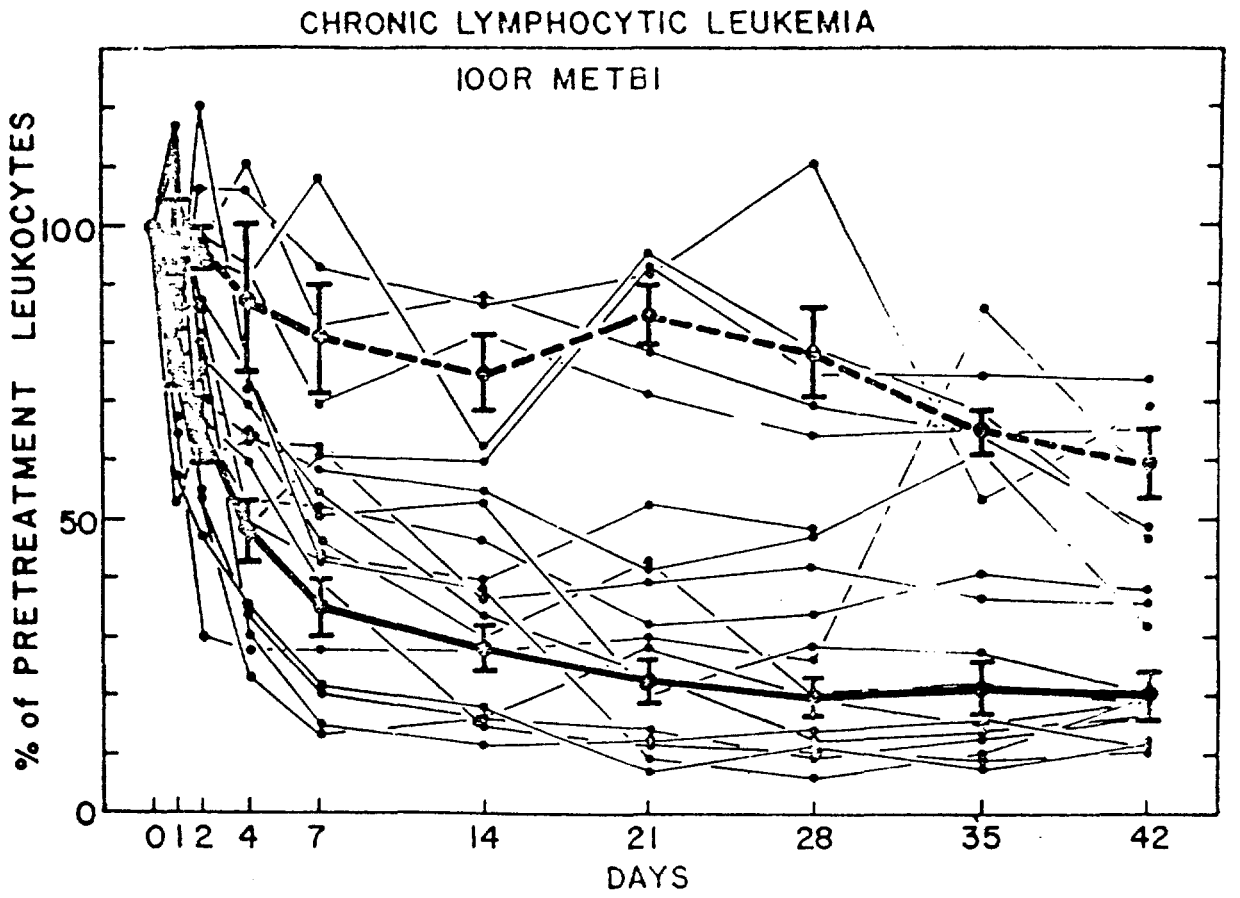

Fig. 2. Changes in the white blood counts (shown in Fig. 1) of 19 patients with chronic lymphocytic leukemia after 100 R. As in Fig. 1, the two geometric means are those for the 14 "sensitive" and five "resistant" patients and are significantly different at the 95% level from the second day onward.

The response of leukemic lymphocytes to 100 R was unrelated to the level of the pretreatment leukocyte counts, nor did it correlate with lymphocyte size, notching of nuclei, or tendency to smudge. The degree of marrow infiltration as judged by histologic examination of marrow aspirated did not tell us why some patients had "radioresistant" lymphocytes. Furthermore, we found no correlation between the lymphocyte response and the clinical response or length of "remission"; eight patients required no other treatment for seven and a half or more months, while nine patients needed additional treatment for leukemia shortly after the study period, less than three months from the irradiation.

While the leukemic lymphocytes responded similarly to 50 R and 100 R, the effect of these two doses on the platelet levels differed strikingly as shown in Figs. 4 and 5. These graphs show also that the responses of patients given 50 R vary more than those of patients given 100 R, suggesting that recovery may be manifested more variably with the lower dose. A trend toward recovery

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is definitely established during the fifth and sixth weeks after exposure. As can be seen in Fig. 6, the recovery in numbers of circulating platelets after 50 R occurs earlier and more rapidly on the average than after 100 R. The standard errors of these geometric means are also larger with the lower dose indicating the greater variability of the response to the lower dose.

Hemoglobin values remained stable in the 10 patients not anemic before treatment; those that were anemic usually had no rise in their hemoglobin levels or became more anemic during the six weeks following irradiation. In a few patients who had been requiring transfusions before treatment, the 100-R exposure increased the number of transfusions needed while 50 R did not (see Table 2).

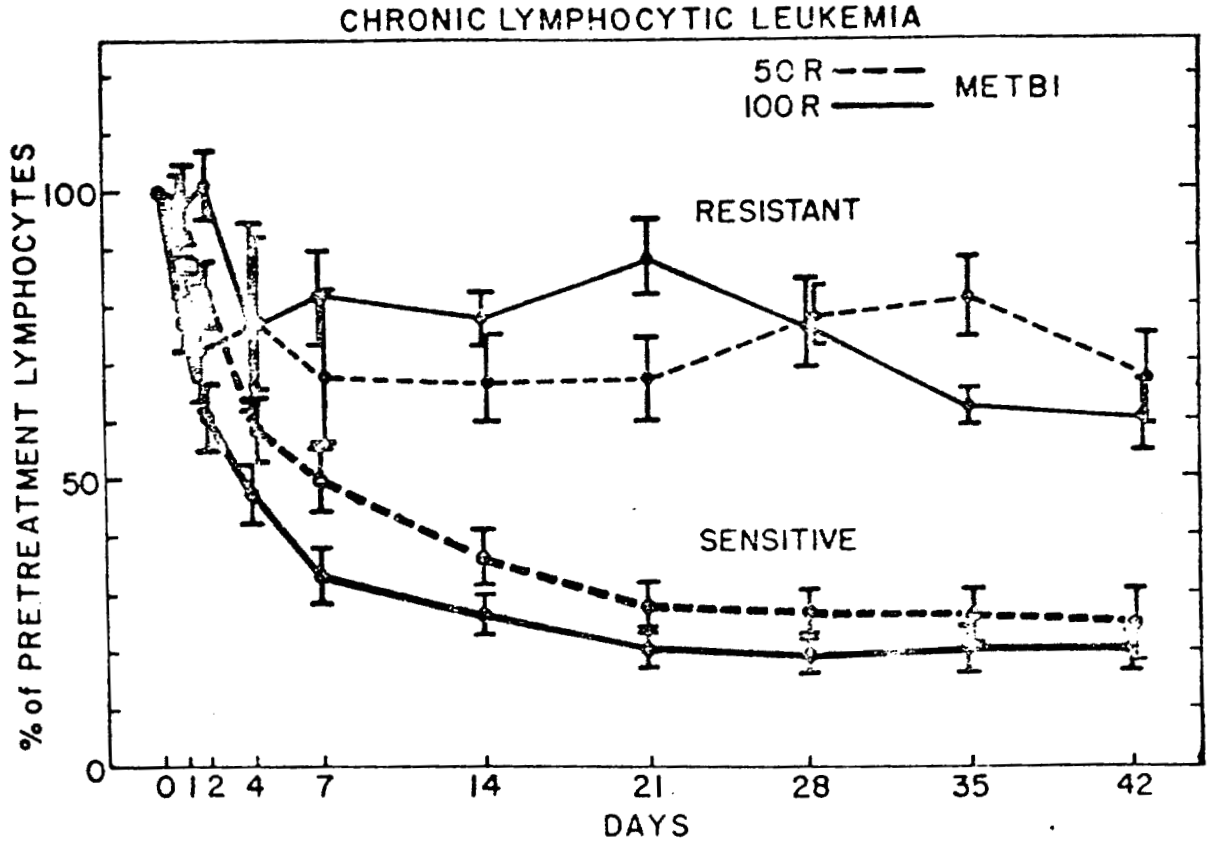

Fig. 3. Changes in the geometric-mean blood lymphocyte values (shown as normalized percentages of pretreatment differential lymphocyte counts) for the patients with chronic lymphocytic leukemia whose changes in white blood cell values are shown in Figs. 1 and 2. There is no statistical difference between the computed mean changes after 50-R and 100-R exposures in either the "sensitive" or "resistant" groups but the statistically valid difference between the mean responses of the two groups is obvious.

Malignant Lymphoma

This group of 20 patients included five who were given 50 R, two of whom subsequently received 100-R treatments. Of the 17 patients who received 100 R,

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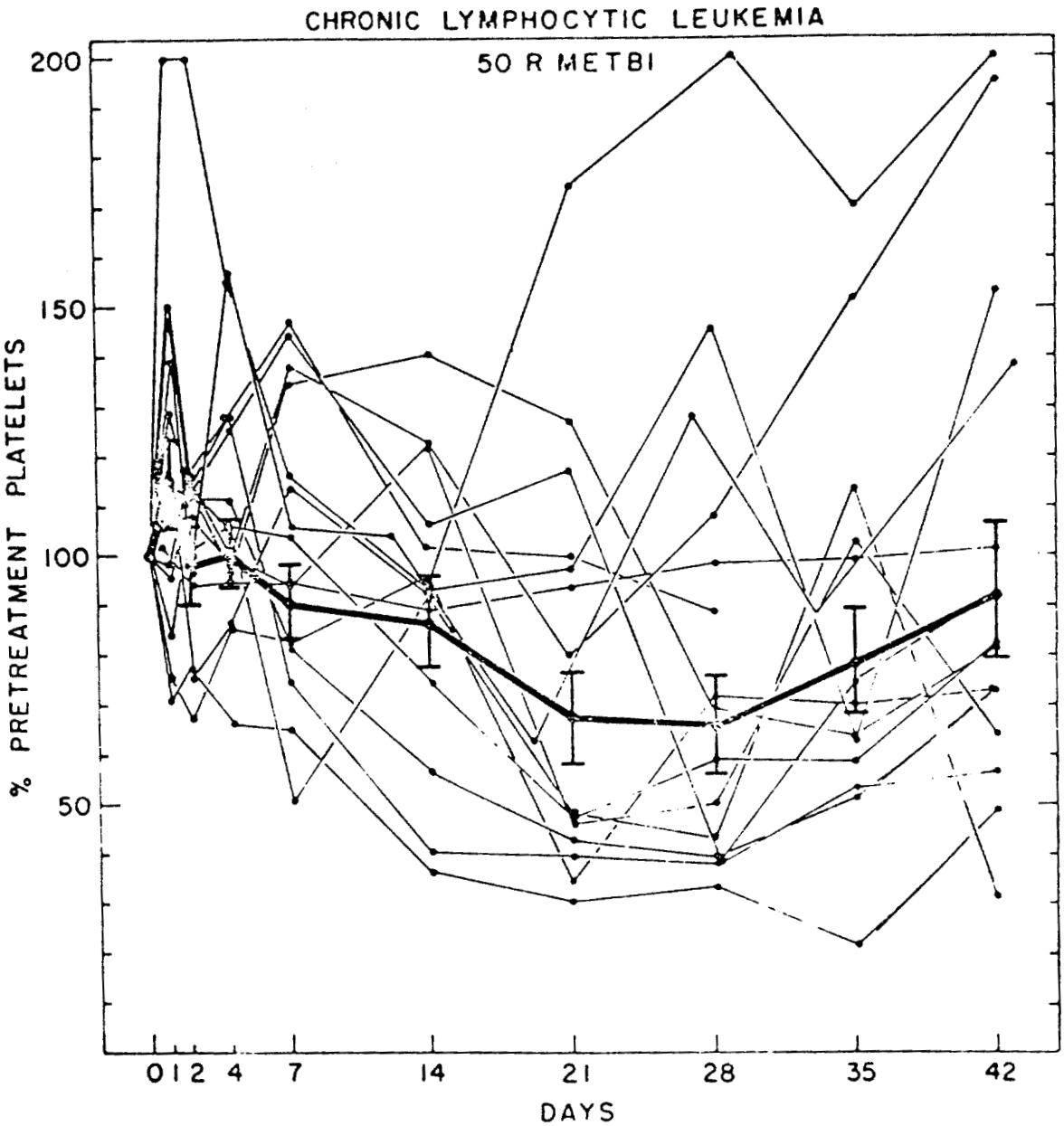

Fig. 4. Changes in the individual and geometric mean percent of pretreatment platelet levels in 15 patients with chronic lymphocytic leukemia after 50 R.

five were given a second 100-R treatment. There were 27 exposures in all.

During the first six weeks after treatment there was no clear difference in clinical responses between the 50-R and 100-R groups. In the 27 treatments, 23 of the 27 patients showed at least some degree of shrinkage of lymph nodes; 17 responded moderately or substantially, while in three the nodes remained unchanged and in one they enlarged after therapy. In the eight patients with palpable spleens, only two spleens definitely regressed, while five others

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remained large and one was questionably changed. Nine palpable livers regressed while eight remained unchanged or enlarged. There was no consistent pattern of change in body weight. The subjective general feeling of well-being remained poor or unchanged in 17 patients, while 10 expressed some degree of improvement.

Most of these patients had at least a few atypical lymphocytes in the blood, and we were unable to separate definitely those that should be considered as having a "leukemic" stage of lymphosarcoma, except for two who had larger numbers of abnormal cells. These two patients described in a later paragraph responded

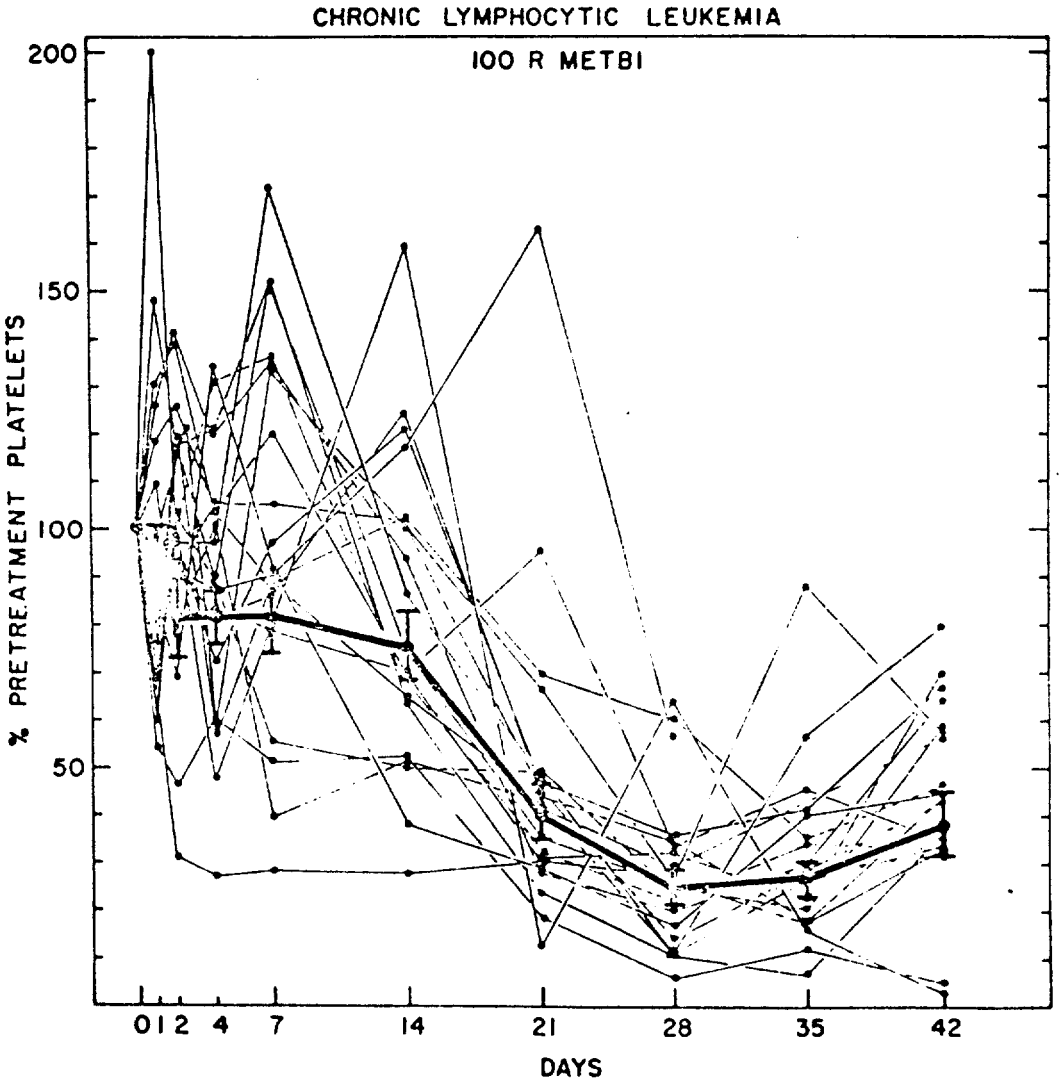

Fig. 5. Changes in the individual and geometric mean percent of pretreatment platelet levels in 20 patients with chronic lymphocytic leukemia after 100 R. Comparison of the geometric means and their standard errors in this figure and in Fig. 4 shows that the degree of response in the two dosage groups differs significantly from 21 days on. Five individual patients who received 50 R, however, reacted as the 100-R group, while three in the 100-R group responded similarly to the 50-R patients.

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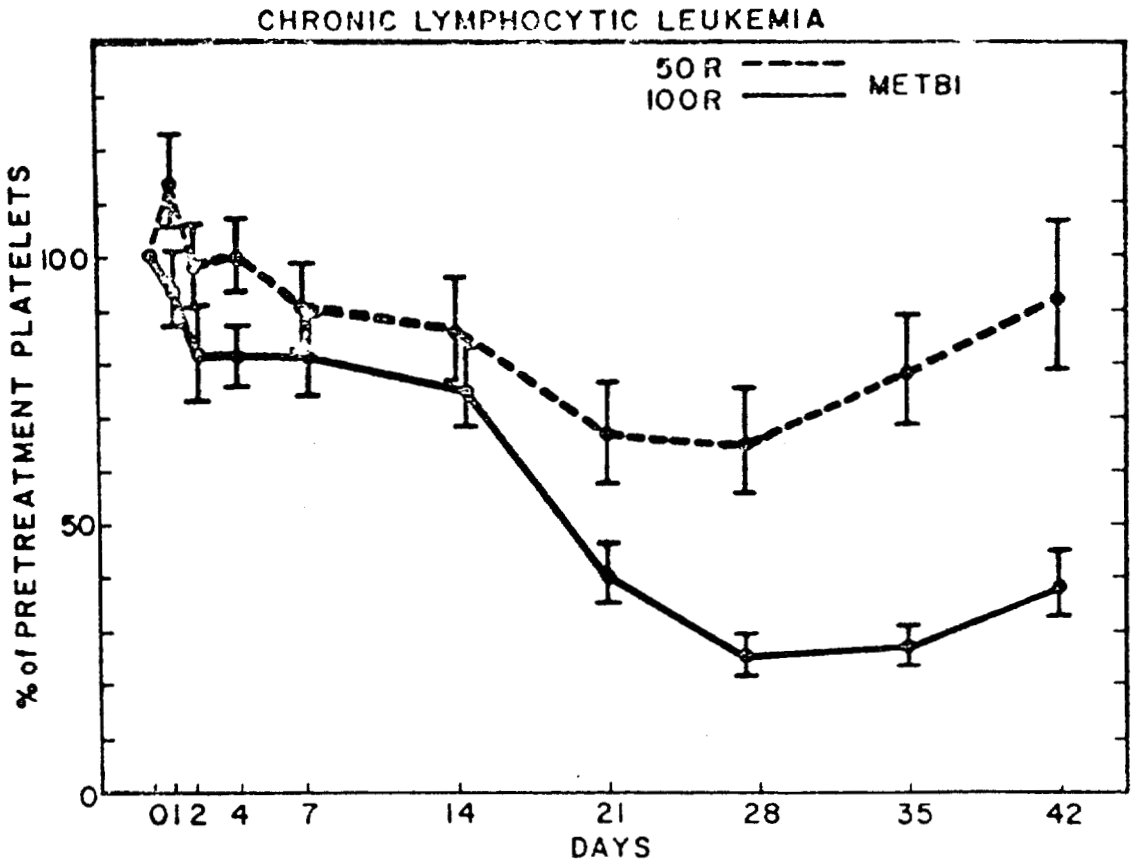

Fig. 6. Comparison of the geometric means for blood platelet levels in patients with chronic lymphocytic leukemia after 50 and 100 R. The curves become statistically different only after 21 days.

quite differently from the rest of the group. All the others had pretreatment leukocyte counts of less than 15,000/mm^3; the numbers of lymphoid cells were less than 11,000/mm^3. The subsequent decrease in lymphocytes was not great (the lowest value was about 50% of pretreatment level, reached at seven days). In the majority of the patients (11/17) lymphocyte levels began to recover from this decrease by 14 days; this was unlike the response in CLL. In Fig. 7 the geometric means for the leukocytes of the main groups of patients with malignant lymphoma who received 100 R are plotted, along with one standard error of the mean. The changes in total leukocytes after 100 R in patients with malignant lymphoma have been graphed in Fig. 7 for comparison with later graphs in this study and with those of other investigators who have not differentiated the hematologic response of the various white blood cell types. In Fig. 8 the sequential changes in lymphocyte counts in individual patients can be seen varying widely.

By contrast, in the two "leukemic" patients with high numbers of abnormal lymphoid cells in the blood before irradiation (16,000 and 26,000/mm^3) these cells decreased profoundly and rapidly after 100 R. Their course differed

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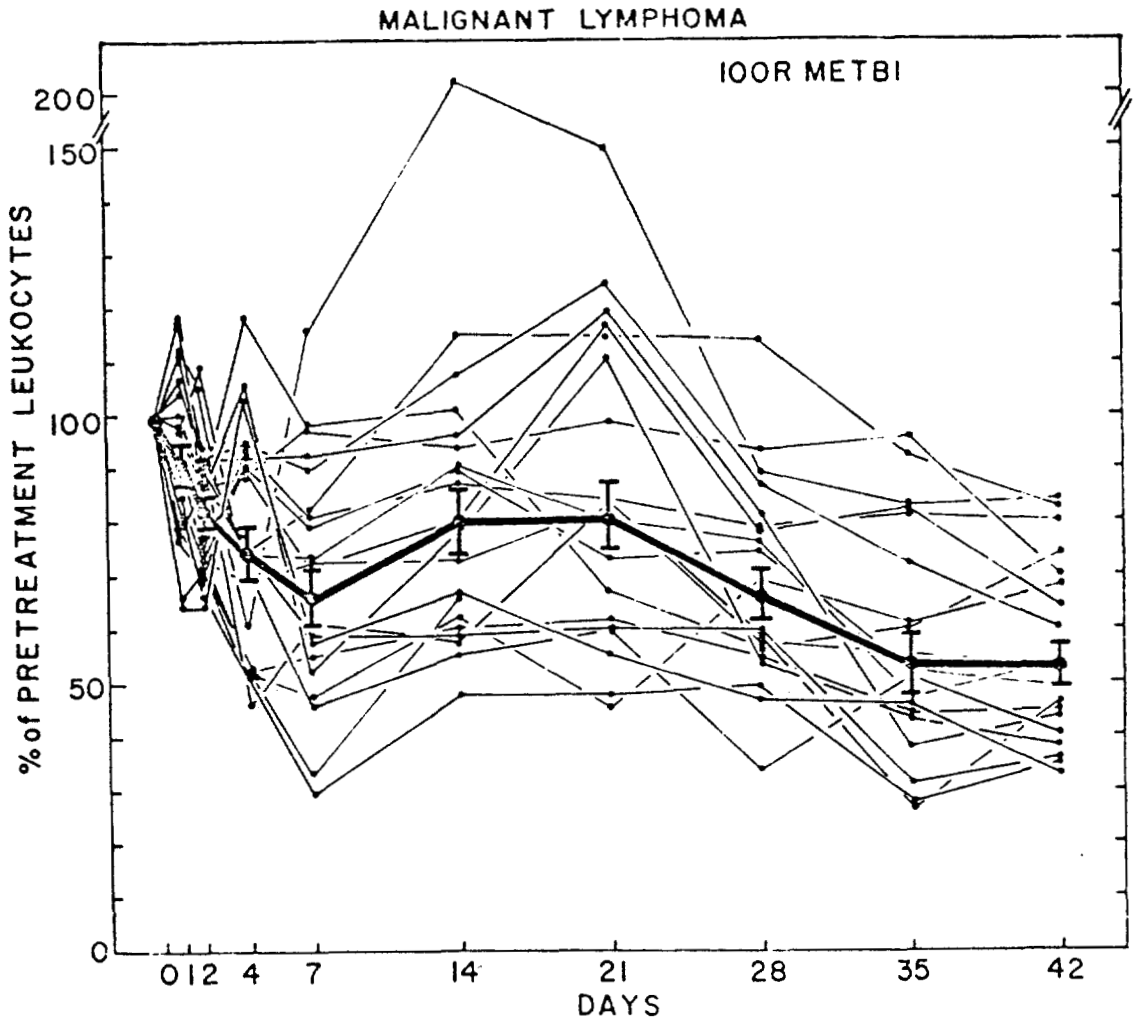

Fig. 7. Changes in blood leukocyte values in 20 patients with malignant lymphoma after 100 R. The actual WBC counts have been normalized to individual pretreatment levels and the geometric mean and its standard error computed on this basis.

considerably from that of the other members of the lymphoma group and resembled more closely the extreme responders of the chronic lymphocytic leukemia groups. (See Figs. 1-3).

The platelet values for the 50-R group dropped only slightly on the average and varied widely from patient to patient. In the 100-R group, the platelets responded more consistently; a steep drop appeared during the third and fourth weeks and reached a nadir of 27% of the pretreatment values. This curve resembles quite closely that of the patients with chronic lymphocytic leukemia given the same dose (Fig. 4). All showed a trend toward recovery during the fifth and sixth weeks (Figs. 4 and 10). Hemoglobin values did not change significantly during the six weeks after irradiation with either 50 R or 100 R.

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Hodgkin's Disease

Only three patients with Hodgkin's disease were treated. One patient who received 50 R early in her disease failed to respond and was quickly transferred to more conventional therapeutic regimens. The second patient, who received 100 R, showed similarly no benefit, and the third one failed to return after two weeks for further follow-up studies. The platelet and lymphocyte responses for the 50-R and 100-R exposure behaved as in patients with other types of lymphomas.

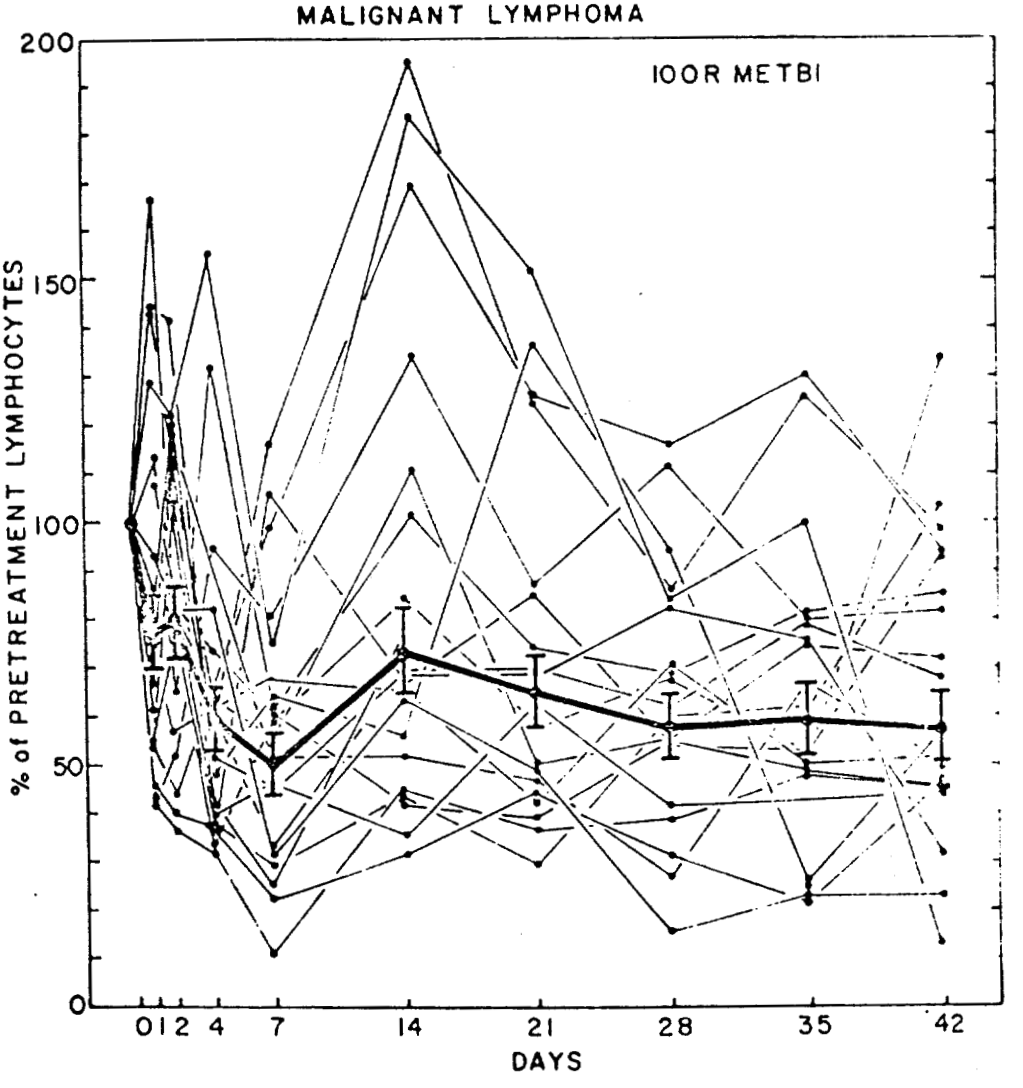

Fig. 8. The changes in Fig. 7 are shown here as changes in lymphocyte levels computed from individual absolute lymphocyte counts before and after exposure. These extremely variable responses of individual patients reduce to a geometric mean not statistically different from that of the "resistant" type of response in lymphocyte levels of patients with chronic lymphocytic leukemia treated with either 50 or 100 R (see Fig. 3). In several of these patients total-body irradiation obviously resulted in lymphocytosis in relation to pretreatment levels.

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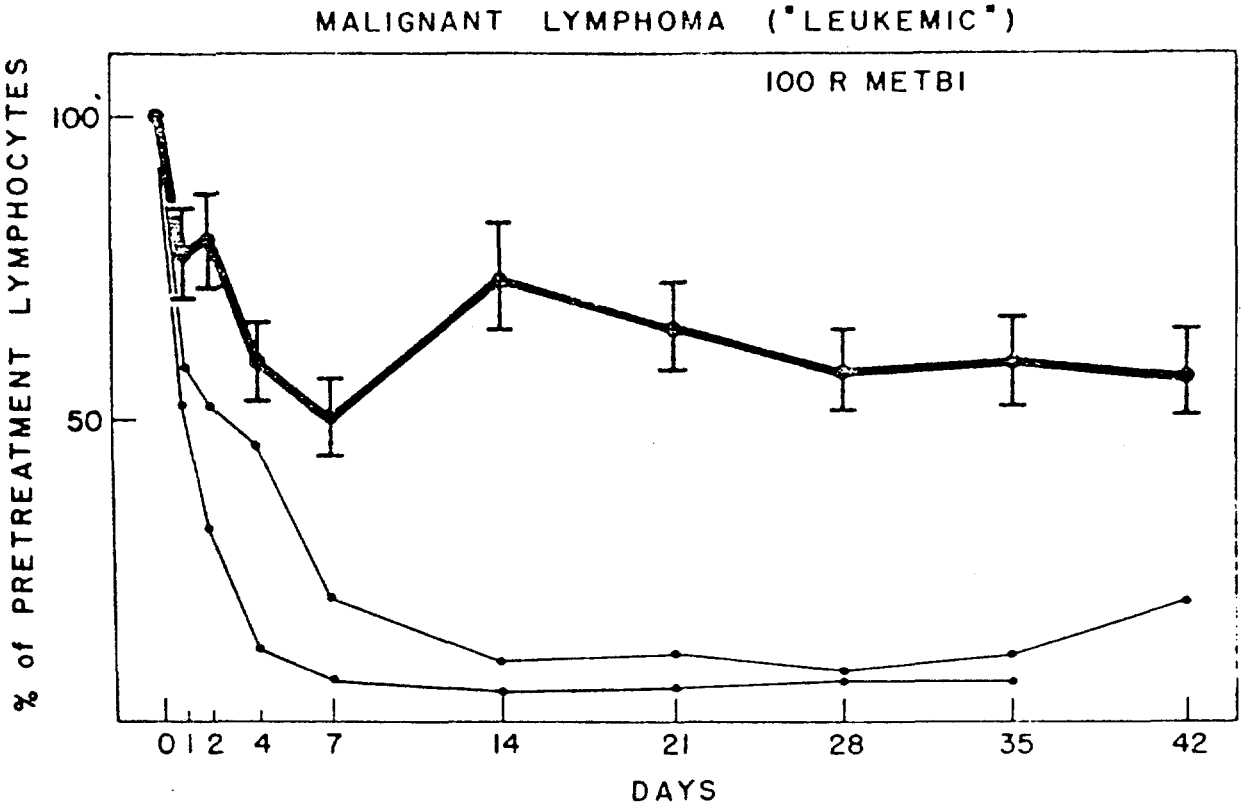

Fig. 9. The lymphocyte response curves of two patients with "leukemic" malignant lymphoma were so atypical in comparison with those of the 20 other patients with this disease (Fig. 7) that they are shown here separately along with the geometric mean of the other 20 patients. These two individual lymphocyte response curves fit within the 95% confidence limits of the "sensitive" type of lymphocyte response curves shown for chronic lymphocytic leukemia in Fig. 3.

Chronic Granulocytic Leukemia

This group included eight patients exposed to 50 R and four exposed to 100 R. Their spleens remained palpable and unchanged in size in eight, became slightly smaller in one, and distinctly smaller in one. In the other two, the spleen was not palpable before or after treatment. A definite decrease in liver size was recorded in only one patient. The general feeling of well-being was improved in eight patients but unchanged in three and poorer in one.

All patients had high initial leukocyte counts consisting predominantly of mature granulocytes. Nongranulocytic elements were so few that the curves shown in Figs. 11 and 12 can be considered as representing chiefly changes in granulocytic numbers. The numbers of leukocytes began a decrease promptly after these doses and the degree of fall indicated a greater radiation sensitivity than we see in normal granulocytes (see Fig. 7). Further, this depression usually persisted longer than would a similar degree of depression produced in normal persons by a higher dose as in radiation accidents. After 50 R the decline

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in values began promptly, the mean dropping to 55% on day seven, 48% by day 14, then staying in this range for the six-week period of observation (Fig. 11). The response of the four patients given 100 R (see Fig. 12) was similar to that of the 50-R group, but the degree of depression was greater: 35% on day 7, 21% on day 14. By day 21, three of the four patients had granulocyte levels below 20% of pretreatment levels; one patient showed a transient partial recovery pattern. This suppression persisted throughout the 42-day period at the end of which there was still a trend toward even lower levels.

The platelets in CGL before treatment were either in the normal range or elevated; in a few instances they were at levels over 1,000,000/mm^3. After 50-R exposures, the platelet counts rose to a mean level of 136% by day 14 before declining to a nadir of 82% on day 28. The means then returned toward the pre-

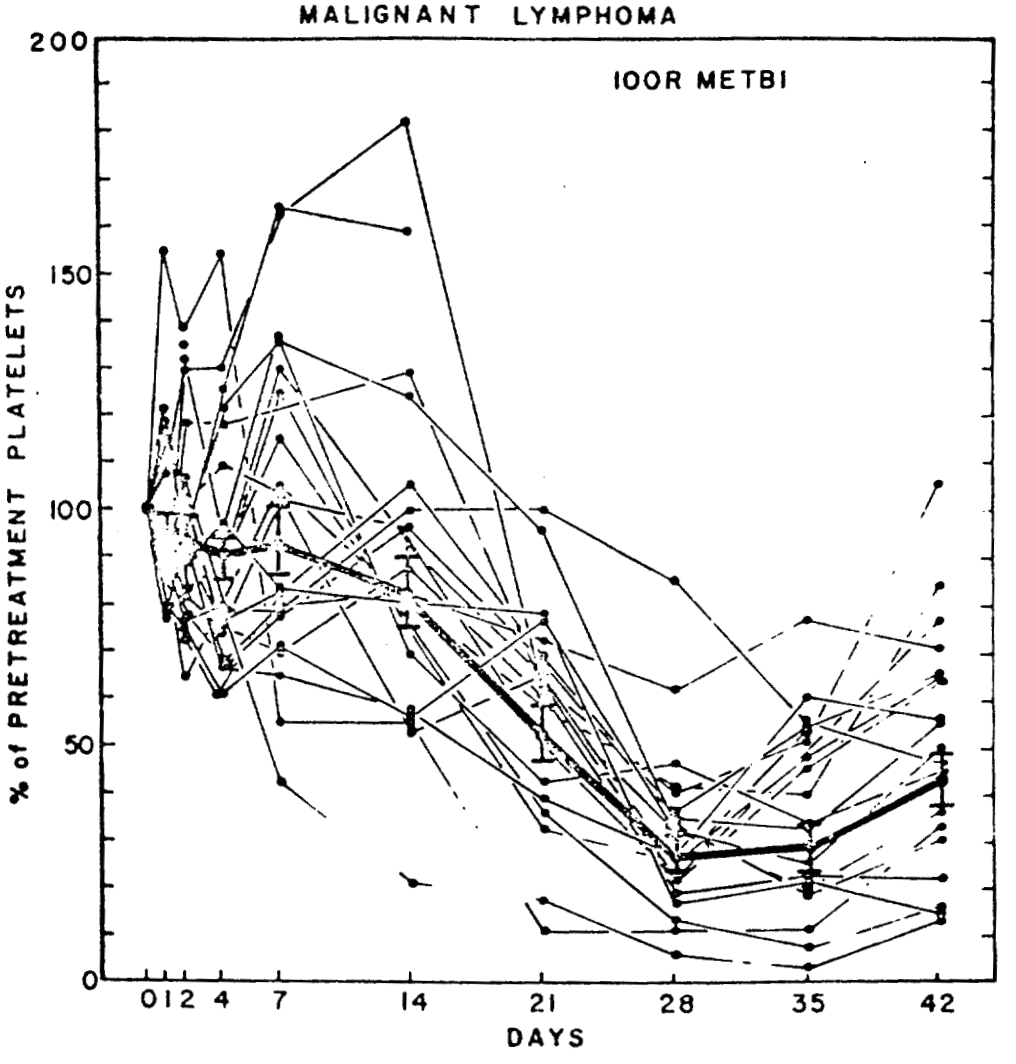

Fig. 10. Platelet response curves in patients with malignant lymphoma exposed to 100 R. The heavy solid line represents the geometric means and their standard errors. The curve closely resembles that in Fig. 6 of chronic lymphocytic leukemia after 100 R.

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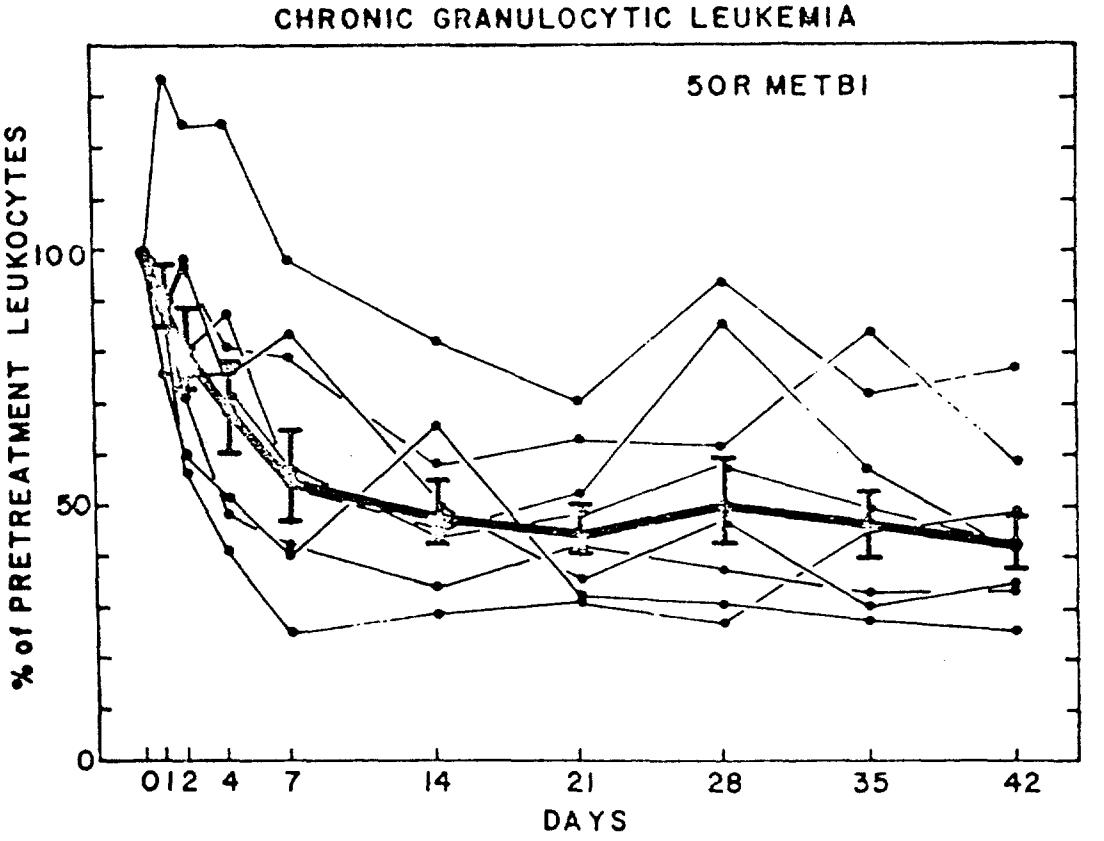

Fig. 11. Changes in blood leukocyte values, expressed in terms of individual pretreatment WBC counts, of eight patients with chronic granulocytic leukemia exposed to 50 R. The dark solid line represents the geometric means and their standard errors.

treatment range during the fifth and six weeks (Fig. 13), but the values ranged widely (53% to 191% of pretreatment values).

The platelets of the group exposed to 100 R also rose during the first two weeks but much less conspicuously (Fig. 14). The subsequent depression followed the usual temporal pattern and reached a nadir of 48% on day 42. This progressive decrease which persisted beyond 42 days is presently being observed also in our ongoing studies with fractionated and low-dose-rate exposures. A comparison of mean responses for platelets and leukocytes after 50 R and 100 R is made in Fig. 15.

The percent response (relative to pretreatment values) of the leukemic granulocyte appears from this graph (Fig. 15) to be about a factor of two greater than that of the platelets. The comparison here shows that in the occasional patients where injury to the platelet system is to be avoided because of borderline thrombocytopenia, a 50-R exposure would offer some therapeutic effect on granulocyte numbers while sparing platelet numbers.

Mean hemoglobin values were not significantly altered during this period of study. Figure 16 shows the hemoglobin values for the patients who received 100 R.

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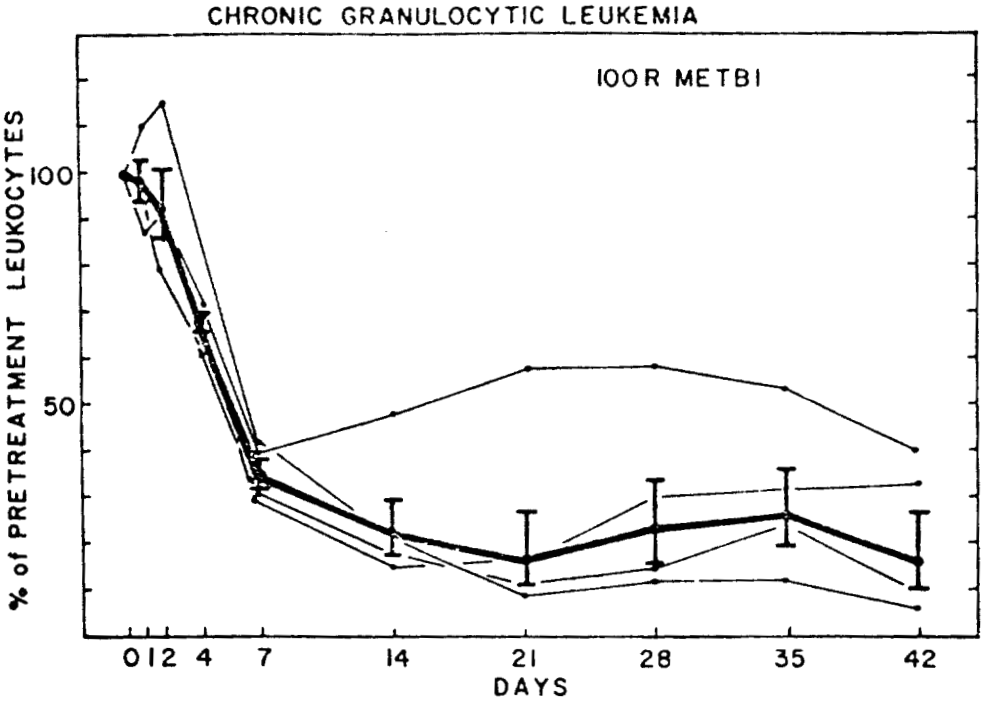

Fig. 12. Changes in blood leukocyte values, expressed in terms of individual pretreatment WBC counts, of four patients with chronic granulocytic leukemia exposed to 100 R. The dark solid line represents the geometric means and their standard errors.

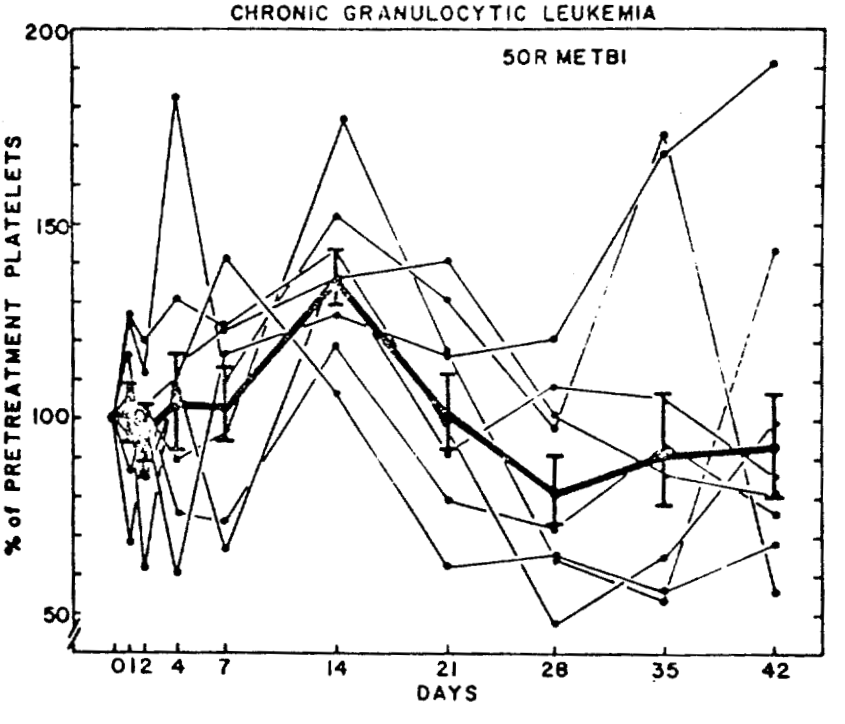

Fig. 13. Changes in platelet values expressed in terms of individual pretreatment platelet counts of eight patients with chronic granulocytic leukemia exposed to 50 R. The dark solid line represents the geometric means and their standard errors.

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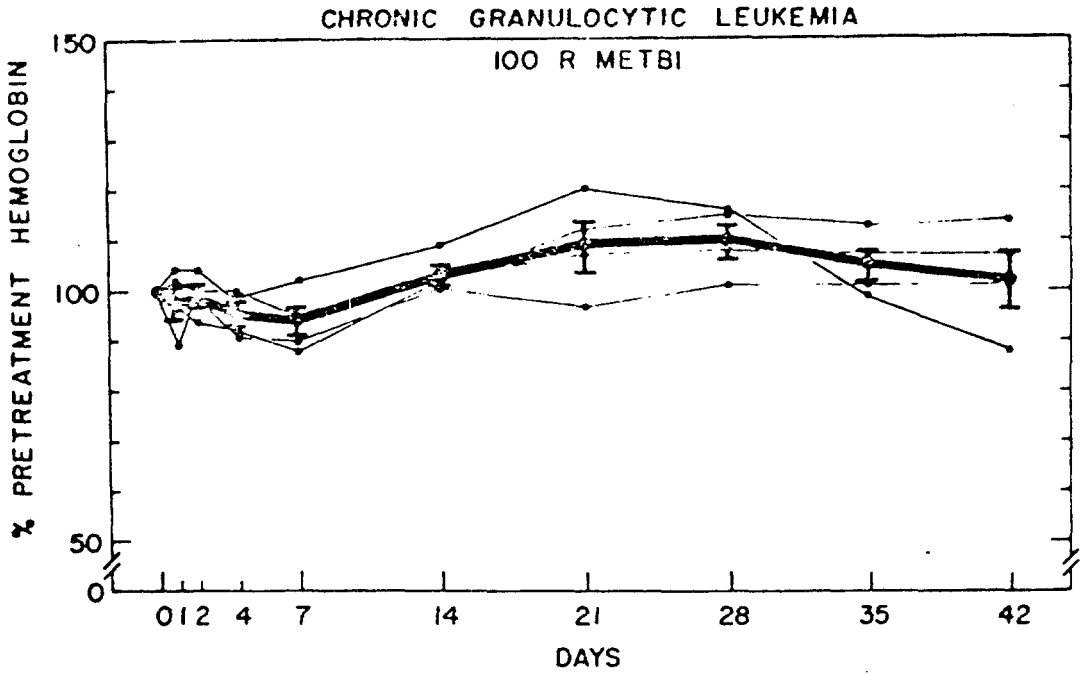

Fig. 16. Changes in blood hemoglobin values in four patients with chronic granulocytic leukemia exposed to 100 R showing a slight improvement relative to initial hemoglobin levels.

Polycythemia Rubra Vera and Primary Thrombocythemia

This group included eight patient-exposures to 100 R. Six patients had polycythemia rubra vera (PRV); one received two separate treatments (seven treatments); the seventh patient had primary thrombocythemia. In five patients there was an improvement in general feeling of well-being; in three there was no change. Of the large spleens, the size decreased in three, increased in one, and remained unchanged in two. The effects on liver size were slight and variable. In six patients a significant gain in weight was recorded.

All the PRV patients had initial leukocyte counts above 10,000/mm^3. These ranged up to 41,000/mm^3 pretreatment. As is shown in Fig. 17, leukocyte values began to drop after one week and reached their nadir at the six-week point, considerably later than has been observed in normals or in patients with most other diseases. As with platelet values (see below), the return of the leukocyte level toward normal was slow and was prolonged up to six months. The changes in absolute lymphocyte values in relation to pretreatment levels after 100 R (Fig. 18) were more like those after 100-R accident cases. Typically no return to normal was seen during the 42-day observation period.

Except for one patient with a normal platelet count, all had pronounced elevated platelet counts ranging from 575,000 to 1,600,000/mm^3 before treatment. The qualitative platelet responses to 100 R were similar to those of accidentally irradiated normal persons and of patients without leukemic diseases in that a nadir was reached at about 30 days (Fig. 19), but characteristically the fall in

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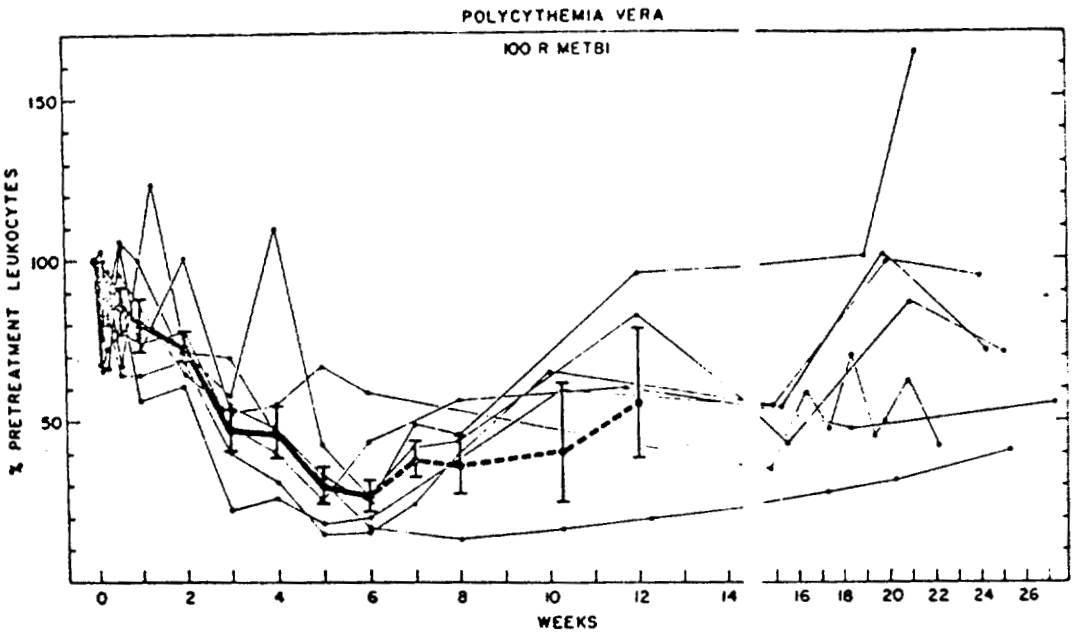

Fig. 17. Changes in blood leukocyte levels in eight patients with polycythemia rubra vera after 100 R. The solid heavy line is the geometric mean of these values through the usual 42-day postirradiation study period; the dotted line extends this mean through less regularly obtained data points over six months.

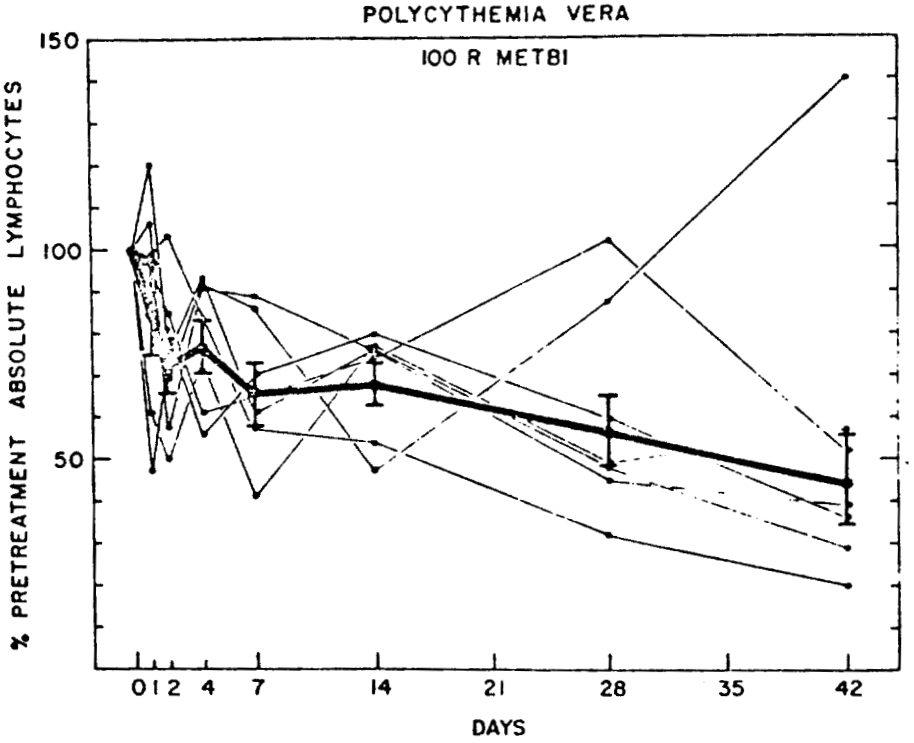

Fig. 18. Changes in blood lymphocyte values in seven patients with polycythemia rubra vera exposed to 100-R total-body irradiation. To improve statistics, 400 leukocytes were counted at each data point. One patient whose baseline values were believed to be unreliable is excluded from this figure.

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count either did not begin for two weeks or was slight until that time. The return toward normal, however, was much delayed and did not reach pretreatment levels for many months. This temporal pattern differs distinctly from the response of accident victims where a return to normal (or even a rebound elevation) occurs within six weeks. It appears that some homeostatic mechanism tends to prevent platelet values from returning to abnormal pretreatment values. Figure 19 shows the platelet response during the usual six-week study period and for the following six months.

Hemoglobin values for this group were not significantly elevated at the time of treatment; excessively high platelet and leukocyte values dominated their blood picture. Evaluation of changes in red cell numbers and morphology was complicated by pretreatment phlebotomies, stage of disease, and previous marrow-depressing treatments with ^{32}P or drugs (only two of the six were new, untreated cases). Hemoglobin and hematocrit values changed little after treatment (Figs. 20, 21) with 100 R. We believe, however, that this dose suppressed the rise that usually would have occurred with therapy. The mean corpuscular hemoglobin concentration before treatment was invariably low, due to phlebotomies and intestinal bleeding. It did not change in the postirradiation period (Fig. 22).

There was a 12% decrease in numbers of RBC and 12% increase in mean corpuscular volume that offset one another so that little or no change was seen in hematocrit values. Blood volume studies, however, were not done. Generally the mean corpuscular hemoglobin concentration did not change significantly

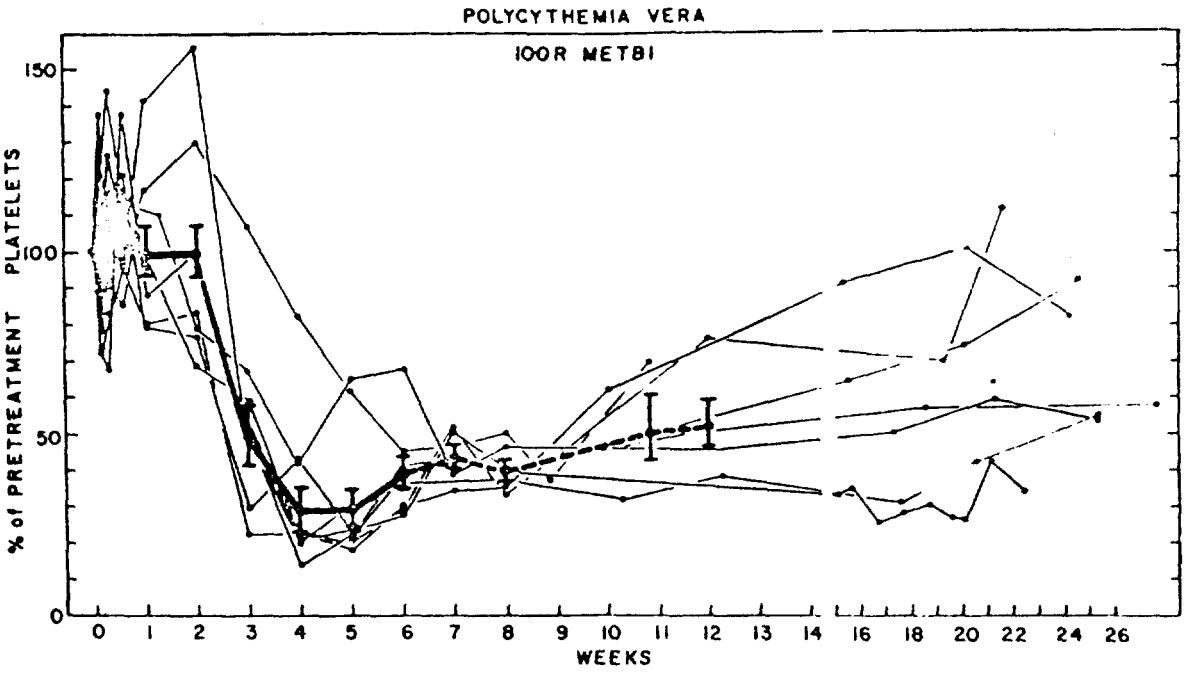

Fig. 19. Changes in blood platelet levels in eight patients with polycythemia rubra vera exposed to 100 R. Geometric mean is shown on a solid heavy line for 42 days of the protocol and as a broken line after that time when data points were less rigidly obtained.

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but in some individuals it rose 10 to 20% (Figs. 22 and 23).* Detailed red cell values in one patient are shown for a 26-week period (Fig. 23). The principal clinical problem in this patient was her excessively high platelet count which ranged above 1,000,000/mm^3 and was believed to be a factor in intestinal hemorrhage and its associated iron loss.

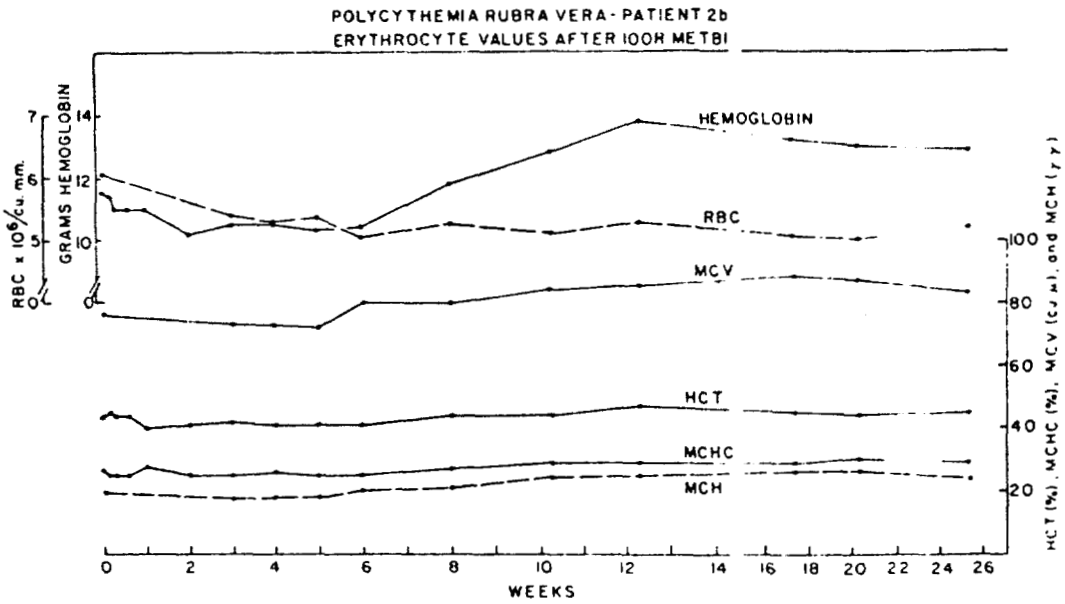

Fig. 23. Changes in actual values of blood erythrocyte parameters in one patient with polycythemia rubra vera treated with an exposure of 100 R.

Changes in Uric Acid

In all disease categories and both dose groups, we examined serum uric acid levels. After exposure, the levels changed, as might be expected from previous observations, but in this series of patients the changes were, in general, small, inconsistent, and of little clinical value. In some patients an early increase and subsequent decrease were sufficiently large to be accepted as indicative of the tissue destruction caused by the radiation exposure.

In 100-R treated lymphosarcoma and CLL, there were increased average levels on postirradiation days through four or seven (Table 7). Among the patients given 50-R exposure the CGL group showed elevated uric acids on only the second day

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* In a study of RBC size distribution after low-dose-rate total-body irradiation (to be reported elsewhere; see ORAU Medical Division Research Reports 1968, 1969), we have found by electronic measurements of red cell size that irradiation produces changes in cell volume that are not demonstrated by measurements of hemoglobin, hematocrit, and cell numbers/cm^3. We are finding that the erythron returns to normal within 120 days in this study only if iron stores have not been depleted by phlebotomy or hemorrhage.

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Table 7

STATISTICAL SIGNIFICANCE OF OBSERVED MEAN SERUM URIC ACID LEVELS AFTER TBI

Disease Category	TBI (R)	Days 1	2	4	7	14	21	28
Lymphosarcoma	50	0 (5)*	0 (5)	0 (4)	0 (5)	0 (5)	0 (4)	0 (4
	100	0 (15)	+ + (16)	+ + (17)	0 (17)	0 (17)	0 (15)	0 (11)
Polycythemia	100	0 (7)	0 (5)	0 (7)	0 (7)	0 (7)	0 (7)	- (6)
Chronic Granulocytic Leukemia	50	0 (7)	+ (7)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)
	100	0 (3)	0 (2)	0 (3)	0 (4)	0 (4)	0 (2)	- (3)
Chronic Lymphocytic Leukemia	50	0 (15)	0 (14)	0 (14)	+ (15)	0 (15)	0 (14)	0 (13)
	100	0 (14)	+ + (13)	+ + (15)	+ (14)	0 (15)	0 (15)	0 (13)
All Disease	50 or 100	0 (66)	+ + (61)	+ + (68)	0 (69)	0 (69)	0 (64)	- (57)
	pre-treatment							
Uric Acid $\bar{X}$	5.82	6.18	6.48	6.38	6.04	5.67	5.68	5.38
mg/100 ml ± S.D.	1.75	1.73	1.82	2.02	1.99	1.75	1.60	1.71

*Figures in parentheses indicate the number of patients in each group.

0 = No statistically significant change from pretreatment levels.
+ = Increase $P \leq 0.05 - 0.01$; + + $P \leq 0.001$
- = Decrease $P \leq 0.05 - 0.01$

and the CLL group on only the seventh day. In other disease categories and exposure groups no statistically significant early changes were found in the mean values from day to day, although some individual patients, even in these groups, showed alterations that possibly reflected increased cellular destruction. On day 28 following 100 R a decrease was seen in some disease categories and in the averaged data for all, but was not found in individual groups after 50 R.

These observations are compatible with the view that change in uric acid level is a dose-related response that is modified by at least three factors: the amount of radiosensitive tissue present at exposure, the degree of radiosensitivity, and the rate of uric acid production in relation to renal excretory capacity. Appraisal of radiation-induced perturbations in this metabolic system might be better elucidated from study of total urinary uric acid and other protein-related excretory products rather than serum levels.

DISCUSSION

This large amount of hematologic data suffers from the usual variabilities of most clinical investigations — wide range in laboratory values, many of them unexplained, and the lack of a true control population. The information derived, however, is clinically useful and meaningful for radiation biology. The differences

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in response in different clinical disorders are of special interest and give some insight into the relative dependence of these disease processes on cellular survival and replication. In this discussion "sensitivity" is used to mean simply a response in cell numbers after irradiation; it is not meant to imply any specific mechanism for altered numbers.

Most of the rapid major alterations in blood values during the six-week post-treatment period were the result of irradiation. To be valid, this statement requires us to assume that all peripheral blood cell values would have remained stationary if no treatment had been given. This steady state was not always present. In fact, therapy was often indicated because certain cellular systems were changing, but the rate of change was usually slow in comparison with that induced by irradiation. Patients with chronic leukemia, polycythemia, or lymphoma were in reasonably good condition and the changes in hematologic status that would have occurred in the absence of treatment during the observation period could be predicted with some certainty. For example, most of the patients with chronic leukemia were becoming worse only gradually; white cell levels and symptoms were increasing slowly. Some with lymphocytic leukemia had falling red cell values that required transfusions. Patients with polycythemia were in need of treatment to alleviate symptoms and to lower hazardous elevations in platelet values; two had phlebotomies shortly before irradiation. A rise in red cell values might have been expected had no therapy been given.

Problems of interpreting the quantitative nature of radiation-induced hematologic response have recently been reexamined by Bergner with theoretical and stochastic mathematical models (18). He points out that all curves of blood cell counts are a composite of the effect of radiation damage and its repair, and variations introduced by data that is poor in reliability and numbers. From his theoretical viewpoint he demonstrates that an increase in dose augments the speed of "the response process" as well as the maximum response itself. He feels, however, that large numbers of patients and observations do little for quantitation of the hematologic response and that biologic variation in patients and its many causes force the development of a qualitative rather than a quantitative theory. In attempting this task he shows that the onset of repair processes and their continuance cause the "spread" of the hematologic response data to increase with time. Since larger doses more effectively suppress repair processes and thus tend to reduce one contributing cause to variability, especially later in the course of response, one would expect that larger doses would give more uniform responses. This effect is seen in most of our data but not in all of it. Bergner's analysis of the patients with chronic lymphocytic leukemia, where maximum response of lymphocytes to 50 and 100 R was the same, revealed unexpectedly that greater variability in response (evidence for greater reparative efforts) occurred with the 100-R dose rather than with the 50 R. Since this greater reparative effort after 100 R resulted in a response curve similar to that of 50 R, these observations suggest together that the expected additional cell-damaging response to 100 R was offset by the reparative processes stimulated by the 100 R, thus providing another basis for considering the 100-R dose in this disease unnecessary as well as undesirable. Further analyses, based on Bergner's "Theory of Quantitative Radiation-Response Time-Data," or on other such analytical models, are needed in radiobiology.

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When examined from a cytokinetic viewpoint the mechanisms of the changes in blood cell values produced by the irradiation are, of course, complex. This problem has been well discussed by Mathé (19) and Bond et al (20). Presumably radiation-induced death of circulating cells cannot account for much of the total effect of the exposure. Alterations in patterns of tissue sequestration and release of abnormal numbers of cells may have a significant effect upon peripheral blood cell values. The basis for most of the reduction in the cells of the blood, however, is undoubtedly interference with cell proliferation brought about most likely by a radiation-induced decrease in stem cells. Therefore, it may be necessary to relate the patterns of radiation effects to a balance between cell production, release, "normal" life span or turnover rate for each cell type as it occurs in the various disease states, and cellular radiosensitivity. Table 8 lists the geometric means of the minimum blood values reached during the six-week study period in the various diseases studied after the 50-R and 100-R doses.

The patterns of hematologic response to irradiation are influenced by the dose and also by the altered cytokinetic state in each disease. We have attempted, as yet, only preliminary interpretation of our results in the light of these factors.

Lymphocytes

Patients with polycythemia rubra vera provided data on the response of presumably normal lymphocytes to 100 R. An early drop occurred by day two to 76% of pretreatment levels and a gradual decline continued to 53% at the end of the 42-day study period, so that we do not know the precise time when the lowest lymphocyte values were reached but this curve was most like that of normal men accidentally irradiated.

Table 8

Minimum Geometric Mean Values During 6 Weeks after TBI
Expressed as Percent of Pretreatment Level

	50 R	100 R
Total WBC		
CLL	34.8 (26.5 good response) (68.3 poor response)	29.7 (19.7 good response) (59.5 poor response)
Malignant Lymphoma	61.8	53.1
CGL	44.4	17.3
PRV	-	26.7
Lymphocytes		
CLL	31.9 (23.7 good response) (66.9 poor response)	26.7 (19.3 good response) (60.6 poor response)
Malignant Lymphoma	59.3	50.0
CGL	49.4	48.5
PRV	-	44.4
Platelets		
CLL	65.0	25.2
Malignant Lymphoma	70.9	27.3
CGL	81.5	48.5
PRV	-	28.6

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Perhaps the most striking observation related to radiation sensitivity of lymphocytes is their response in chronic lymphocytic leukemia to 50 R and 100 R. The two curves are not significantly different. The two series were not entirely comparable and the stage of illness may limit the interpretation of this fact. Our data suggest, however, that if the clinical objectives can be equated with reduction of only the lymphocyte count, the lower dose may be preferable since 50 R appears to reduce lymphocyte numbers adequately with less depression of platelets. Lymphocytes in chronic lymphocytic leukemia are certainly most sensitive to 50 R, and using the lymphocyte response data of the patients with PRV (Fig. 18) as a substitute for our lack of normal control data we can say that those with leukemia are almost three times as sensitive. A comparison with the lymphocyte counts of the Marshallese normals on Rongerik Island (Group III) who were estimated to have been exposed to 78 R (21) also shows that lymphocytes of normal people are less sensitive than those patients with lymphocytic leukemia.

Schrek (22) has reported that some patients with chronic lymphocytic leukemia have radioresistant lymphocytes. In our study (Figs. 1, 2, 3) several of the patients given 50 R or 100 R showed a significantly decreased response, in contrast with the common pattern of a drop to 50% or less of initial values in four or seven days. We have been unable to discern any clear-cut clinical or hematologic correlations with this nonresponsiveness. In some of these patients the resistance of the lymphocytes is actually greater (compare Fig. 3 with Fig. 18) than that of those in PRV (considered to be "normal").

On the other hand, two cases of "leukemic" lymphosarcoma showed inordinately sensitive lymphocytes with an early precipitous drop to 10% of the pretreatment values (Fig. 9). The remainder of the patients with malignant lymphoma had depressions of the mean lymphocyte values that were less than the response in polycythemia and must be considered more resistant than normal. We wondered whether the numbers of circulating lymphosarcoma cells in the peripheral blood of these patients before treatment might be related to radiosensitivity, but when the values were graphed after sorting the patients into two groups (those with lymphocyte counts above 4,000/mm^3, and those with counts less than this level) no differences in response could be detected. We found no clear relation between height of the initial lymphocyte count in CLL and the subsequent percentage fall with therapy. There is a slight suggestion that when the initial counts are low a somewhat exaggerated response may be anticipated. In general, however, from a clinical viewpoint, one cannot prescribe the amount of treatment needed on the basis of the height of the initial count.

Granulocytes

Granulocytes in chronic granulocytic leukemia begin to drop promptly and appear to be more sensitive to radiation than in other patients and in normal man. Mean values after 50 R can be superimposed on the responses of lymphocytes in lymphocytic leukemia even though we are comparing different cell types. However, the degree of change in granulocytic leukemia is related to the initial

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white cell level, a relation that does not exist for lymphocytic leukemia*. As noted earlier, leukocyte values were elevated in patients with polycythemia rubra vera before treatment, in some instances to a moderately pronounced degree. The drop after 100 R was less precipitous in PRV than in patients with chronic granulocytic leukemia, with a mild decrease during the first two weeks continuing to a nadir on day 42 in contrast to the response expected in normal persons. This depression from pretreatment values persisted for a number of months, although the pattern of climb toward pretreatment values varied considerably.

Platelets

Platelets usually reach their lowest level between the 21st and 35th days. In every group, responses to 100 R were significantly greater than to 50 R, and there was little overlap; 50 R produced little change in the patients with lymphoma, lymphocytic leukemia, and with chronic granulocytic leukemia. Individual variations were rather pronounced. Patients with polycythemia rubra vera who usually have moderate or high platelet values were not rebounding toward normal by the end of the six-week study period but had leveled off, remaining for many weeks or months at values considerably below the pretreatment ones (Fig. 16). This desirable effect from the point of view of therapy perhaps indicates that a new cellular steady state has been achieved either through the establishment of normal homeostatic mechanisms or depletion of stem cells to limiting levels of cell production.

SUMMARY

Eighty-nine treatments of total-body irradiation were given in single exposures of 50 R and 100 R at 1.5 R/min to patients with lymphoma, chronic leukemia, or polycythemia rubra vera. The clinical and hematologic responses during a 42-day study period were analyzed according to disease and dose; not unexpectedly the therapeutic responses varied. In lymphoproliferative disorders measurable clinical benefit did not depend solely on the radiation dose; the majority showed some shrinkage of enlarged lymph nodes, liver, or spleen, but the larger dose was not proportionally more effective in all cellular systems. Many required additional therapy within three months but this was not surprising in view of our use of only a single exposure. In granulocytic leukemia, improvement occurred in more than half of the patients. For polycythemia, the most clinically beneficial response appeared to be a decline of the dangerously elevated platelet counts to more normal levels that were maintained for many weeks or months.

The hematologic responses to 100 R usually but not invariably exceeded those to 50 R. A notable exception was the lymphocyte response of CLL in which the mean values of the responses of two groups were statistically the same. In general the abnormal proliferating blood elements did not return to pretreatment

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* This analysis is to be the subject of a separate report by J. Yuhas (ORNL), C. C. Lushbaugh, and T. Stokes (ORAU).

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values in the same time sequence that is seen in recovery of normal cell lines in the acute radiation syndrome, suggesting that homeostatic mechanisms have been reestablished to hold the values within normal ranges. For example, elevated platelets in polycythemia rubra vera were depressed by the treatment but did not return toward normal by day 42, in contrast to events in lymphocytic leukemia where initial platelet levels are usually normal or low and recovery of platelet values is usually well under way by day 42.

The detailed graphs of blood cell values, together with their geometric means for each disease and exposure group form a useful reference for radiobiologic comparison with patterns in normal persons accidentally exposed, and relate the radiosensitivity of the various blood cell lines in the diseases studied.

The graphs also show the most probable or predictable response of the average patient with these diseases for 42 days after 50-R and 100-R exposure, providing a temporal course for comparing the relative effectiveness of similar total exposures of radiation given in small daily fractions at high or low dose rates. Such a comparative study of dose-rate effects upon therapeutic effectiveness is in progress.

Acknowledgements

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TABLE A APPENDIX

RESPONSE TO 100 R METBI - POLYCYTHEMIA

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x (approx. amt.)	Interval from last R_x to TBI	Spleen Change in Size	Systemic Symptoms + = Improvement	Pruritis + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to next R_x	Follow-up Interval (3)
1	F	62	3 mo.	Phlebot. 6 x	1 mo.	N	NC	NC	Phlebotomy	2 yr. 4 mo.	4 yr. 6 mo.
2 a	F	73	1 mo.	None	-	- 2	NC	N	^{32}P 5 mc METBI 100 R Busulfan	3 mo. 23 mo. 3 yr.	4 yr.
2 b	F	75	3 yr.	METBI 100 R ^{32}P x 1	20 mo.	- 1	+ 1	N	Busulfan	13 mo.	2 yr.
3	F	64	7½ yr.	^{32}P x 1 Myleran Phleb. 25 x	2½ mo.	NC	+ 1	+ 1	Phlebotomy	7 mo.	4 yr.
4	M	55	15 yr	Phleb. 50 x ^{32}P 7 x	6 mo. 6 mo.	NC	N	N	Phlebotomy	4½ mo.	4 yr.
5	M	68	6 yr. 7 mo	Phleb. 15 x ^{32}P 7 x	17 mo.	NC	+ 2	+ 2	None	-	D 1 yr. 7 mo.
6 (1)	M	59	1 mo.	None	-	-	+ 2	+ 2	LETBI 100 R LETBI 250 R	23 mo.	2 yr.
7 (2)	M	60	4 mo.	^{32}P 2 x	3 mo.	N	N	N	LETBI 150 R 2 x	15 mo.	2 yr.

(1) Splenectomy 4 yrs. earlier after abdominal trauma
(2) Primary thrombocythemia
(3) All patients alive at latest follow-up except patient 5; none with leukemia

Change in Size:
NC = No change - abnormal before and after treatment
N = Normal or absent before and after
+ 1 or + 2 = Larger
- 1 or - 2 = Smaller

Systemic Symptoms:
NC = No change - abnormal before and after treatment
N = Normal or absent before and after
+ = Improvement
- = Worse

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TABLE B APPENDIX

RESPONSE TO 50 R CHRONIC GRANULOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size		Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
						Spleen	Liver				
1	M	67	3 days	None	-	NC	NC	+ 2	Ext. rad. to spleen Busulfan Splenectomy Hydrocortisone Prednisone Hydrocortisone	$2\frac{1}{2}$ mo. $5\frac{1}{2}$ mo. 14 mo. 14 mo. $14\frac{1}{2}$ mo. 15 mo.	D 15 mo.
2	M	48	3 days	None	-	- 2	- 1	+ 2	Ext. rad. to spleen Busulfan 6-MP	$2\frac{1}{2}$ mo. 6 mo. 2 yr. 1 mo.	D 2 yr. 3 mo.
3 a	F	52	5 days	None	-	- 1	- 1	+ 1	Busulfan METBI 50 R	1 yr. 4 yr. 4 mo.	D 6 yr. 7 mo.
3 b	F	57	4 yr. 4 mo.	METBI (50 R) Myleran	$8\frac{1}{2}$ mo.	NC	NC	NC	Ext. rad. to spleen Ext. rad. to liver 6-MP Prednisone Cyclophosphamide Methotrexate Hydrocortisone	9 mo. 18 mo. 23 mo. 23 mo. 2 yr., 3 mo. 2 yr., $3\frac{1}{2}$ mo. 2 yr., $3\frac{1}{2}$ mo.	D 2 yr. $3\frac{1}{2}$ mo.
4 a	F	60	34 days	None	-	N	N	+ 1	Busulfan METBI 50 R	3 mo. 3 yr.	D 5 yr. 7 mo.
4 b	F	63	3 yr. $1\frac{1}{2}$ mo.	METBI (50 R) Myleran	$1\frac{1}{2}$ mo.	NC	NC	NC	Ext. rad. to spleen Ext. rad. to liver METBI 100 R (See Table C, Case 2) Busulfan Prednisone 6-MP Hydrocortisone	2 mo. 9 mo. 11 mo. 13 mo. 2 yr. 5 mo. 2 yr. 5 mo. 2 yr. 7 mo.	D 2 yr. 7 mo.

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TABLE B APPENDIX - Continued

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size		Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
						Spleen	Liver				
5	M	59	1 yr. 9½ mo.	None	-	NC	NC	N	Ext. rad. to spleen Busulfan 6-MP Prednisone Hydrocortisone	2 yr. 10 mo. 3 yr. 8 mo. 3 yr. 10 mo. 3 yr. 10 mo. 3 yr. 10½ mo.	D 3 yr. 10½ mo.
6	F	53	1 mo.	None	-	NC	NC	+ 2	Ext. rad. to spleen (x 2) Ext. rad. to liver Ext. rad. to spleen (x 2) Hydrocortisone Prednisone 6-MP Prednisone	1½ mo. & 21 mo. 3 yr. 3 yr. 5 mo. & 4 yr. 3 mo. 4 yr. 9 mo. 4 yr. 9 mo. 4 yr. 10 mo. 4 yr. 10 mo.	D 4 yr. 10 mo.

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TABLE C APPENDIX

RESPONSE TO 100 R CHRONIC GRANULOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size Spleen	Change in Size Liver	Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
1	F	64	4 yr	METBI 50 R (See Table B, Case 4) Myleran METBI 50 R (See Table B, Case 4) Ext. rad. to spleen Ext. rad. to liver	$2\frac{1}{2}$ mo.	NC	NC	+ 1	Busulfan Prednisone 6-MP Hydrocortisone	2 mo. 18 mo. 18 mo. 19 mo.	D $19\frac{1}{2}$ mo.
2	M	53	16 mo.	Cytoxan Ext. rad. to liver Ext. rad. to spleen Ext. rad. to spine Ext. rad. to spleen x 2	$2\frac{1}{2}$ mo.	NC	NC	+ 1	Ext. rad. to rt. ilium Alkeran Ext. rad. to spleen 6-MP	$4\frac{1}{2}$ mo. 5 mo. 16 mo. $17\frac{1}{2}$ mo.	D $17\frac{1}{2}$ mo.
3	M	44	4 yr., 10 mo.	Ext. rad. to spleen x 8 Ext. rad. to liver Ext. rad. to spleen	6 mo.	NC	NC	- 2 (1)	Ext. rad. to spine	24 days	D 50 days
4	F	46	20 mo.	Ext. rad. to liver Ext. rad. to spleen LETBI 100 R	3 mo.	N	N	+ 2	METBI 100 R (divided dose)	5 mo.	A $13\frac{1}{2}$ mo.

(1) Paraplegia - terminal blastic state

Organ Size:
NC = No change - abnormal before and after treatment
N = Normal or absent before and after
- 1 or - 2 = Smaller
+ 1 or + 2 = Larger

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TABLE D APPENDIX

RESPONSE TO 50 R CHRONIC LYMPHOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
1 a	M	67	3 yr., 8 mo.	^{32}P x 4	$6\frac{1}{2}$ mo.	- 2	N	- 2	+ 2	Chlorambucil Prednisone Ext. rad. to spleen ^{32}P x 2 METBI 50 R	$6\frac{1}{2}$ mo. $6\frac{1}{2}$ mo. 10 mo. 2 yr., 4 mo.& 3 yr., 2 mo. 4 yr., 7 mo.	A 9 yr., 3 mo.
1 b	M	72	8 yr., 3 mo.	^{32}P x 4 METBI 50 R Chlorambucil Prednisone Ext. rad. to spleen ^{32}P x 2	17 mo.	- 1	NC	NC	+ 1	Prednisone	5 mo.	A 4 yr., 9 mo.
2 a	M	51	23 mo.	None	-	N	N	NC	N	Prednisone Ext. rad. to neck x 2 Chlorambucil ^{32}P x 4 Prednisone ^{32}P Ext. rad. to axilla Ext. rad. to axilla and groin METBI 50 R	9 days 14 days & 27 days 5 mo. 12 mo. 14 mo. 16 mo.& 21 mo. 22 mo. 23 mo. 2 yr., 1 mo. 2 yr., 2 mo. 2 yr., 9 mo.	D 6 yr. 4 mo.

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TABLE D APPENDIX - continued

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
8 a	M	68	3 days	None	-	+ 1	+ 1	- 1	NC	Prednisone METBI 50 R	5 mo. 3 yr., 5 mo.	D 6 yr., 7 mo.
8 b	M	71	3 yr., 5 mo.	METBI 50 R Prednisone	23 mo.	+ 1	+ 1	- 1	+ 1	Chlorambucil	15 mo.	D 3 yr., 2 mo.
9	M	74	5½ mo.	Prednisone 32P x 2	3 mo.(3)	N	N	- 2	+ 2	Prednisone Hydrocortisone	Cont. (3) 11 mo.	D 11 mo.
10	M	82	14 days	None	-	NC	NC	- 1	UD (4)	32P	2 mo.	D 1 yr., 2 mo.
11	M	63	14 days	Prednisone Hydrocortisone	(3) 7 days	- 2	UD	- 2	NC	Prednisone Hydrocortisone Ext. rad. to spleen	(3) Continuous 28 days 1 mo.	D 3 mo.
12	M	79	23½ mo.	METBI 100 R (See Table E, Case 15) Prednisone	- 18 days	- 1	NC	NC	+ 1	Prednisone Hydrocortisone Ext. rad. to spine Hydrocortisone Prednisone 6-MP Hydrocortisone	42 days 2½ mo. 3 mo. 5 mo. 5½ mo. 7 mo. 7½ mo.	D 7½ mo.

(1) Hospitalized for acute meningitis days 25 - 54
(2) Hospitalized with hemolytic anemia days 14 - 44
(3) On Prednisone during and after treatment
(4) Hospitalized with pneumonia days 35 - 45

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TABLE E APPENDIX

RESPONSE TO 100 R CHRONIC LYMPHOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval From TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
1	F	40	2 mo.	Ext. rad. to spleen	11 days	NC	+ 1	- 2	N	Ext. rad. to abdomen 32P Prednisone Ext. rad. to neck & chest Ext. rad. to pelvis Ext. rad. to neck & rt. axilla Dexamethasone	3 mo. 4½ mo. 7 mo. 15 mo. 2 yr., 6 mo. 2 yr., 10 mo. 5 yr.	D 5 yr., 9 mo.
2	M	49	2 yr., 1 mo.	TEM Ext. rad. to rt. axilla Ext. rad. to naso-pharynx Chlorambucil Ext. rad. to lt. axilla	12 mo.	NC	+ 1	NC	UD (1)	Prednisone 32P	2 mo. 4 mo.	D 3 mo.
3	F	49	3 days	Ext. rad. to neck and abd., axill. & ing. nodes	- 12 mo.	NC	NC	NC	NC	Prednisone Ext. rad. to liver Hydrocortisone	1½ mo. 2 mo. 4 mo.	D 4 mo.
4 a	M	54	2 yr., 2 mo.	METBI 50 R (See Table D, Case 4) 32P x 3 Prednisone	1½ mo. (2)	- 1	- 2	- 2	NC	Hydrocortisone Prednisone METBI 100 R	2 mo. (2) 16½ mo.	D 21 mo.
4 b	M	55	3 yr., 6 mo.	METBI 50 R (See Table D, Case 4) 32P x 3 Prednisone METBI 100 R Hydrocortisone	3 days	+ 1	+ 1	NC	+ 1	Hydrocortisone Prednisone	11 days 1½ mo.	D 4½ mo.
5	M	88	4 yr.	Chlorambucil	1 mo.	N	N	+ 2	- 2	32P	1½ mo.	D 1 yr., 1½ mo.

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TABLE E APPENDIX - continued

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval From TBI to Later R_x	F D
						Spleen	Liver	Lymph Nodes				
6	M	57	6 days	None	-	+ 1	• 1	NC	+ 1	^{32}P Ext. rad. to neck Prednisone Hydrocortisone	$3\frac{1}{2}$ mo. 7 mo. 9 mo 2 y 5 m.	-
7	F	54	13 days	None	-	+ 1 ?	N	- 1	N	Chlorambucil Prednisone Dexamethasone Hydrocortisone Cortisone Acetate Splenenectomy	$2\frac{1}{2}$ mo. 4 mo. 2 yr., 2 mo. 3 yr., $4\frac{1}{2}$ mo. 3 yr., $4\frac{1}{2}$ mo. 3 yr., $4\frac{1}{2}$ mo.	A
8 a	M	61	7 days	None	-	- 1	NC	NC	+ 2	METBI 100 R	22 mo.	D
8 b	M	63	22 mo.	METBI 100 R	22 mo.	- 1	NC	- 1	+ 1	Prednisone	$2\frac{1}{2}$ mo.	D
9	F	82	1 mo.	None	-	N	N	N	NC	None	-	A
10 a	M	74	3 days	None	-	N	N	- 1	N	METBI 100 R	18 mo.	D
10 b	M	75	18 mo.	METBI 100 R	18 mo.	N	N	- 1	+ 1	Ext. rad. to lt. ear LETBI 100 R LETBI 100 R Prednisone	8 mo. 16 mo. 21 mo. 2 yr.	D

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