DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Northeast Region
Boston District
One Montvale Avenue
4th Floor
Stoneham, MA 02180-3500
Tele: 617-279-2048

March 2, 1992

John Lauritsen
26 St. Mark's Place
New York City 10003

Re: F91-40665
Add'l Information
Robert Schooler, M.D.
Massachusetts General Hospital
Boston, MA

Dear Mr. Lauritsen:

This is in response to your request for records from the Food and Drug Administration pursuant to the Freedom of Information Act.

X In order to help reduce processing time and costs, certain material has been deleted from the record(s) furnished to you because a preliminary review of the records indicated that the deleted information is not required to be publicly disclosed. If, however, you desire to review the deleted material, please make the additional request at the following address: Food and Drug Administration, Freedom of Information Staff HFI-35, 5600 Fishers Lane, Rockville, Maryland 20857. Should the Agency then deny this information, you would have the right to appeal such denial. Any letter of denial will explain how to make this appeal.

___ As you will note, the enclosed record(s) contains certain business or personal information which is disclosable only to you or your firm. Copies of these records will be disclosed to other requesters only after thorough review and deletion of those portion which are not disclosable to the general public.

"The following charges may be included in a monthly invoice:

Reproduction 7.60 Search 2.75 Review 5.50 Total $ 13.10

The above total may not reflect final charges for this request. Please do not send payment unless you receive an invoice for the total monthly fee."

X Other: Enclosed EIR & FD483 dated 10/86.

Barbara A. Recupero
FOI Specialist
Boston District Office

cc: HFI-35 With attachments

B92-24

Note: The "Monitor" = Ron Beitman (p. 48), an B-W employee (p. 66)

SUMMARY OF FINDINGS:

i.e., not routine?

This was a For Cause Inspection of a clinical investigator of [redacted] Robert T. Schooley, MD., Principal Investigator. Martin S. Hirsch, MD., was the Co-investigator. The Study was conducted at Massachusetts General Hospital between April and September 1986. This double-blind study was sponsored by [redacted] nineteen subjects were enrolled, but the Study ended early when a National Data Safety Board reviewed the first few months of data and concluded that Placebo patients were dying at a greater rate than those on the drug.

Dr. Schooley has not been inspected previously; Dr. Hirsch has, in 1979, covering an Interferon Study. That EIR revealed errors in the Protocol; no notification of the IRB re Protocol changes or other Study medications used; subjects were given each other's drugs; and some of the label color was visible, thereby breaking the code.

The current EI revealed numerous deviations, many of them similar to those cited above in the 1979 EI. The observations listed on the FD-483 included: Deaths (two, so far) and adverse reactions have not been reported to the IRB; undocumented Protocol deviations including: concomitant meds, subjects not meeting entrance criteria admitted (two); tests not performed as frequently as required by the Protocol; adverse reactions not reported as such on Case Report Forms ("CRF's"). There were changes made on photocopied CRF's usually with no explanation, date, or initials; significant observations were not addressed on CRF's by clinical investigator; some raw records could not be located and were explained to have been discarded. Accountability of the Study medication is inadequate; 87 bottles/containers shipped cannot be accounted for; Pharmacy kept the inventory and it does not correlate with shipping records; Study medication returned by subjects was not counted, stored properly, or signed off by the clinical investigator.

Dr. Schooley indicated he understood these observations and that he would correct his operations in the future.

This assignment was received on 9/30/86 and I called Dr. Schooley the same day. I was instructed to try to begin the EI after the week of 10/6/86, so we scheduled it for the next week, 10/14/86 (10/13 was a holiday). The first four days of the EI were conducted with Tony El Hage, Ph.D., Pharmacologist, Div. of Scientific Investigations.

HISTORY OF BUSINESS & INDIVIDUAL RESPONSIBILITY:

[redacted]

Dr. Schooley is an attending physician and lecturer at MGH and is an Assistant Professor of Medicine at the Harvard Medical School along with numerous other appointments. See Exhibit A-1 for Dr. Schooley's CV. Dr. Schooley has a lab in the Infectious Disease Unit of MGH. This is where some of the work on the [redacted] Study was performed. Dr. Schooley described himself as a research physician, not as a primary care doctor. So generally he saw the subjects on the Study as a reseach physician and they usually had their own primary care physician in addition. A list of Studies that Dr. Schooley did concurrent with the [redacted] Study and prior to it, for the previous two years, is attached as Exhibit A-2. Dr. Schooley said that he had never had 20 patients at one time on a Study before. Added notes on A-2 indicate the number of patients that were on those Studies.

Dr. Hirsch is the Head of the Virology Lab in the Infectious Disease Unit. He also has numerous appointments at MGH and Harvard Medical School. Dr. Hirsch is over Dr. Schooley but they have separate labs.

Most of the paperwork and some of the clinical work on this Study was done by Teri Flynn, Research Nurse. Dr. Schooley said prior to the inspection that she was over extended and after the inspection that there should have been clerical assistance provided for the Study. He indicated that since the Study was to have been short term that he did not consider hiring someone to do the paperwork. However, in retrospect he thinks he should have hired someone for that task. During the last Week of May and the first Week of June Ms. Flynn was away on a honeymoon and was replaced by another nurse. That ment that the replacement nurse covered for Ms Flynn for four clinic visits when subjects for the Study would have been seen by the Clinical Investigators. That substitution of Research Nurses is not stated in the Case Report Forms. Ms. Flynn was pretty sure that the replacement nurse was Eileen McCauley, RN. Ms. Flynn did not change her name subsequent to her marriage so CRF's, will list the same name.

Another Investigator listed on the FD-1572 (Exhibit B) is Dr. Ho. Ms. Flynn explained that Dr. Ho filled in for Dr. Schooley or Dr. Hirsch on clinic day when they were not available. It is not possible to determine from the Case Report Forms which days Dr. Ho. worked on the Study. When asked, Ms. Flynn said there should be no other names on the CRF's.

The Laboratory which performed the [redacted] tests, under Dr. Schooley is run by Roy Byington, Supervisor.

Rowena S. Wilder, Research Pharmacist and Coordinator of Investigational Drugs was responsible for storage and dispensing of the study substance in the Pharmacy in the basement of the Burnham Building. She explained the procedures and record keeping. She introduced us to Harold DeMonaco, Pharmacy Director and to Carol Cronin, Associate Director of the Pharmacy. We commented briefly to them on the pharmacy records regarding this study.

20 centers? or 12?

STUDY BACKGROUND:

Several studies are related and will have to be distinguished for the purposes of this report. This EI covers what will be referred to as [redacted], or the Double Blind Study. The Double Blind Study was conducted at 20 Centers in the country. Subjects on this Study were offered entrance on to a subsequent, open-label Study in September when the Double Blind Study was ended. In the Fall of 1986, a third Study has begun, this time open-label and not limited to the original 20 Centers. This Study will be described in the last section of this report entitled "New Study".

In addition, MGH has been conducting its own large scale "Prospective Study". Over [redacted] people with [redacted] are on this Study. It is being conducted to track P[redacted] over time. It is also the source of a number of the subjects for the [redacted] Double Blind Study of this EIR. Study numbers for the Prospective Study are three digit numbers such as "114", "170", etc. These numbers will be seen identifying subjects on the Double Blind Study in additional to their Double Blind number which is four digits long.

Dr. Schooley first wrote to the IRB on January 22, 1986 to describe the Study (see Exhibit G-1). The Study was approved by the IRB as of February 25, 1986 (Exhibit G-12). The first subjects were entered on the Study in late March and early April. The last subject was entered on the Study on June 16, 1986. The Study ended on or about September 19th when a Press Conference was held to announce that the results of an independent Data Safety Monitoring Board showed that there were more deaths with Placebo subjects than with those who were taking the drug, [redacted] (Note: The statement was that there were more deaths in Placebos as opposed to better results than those on the drug.)

At that point the code was broken and the subjects on the Study were notified whether or not they had taken drug or placebo during the previous months. Dr. Schooley explained that the Data Safety Monitoring Board had been scheduled to meet one month later, but that apparently the preponderance of the data had shown results that convinced the Sponsor and other Clinical Investigators that this Study should be terminated prematurely. Exhibit C-13 is a List of the Subjects who were "Placebos" on the Study. In the series of

T-4 counts?

subjects with [redacted] of < 100 "Group A", are six whose numbers were between 1001 and 1010. For those subjects whose [redacted] value was greater than 100 but less than 500 "Group B", the numbers were between 1052 and 1059. The listing of the Code Numbers for the Placebos are Exhibit C-13, pages 1 & 2. The numbers greater than 1010 or 1059 on these lists were at another Center(s).

Exhibit D consists of summaries of data from the Study. Exhibit D-1 lists the subjects by number on the [redacted] Next to that number if the individual has gone on the Open Study there is a Capital "O". The three digit code for the long term MGH Study as well as initials and dates of birth for each person on the Study are the next two columns. There is a column of the subject's status, whether they were [redacted] whether they were on Placebo (P) or on drug (D); if they were hospitalized during the Study; and the dates of: their Informed Consent, and when they began and ended the Study. Dates of transfusions during the Study are listed and the referring physician and additional notes are written as well. The adverse reaction column may include reactions that the Clinical Investigator did not designate as adverse reactions.

P=?

P=?

P=?

According to this record [redacted] subjects on the original Study of [redacted] AZT have opted not to continue on the Open Label Study. [redacted] of those were subjects who had been taking Placebo and [redacted] were taking the drug. Those taking the drug were Subject numbers [redacted] An extra copy of the monitors listing of returned medication is attached as Exhibit D-2. Please note: This record may be misleading in that it indicates four subjects completed the Study: four others came within three to four Weeks of being on the Study for six months and six went halfway. That may not always be the case due to how the Study was administered. Some subjects were ill and sometimes hospitalized and therefore dropped for a while during the study, but CRF's were generated as though they continued on the study. The reader is referred to the observations for individual subjects in the Case Report Form coverage below and to observations of pharmacy and inventory errors in the Accountability Section also below.

AIDS? AZT? ARC?

Two subjects have died since this Study. In each case they were off the Study medication prior to their death. They are Subject numbers 1001 and 1009. As it turns out each of these was an [redacted] patient. And each was on Placebo during the time of the Study. Number 1001 died August 15, 1986. He had been on the Study from the 3rd of April to the 14th or the 26th of April. Number 1009 was on the Study from May 29th to June 26th and died on August 20, 1986. When I asked T. Flynn why [redacted] patients had died as opposed to [redacted] patients she explained that some [redacted] are more sick than [redacted] patients. These two subjects had been sick for a long time and had lost a lot of weight and in fact were more ill than some of the people with [redacted] However, she noted that those who were classified as [redacted] did not have the opportunistic infections that would be true criteria for the CDC definition of [redacted] Dr. Schooley echoed her comments about how ill the [redacted] patients were.

* treated for 1-4 weeks each

AIDS

A summary of the [redacted] values was generated by T. Flynn over the course of the Study. Her results, including those that were highlighted by her, are attached as Exhibit D-3. The subjects are divided into Group A and Group B for these Charts. Ms. Flynn also generated a record at the beginning of the Study which was not maintained of tests that were required for the Study. That is attached as Exhibit D-4.

The Protocol used by the Study is attached to the Home District copy of this report. It is Exhibit - E.

COMPLIANCE PROGRAM FOR CLINICAL INVESTIGATORS:

A. Visits to the Clinical Investigator

1. When I asked Dr. Schooley if he were visited on site by the Monitor prior to his participation in the Clinical Investigations, he said he was and he gave as examples a meeting at [redacted] and a meeting [redacted] However, in the File of Records that was provided to us there was a draft quality personal computer note to Teri dated October 3, 1986 from the monitor, [redacted] stating that (during our inspection) she would likely be asked about visits by the monitor. The note included a listing of these dates. This is attached as Exhibit F to this report. It states that there was a prestudy site visit on February 19, 1986.

2. Dr. Schooley said that the monitor explained in advance of the Study the investigational status of the article, the nature of the research protocol, and his obligations. Copies of correspondence in Exhibit C verify his response. Exhibit C-1 is a November 22 letter to Dr. Schooley from [redacted] Dr. Schooley responded on January 23, 1986 to [redacted] The letter primarily discusses the issue of the Safety Monitoring Board. Dr. Schooley and Doug Richman (title unknown) recommended that the Board be used "to terminate the Study if clearcut clinical benefit or significant toxicity is observed in the drug Recipient Group". This letter is Exhbit C-2.

3. Dr. Schooley was the Principal Investigator for the Study and he explained that Dr. Hirsch was his Co-Investigator. Dr. Schooley's description of his workload included that he is a teaching attendent at MGH which account for 3-5% of his time and an Assistant Professor of Medicine at Harvard Medical School in Infectious Diseases and Immunology which accounts for 2% of his time. The bulk of his time, he said, is spent in [redacted] related research which is [redacted] funded.

4. The monitor's listing of dates of visits did show that he visited the investigator at the site of the Study during the investigation. From Exhibit F the following dates are noted. After the prestudy visit,

he came to the site on March 20, April 23, May 15, June 5, 23 and 24th. Other dates were July 8th and 30th, September 4th and 23th, and October 7th and 8th. We know in addition that after the investigator was notified of this inspection and prior to our arrival that the monitor also visited apparently for a few days and did work on the Study including Accountability Records and return of Study medication records (see below).

Are these deletions intended to prevent further FOIA requests?

5. When I asked about additional meetings with the monitor during the Study, Dr. Schooley mentioned the meeting at [redacted] This [redacted] that Mr. Byington, Lab Supervisor, attended. He also (repeated) a meeting in [redacted], "several Saturdays ago" where [redacted] presented data prior to the Press Conference explaining the results of the Study.

Also in response to this question, Dr. Schooley said that one of the problems in organizing or running the Study was that the [redacted] overlap with each other and with the Study. The [redacted] are funded wholly by [redacted] Drs. Hirsch and Schooley are in charge of these Units in Boston. Dr. Schooley said they are not doing anything with these groups yet. It will be six Weeks to two months before they begin. It was my understanding that what he meant by a conflict was that these Units, once established, will be a more organized way of dealing with new substances to treat AIDS. [redacted] Dr. Schooley and Ms. Flynn mentioned several times that the subject Study was organized quickly and it's my understanding that they felt that some of the disorganization, both theirs and [redacted] was due to the fact the the Units were not in place and there is no standard way of dealing with all these Studies. As an example, personnel have not been put in place to perform clerical functions for the [redacted] and since the units have not yet been established, the committment to hiring additional people prior to that time has not yet been made.

Correspondence regarding the Study is attached as Exhibit C to this report. In this section we will mention briefly the review made of the correspondence. It appears that this correspondence file was incomplete. In one case (Ex E-2) only page one of a two page letter was made available to me. PAS 12-30-86

Exhibit C-1 - Is a letter to Dr. Schooley from L. [redacted] dated November 22, 1985. [redacted] explained that a Tentative Outline for the Double Blind Study is enclosed and he asked for Dr. Schooley's comments. He also recommends that the outline be submitted to the IRB for their consideration and Dr. Schooley "start screening patients based on the entry and exclusion criteria of this Outline".

Exhibit C-2 - Is a January 23, 1986 letter from Dr. Schooley [redacted] Dr. Schooley discusses the Safety Monitoring Board and recommends that they be in a position to terminate the Study "if clearcut clinical benefit or significant toxicity is observed in the

* So, even the FDA has info withheld from it.

drug recipient group". Dr. Schooley also recommends the Study be stopped if there were "statistically significant differences between the treatment and placebo groups" for some specific variables. He recommends as an example that Grade III or IV toxicity be one of the variables that is tracked.

Note that this January 23th letter does not appear to be a response to the November 22nd letter in the previous Exhibit.

Chip Schooley!

Exhibit C-3 - Is a February 5, 1986 letter to Dr. Schooley (referred to as "Chip"). The letter is from S[redacted] She says that a detailed Protocol is attached for processing patient samples for [redacted] isolation and for maintaining the cultures and determining reverse transcriptase activity. She also asked for copies of the Radioisotope Broad License and indicates that the trial should be underway within the next month.

Exhibit C-4 - Is a letter to Dr. Hirsch dated February 7, 1986 from [redacted] She explains that [redacted] will perform the majority of laboratory tests. ([redacted]rates have to be done on-site as soon as possible after the blood is drawn.) [redacted] contracted to provide hard copy results of the tests within 24 hours of pickup. [redacted] would also supply results via magnetic tape to [redacted] once a week that could be evaluated quickly and therefore not require additional data entry. She explained that this meant that the Study Nurse would not have to transcribe the data onto the Data Collection Forms. She also refers to the fact that a decision on the final dose to be used in the Study had not yet been made and to proper packaging of [redacted] specimens. She also notes that IRB Approval, Consent Forms and Statement of Investigator and C.V.'s are needed before the Study can begin.

Exhibit C-5 - Is a letter to Dr. Hirsch fro[redacted] (see above). The letter is dated March 12, 1986 and it covers financial arrangements for the Study. Basically the Investigator would be paid [redacted] per patient which covers special laboratory work, clinical evaluations, neuropsychological assessments and personnel time. It does not include the cost of running the [redacted] ests. For patients who drop out of the Study the cost would be "pro-rated based on the amount of time the patient was in the Study. However, patients that are clear Protocol violations who are entered in the trial would not be considered for any reinbursement".

$??

So?

Please note that the request made in the previous letter about copies of the IRB Approval and Patient Consent Form and Statement of Investigator were not addressed in any letter to which we had access.

Exhibit C-6 - Is an April 9, 1986 note addressed to [redacted] from [redacted] (the Monitor). He says that a stamp for Dr. Hirsch's name was enclosed. That stamp or Dr. Schooley's could be used on the Case Report Forms. He also said that 10 sets of the first volume of DCF's

Why do we not have a right to know how much ~~Schl~~ Schooley was paid per patient?

(Case Report Forms) would be sent ASAP.

Exhibit C-7 - Is a note with [redacted] name (presumeably addressed to her) and a statement, on 4/16/86 "mailed" the 10 sets of Study forms referred to above and 12 employment questionnaires and a packet of patient diaries.

Exhibit C-8 - Is a April 29, 1986 letter to [redacted] from [redacted] It welcomes [redacted] and says that "a number of questions have come up that need immediate attention". It refers to coordinating and trouble shooting the [redacted] Virology.

Exhibit C-9 - Is a May 20, 1986 letter to Dr. Hirsch from [redacted] He says that patient enrollment into the Study will stop as of June 6th.

Please note that Exhibit D-1, The Summary of Subjects, states that four subjects entered the Study after that date. They are numbers 1008, 1011, 1012, and 1059.

Exhibit C-10 - Is a letter to [redacted] from [redacted]. The letter is not dated, however, it refers to his next visit as being the end of July or early August. The letter addresses mailing the [redacted] Test Results and the Marketing Questionnaire Forms. (Please note: This Marketing Questionnaire Form was something I asked Ms. Flynn and Dr. Schooley about and neither recalled the Form.) [redacted] thanked [redacted] for the excellent work she had been doing on the Study.

Exhibit C-11 - Is a draft copy of a personal computer letter from [redacted] to Drs. Schooley and Hirsch dated July 14, 1986. It explains the status of payments for the Study and the viral cultures.

Exhibit C-12 - Is another apparent draft copy of a note from [redacted] to [redacted] dated September 19, 1986. It confirms that fact that he had called the previous day to say that the Double Blind portion of the Study was to be ended. Subjects on the drug should have their dose reduced to [redacted] and all Placebo patients were to be allowed to change to [redacted] They were to take [redacted] for the first 4 Weeks and thereafter to take [redacted] The [redacted] capsules, that had been used in the Double Blind Study, were to be returned. A list of the numbers of the Placebo patients was attached. It is identified as Exhibit C-13. The code numbers for subjects at this location in that Exhibit are first, patients with [redacted] less than 100: 1001, 1002, 1005, 1007, 1009, and 1010. Patients with [redacted] between 100 and 500 were: 1052, 1054, 1056, 1058, and 1059.

Test Report Forms were also enclosed for use after termination of the Double Blind Study. [redacted] said he would visit each site the Week of September 22, 1986 and he reminded [redacted] to have all Case Report Forms completed of significant events up to September 18th.

Please note: The following six exhibits were apparently out of order.

Exhibit C-14 - This is another draft quality note to [redacted] from [redacted]

[redacted] saying that two memoes are attached regarding the [redacted] Assays. They were not attached to a copy of the letter that I was shown. [redacted] says in the letter that one memo dated July 2, 1986 requests that [redacted] samples to sent to [redacted] the Week of August 11, 1986. (I do not know if this shipment was made.)

Exhibit C-15 - Is a July 22, 1986 letter from [redacted] to Drs. Hirsch and Schooley saying that some of the Study Drug, [redacted] had been purchased "on the street". Clemons asked them to be sure that the Study medications be kept under a "double-lock system".

A number of observations of deviations from appropriate accountability procedures are noted under section C. below, Test Article Accountability.

Exhibit C-16 - Is a "telcon (telephone conversation record)" from the [redacted]. The date is hard to read but is, according to Dr. Schooley, August 5, 1986. [redacted] recorded a conversation with Dr. Schooley on that date. [redacted] month old child had ingested some of the patient's Study medication. The second sentence says "code showed capsules contained [redacted]. The medication count indicated the child had taken [redacted] apsules or [redacted] (Other records indicated that the child was a girl.) She was given Ipecac and Dr. Schooley asked about the possibility [redacted] "as a rescue". Drucker apparently discussed this with three other physicians and the decision was made that unless there were repeated exposure that [redacted] rescue would not be appropriate. "Monitoring and supportive transfusions were used prm otherwise." The note ended by saying that Dr. Schooley would send blood for [redacted] levels. See also the discussion of this incident in the text for 1006, Week 14.

Please note: There was no further followup in the records regarding this incident.

Exhibit C-17 - Is a letter dated August 20, 1986 from [redacted] and it appears to be a form letter. The heading says Dear: with no additional name or title. Attached to the 2 page letter is a listing of physicians who presumably were working on this Study. The listing shows Dr. Hirsch and not Dr. Schooley. The letter appears, to this reader, to be contradictory in that it says in paragraph 2 that some have interpreted the Company's intention to be, that each patient on the Study could be moved into an open Study after the Double Blind one was completed. However, they say that current safety and efficacy data do not support doing that. However, they also say that since there is no alternative to the therapy that patients could continue on their present treatment and not be required to have a "washout" period. If they chose not to, they would still be eligible for an Open Study later on.

Additional provisions were made for subjects who would have a "event" such as opportunist infections or other problems that would require experimental or contraindicated drugs. So an interim open study would be available to those patients which would give information about drug interactions and end points. Specific categories of patients were listed for those purposes.

* And yet Schooley was P.I.

Then there is a statement (page 2) that 24 Weeks after a patient's first [redacted] treatment (presumably Placebo or drug) he would be eligible for the Open study.

Exhibit C-18 - Is an August 29, 1986 letter to J[redacted], at [redacted] in Boston, from Richard Clemons. (Dr. [redacted] conducting the [redacted] It appears that at least this letter was shared between the two locations.) R. Clemons refers in the letter to Dr. [redacted] letter of August 20th about how to deal with subjects when they complete the six months of Study drug treatment. The Amendment to the Protocol, "which is being submitted to the FDA" is attached in the letter and is also attached to Exhibit C-18. It does verify the previous letters that subjects who were on the Study for 24 Weeks could continue on either the drug or Placebo (blinded) after the initial 24 Weeks of therapy. If they did develop certain medical conditions they would be eligible to go on Open Label.

Please note that there is no indication in this file or elsewhere that the IRB was notified of this Protocol Amendment.

Exhibit C-19 - Is a letter dated 9/11/86 from [redacted] to Dr. Hirsch. The letter says that data was being tabulated for the next scheduled meeting of the Data Safety Monitoring Board. Apparently informaton that had been conveyed over the telephone had been reduced to writing and the investigator was being asked to verify the accuracy of the information. There is no return letter in the file. It appears a record kept in the front pocket of the looseleaf binder for each subject was likely the response made at this location to this request. Those notes will be discussed below in each patient's record. For those copies that were dated the date was ordinarily September 19th. In the exhibits below this record is usually the first page for each subject. The records were handwritten and sometimes had comments made by Dr. Hirsch on them. [redacted] said that the monitor had used [completed?] the form and sent them express mail the day before the code was broken. She showed them to Dr. Hirsch and "he signed off".

Exhibit C-20 - This is a September 24, 1986 letter to Dr. Schooley from [redacted] He discusses the results of the independent Data Safety Monitoring Board from September 19, 1986; they unanimously decided to end the Double Blind Study. The decision was based on "an unacceptable mortality rate in the Placebo Arm of the Study". A summary of the results of the data analysis was said to be attached. It was not in the Correspondence File.

[redacted] also said that the Study would be continued open label. He added, "Because of the suggestion of marrow suppressive activity of [redacted] AZT in the Controlled Study, the dosage would be changed. Former Placebo recipients would get [redacted] every [redacted] hours for [redacted] Weeks and then [redacted] hours thereafter. Former drug [redacted] recipients would immediately have their dosage reduced to [redacted] every [redacted] hours. Dr. Schooley said the dosing for the open label study has been changed several times.

Why are dosages lower?

Exhibit C-21 - Is a letter dated September 25, 1986 to Dr. Schooley from [redacted]. He reiterates what was in the previous day's letter about the change in dosage. He also suggests that questions about changing the dose especially for those on the drug should be addressed to the monitor. He refers to circumstances where the physician might wish to alter the dose indicated by the Sponsor firm. A new Protocol and Case Report Forms would be sent soon and the budget would continue so that funds remaining from the Grant would be calculated on a per visit basis, and supplemented as necessary.

Please note the letter also says, at the bottom of page 1, and the beginning of page 2, "As specified in the New Drug Regulations, we anticipate that the FDA will request an updating of all patients and data just prior to the approval". It is unclear what was meant by this "approval". I.e., he knew in advance AZT would be approved!

Institutional Review Board (IRB)

1. The Study was subject to IRB review, by the Massachusetts General Hospital "Committee on Research, Subcommittee on Human Studies". Exhibit G includes the correspondence with the IRB. It was obtained in it entirety from the IRB from [redacted] IRB Administrator, not from Dr. Schooley.

2. Dr. Schooley submitted a copy of the Protocol. He first wrote to Dr. [redacted] Executive Secretary for the IRB on January 22, 1986. In the letter Dr. Schooley describes the Study and asks for comments by the IRB. That letter is Exhibit G-1.

The Application for Approval by the IRB is attached as Exhibit G-4. The records of the IRB were in order such that it appeared that ExhibitG-6 was a copy of the first page of the Protocol submitted to the IRB. The last date on this edition is January 22, 1986. However, that is not the final edition of the Protocol and it appears that the IRB did not receive the final edition of the Protocol which was dated February 18, 1986 (Exhibit E for the Home District copy) in time for their approval of the study.

He lies, When I asked Dr. Schooley if he had submitted a report of prior investigations to the IRB he said "yes". I did not see reference to it in the correspondence with the IRB.

Appendix V of the Protocol was the Suggested Informed Consent from [redacted] It appears that this is what Dr. Schooley submitted to the IRB for their initial review. Page 1 of this Appendix is attached as Exhibit G-7. On it is a note Dr. [redacted] "Looks good, no mention of giving drug to Placebo assigned patients if Study proves it is effective".

The Study was reviewed by the Subcommittee on January 28, 1986. A summary of the discussion is Exhibit G-8 of the same date written by Dr. [redacted] It is in this summary under "Considerations" that Dr. [redacted] mentions the seventh month of the Study being a drug washout. And the offer of [redacted] to all participants "if it is showned to be beneficial and

if a sufficient supply is available at that time". Dr. [redacted] also notes that "the usual Phase II clinical trial of the Safety and Efficacy of [redacted] had been bypassed". AZT given even before Phase II trials began?

Exhibit G-9 is the Subcommittee's Form which states that the Study was "Provisionally Approved". In Dr. [redacted] summary there was a comment that the Consent Form required some changes.

Exhibit G-10 - is a cover letter from Dr. Schooley dated February 10th to Dr. [redacted] saying that the revised Consent Form was enclosed. The subsequent Administrative Approval dated February 25th from Dr. [redacted] (Exhibit G-11) explains that the change in the Consent Form included "the availability of the drug to all participants should the Study prove its effectiveness". The revised Form was acceptable. An approval by the Subcommittee is dated February 25, 1986 (Exhibit G-12). It states, "ANY ADVERSE EXPERIENCE BY A STUDY SUBJECT IS TO BE REPORTED IMMEDIATELY BY TELEPHONE, FOLLOWED BY A WRITTEN REPORT".

The IRB requirement that all adverse reactions be reported was not met. None of them were reported. See G.1.e. below. The informed consents (one for [redacted] (Ex. J-1, pp. 18-23), and one for [redacted] (Ex. J-4, pp. 40-45) are attached.)

Dr. Schooley said he did give the sponsor a copy of the consent form. There is no documentation of that in the correspondence file (See Ex. C.).

3. Dr. Schooley did supply IRB with a copy of the final version of the [redacted] Protocol. The cover letter that he used for that is dated February 26, 1986 (Exhibit G-13). This was after the IRB had approved the Study. No where in writing is there a record of Dr. Schooley's notifying IRB of changes that have been made in the Protocol between the different versions. These changes included droping the Lumbar Puncture, reducting the dose of the drug for those subjects who were on it, inclusion criteria (patients could be entered no more than 120 days after diagnoses and within 90 days of recovering from PCP), plasma level of [redacted] would be drawn only a certain centers and the rating of the Toxicity Chart was modified somewhat. The list of these changes is the first page of the Protocl Exhibit-E. When I had asked Dr. Schooley if there had been changes to the Protocol that he submitted to the IRB, he said, "No". Another lie,

4. See also Number 3 above. Correspondence with the IRB has been described above in Section B, Numbers 2 and 3. In addition there has been correspondence with the IRB since the Sponsor said on September 19, 1986 that the Double Blind Study would no longer proceed. Dr. Schooley informed the IRB in a letter dated September 19, 1986 (Exhibit G-16) of the results of the Safety Monitoring Board who noted an excess of deaths in Placebo recipients at month 4. Therefore, Dr. Schooley said they would like to put all the participants in the Study on active drug. He refers to the (new) Consent Form, attached, for this new open study. In fact there are two Consent Forms, one for subjects who had received the drug [redacted] and a different one for those who had received the Placebo.
AZT

Open Study:

These Constent Forms are attached as Exhibit G-19.

The new Protocol for this part of the Study is also attached, as Exhibit G-20. It appears that the cover letter for this Protocol is dated October 9, 1986 to Dr. [redacted] from Dr. Schooley, Exhibit G-21. It appears that this part of the Study was approved on October 21, 1986 by the IRB. However, that was a month after the first subjects would have been transferred from one Study to the other. The approval by the Committee is Exhibit G-22. Exhibit G-23 is Dr. S[redacted] Summary of an Administrative Approval dated September 23, 1986; his Report is dated October 21, 1986. Dr. [redacted] notes in his Summary that the Sponsor's Protocol and the investigator's proposal differ in that the investigator would drop the AZT [redacted] dosage to [redacted] every [redacted] hours after certain time intervals, but not wait for adverse hematologic effects (as in the Sponsor's Protocol). He also points out that no new patients would be added to the Study (he refers to FDA's policy) as only those subjects on Studies could have access to the drug.

5. As mentioned above, all records of submissions to the IRB were obtained from the IRB, not from Dr. Schooley.

~~But this was supposed to be a BLIND study.~~

C. Test Article Accountability

1. In addition to the Investigator, Drs. Hirsch and Ho and Teri Flynn, RN, were authorized to administer the test article. Dr. Hirsch and Dr. Ho were listed on the FD-1572.

2. Accounting procedures were not adequate to explain all use of the test article (see FD-483 Nos. 9, 10, and 11) as follows:

a. There is no running record of dates of receipts of the Study substance and quanity. Copies of shipping records were kept (Exhibit H-1) but they were not verified (FD-483, No. 9) by the investigator, research nurseor pharmacy (where the Study substance was stored). These records show the following shipments:

Shipping Date	Amt/Kind Rec'd AZT [redacted]	Placebo	Unknown
3/11/86	60	60	
4/7/86		60(?env)	
4/14/86			16
5/5/86			84
6/23/86			60
8/14/86			1

9/11/86 4

(PAS totals) 60 120 165 = 345 ,

The second shipment dated 4/7/86 referred to "env", envelopes of Placebos. No one recalls any envelopes. Usually the product was in amber bottles. This record said the monitor would replace the old Placebo with the new. There was no explanation given beyond that. Otherwise the shipping records were inconsistently completed, and there were different codes for Placebo and drug. Sometimes the subject numbers were listed and sometimes they weren'st. Shipment on 5/5/86 said it would be re-labeled with Dr. Schooley's code. This was not documented.

The pharmacy made their own count, but did not correlate it with the shipping records. Their count shows the following on the monthly inventory (Exhibit H-2):

Group A Receipts (Ex. H-2, p-1) (Bottles of 50 or 100 capsules each)

March	60
April	39
June	30
	129

Group B Receipts (Ex. H-2, p. 2.)

March	60
April	39
June	30
	129

(PAS Total 258)

Note: These records do not (1) show the count per bottle. (2) Some of theseinventory entries were in pencil and (3) the pharmacist also recalls a shipment of bottles with handwritten "50"(count) on the label. This was not documented (FD 483 no. 10.). (4) These records show 87 fewer bottles were received by the pahrmacy than were shipped (345 shipped - 258 received = 87) FD 483, no. 9.

This inventory record also shows the following returns:

Group A	25
Group B	34
	59

R. Wilker tabulated these results during this EI:

Group A
129 rec'd
102 dispensed (inventory erroneously says 103)
27

-25 returned
2 unaccounted for

Group B
129 rec'd
-89 dispensed (inventory off by 2)
40
-34 returned
6 unaccounted for

b. The pharmacy kept a running inventory, but that has been destroyed. (FD-483 N0.10. They do have on file the prescription slips and they generated a computer list of who received Study meds, how much, when, and who wrote the Rx (Ex H-3). Problems noted with this record are listed below, No. 3, para. 4.

The pharmacy also generated an actual and theoretical inventory once a month which was sent to the C.I. As of the last day of this inspection, T. Flynn said she still had to get this information together.

c. The remaining Study substance was taken by the monitor. Until then unopen bottles which T. Flynn had taken were kept in a locked drawer in a cabinet in Ms. Flynn's office. Open bottles were stored in a bag under he desk and were therefore not locked up at all times (FD-483 No. 11). Two other people share that office. It opens into a lab in which other people might work. The lab door to the hall does lock according to T. Flynn.

When I first asked (day 1 or 2 of the EI) for the count of what the monitor took I was referred to the listing he wrote by hand (Ex H-4). I noted that there was no final count to show how many bottles he had taken with him. I counted 116 returned and 3 not received by the monitor. Then I compared that to what the pharmacy said they returned, which was 59 bottles. Subtracting that from 116 leaves 57.

Also when bottles are "B" (broken) there is no documentation of the disposition of the bottle's contents--are they discarded, saved? On one of the last days of the EI, T. Flynn showed me two "Drug Disposition Forms' (Ex H-5). These records are not signed by the CI. In that slot is "NA [redacted] on each of these forms (FD-483, No. 11). They indicate the following returns:

		FULL	PARTIALLY FULL
Form 1:	From Pharmacy 10/6/86	113	1
Form 2:	T. Flynn 10/10/86	13	162
PAS Totals		126	163

Each form has attached a listing by subject numbers of the number of "F"

(full) or "P" (Partial) bottles by week. By matching these 2 records, it is possible to determine what bottles are not accounted for by these two records as follows:

Subject Number	Weeks
1001	4,6
1002	1,2
1003	
1004	1,2 20
1005	" 22
1006	6 22
1007	
1008	3
1009	4
1010	6,8,10,12,14,16,18,20,22,24
1011	Ø 14
1012	
1051	
1052	24
1053	20,22,24
1054	16
1055	2,3
1056	
1057	
1058	No. not used (no entry wks 6-24 - may not have been shipped?)
1059	
1060	No. not used.

This is 21 bottles not accounted for (excluding 1058, whose number was not used and 1010. Each of these did not have medication for Weeks 6-24 shipped to them) according to Exhibit H-4.

3. It is not possible from these records to compare the test article useage against the amount shipped to the C.I., and as compared to the amount returned to the Sponsor. (FD-483, No. 9). In fact, the number of bottles (or amount of capsules) used or unaccounted for varies with the system checked.

For example, the shipping records (see 2a above) show a total of 345 bottles were received. The pharmacy says that 258 bottles were received. That difference of 87 bottles (FD-483, No 9) is not accounted for by the 13 full bottles returned by T. Flynn. From records of returns, 310 partial or full bottles were picked up by the Monitor. That leaves 35 unaccounted for or not returned by the subjects.

My count of the containers returned by the pharmacy (Ex H-5, p-1) is 117 full and 1 partial, not 113 full, as written n the Monitor's copy. I did not check the other record, of returns from T. Flynn.

The computer print-out of dispensing the Study medication (Ex H-3) does not function as a check on the system and is not a running inventory for several reasons. We had been told that T. Flynn often got the Study meds from the pharmacy on the first day of the EI. I learned that T.

Flynn often got more than one visit's supply per subject. She said she only gave the subject the amount he was supposed to get that week, and she kept the additional in her office. Besides being more convenient, she did not say why this was done. So the computer generated record only lists when the Study substance was removed from the pharmacy, not when it was used by the subject. Numerous instances of issuing more medication at a time is noted in Ex. H-3 by brackets connecting Rx's filled the same date. Originally, T. Flynn said she locked only a few bottles "4-5 maximum" in her file cabinet on the Friday or Wednesday before clinic (Mon or Thurs). Later she said she sometimes took enough for a few weeks for the same subjects.

Also, this record notes the quantity dispensed and the time during which it is to be used. However, the latter entry is not completed consistently. On page 5, note that 50 capsules are said to cover 7 days [redacted] which is correct, or 30 days [redacted] which is inaccurate. Similarly, 100 capsules are described to cover 30 days [redacted] or [redacted] on 7/9/86) or 7 days [redacted] on 7/11/86, [redacted] or [redacted]. These comments apply to entries on one page only. There are similar entries on many of the other 14 pages.

why not? The second copy of this print-out is generally not legible, but can be correlated with the first. R. Wilker added a number of comments as follows:

Page	Subject	Comment
1	[redacted]	QA label missing on Rx
2	[redacted]	QA label missing on Rx
4	[redacted]	50 were issued, not 100.
RB	"Deleted, Rx	missing, no wk 16". [not given according to the computer].
8	[redacted] (3-26-86)	2 bottles of 50 ea issued.
8	[redacted] (4-9-86)	one botte of 50 ea issued (not 100)
8	[redacted]	Week 2 and 3 were issued on the same day. Wk 3 entry is on page 14.
10	[redacted]	Wks 3&4 issued the same day (see p.14).
11	[redacted]	Wk 14 Rx #77 not listed in print-out.
11	[redacted] 6/27	no Rx; deleted

11	[redacted]	2X50 issued, (not 50 only).
11	[redacted]	Wk 18 Rx #22, 7-9-86 not on print-out. R. Wilker explained that when the wrong entry is made and then corrected the same day, that neither shows up on the day that neither shows up on the print-out.
12	[redacted] - 1056	CF's Week 10 was given to 1057; the wrong code was on the Rx. It was realized next visit.
13	[redacted]	The "extra bottle" of 50 was dispensed (it is also referred to as wk 0).

Several entries [redacted] p.8 and [redacted] p. 2 list Dr. Greg Hirsch, Surgery". Apparently this is an error, but it also is a violation of the Pharmacy policy (Ex 11-9, pp 1 and 3) to only dispense to an authorized physician. Those authorized for this Study are Drs. Schooley, Ho and Martin Hirsch (Ex 8H-8,p.1).

It was not possible to review the label of the Study medication since we were told the monitor had picked up all the empty and full bottles the week before we arrived and he had subsequently destroyed them all since. Ex H-6 is a copy of what the label would have looked like according to R. [redacted] Ex H-7 is a copy of the label on the open Study, front and back. Ex H-8 are Pharmacy labels. A seven digit code was written on two records and crossed out but not explained (1003, and 1005). T. Flynn explained it may be a product code. On 1003's CRF (p. 82) the code was "1017401"; on 1005's CRF, p. 199, wk. 6, the number is "1118401".

RCB AZT

Directions for Dispensing the Study medication (Ex H-9) include a statement that the returned capsules should be counted. They were not counted when returned. T. Flynn ~~said she was~~ too busy to check at the time so she estimated the amount returned, and the week before we ~~arrived, she and/or the monitor~~ made an actual count, and changed the CRF's accordingly (FD-483, No. 11). The record was changed like this for some if not all return visits for 1003, 1005, 1006, 1009, 1011, 1012, 1051, 1053 and 1057. Some of these changes, however, were from 0 returned to some number higher than zero, which is not explained by "making estimates" (FD 483, No. 11.).

Directions for the Pharmacy for this Study are Ex H-10 and for studies in general, Ex H-11.

8. Dr. Schooley said he did not advertise for patients for the Study. Exhibit G-15 is the copy for an Ad that was shown to the IRB. However, it was not used, according to T. Flynn. She explained that at first they thought they might have a problem getting subjects but they found that they got referals easily.

Another lie?

There were three sources of subjects. One was people who had been

hospitalized in the preious month with [redacted] so they had been seen by the Infectious Disease Unit. Other patients came from the Prospective Study being conducted by MGH (see History above). These were noted to be usually [redacted] patients. Others were said to come from outside physicians who had read about the Study in newspapers and journals. Probably 50 to 60% were from the first two categories and 30 to 40% from the last one. I asked if patients had self referred themselves. Dr. Schooley said that the [redacted] community did seem to know a lot about the Study. He said the local [redacted] did interact and still do. He said he talked with the Director [redacted] a lot. Dr. Schooley said the patients were very well educated and were well informed about the Study.

D. PROTOCOL

1. The investigator had a written Protocol. However, the edition of the Protocol that the Research Nurse was using was the edition prior to the final version.

2. Changes to the Protocol were covered in B (3) above. There were changes in subject selection, doseage, blinding procedures, tests performed and also in certain cases admission criteria.

3.a. The changes to the Protocol were not specifically documented by the Investigator, but he had a current copy of the final version of the Protocol.

b. and c. See 3.a. above.

d. The effective change to the Protocol that was not documented as reported to the Sponsor was the admission of a couple of patients who did not meet the admission criteria. These were number 1055, who was diagnosed as having [redacted]. Massachusetts General Hospital decided it was not [redacted] However, the Clinical Investigator did not so document on the Case Report Forms and the subject was classified as an [redacted] patient. There is also no documentation of "special permission" received to admit number 1011 since the timing of his [redacted] was outside the Protocol requirements. (FD-483, No. 3B).

Other deviations from the Protocol included undocumented approval by the Sponsor for concurrent medication used for 11 subjects. This is noted on the FD-483, No. 3A:

3.) Deviations from the Protocol were allegedly approved per telcons. These calls were not documented, or noted in the Case Report Forms (CRF's). These deviations from the Protocola were not reported to the IRB:

A. Concurrent Medication
1001: Cefadroxil, Erythromycin (within 2 wks prior to the Study);
1003: Acyclovir, Wacomil*, Ranitidine (Zantac); *[Correction: Ludiomil]
1005: Hydrocortisone Cream (topical), Benadryl, Dilantin;
1006: Stelazine, Xanax, Halcion, Colace;
1008: Compazine, Tylenol, Lomotil;
1009: Tylenol;

1011: Benadryl, Excedrin;
1012: Keflex;
1051: Erythromycin;
1055: Streptomycin, INH (Isoniazid), Ethambutol, Pyridoxine;
1057: Lithium.

There were also numerous tests on 11 subjects that were not done as frequently as they were called for in the Protocol. These included subjects numbered 1004, 1005, 1006, 1008, 1009, 1011, 1012, 1051, 1053, 1055, and 1057 (FDA 483, No. 3 C.).

E. Consent of Human Subjects

1. Informed Consent was obtained from all subjects prior to their entry into the Study. In Exhibit D-1, the Summary of Subjects, there is a listing of the dates of the Informed Consent and the dates the individuals went on the Study. Number 1005 had two Consent Forms, 1 dated 3/24/86 and the other 6/17/86 and he started on the Study on 4/16/86. I asked about this and T. Flynn said that the original Consent Form had been misplaced (and later on was found) and so the Form dated 6/17/86 was generated. However, neither Form explained this.

2. Written consent was obtained in all cases. A copy of a typical Form, one each for [redacted]patients are attached as Exhibit I to this report. Once the subject went on the Open Label Study in September of 1986, an additional Consent Form was generated. I did not check all the records for these. An example of a copy of this Consent Form is also attached as part of Exhibit I.

G. Records Regarding Subjects

1. The Investigator maintained some records which are supportive of Case Reports on each subject, but other records were not maintained. Frequently the Case Report Form is the only record of the subject's visits. Observations specific to the individual cases are covered in G.1.e. below. Generalized observations are in G.1.a. through d. as well as in the above IRB and Informed Consent sections above.

a. Some of the observations, information, and data on the condition of the subjects at the time they were entered into the Study was noted on Case Report Forms. However, telephone calls to determine whether or not the subject was qualified to be on the Study were not always documented. T. Flynn provided me with a copy of notes from her Telephone Log. She crossed out the names of individuals who were not entered into the Study. I subsequently made those other names illegible by using a black crayon. This record is attached to this report as Exhibit J. I noted that it was not always clear whether the patient or his physician had called. The information noted on the Log did not address all prerequisites of the Study. However, since patients were seen at least once and often more times prior to entering the Study, it is possible that other information was obtained during those initial visits.

At the same time however, tests that were to have been performed on the subjects prior to entering the Study were not always done, and some of

the original documents ("raw records") no longer exist. Example of these observations are the following: for subject 1004 pre-entry lymph panel was done only once during pre-entry instead of twice as called for by the Protocol; 1004's clinical chemistry and B-12 and Folate tests were not done pre-entry or during the first treatment visit; and 1004's CMV and EBV Serology at pre-entry were blank.

The pre-entry hematology and clinical chemistries were not done for 1006.

The pre-entry chest X-ray was not done for 1009.

The pre-entry clinical chemistries for 1051 were not done.

Otherwise missing raw data records included the following:

For 1004, Hematologies numbers 1 and 2; 1005 Hematology Week 14; 1003's Urinalysis at Week 0 and Week 1; 1011 Hematology at pre-entry and raw data for T4/T8 values before 6-18-86 not located for 1005.

There were also tests that were not performed when the subject first entered the Study. They were not called "pre-entry tests" ; they were identified as "Week 0" for the first day the subject went on the Study. Therefore, test results on this day would reflect the subjects condition before being on the Study medication. These included CMV and EBV Serology at Week 0 were blank.

Number 1005 at Week 0 had the following tests not done: Hematology, Clinical Chemistry, Lymphocytes, EBV and CMV Serology.

Number 1006 had no clinical chemistry performed at Week 0.

Number 1008's Week 0 lymphocyte panel was not done.

The hepatitis B, CMV, and EBV tests were not performed for 1009 at Week 0.

The Week 0 lymphocytes were not done for 1012.

Number 1011's Week 0 hematology and clinical chemistry, and lymphocyte panel were not done. Also the B-12 and Folic Acid were not done at Week 0. The latter two test were done at the end of the first week that this individual was on the Study medication.

Number 1057 did not have the hematology and clinical chemistry tests done at Week 0.

Number 1055 did not have data for the clinical evaluation sheet at Week 0.

b. Documentation regarding the consent of subjects is listed in E. and F. above. Note also that the informed consent for number 1053 had a changed date on it. The date that appeared beneath the final date

cannot be read clearly but could be on or after the date that 1053 started the Study which was 4-10-86. This could have been a simple error and that is how it was explained verbally by T. Flynn. However, it was not documented in writing.

c. Information about the exposure of the subjects to the test article is in the Case Report Forms. The subjects took the medication on their own time and they were all out-patients. They were asked to maintain patient diaries. Usually the subjects used pencils to make the notations on the diaries. Some had erasures. The diaries had been taken by the monitor and were therefore not available for much of the inspection. When I did receive them I compared some of the entries in the diaries to the case report forms (see below). It was not possible in the time allotted to determine whether or not the set of diaries shown to me was complete.

T. Flynn said that the subjects had been told to make an entry in the diary only if they took the medication. That meant that missed doses would not be listed. I mentioned to T. Flynn at the end of the inspection that if the subjects were to write down all doses and then whether or not they took them it would be easier for her to check and determine how many doses the subject had missed. I explained that it would then function as a double check on the number of capsules remaining in the bottle that was returned by the subject. As described above, the records of drug accountability, especially those that listed the amount of medication returned by a subject and by inference the amount he had taken, were frequently changed. This happened on five out of 12 visits for 1003; for 4 out of 12 visits for 1005; 3 out of 10 visits for 1006; 3 out of 3 visits for 1009; 4 out of 8 visits for 1011; and 4 out of 9 visits for 1012. There were also changes on 7 out of 14 visits for 1051; at least 1 visit out of 9 for 1053 and 3 visits out of 7 for 1057.

d. Records of exposure to any concomitantly or concurrently admistered drugs were not kept by Dr. Schooley separate from the Case Report Forms. Since Dr. Schooley and Dr. Hirsch were not primary care physicians, the Study subjects might have received other medications from their physicians. They were instructed not to take other medication if possible, especially [redacted]. We were told that they were asked to note when they took the latter on their patient diary cards.

The Protocol specifically states what concurrent medication would be acceptable. This is stated in Appendix IV, page 27 of the Protocol. It states "Any regimen not listed must be approved by Sponsor". A similiar statement is made in the body of the Protocol, pages 13 and 14. [redacted] was allowed for treatment of [redacted] We noted that frequently patients were also taking B[redacted] instead. Dr. Schooley said that at the initial [redacted] meeting in early 1986 that an investigator had questioned [redacted] of [redacted] about substitution of [redacted] since the latter is manufactured by [redacted] had responded that there is no difference between the two. Dr. Schooley mentioned that pharmacists in Massachusetts must give the cheaper product unless the physician says otherwise on the prescription.

Otherwise the concurrent medication that was taken during the Study and not "cleared" by the Sponsor in any documentation was listed above under Protocol Deviations (see D.3.d., the Protocol Section above). In addition to those comments I would note that the hospital record copy that I had to view for the subject 1059 was not legible. It is possible that the words Dilantin and Codeine and Pyromethamine were listed on the record. I asked to see this subject's hospital record and was told that it could not be located. A number of subjects were on [redacted] but I did not note that the Protocol specified that they could be on certain doses for 21 days. Therefore, I did not check that in the Case Report Forms.

Sure!

??

e. Observations and data on the condition of the subjects throughout their participation in the investigation were, as above, generally recorded directly on Case Reoprt Forms. There were very few raw records with which to compare. In this section I will list the subjects by number and in the first paragraph for each subject I will focus on the most significant observations/deviations from the Protocol or the Regulations.

Mr. Breitman?

Prior to that however there are some issues that cut across subjects and should be described. To begin with T. Flynn completed most of the Case Report Forms and also the monitor, [redacted] made numerous entries on the records. However, it is often not possible to determine who made the entries on the records. In addition to these two individuals Dr. Schooley and Dr. Hirsch and occasionally Dr. Ho also made entries. T. Flynn was on a honeymoon during the last week of May and the first week of June and during that time she was replaced by another nurse as discussed above. Again, however, because entries were ordinarily not initialled it is not possible to tell exactly what entries were made by that individual as opposed to T. Flynn at some point after she returned.

There was a lot of discretion exercised during the course of this Study. Examples include such as 1055 [redacted], who was discharged from [redacted] on 10-14-85 with a final diagnosis of [redacted]. He had been on [redacted] but had experienced adverse reactions to that, so he was then on [redacted]. However, 1055 was diagnosed to be an [redacted] patient because MGH decided it was not [redacted] I did see evidence in the file for 1055 that slides had been sent from the [redacted] Hospital to MGH. I did also see on the entrance Case Report Form that this subject was diagnosed as an [redacted] patient. I did not see any statement in the record that explained that any particular individual at MGH was taking responsibility for the fact that this patient's previous diagnosis was denied by the physicians in Massachusetts.

Other examples of the discretion exercized include:

Subject [redacted], 1001, had medical records from [redacted] with a note dated 5-16-85 that a lesion on h[redacted] was diagnosed as [redacted]. The summary diagnosis was [redacted]. Again on the entrance record, Case Report Form, page 2, was a statement that this individual had no [redacted] I asked Dr. Schooley if he did any followup biopsy as an example for this subject. He said he would do that if the lesion got large over time. He said it is a hard call for a pathologist to make. He said sometimes its "yes" and sometimes "no". He said you

go on behavior. He said he was agreeing with the diagnosis [redacted] made in [redacted]

Number 1006 [redacted] had a medical history that included [redacted] I asked why this did not change his classification from [redacted] to [redacted] T. Flynn said that they were unable to grow the culture on a [redacted], so he was classified as [redacted] This individual also was on Stelazine and in the Medical History (page 3) was said to have depression. T. Flynn explained that the depression was not bad enough for this individual to have a Lumbar Puncture.

Then after the pre-entry visit for 1006 were three added pages. They were entitled, "Infections Other Than OI". These three pages were added according to T. Flynn later in the Study to document opportunistic infections. These pages were not numbered. The first of the three noted that the infection, [redacted] had been, "(Seen earlier, onset date per Sponsor request)". T. Flynn explained that this statement was written by the monitor. It was seen on other records of opportunistic infections for other subjects and ordinarily referred to [redacted] She said it meant that there had been symptoms earlier but that the date used was the one requested by the Sponsor firm. The second of these three pages said that there were not tests performed for this diagnosis; "Dx by clinical observation". The last of the three pages was dated 6-26-86 and was identified as an update. It said that the [redacted] had started on 5-1-86 and ended on 6-26-86. No raw records substantiates the observation of [redacted] T. Flynn said that was true, that it was based on observation alone.

When I asked T. Flynn about this situation, she said they would prefer to have a culture. However, if they are not able to grow it then this happens. She said they do treat for it because it can lead to Esophogitis.

Subject 1055, [redacted] had [redacted] according to Fungal Tounge cultures done on 3/11 and 3/31/86. However, he later had a record that said that there is "no involvement" (for [redacted]). T. Flynn said that this can happen because the condition can clear up and it will not appear again. Medication such as Nystatin, Konketazol and Chlortrimozol can have this effect.

Subject number 1051 [redacted] had no record to support the claim in the Case Report Form, Pages 1 and 4, that the patient had a history of Oral Candidasis. This subject was classified as an [redacted] patient. T. Flynn said that he had a negative culture but presented on physical examination. She said that this often happens.

Number 1053, [redacted] had an entry in his physical examination under "EENT" for Oral Candidasis. Both the normal and abnormal responses were checked for this entry. It appeared that the decision had been to call it normal then abnormal and then normal. T. Flynn said that she could not tell from the record. I saw no history of medication for this indication. She said it was necessary to culture him because he was a [redacted] patient. That is apparently based on his [redacted] history in November

1985 (page 4).

violate if positive upon entry!

Subject 1005, [redacted], at Week 1, that is after one week on the drug, had a Hemoglobin value of [redacted] The Protocol required that for entry onto the Study the subject have a [redacted] Hemoglobin. Dr. Schooley explained that it is only when starting on the Study that the hemaglobin is an issue. He said later the subject can be transfused. He also said that the subject should not be on the Study if the value is below [redacted] before being entered and he said something about probably the individual should be transfused. There was at least one case where the subject was transfused a week before entry on the Study. That was subect 1009, C.S. He received 4 units on 5/22/86 and began the Study on 5-29-86.

Subject number 1006, [redacted] had a Discharge Summary from [redacted] Hospital on December 11, 1985 which included a note of CMV of 1:64 (normal 0.2521.3). This was accompanied by a comment which said "suggestive of recent infection". T. Flynn said that this individual could still be on the Study and was an [redacted] patient. She, at another point, had said that the CMV would have to be disseminated (it is my understanding to be classified [redacted] patient").

One last observation of about issues that might be described as discretionary is the fact that those subjects who became so week during the Study that they had to be treated, usually with a blood transfusion, went to the Emergency Room to be treated. T. Flynn explained that the [redacted] cannot perform blood transfusions and that the Blood Bank also would not do it. However, my observation is not that the subjects had to go to that location, but that they became so ill that on their own they went for treatment. Subjects who received transfusions during the Study included 1004, [redacted]; 1008, [redacted]; and 1053, [redacted] three different occasions).

Adverse Reactions were noted, but were not always identified as such in the Case Report Forms. In other words, symptoms might be listed as part of the physical exam or as part of clinical chemistry results, but they were not identified as adverse reactions on the adverse reaction Case Report Form. The Adverse Reaction Case Report Form for this Study requests whether or not in the judgment of the investigator the reaction is related or possibly related or not related to the Study.

The listing of Adverse Reactions on the FD-483 is as follows:

4.) Adverse reaction of high SGOT is not mentioned on CRF for 1003 (CRF p.73 says "none"). anemia

1004 Severe coughing not addressed if adverse reaction or not in CRF, (wk. 14.).

1004, 1008 and 1053 were treated in the Emergency Room during the study due to need for blood.

1005's ataxia and "wobbly-transient" were not reported as adverse reactions, nor explained.

1008 was hospitalized during the study, which was not stated in

CRF's and was said to have no adverse reactions. Wks. 1,2,3,4,8,10,12 had moderate headaches, diarrhea, lethargy, abdominal cramps, dizziness, but no adverse reactions.

1012 had rash wk 8, but no adverse reaction; wk 10 had moderate loss of appetite, but no adverse reaction.

1051 had SGPT value of 58 during wk 3, and in wk4, SGPT value of 57, but no adverse reactions.

1053 wk 2 listed nausea and marked fatigue, but no adverse reactions; wk 3 WBC's were 1.6 and granulocytes were 944, but no adverse reactions. During wks 10 and 12 Pt. diary says blood counts were too low to take the drug, but adverse reaction CRF says patient took drug during part of that time. Week 14 WBC 1.6; no adverse reaction.

1059 went to the emergency room during the study and had NMR and CT tests, but this is not stated in the CRF's nor are there any adverse reactions reported.

In addition number 1005, [redacted] had a seizure during the course of [redacted] Study. Dr. Schooley had talked with his attending physician at [redacted], but did not have any record on [redacted] incident.

No adverse reactions were reported to the IRB.

Another general issue applying to a number of subjects in the Study is that a cursory review of their Case Report Forms would indicate that they had been on the Study longer than actually happened. Generally this is due to the fact that Study records continued to be generated even when the subject had been dropped from the Study for a period of two weeks to a month. Examples include: number 1053, [redacted] dropped out of the Study for two week from June 19th to July 3rd. and he was off the Study again on August 11 for a final time due to decreased white blood cell count. CRF were generated as though he were on the study through 9-8-86. Number 1057, [redacted] was on the Study for 13 to 14 weeks but the Monitor's Accountability Sheet indicates that he was on the Study for 16 weeks. The Case Report Forms showed that he last came to the Clinic during Week 14 and nothing was returned thereafter. Subject Number 1008, [redacted] was off the Study for a month even though the Accountability Record indicates that he never left it. He was off the Study during the Week 6 visit. It is unclear if the Week 8th's medication was dispensed. In fact during Week 4 the Case Report Form states that he had pneumonia beginning July 7th and ending August 7th. And during the week four visit he was not dispensed any medication. In fact it appears that he was hospitilized then or soon after although the Case Report Forms do not state that he was hospitilized. So he was off the Study medication for at least a month but to view the Record of Dispensing of Medication to him, as an example, D-2 it appears that he was on the Study pretty regularly for 12 weeks.

Another observation that applied to numerous Study subjects was that there was no comment by the clinical investigator about significant observations and abnormal values (FD-483 No. 6). Some examples of significant observations about which there were no comment are the following:

FD-483 No. 6. There is no comment by the clinical investigator re several significant observations (including subject left the study) and abnormal values, eg.:
1003: IgG value out of range-high - 2589, (Range 540-1480), wk 12; Note of "neck mass" not explained, initialed, or dated at wk 20 (noted on study med record). When it was explained on record 2 wks later, there were no initials and the subject was removed from the study.
1055: "fevers to 105 - admitted to hospital. Drug held", CRF not say why ended study.
1056: a placebo subject, received 1057's medication (AZT drug) for two weeks; this is not explained on his (1056's) CRF. 1057's record does not reflect this. There should be an extra bottle of 100 for 1056, but it is not accounted for.
1057: had HGB value below entrance criteria; repeat HGB value was used instead.
1059: not say why ended study.

they missed one!

The Case Report Form packages have not been signed off by the Clinical Investigator to indicate that the Study has been completed or to say why the patients stopped. This is true for most patients except for those who developed opportunistic infections. (Examples include: 1003 C.H. 1057 PAS 12-30-86. PAS 12-30-86

There is no comment by the Clinical Investigator for Hematology and Clinical chemistry values that were out of range on numerous weeks (FD-483, No. 6) for the following subjects: the subjects in this Study were so ill that it was the norm to have some of these values be out of range. When a record is not listed below as having values that were out of range is ordinarily because the test was not done or the record could not be found.

1001, [redacted] had an abnormal hemoglobin of 11.6 on Week 0 and an abnormal white blood cell count of 2.7 (range 4.0 to 10.0) on Week 1 (CRF page 38 attached).

1003, [redacted] had abnormal values and no comments for Weeks 3,4,6,8,10,12,14,16,18.

1004, had abnormal values and no comments for Weeks 1,2,3,4,6,8,10.12,and 16.

1005, [redacted] had abnormal values with no comments twice during pre-entry testing, and again during Weeks 1,2,3,4,6,8,10,12,16, and 20.

1006, [redacted] had abnormal values with no comments for Weeks 0,1,2,3,6,8,12,14,and 16.

1008, [redacted] had abnormal values for Weeks 0,2,3,4,8,10, and 12. His Week 0 B-12 and Folate test results were out of range with no comment.

1009, [redacted], had abnormal values and no comments on Weeks 1,2,and 3. On Week 2 his Alkaline Phosphatase was high and on Week 3 his Eosinophils were low. (Week 0 values for 1009 were also out of range.)

1011, [redacted] had abnormal values and no comments on Weeks 2,4,6,8,10, and 12.

1012, [redacted] had abnormal values with no comments at pre-entry, and Weeks 0,1,2,3,4,6,8,10, and 14. And at Week 0 the T4 value was less than 100, again with no comment.

1051, [redacted] had abnormal SGOT/SGPT values during Week 24.

1053, [redacted] had abnormal values and no comments at pre-entry Week 1, 2,3,4,6,10,12,14, and 16. At Week 6 his Urinalysis showed marked amorphous urates and moderate bacteria and moderate calcium oxalate crystals. There were no comments about these results. On Week 12 his IGG value was 2364, where the normal range is 540-1480. His IGA value was 558 and the normal range is 65-380. His white blood cells for that day were 1.2 and the record noted that this was verified by repeat analysis. However, none of these results were commented on in writing by the Clinical Investigator.

1055, [redacted] had abnormal results with no comment for Week 0, 1,4, and 5. No Urinalysis was conducted for 1055 on Week 3.

1057, [redacted], had abnormal results with no comment for both tests at pre-entry, Week 0,1,2,3,4, and 10.

Another general observation that was made about a number of subjects was that tests which according to the Protocol, were to be done twice before the Study began, again during the first Week of the Study, and also later were not always performed according to schedule and the Case Report Forms do say why, nor are they initialled and dated. Please note that the following tests were not done at this location: skin tests at 24 hours, Plasma Concentration levels, Serum Interferon levels, Nitrogen testing, Quantitative Immunogens, Cytomeglovirus and Epstein Barr Virus, and Immunoglobulins. Examples include the following:

1003, [redacted] had no Hematology Tests run and no explanation for Week 4 and no Reticulocyte and Erythrocyte SED Rate done for Week 4.

1004, [redacted]s pre-entry Lymph panel was done only once; his clinical chemistry and B-12 and Folate tests were not done at pre-entry or during the first treatment visit; during week 1 no Urine sample was received and there was no comment on the Case Report Form, page 107.

1005, [redacted] at Week 0 had all of the following not done: Hematology Clinical Chemistry, Lymphocytes.

1006, [redacted], had the following tests not done: the first set of lab tests at pre-entry (Hematology and Clinical Chemistry), his Week 0 Clinical Chemistries were not done; and at Week 8 the HTLV-III was also not done.

1008, [redacted] had no Lymph panel done at Week 0 and the same test was not done at Week 4 along with the HTLV-III test.

1009, [redacted] had no pre-entry Chest X-Ray, Week 0 Hepatitis B test, Week 3 Urinalysis, or Week 4 Hematology.

1011, [redacted] did not have the following tests run at Week 0: Hematology and Clinical Chemistry, Lymphocyte Panel, B-12 and Folic Acid. These last two tests were done at the end of the first week that the subject was on the drug. At Week 12 he also did not have the following tests done: Hepatitis B, Immunoglobulin, Lymph Panel. The Study ended the day after this person's visit at WeeK 12.

1012, [redacted] had no Week 0 Lymphocytes or T4/T8 tests. He was also missing a Week 1 Urinalysis; a Week 4 T4/T8; and Week 12 Clinical Chemistry and Hematology.

1051, [redacted], had no pre-study clinical chemistry; clinical chemistry and Urinalysis at Week 6 were not done; the HTLV-III test was not done at Week 12.

1053, [redacted], at Week 0 had no Hematology and Clinical Chemistry; no Week 1 Urinalysis; no Week 8 Hematology (clotted) followed in two weeks by blood transfusions; Week 16 T4/T8 not done; Week 20 Urinalysis not done; Week 22 no vital signs and Clinical Chemistry and Urinalysis not done and Hematology invalid.

1055, [redacted], had no Clinical Evaluation Sheet at Week 0.

1057, [redacted] had no Blood Lymphocytes or T4/T8 values for Week 0.

In this section observations by subject will be listed. These observations will overlap with those made above that were common to groups of subjects, but they will be repeated in order to assess the experience of each subject. Some records were reviewed for all subjects, EG the Informed Consent. Records for five subjects were not completely reviewed although some records for these individuals were seen: 1010, 1052, 1054, 1056, and 1059. The few observations made about these individuals will be included in order with the rest of the subjects.

The most significant observations about each subject will be included in the first paragraph about them.

Number 1001 [redacted] is an [redacted] patient. His initials might also be [redacted] on some records. He is one of two subjects who died while the Study was on-going, however, in each case the subject was off the Study at the time of his death. [redacted] was on the Study from April 3rd until April 14 or 26th (Case Report Form, page 245 states 4-26-86). He was a Placebo patient. His death was said to be caused by Klebsiella Pneumonia which had been cultured from his lung in February 1986 by his

in study for only 1-2 weeks.

died 15 Aug. - 4 months after leaving study. Yet, he was counted as a death in the placebo group.

#1001 - allegedly + Lactic - died

referring physician, [redacted]. His record also had a note dated 5-16-85 that a lesion on his scalp might possibly Kaposi's Sarcoma. T. Flynn explained that the final diagnosis was Hemangioma and not KS. This issue was discussed above, when I asked if they would do a followup biopsy to which Dr. Schooley said,"No", unless it got larger or there were new lesions. In the Summary Sheet for Number 1001 dated 9-18-86, page 1 of Exhibit J-1 is a statement of this patient's condition at the time that the Study was ended. It includes a correction which states "PT died of [redacted] with moderate neurological impairment". (However, on the second page the statement of the subject's discontinuation from the Study is a statement that he discontinued from the Study due to generalized debilitation and Klebsiella Pneumonia. The first of those two records was generated most recently and is probably the most accurate.

"neurological impairment" sounds like AZT,

Number 1001 had a note on page 3 of his Case Report Form of personal medical history of "CMV lungs Klebsiella infection" with a date (5/85). We were told that the CMV would have to be clinically manifesting that is, giving him problems to be a concern for the Study. We were told that you could probably find CMV or PCP in his lungs but it would not be treated if it were not causing him problems. Note also that this record of the personal medical history, Case Report Form page 3 and Exhibit J-1, page 5 is not dated as to when it was completed and does not show who completed the Record. That same observation is true for most of the Case Report Forms, although in some cases it is not as relevent as others. The very first page of Exhibit J-1 has at least two kinds of handwriting, one by Dr. Hirsch and the other maybe by T. Flynn.

Page 6 of 1001's Case Report Forms includes his T4/T8 values. Note that the OKT4 Absolute value is 31.25. A chest X-Ray in the file for this subject included a note that on 3/17/86 he started on Erythromycin. However, page 15 of the Case Report Forms (Exhibit J-1, page 7) states that there were no concurrent medications for four weeks prior to entering the Study. He started on the Study on 4-3-86. Another record (not copied) said that he had Candida on his tongue dated 4-6-86. On the Case Report Form, page 3, Exhibit J-1, page 5, the date used was 4-22-86. He entered his participation on the Study on 4-26-86. Although his record of concomitant medication said that he was taking none during the four weeks prior to this Study, it was not possible to verify this since there were few records other than the Study records available for review.

During Week 1 of the Study Number 1001's white blood cell count was 2.7 where the normal range is 4.0-10.0. This was described above as an out of range value about which the Clinical Investigator did not comment. The record of this result is attached as Exhibit J-1, page 8. Also during Week 1 the B-12 Value was 33. The normal range is 205-876. There is no comment by the Investigator or anyone else about this. T. Flynn said that it was understood by the physician to be disease

related. The same week his hemoglobin value was 11.6 (which was low).

During Week 2 the Case Report Form (Exhibit J-1, page 9) stated that 1001 had been on Erythromycin for one day beginning 4/10/86 to 4/11/86 and then was on Cefadroxil from 4/11/86-"con't". This record is also an example of not stating the day on which the entries were made, except that it refers to the week to visit. When I asked T. Flynn about this she said that the subject's personal doctor has put him on the Cefadroxil due to the Klebsiella Pneumonia, a recurring infection.

The record for dispensing the Study medication for Week 3, page 58 (Exhibit J-1, page 10) shows that [redacted] returned six capsules (later changed to 8) on 4-24-86. He was also dispensed 50 more capsules for the 4th week. Then there are two additional notes to this record on the bottom. The first says, "4/26[redacted] The second says , "Bottle not returned. Hosp (italized) in Maine-Klebsiella Infection". This note is not dated or initialled to say who was taking responsibility for making it. It appears to be T. Flynn's writing. T. Flynn explained to us that this subject's physician had called her on the phone to explained that he had died. According to the first pages of this Exhibit his death was on August 15, 1986.

Number 1002, J.J.S., was an [redacted] patient who had been on Placebo. This subject requested to be dropped from the Study and it appears that he was on the Study for only two weeks, from April 3rd to April 14, 1986. The record generated the day before the code was broken for the Study (Exhibit J-2, page 1, states, "Developed [redacted] Week 2 {4/14/86}, maximum severity=moderate". The updated Karnofsky score was 80-90, according to T. Flynn whose source was the subject's brother.

[redacted] date of birth is 11-25-30. According to T. Flynn his physician, [redacted] first called her about this subject on 3/3/86. From my review of the telephone log,(Exhibit J) it is not clear to me that it was [redacted] who made the call. There is no other information to indicate how this patient was referred to the Study. She also said that his doctor said that he was not on any medication. I do not see any information on the telephone log that verifies that.

The second page of J-2 is the Investigator's statement which is page 246 of the Case Report Form. It is one of the few closing records which states that the entries of the data in the Collection Forms on this patient have been examined and are correct to the best of the signer's knowledge. Dr. Schooley signed this Record and it is dated 10-9-86. When I asked why it was dated then since the subject had been off the Study since the 14th of April, T. Flynn said that they did not know how the Sponsor Firm wanted the Study to be ended.

The Record of Discontinuation of the Study, Case Report Form 245, (Exhibit J-2, page 4) said that the patient requested to be discontinued from the therapy and that there was moderate Opportunistic

Infection after the patient entered the Protocol. This record is dated 4-14-86.

The third page of J-2 shows the Study Medication Record accountability for Number 1002 at Week 1. This record states that four capsules were returned on 4-10-86 and the last page of Exhibit J-2 shows that 4 capsules out of the original 50 were returned from the Week 1 bottle. However, Exhibit D-2, the Monitor's Medication Summary states that the first week's bottle for Number 1002 was "LOST'. The next week's medication had been dispensed on 4/10 and the subject discontinued the Study on 4/14, however, the bottle was not returned.

AZT

Subject Number 1003, [redacted] was on the drug and is a [redacted] patient. He was eventually discontinued from the Study due to developing TB. My review of his Case Report Forms indicated that that happened during Week 20 of the Study. The monitor's Medication Summary (Exhibit D-2) indicates that he went for 22 weeks. PLEASE NOTE: Ordinarily one paragraph is used to describe the significant events for a subject but for this subject it will take two. CH was on Septra or Bactrim from November 25, 1985 until at least August 28, 1986. This deviation from the Protocol was not noted on the FD-483. There were no Adverse Reactions listed on Case Report Forms for this subject. However, he had significantly elevated SGOT, and IGG values and significantly low T4 value and white blood cell counts. His Hematology values were so low for so long that I asked if he had received a blood transfusion. I was told (verbally) that he did not.

His week 16 T4 value was 29 (very low).

As of Week 18 an observation of "neck mass" was made but with no comment, date, initials or explanation. This was the same week that there was no record of concomitant meds in the binder. By the following visit, Week 20, it appeared that a biopsy had been done by the patient's physician in [redacted] and the diagnosis of presumed TB was made. See Summary Sheet dated 9-18-86 (Ex. J-3); cultures were pending as of that date. Toward the beginning of the Study, Week 6 and Week 8, this subject returned a large number of capsules, 32 and 25 respectively. There should be approximately 14 to 16 returned if the medication is taken according to the Protocol. T. Flynn said that he probably slept through the night. She said they encourage the subjects to take the medication as directed.

[redacted] was treated for [redacted] from 11/16 to 12/12/85 (see Exhibit J-3, pages 32 through 34). Based on the date of discharge, then his entry into the Study was within the 120 days. When he entered the Study, what is referred to as "Week 0" a clinical evaluation was done. It is page 19 of the Case Report Forms (see Exhibit J-3, page 4). Later a second page 19 was also generated which has more specific information. It can be seen as page 3 of Exhibit

"RB" as The Monitor

#1003 (AZT)

J-3. It has a note, "Transcribed 6/23/86 RB". I asked what this meant and was told that the Sponsor Firm had decided that the longer form should be used and not the short form. However, the short form , includes information not on the long form, such as Candida Colonization and Cutaneous //// Skin Eruptions. T. Flynn noted that the longer form had been completed by the monitor, R.B., and that he had transcribed the information from the previous form. However, the long form asked for information that was not present on the short form such as, "Fever, Chills, Night Sweats, etc. I noted that on this Case Report Form that the monitor did not complete those entries for which there was no information given on the original form. T. Flynn also said that the Sponsor Firm had asked that the short form be destroyed but this was done not at this location. Also during Week Ø there was no data to support the Urinalysis Data on Case Report Form page 24 (Exhibit J-3, page 6). T. Flynn said that it was not always kept. I explained that it should be. The antibody HTLV-III Test was done later after the subject was on the Study.

When [redacted] returned for the Week 1 visit he returned some capsules. It was difficult to read the number returned; see CRF page 42 (Exhibit J-3, page 13). T. Flynn said that 9 capsules were returned. I noted that there were no

Hematology, Clinical Chemistry, or Urinalysis data entered in the Case Report Forms for Week 1. However, there was a print-out from [redacted] (Exhibit J-3, page 8; see also pages 9 through 11. The Reticulocyte Count was performed at MGH. The Erythrocyte Sedimentation Rate should have been done at MGH (Exhibit J-3, page 9). There was however no Urinalysis done for that week and no explanation made as to why. The fact that the Case Report Forms were not completed was explained when I reviewed the correspondence and it indicated that the [redacted] values would be transmitted to the Sponsor directly. So there many pages of Case Report Forms that were not completed and there were no comments on out of range values either on the [redacted] Slips or on the blank Case Report Forms.

The review of the Study Medication Record for Week 1, see CRF, page 42 (Exhibit J-3, page 13) showed that there was writing on the photo copy of the Form. In other words since a copy had been made of the original and it was shipped to the Sponsor, the copy has been altered. "RB" the Monitor, had corrected the bottle identification number. "tf" had altered the date the bottle was dispensed. Both of these changes were initialed and dated, but not explained. The dates that the next prescription were good for were also changed but the original dates could not be read and there were no initials, dates, or explanations. Likewise on page 43 (see Exhibit J-3, page 14) the Listing of Concurrent Medications was changed to read that there were none to list. Bactrim and all of the entries on this page were written on the photo copy.

The Week 2 [redacted] printout lists [redacted] as being 36 years old, where as previous records said he was 44. A Urinalysis was performed during Week 2 and he continued to be on Bactrim.

When I saw a note in the Clinical Evaluation that 1003 was depressed at the Week 3 visit, I asked if that was enough for a Lumbar Puncture. T. Flynn said he did not have enough depression for this procedure. The [redacted] Slip for this visit, 5-1-86 (Exhibit J-3, page 15) showed low red blood cell counts, Hemoglobin, Hematocrit, and white blood cell counts and an elevated LDH. His Amorphous Urates were "marked". There were no comments on any of these out of limits values. His record of return medication for that date was changed from an original entry of 6 capsules returned to 10 capsules. This note was written on the photo copy and was not dated or explained (Exhibit J-3, page 16). The Record of Concurrent Medication (Exhibit J-3, page 17) has a note that he did not take the Acyclovir according to direction and "took only one" every four hours. The Record also notes that 1003 was taking Ketoconazole for Candida as did many other subjects. Note: The Protocol approve use of "Clotrimazole Troches".

For the Week 4 visit the Hematology, Reticulocyte, and Erythrocyte Sedimentation Rate were not done. The SGOT Value was three times normal at 61, the SGPT was also elevated at 116 as was the LGH at 557. There were numerous other out of range values on this record and no comments (Exhibit J-3, page 18). The T4 and related tests values were "not valid". T. Flynn said that the tests did not go right. See Exhibit J-3, page 19. I asked about the Serum Interferon samples and was told that they were banked and ready to go but they had not been called for yet. The Adverse Reaction Form for Week 4 said that there were none. We explained to T. Flynn that the SGOT Values should have been mentioned.

The returned Study Medication Record for Week 4 was altered from an original entry of 7 capsules returned to make it 12 returned. There was no date or explanation as to why the change was made (Exhibit J-3, page 20). The next page of the Case Report Form and Exhibit is concurrent medications for Week 4. The line listing Ketoconazole is added to the photocopy. It states that CH was on that drug until 5/7/86.

Week 6 results showed the Lymphocytes were high at 60 (range 20-45) and white blood cell count was low at 2.9 (normal range 4.0-10.5). The Clinical Evaluation Sheet (Exhibit J-3, page 22) mentions L Flank Pain-intermittent especially with walking (rated "2") and no mass or pain with Palpation. There was also some question of a Fungal Infection in his right great toe. This is the date on which he returned 32 capsules from the previous 2 weeks. Also during this visit the Record of Medication Dispensed includes a seven digit code that could not be explained by the Research Nurse. That number is "1017401" (see Exhibit J-3, page 23). We asked numerous times what the meaning of this number was and were told that it might be a product number code, but it was never satisfacterly explained and it was not possible to see an original label. A similiar seven digit code was seen on the label of No. 1005, described below.

The Week 6 Concurrent Medication included two additional prescriptions: Ranitidine and Ludiomil, both of which were started on 5/18/86. The

latter was to end on 5/23 and the former was to be continued (Exhibit J-3, page 24). Please note the FD-483 lists the latter drug as Wacomil. The correct name Ludiomil is an antidepressent by Ciba. , Ranitidine is an anti TB drug.

During the Week 8 visit, 6/5/86, there were numerous blood chemistry and Hematology Values out of range and no comment was made by the Investigator. [redacted] Karnofsky Score was up to 100 (from 80 during previous visits). He complained of headache. This is the visit when 25 capsules were returned. The concurrent medication for this date continued to include Septra and Zantac (Ranitidine). The dates were changed for both of these; the Septra date had been explained above. The Zantac was changed from 4/22/86 to 5/18/86. There was no explanation why this change was made. During the Week 10 visit the Clinical Evaluation (CRF, page 103) showed no blood products, feels well, and 1-10% Candida. The red blood cell count, Hemoglobin, Hematocrit and white blood cell count continued to be low and there was no comment made. There were no adverse reactions listed and 19 capsules were returned. The date on the concurrent Septra medication was changed from February 1986 to November 25, 1985. T. Flynn said that she made this change. It was not initialled, dated, or explained.

During the Week 12 visit, 7-22-86, the IGG was 2589 with a normal range of 540-1480. This result was verified by repeat analysis and there was no comment made. (See Exhibit J-3, page 27). An abdominal check during that visit found a small module, 4 CM. Seventeen capsules were returned. The moniotr's study meds record for week 12 said wk. 12 was returned intact from the Pharmacy. He continued to be on Bactrim, DS, and Zantac.

The Week 14 visit was on 7-17-86. One blood cell count was 1.7 which was its lowest level during this Study. The red blood cell Hemoglobin and Hesmatocrit were also all low and no comment was made about any of these. There continued to be no Adverse Reactions and 18 capsules were returned. The Record of Study Medications was altered with a note written on the photocopy that "Week 18 was issued". The Concomitant Medication Listing for this week did not list Zantac and did not say if the subject had stopped taking it.

By Week 16, 7-31, [redacted] had gained 3 kilograms. His T4 value was 29, very low but no comment was made about that. The [redacted] Printout showed that white blood cell counts and Hemoglobin were low and no comment was made. In fact the WBC's were so low at 1.9 that they were "verified by repeat analysis". Returned Study medication for that week was changed from 6 to 14 on the photocopy. He continued to be on Bactrim, DS.

During the Week 18 visit, 8-14, [redacted] had the same low Hematology values with no comments and no adverse reactions. The Study Medication Record (Exhibit J-3, page 29) had the two words "Neck Mass" and no further explanation. This same record changes the number of capsules returned from 6 to 12 and there is no record of concomitant medications for this week although during the following week it will indicate that they continued throughout.

The Week 20 visit of [redacted] was on 8-28. The Brief Physical Exam made the following note of abnormal findings for EENT, "swollen R interior neck nodes and soft tissue post biopsy 8/22/86-Dx multiple acid fast bacilli, will begin INH, Ethambutol, Rifampin (per Dr. [redacted] will D.C. Study drug". There was no initialling of this note. I was told Dr. Hirsch made it. It is attached as Exhibit J-3, page 30. The Record of Return Study Medication for this day was changed from 5 to 13 capsules. The concomitant medication listed was Bactrim, DS. Dr. Schooley had explained that the diagnosis of the acid fast bacteria was from the subject's [redacted] physician.

[redacted] was discontinued from the Study due to opportunistic infections. This is stated on page 245 of the CRF. Dr. Schooley signed the Investigator's Statement, CRF, page 246, on 10-9-86. In fact, this record was a photocopy of an original which listed the date and patient number at the top. Dr. Schooley's signature was written on the photocopy at his site. T. Flynn said that he was taken off the Study drug because he could not take the TB drugs at the same time. She said they later determined, after 9/19/86 that they could do both. This record is attached as Exhibit J-3, page 2.

Subject Number 1004[redacted] was an [redacted] subject on the drug. I did not have the hospital records to review at the same time as viewing the Case Report Forms for [redacted] He stopped his participation in the Study on or about the 14th week. However, records were generated through Week 20. He developed [redacted] during August, at which time he stopped taking the Study medication. During the Study over time his white blood cell counts decreased from 5.4 on 4/17 to 2.3 on 7/18. Three days later he received three units of Packed Cells. At about the same time, 7-17, he was noted to have coughing with a severity of "3". T. Flynn said this was "severe" but not deemed an adverse reaction. On July 30th he had another two units of Packed Cells. The 9-16-86 summary said that he was off the Study as of 9-9-86 telephone call while he was being treated for [redacted] In addition it says that [redacted] moderate at week 18. D/C Study medication. Probably will restart Study after recovery [redacted]

[redacted] was hospitalized twice in 1986 at MGH prior to entering this Study. The first admission was from January 2nd to the 16th. The second admission was January 23 to February 11th. The Hospital Summary at the beginning of his Patient Chart said that the first visit was for [redacted] and the second was for [redacted] Bronchial Lavage. He had been well until August 1985 according to the first visit Admission Note, when he presented to an "Outside Clinic" (not related to MGH). He was told he had Bronchitis and again in November he did the same and was told that he had "Pneumonia" in the left lung. I did not see a record to clarify whether or not that bout of Pneumonia might have been [redacted] During his first visit at MGH his HTLV-III was found to be strongly positive by Elisa. His chest X-Rays during that visit indicated on 1/5 that [redacted] is possible and on 1-12 "could be resolving Pneumonia". I asked T. Flynn if this was ever decided and she said that it is not possible to rule out [redacted] unless a Bronchial Lavage is done. Copies of [redacted] hospital records prior to the study are pp. 46-64 in Ex. J-4 since

there was some discussion of how often he had [redacted] before the study.

His second hospital admission on 1/23/86 was via the Emergency Room where he had difficulty breathing. The Pulmunary Fellow's note said that during the previous visit he had Pneumonia of "uncertain etiology". Two days later his Hematocrit was 24 and K+ was 5.0. The accompaning physician's note indicated that this was due to his chronic disease. On January 28th Dr. Weinberg, his physician, asked for the Retina Service to check for fundus changes due to using six liters of Oxygen. A nutrition note on January 24th noted that he had lost 20 pounds since his last admission and 40 pounds since November of 1985. On February 2, 1986 his was 27.1 and white blood cell count 2.9. [redacted] was discharged on February 11th and a followup Chest X-Ray was done on February 27th. There were other laboratory studies ordered by Dr. [redacted] in March.

[redacted] is a part of the long term study at MGH, which accounts for the code number, "170", eg. Exhibit J-4, page 35. This record lists the T-Cells Subset Value for January and early April for [redacted] The following page has the same information dated 4-9-86.

In the Case Report Forms for [redacted] page 4, is a note that he had [redacted] on 1-20-86 and recovered from it on 2-14-86. The first of these two dates is between the two hospital admissions described above. (Exhibit J-4, page 1). There were no records for the Raw Hematology one and two (CRF pages 5 and 7) above the white blood cell count value. Only one pre-entry lymp panel was done (CFR page 6,8). T. Flynn agreed that for some reason only one was done. His informed consent is Ex. J-4, pp. 40-45.

At Week 0, 4-10-86, [redacted] Hemoglobin, Hematocrit, and red blood cells were all low and there was no comment made. They were respectively 10.5, 31.8, and 3.59. The Clinical Chemistry and B-12 and Folate tests were "ND" or not done (Exhibit J-4, pages 2&3). These tests are required by the Protocol. There were no initials accompanying these notations nor dates or explanations. T. Flynn said that these tests were not done due to neglect on her part. Note that they had not been done on pre-entry either. All entries for the CMV tests were written on the photo copy including for titer, "not able to do". (CRF page 27). The Mitogem testing was not done and there were no initials or explanation (Exhibit J-4, page 6). During the Week 0 visit the Concomitant Medication Record was not in the file for that week however page 15 which was the Concomitant Medication Record for the pre-entry visit was in the file. It is attached as Exhibit J-4, page 7 and it lists a multi-vitamin, Vitamin C, and "SLO K". The Week 0 T/4 and T/8 were not done.

Week 1 was dated 4-17-86. On the Clinical Evaluations Form (Exhibit J-4, Page 8) is a notation that he had episodes of dizziness 2-3 times during the week and one day of "Flu"-like symptoms. The initials MSH/tf are written after this note to indicate that Dr. Hirsch made the observation and T. Flynn wrote it down. These reactions were written as adverse reactions on Exhibit J-4, page 11. The Urinalysis for this week was not done (Exhibit J-4, page 10). T. Flynn said that if the

#1004 (cont'd)
AE

subject is not able to supply a urine sample then they do not ask them to return again for that reason only - they just try again at the next visit.

The Week 2 visit for [redacted] was on 4-24-86. He had the same low Hematology values with no comments and he had high liver values, again with no comments (see Exhibit J-4, page 12). He had gained weight and was 149 pounds. The Week 3 visit was on 5-1-86; again the same Hematology values were low as well as high liver values with no comment. He was 151 pounds and the concomitant medication was the same all along. The Week 4 visit was on 5-8-86 and the Hematology values were again the same with no comment.

The Week 6 visit for [redacted] was on 5/22. The Hematology values were like those above. This time on the Hematology Case Report Form, page 78 (Exhibit J-4, page 14) there was a note as follows: "Note decreasing Hemoglobin" followed by a listing of dates starting with 5/8/86 and at the bottom 3/27/82 and 4/3/86. The most recent Hemoglobin value showed 9.6 and the two earlier ones showed 8.9 and 10.5, respectively. There was no date for this comment nor initials. The concomitant medication, Slo K was increased by one per day. The Week 8 visit was 6-5-86. As of this date his weight was 160. There were even more low values on the Hematology Report this time and there were no comments about it (Exhibit J-4, page 15). The B-12 and Folate tests were "ND" (Exhibit J-4, page 17) as were the Mitogen Tests. The Slo K concomitant medication was reduced to three.

The Week 10 visit of Number 1004 was 6-19 and his weight was 163. There was no Urine sample received according to the Roche Printout (Exhibit J-4, page 18), but there was no comment on the Urinalysis Case Report Form (page 107).

[redacted] 12th Week was on 7-2-86. His IGG value was 2081 (normal range 540-1480) and IGM was 566 (normal range 65-380) (Exhibit J-4, page 20). It was at about this time that I noted that 1004 was returning less of the Study Medication then he should. During this visit and the following one he returned 10 capsules instead of 14 to 16. The 14th Week visit was dated 7-17-86. This was the visit where the clinical evaluation was "3" (see Exhibit J-4, page 21) for his coughing. His concomitant medications were written on the photo copied record. Case Report Forms for this visit include a notation of 3 units of packed red cells given five days later on 7/22 due to decreased Hematocrit and Hemoglobin. However, the Hospital Record for this individual indicates that he went to the Emergency Room to be treated and that is where he got the transfusions. There they found he had a decreased Hematocrit and noted that he had [redacted] There was a note that the Blood Bank had refused to see him and therefore he went to the Emergency Room. T. Flynn noted that the Blood Bank does not have the personnel to take care of additional patients. I asked if there were any provisions made for such a situation where a subject would end up needing a transfusion and go to the Emergency Room for it. She said the patients knew that they might need blood; they knew the doctor was checking those perameters. She said that they were really prepared for anything. The

#1004 (cont.) an AZT patient

Case Report Form does not indicate the individual went to the Emergency Room. The [redacted] Printout for this date states that the WBC's were at 2.3 and this result was verified by repeat analysis.

An Adverse Reaction Form was completed for this visit stating that he had anemia from 7/17 to 7/30. They noted that he was given 3 units on 7/22 (see Exhibits J-4, pages 22 and 23).

Again on 7/30 the subject was transfused with 2 units of red cells. This observation ended up on the records for the Week 16 visit which was the next day, 7/31/86. He had the same low hematology values. MGH Hematology and other tests were done on 7/29 (see Exhibit J-4, page 24) with a handwritten note, "Transfused 7/30/86 2 Units). This note was added to the original form and it is not initialled or dated. The Adverse Reaction Form for Week 16 repeats the fact that 3 Units were transfused on 7/22/86. However, it does not mention the two units that were transfused the day before this visit. T. Flynn agreed that either both should be listed or the more recent one should be. She said it might be listed in Week 18. Another Case Report Form (page 160) on this date said that 2 Units had been given on 7/22 but a comparison with the Hospital Record made it clear that 3 Units had been given. During this same visit, [redacted] returned only 8 capsules instead of the 14 to 16 that should have been returned. There was no comment made about this on the Case Report Form.

The Week 18 visit was dated 8-14-86. His weight had decreased to 136 (Exhibit J-4, page 27). The Case Report Form for Hematology noted that the results were from the "MGH Lab" which ordinarily meant that the subject was either not on the Study, or in the hospital, but somehow not on the usual test track. The listing of Study Medication (Case Report Form page 166, Exhibit J-4, page 28) noted that, "stopped [redacted] 8/18/86-started on Bactrim". The Listing of Concomitant Medication (page 167, Exhibit J-4, page 29) noted that he was on Dalmane as of 8/14/86 and on Bactrim DS as of 8/18/86. The entire line of information about Bactrim was added to the photocopy. There was no explanation why this occurred and I noted that his difficulty sleeping was only rated as "1" (mild). I asked T. Flynn if she could explain this and she said he probably had a new bout of [redacted] that was evident on exam though perhaps not in the labs. She noted that there were several X-Rays at that time that he was problem. She also recalled that his visit during Week 18 was on Thursday and that he returned on Monday of the 19th Week after being sick during the weekend. Then Week 19 Opportunistic Infection Forms were completed for him. I asked T. Flynn why it was stated on his Study Medication Record that he was off [redacted] and she said that they used that as a short form of referring to the Study Medication, even though they did not know whether they were giving drug or Placebo to the subject. The Case Report Form for adverse reactions said that there were none. T. Flynn said that was changed later.

??? we was on AZT

A Week 20 Case Report Form was generated and included a [redacted] Printout dated 8-25-86 although the other Case Report Form date used was 8-28-86. There was no Urinalysis and no Hemoglobin results. Oddly enough, however, the Study Medication Record for this week, page 181

#1004 (cont)

(Exhibit J-4, page 30) has a notation in what I believe to be T. Flynn's handwriting that says, "still off drug as of 8/18/86", and on the same record it says that from 8/28/86 to 9/11/86 he took no doses. This does not agree PAS 12-3-86 with the note on the Grad consultation dated 8/18/86 (Exhibit J-4, page 34), "started Bactrim DS (2 QID) Monday 8/18/86 D/C [redacted]. This latter notation makes more sense generally however the first statement which I believe is in T. Flynn's writing might help to explain the fact that MGH Laboratory results were used for Hematology that week.

In either event he was off the Study by that time, and Case Report Form, page 182 says that he was on Bactrim DS. Exhibit J-4, pages 32 and 33 include hospital notes by Dr. Hirsch. However, they are incomplete and it appears that they were with the Study Records as opposed to the Hospital Record. The second note (Exhibit J-4, page 33) says that it is presumed that he is having a reoccurrance of PCP and that since he had a reaction to Bactrim that he would be given Pentamidine IV by a Home Care Group. However, they require that the first three doses be given in the hospital. So appears that he was treated in the hospital and then discharged and treated for three days. This note is signed by Dr. Hirsch. When I asked why the Week 20 results were not in the Case Report Forms, T. Flynn said they probably are there but are not filed.

The Hospital Record included a note dated 8/18/86 of a Chest X-Ray with "marked worsening of chest". By 9/10/86 the Chest X-Ray said, "marked clearing of [redacted] since 8/25 when there had been increased defuse lung disease consistant with [redacted]. At another point when I asked T. Flynn to explain the 8/18 note that he was still off the drug she said that he went off the drug on 8/4. However, that was not in any of the records that I reviewed and it means that he did not go even 18 weeks on the Study.

A chart of 1004's white blood cells over time is the following:

What AZT does to white blood cells

4/17	5.4	6/5	3.5
4/24	4.4	6/19	3.6
5/1	3.6	7/2	4.4
5/8	4.2	7/18	2.3
5/22	4.7	7/21	3 Units Packed Cells

FLOW CYTOMETRY RECORDS PAS 12-3-86

There are also ~~(SOUNDS LIKE CLOSED SYTOMOTRY RECORDS)~~ for this subject dated 4/9, 4/15, and 4/20/86. These are attached as Exhibit J-4, pages 36,37 and 38. There is also a Lymphocyte Diff. Profile dated 6/2/86 which is page 36 of Exhibit J-4.

Number 1005, [redacted] was an [redacted] patient who was on the Placebo. This is the subject whose Hemoglobin was 9.1 (Protocol entrance requires greater than 9.5). Since he had been on the Study medication one week, that was considered acceptable for the purposes of the Study. By Week 2 he developed a rash on his face and was given Hydrocortisone Cream. At the Week 4 visit he had a 9.2 Hemoglobin. Some weeks he returned as many as 22 or 23 capsules. He had a seizure

#1005 (PCB)

on August 9th and he was treated for Anemia on August 27 and 28. Each of these was considered an adverse reaction, however, the followup to the seizure is incomplete since records from the attending physician and other hospital had not yet been obtained. As a followup to the seizure, he was seen at MGH for a Cat Scan and NMR. At that time T. Flynn did supply him with additional Study medication. However he took the Study medication sporadically at this point and the Case Report Forms do not specify what actually happened.

[redacted] started on the Study on April 16. He had recovered from [redacted] on 3/10. He had severe Candidiasis and was treated with Ceftiroxime I.V. and Erythromycin on or about 3/4. He was treated for Anemia and a Hematocrit of 26 with 6 Units of Packed Red Blood Cells (date unknown, from physician's note). The physician's notes indicated that he was on Ketoconazole, 200 TID and Mycostatin. He received two units of red cells on or about 3/5. His records of hospitalization prior to the study is Ex. J-5, pp. 27-32.

At pre-entry, 1005 had Hematology values including Hemoglobin, Hematocrit red blood cells all below normal range with no comment by the Investigator. There is no lab data to confirm the T4/T8 values reported in the Case Report Form, page 6. From the physician's office visit he was on Acyclovir and Bactrim as of 4/4/86. His second set of Hematology values was again below the normal end of the range with no comment by the Clinical Investigator. The second set of T4/T8 values were also unsubstantiated by raw records. By 4/10 he was on Trimethoprim/Sulfa DS and Clortrimazole (CRF, page 15 attached as Exhibit J-5, page 3).

PAS 12-30-86

For the Week 0 visit, 4/16/86, Number 1005 did not have Hematology, Clinical Chemistry, Lymphocytes, CMV Serology or Immunoglobulin sets done and there was no explanation given in the blank Case Report Forms. T. Flynn said these tests were done pre-entry and not at Week 0. Examples of the blank Case Report Forms are pages 21 and 22 (Exhibit J-5, pages 4 and 5). At Week 1, 4/24, [redacted] had low values for the following: RBC's - 3.32, HCT - 28.7, WBC - 3.6. There was no comment on these low values (Exhibit J-5, page 6, the [redacted] Printout). He also had a Hemoglobin of 9.1 as described above. On this visit the number of capsules returned was changed from six (6) to none (Case Report Form, page 42, Exhibit J-5, page 7). As of this visit [redacted] was on Trimazole and Bactrim. The date of starting the former medication was changed by the monitor from 4/86 to 3/86 as can be seen in Exhbit J-5, page 8.

PAS clo 12-30-86

By Week 2, 5/1/86, 1005 had a Hemoglobin of 9.0 and RBC's - 3.12, Hematocrit-26.9, WBC-3.1. This is the point in the Study where he developed a rash on his face and needed Hydrocortisone Creme. T. Flynn said that they would have checked with [redacted] about using this drug. However, there was no documentation of that in the Case Report Forms. On this date he returned 11 capsules. Other Concomitant Meds were as above. By Week 3 [redacted] again had low Hematology, Clinical Chemistry and lab values could not be found. Case Report Forms for these dates were pages 54 through 56 (Exhibit J-5, pages 10 - 12). The Hydrocortisone Creme did not show on the Concomitant Meds which

#1005 (PCB?)

otherwise remained the same.

The Week 4 visit was 5/16/86. As of this date [redacted] weight was 69 kilograms. It had been 68 kilograms four weeks previously. His red blood cells were 3.23 and Hematocrit 27.4 and the Platelet Count was 148 (normal range 150-500). His Hemoglobin was 9.2. He complained of Ataxia and "wobbly - transiant". These were not listed as Adverse Reactions (see Exhibit J-5, pages 13 and 14 for these Case Report Forms). When Dr. [redacted] mentioned this to T. Flynn she said that they could have included it. Concomitant Medications continued to be Bactrim and Clotrimazole.

By Week 6, dated 5/29 [redacted] weight was 69 kiligrams and again his red blood cells, Hematocrit, white blood count and Hemoglobin were all low. They were 3.52, 29.8, 3.6, and 9.7 respectively. This was the visit on which the bottle identification on the new medication was crossed out. It had read "1118401". This is the code which is discussed above which was never explained to our satisfaction. The number of capsules returned was changed from 9 to 17. (Ex. J-5, p.15). Concomitant Meds remained the same. Week 8 was dated 6/12 and showed no change in weight. Again RBC, Hematocrit, WBC, and HGB were all low at 3.2, 36.9, 2.7, and 9.0. There is no comment by the Clinical Investigator for these low values. Twenty-three (23) capsules were returned out of the original 100 that were dispensed. This week instead of listing Bactrim, Septra was listed a concomitant med. (Ex. J-5, p.16).

The Week 10 visit was on 6/26. There was no comment by the Clinical Investigator for the following low values: RBC-3.12, HCT-27.2, WBC-3.4, and HGB-9.2. The Platlet Count was also low at 134,000 when the normal range is 150-500. Concomitant Meds were the same. The Week 12 visit - 7/10 again showed low values about which there was no comment as follows: RBC-3.31, HCT-29.9, WBC-3.1, and HGB-9.8. His weight was 66.8 kilograms. Other abnormal values included IGG-2014 (normal range 540-1480) and IGM-452 (normal range 45-260). He returned 22 capsules on this date and only Benadryl was listed as a Concomitant Medication. (ex. J-5, p.17).

The Week 14 visit was on 7/24 and [redacted] weight was 64.5 kiligrams. There was no Hematology Lab Slip to support the values in the Case Report Form page 135 (Exhibit J-5, page 18). In the right hand margin is, "MGH", which ordinarily means that the tests were run at MGH. There is no raw record in the file however with which to compare. The listing of Concomitant Medications does include Benadryl which was mentioned during the previous visit but listed the other medication as though it had continued all along and it was not listed in the previous week's CRF. The Week 16 visit was on 8/8/86 and No. 1005 weighed 65 kilograms. His Platelet Count at 89,000 was low (it had also been 89,000 the previous week). In fact both weeks again have low red blood cells, Hematocrit, white blood cells and Hemogloblin, with no comment. During the Week 16 visit those values are respectively: 3.25, 29.0, 3.9, and 9.7. The number of capsules returned was changed from 8 to 16 (Exhibit J-5, page 20). Concomitant medications remain the same but Benadryl was dropped.

* 1005 (PCB ?) adverse reactions were recorded for placebo patients

The Week 19 (Week 18 was really Week 19) visit was on 8/28 although some records said also 8/19. [redacted] weight was 65 kilograms and there was a note of mild weekness in legs and lethargy. He had had a seizure on 8/9/86 after leaving a movie. This is listed on the Case Report Form, page 161 (Exhibit J-5, page 21). It is also listed as an adverse reaction along with Anemia on the next page of Exhibit J-5. We noted that the Case Report Form, page 161, did list the subject number as 1057 and changed it to 1005. The change was not initialed or explained. It appears to have been an error. He appears to have been treated with one unit red cells on 8/27/86 at [redacted] (Exhibit J-5, page 24). His Concomitant Medication now included Dylantin. None of his capsules were returned as of this date. T. Flynn explained that he was hospitalized on 8/9 and was out of the hospital on or/about 8/22 or a few more days. When he was at [redacted] as an in-patient he was sent to MGH for a Catscan and an NMR and at that time she gave him some of the Study Medication. This is not so stated on the Case Report Forms. So his participation from 8/7 to 8/28 is unclear. He was seen by the Study Group on 8/28. He was also hospitalized from 8/28 to 9/11, but I saw no records of that.

The Week 20 visit was dated 9/11/86. [redacted] weighed 64.5 kilograms and complained of generalized weekness. He had again low hematology values and there was no comment about that by the Clinical Investigator. He had missed dosing from 8/28 to 9/11/86 because he was hospitalized. Still the number of capsules that were returned were six changed to 0. T. Flynn explained that number 1005 did continue to come back to the Study and is on the open Study now. He had been on Placebo. According to his Case Report Form, page 181, he switched over to the Open Study on 9/25. It is difficult if possible to reconstruct the use of the Study Medication by this patient. We did not see records of this last hospitalization, if in fact he were hospitalized at this location. However, since he is ordinarily treated at [redacted] by his attending physician it is likely that he was treated there.

Number 1006 [redacted] was an [redacted] patient who was on the drug. His date of birth is [redacted]. He started on the Study on May 1st. This is the subject whose daughter ingested the Study substance in early August. At that time the code was broken but the Case Report Forms do not mention the incident, nor the loss of the capsules, nor the fact that the code was broken. There was no further F/U (documented at this location) of this incident. Prior to [redacted] entrance on the Study he was noted to have Stable Anemia and Leucopenia. However, according to T. Flynn, he met the entrance criteria and was therefore allowed on the Study. He also had a history of depression, but it was thought to be not bad enough to require a Lumbar Puncture. In order to enter the Study as a [redacted] patient he need to have a specific weight loss and/or documented history of Mucocutaneous Oral Candidiasis. He did not have the latter according to his pre-entry record dated 4/7/86, so his weight loss was needed to meet the entrance criteria. Page 1 of his Case Report Form lists a change in his weight three months prior to entry. One Humdred and Thirty One (131) pounds were changed to 170 (see Exhibit J-6, page 2). T. Flynn said she made this correction of Dr. Schooley's original entry. His weight in June of 1985 had been 185, in November, 146 and on 5/1/86 was 141 pounds. A note attached to the

* a relatively healthy patient put on AZT

* a unique form of unblinding (covered up),

#1006 (AZT)

Discharge Summary from his hospitalization in November '85, which is a copy of a stenographer's pad, notes that his weight had been 181 pounds in 1985 and was now down by 33 pounds (Exhibit J-6, page 25). So none of the raw records can explain the 170 pound entry made by T. Flynn. One other weight entry made on or about this time was at the Week 1 visit on 5/8 when his weight was 144 pounds. This is also the Subject who by Week 2 was experiencing tremors. These were thought to be due to the Stelazine that he was on. So the Stelazine was reduced but only that week. Otherwise the Case Report Form showed that this medication has been given since December 1985 and at the same dose.

[redacted] was treated between November 27 and December 11th at the [redacted]. [redacted] was his physician. The [redacted] is attached as Exhibit J-6, pages 26 through 28. This record noted that, "Serial CBC's showed Stable Anemia and Leukopenia". He was noted to have a history of Syphilis and numerous other conditions including depression. His weight in June of '85 had been 185 pounds and in November it was 146 pounds. His T4/T8 ratio was markedly decreased. During this stay in the hospital his HTLV-III result was received and was positive. He was discharged on Oral Erythromycin. His CMV was 1:64 (normal range 0.25-1.3) which was said to be suggestive of a recent infection. His diagnosis upon discharge was:

1, [redacted] 2, Oral Moniliasis; and 3, LLL Pneumonia.

A hand written note on green stenographer pad paper was attached to the front of the Discharge Summary. T. Flynn said, Yes, it was her writing and that it was based on a telephone call. She commented that he had been losing weight since February of '86. However, I do not have notes that indicate that I pressed her further on this issue. Two other records attached to this Discharge Summary are a April 7th Tongue Culture which was negative for Fungi, (Exhibit J-6, page 29) and an April 22nd Vitamin B-12 and Folate Assay from MGH (Exhibit J-6, page 30).

[redacted] Informed Consent was signed on 4/22 and he began the Study on May 1st. Comments about his weight upon entry and prior to that had been made in the first paragraph under this subject's number above. His Medical History, page 3, lists a history of Moniliasis, Hepititas B, LLL Pneumonia (November 85), Peptic Ulcer, and depression. This Medical History does not list [redacted] even though he had been diagnosed with a positive HTLV-III at the [redacted] Hospital. The Medical History is Exhibit J-6, page 3. The next page of the Case Report Form and of the Exhibit includes his [redacted] and his [redacted] disease history. This record says that this subject has not had a positive HTLV-III culture within three months prior to entry to the Study. The note is that it is pending with the date 4/7/86. I did not find any raw records for this date. T. Flynn said that if it is not in the Blue Binder for the Study or in the Red Folder of additional records that she no longer has the record (with the exception of the Clinical Chemistries which were done at MGH on 4/22/86). Then page 9 of the Case Report Form (Exhibit J-6, page 5) shows that the HTLV-III Culture results pre-entry dated 4-7-86 were negative. The HTLV-III antibody (Elisa) test was positive;

#1006 (KZT)

it was dated 4-22. T. Flynn said of the culture that they had hoped to see a change but they had not seen a change there. She said that they did not expect any change with the Elisa test result. On both 4/22 and 4/29 the Skin Tests were not done (Case Report Form, pages 11 and 13). SGOT was not done at entry.

[redacted] Concomitant Medications at pre-entry (Exhibit J-6, page 6) were Stelazine, Xanax, and Halcion. "The level of Stelazine that Number 1006 was 5 milligrams #TID". Again, as above, T. Flynn said that all Concomitant Medications would have been checked with the sponsor but if that was done, it was not recorded. After page 16 of the Case Report Forms was a set of three forms addressing opportunistic infections. These pages are not numbered. The first of these three stated that the subject has Candida and "(Seen earlier, onset date per Sponsor request)". T. Flynn said that this note was in the Monitor's handwriting. The second page of the set says that no tests were done and, "Dx by clinical observation." (Exhibit J-6, page 7). The third page was dated 6-26 and was called an Update. It said that the Candida started on May 1, 1986 and ended on June 26, 1986. Note that May 1st was the first day of this Study for this subject. There was no raw record that substantiated this observation of Candida. T. Flynn that that was true, that it was based on observation only.

For the Week 0 visit, 5/1/86, the physical exam noted oral thrush (Exhibit J-6, page 9). The Clinical Evaluation for that week (Exhibit J-6, page 10) noted malaise and fatigue rated at "2" each.

The [redacted] Hematology Values for the Week 0 visit showed low Hematocrit, red blood cells, and Hemoglobin with no comment (Exhibit J-6, page 8). The Clinical Chemistry and B-12/Folate Tests were "ND". See Exhibit J-6, page 11 and 12. Page 25 of the Case Report Forms shows a WBC count of 4.6 and percent lymphocytes 11 (normal range 20-45% however, these values were on a blue original page not a photocopy) and the OKT4 and T8 values on that page were not entered and in the margin was the note, "? valid". T. Flynn said this was her note; it was written in pencil. She said the values were not valid for that date. The HTLV-III culture results for week 0 were negative. The culture is dated May 1st (Exhibit J-6 page 13). The HTLV-III serology and antibody (Eliza) tests were positive, page 28 of the case report forms.

The week 1 visit for number 1006 was 5-8-86. The [redacted] printout of his Lab analyses show a number of low hematology values including Red blood cells, (3.67), Hemoglobin (10.5); Hematocrit (31.7); White blood cell count (2.0). His weight on this visit was 144 pounds. His low hematology values were not considered an adverse reaction. He had other out of range values including SGOT, iron, etc. His SGPT at Week 1 was 167 (Range 0-50). The week 2 visit was on 5-15. His weight was 150 pounds at this visit and again he had numerous low Lab results with no comment. The clinical evaluation sheet (Exhibit J-6, page 15) showed a loss of mental acuity and tremors both evaluated at "2". The comment about tremors was also on page 45 of the case report form (Exhibit J-6, page 16) with a scratched out note which said, "Comments re adverse effects". The handwriting of the original comment appears to be Dr.

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Hirsch's. T. Flynn had initialed the note and it appears that she was taking credit for crossing out the observation. There is no additional explanation or dating of this change on this record. The adverse reaction case report form this week is page 49 (Exhibit J-6, page 17). It lists both the tremors and the mental confusion and attributes them to Stelazine. It says that after that was decreased that all symptoms abated. However, as described above, the dosage was returned to normal subsequently and there was no further explanation. Case report form page 51 which is the listing of Concurrent Medications for Week 2 shows that number 1006 is on five milligrams bid of Stelazine per day.

The Week 3 visit was on May 22nd. [redacted] had low hematology values in his [redacted] printout. His White blood cell count was 2.2. It was in this record on page 53 (Exhibit J-6, page 19) that there is an unsigned and undated note on reducing Stelazine. I believe this to be Dr. Hirsch's writing. He says, "On reducing Stelazine, all signs of tremors, mental confusion have (decreased)". A listing of Concurrent Medications for Week 3 is attached as Exhibit J-6, page 20. It shows the same reduced level of Stelazine.

Number 1006 Week 4 visit was on May 29th. He weighed 168 pounds (page 77 of the case report form). (The entry for the brief exam for E.E.N.T. was checked normal and then abnormal for oral thrush. T. Flynn made the changes on the record. At Week 6, he weighed the same as the previous visit. His [redacted] printout of White blood cells was 2.8. Other low Hematology values persisted and there was no comment about them. The Concomitant Medications for this week (Case Report Form page 75) remain the same. During the Week 6 visit R.B's Concomitant Meds were the same but Halcion was dropped.

gained 24 lbs. in 4 weeks?

The Week 8 visit [redacted] printout had the same low and high values with no comment. The White blood cell count was 2.4. The HTLV-III test was not done and there was no comment about that. I noted on Case Report Form page 102 that Colace had been started as a Concomitant Medication in June of '86. T. Flynn explained that this is a stool softener and sometimes that is needed to counteract the effect of psychiatric drugs.

The Week 10 Concomitant Medication record shows that [redacted] was on Stelazine at 0.5 milligrams P.O. TID. The decimal in front of the 5 was also noted during Week 4 and Week 8. However, during other weeks prior to this there was no such decimal.

The Week 12 [redacted] printout results again had out of range values that were high or low and no comment. There was an asterisk next to the White blood cell count of 2.4 which indicated that the test had been repeated since the lab techs believed that it might be inaccurate since it was so far out of range. As of this week [redacted] weighed 166 pounds. Their record of return Study Medication was changed from ten capsules returned to nineteen. Concomitant Medication remain the same as above.

The Week 14 visit included laboratory values that were out of range as described above, with no comment. [redacted] weight was 163 pounds. Return Study Medications showed 16 changed from 8 capsules. As of this visit, he was off Colace and Halcion. As mentioned above, this is the

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visit where this subject's 18 month old daughter had ingested Study Medication. The record of Study Medication returns did not make any mention of this incident. The only record of it was in the correspondence file, Exhibit C-16, an August 5th telephone conversation note by Dr. [redacted] with Dr. Schooley (See discussion of correspondence above.) Current review of this record indicates that it does not cross reference the study subject so as to determine which file this relates to. We had to be told by the clinical investigator who the subject was. At one point Dr. Schooley referred to him as [redacted]". T. Flynn said that this subject sometimes went by a different first name and that is why the initials might be different.

This record also gives no indication of what followup was made. Dr. Schooley had told us verbally that the subject had kept the vial of medication at home. He had walked into a room and seen his daughter sitting on the floor with capsules in her hand. He had received a call about the incident from a [redacted] hospital. She had taken an unknown number of capsules. Further followup indicated that between 1 and 3 capsules were missing. Dr. Schooley meanwhile had called the sponsor firm and had determined that this subject was on the drug product. Dr. Schooley mentioned verbally speaking with [redacted] However, there is no mention of his name in the memo of telephone conversation. He made some comment about calling the Poison Center but the memo of telephone conversation indicates that the assessment of the toxicity of the drug was made by [redacted] He said it was "below the acute toxic dose". He made a comment about the hospital planning to draw blood for samples and, in fact, the memo makes reference to that as well. T. Flynn mentioned that the child was taken back (apparently to the hospital) one more time. There is no additional followup to indicate the results of the blood sample or checks on the condition of the child's health. There was no copy of any hospital treatment record from the [redacted] hospital in the study records.

The Week 16 visit was on 8-21-86. [redacted] ENT was normal and his weight was 164 pounds. His White blood cell count was 2.0 and his SGPT was 111 and the vitamin B and folate tests were not done. There was no comment about any of these tests. No raw record could be found to support the case report form, page 149 (Exhibit J-6, page 24) listing the T-4 and T-8 values. Mitogen testing was not done and there was no comment explaining this. Return Study Medication was changed from 7 to 16. His Concomitant Medication remained the same.

There was no conclusion to number 1006's participation in this study. There is no final statement in the Case Report Form. According to T. Flynn, he was switched over to the open study (dated unknown). When I asked if there were a Case Report Form to close out this record, T. Flynn said there should be an investigator's statement in the record similar to those for the two patients who had died. However, the B-W's monitor had said to hold off since they had not yet decided how to do this. I explained that there should be a statement of concluding the study in the case report forms.

The Summary form that was at the beginning of each subject's record and that was ordinarily dated 9-18-86, was not so dated for number 1006 but stated, "No OI reported. doing well." It also noted that he had a Karnofsky score of 1 as of September 5, 1986 via a telephone call. This was not further explained.

Subject number 1007's record was not thoroughly reviewed. For the most part, he was skipped, but a few records were checked or inadvertently reviewed. His initials are [redacted] He was an [redacted] patient who was on placebo. His date of birth is [redacted] He did choose to go into the open study after this study. The date on his informed consent was changed from May 8, 1985 to the same day in 1986. There was no explanation for this change, dates or initials. It appears that number 1007 had low White blood cell counts, Hematocrit, and Hemoglobin values throughout the study. Exhibit J-7, page 2 is a summary list which traces these values from Week 0 through Week 12 of the study. There is no explanation, initials or date for the entries. It appears to be T. Flynn's writing. There is no followup or explanation of what was done with this information. The discharge note for this person from [redacted] (admitted 3/19/86 and discharged 4/11/86) identified among other things, that he had "[redacted] and anemia, Leukopenia with Lymphopenia. He was given Bactrim in the hospital. He went off the Study Medication on, or about, August 24th because of bronchitis. This is noted on Case Report Form page 131 (Exhibit J-7, page 4). The same record of Study Medication use notes that he returned 32 capsules on Week 12 (changed from an original entry of 6 capsules) and a note explained, "didn't take all night doses." The change in the number of capsules was identified by "tf" and it appears that the other note about night does would have also been written by T. Flynn.

Weeks checked for Concomitant Medications were Weeks 8, 10 and 12 and number 1007 was on Bactrim during those visits. He missed visit number 14 and after that he was on Amoxicillan for bronchitis. All the records for Week 14 were identified with a note "missed visit". The date of that visit was August 28, 1986. When the study summaries were generated, the original entries for number 1007 (Exhibit J-7, page 1) identified telephone call on 9/9/86. At that point, it was determined that he was off the drug due to Amoxicillan treatment for bronchitis. The dose was dropped to 0 via the telephone call and this information was as of that time not in the database. The bronchitis was described as "moderate" and, "no OI reported." There is an added note in what appears to be T. Flynn's handwriting that says, "Patient developed a generalized skin rash after being treated with Amoxicillan. Have not restarted study drug as of today. PT. C/0 being severely fatigued with moderate lethargy." It appears from the record though it is not specifically stated, that this additional information was received on September 15th during a patient visit when his Karnofsky score was 80.

T. Flynn explained to me verbally that Ron Beitman, the monitor, had taken the Case Report forms on, or about, September 12th or 13th. Therefore, he did not have the additional information from the

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September 15th visit. She said after he took the Case Report forms and had left that the drug had to be stopped for this subject due to the Amoxicillan for bronchitis. Then the subject never was back on the study. Subsequent to that they found out that he was on placebo and he then entered the open drug study. This does explain some of what happened, but the dates of going on and off the Amoxocillan versus the study substance do not correlate. T. Flynn said that she gave the additional information that he had been off the study drug to [redacted] over the telephone since it would have been information the he did not have in his database (based on the Case Report forms).

The record of returns of study substance per subject that were generated by the monitor (even though they were intended to be a running inventory for the clinical investigator) indicated that number 1007 returned a lot of study medication. Dates noted and the amount of returns made are as follows:

Study Visit Date	No. of Capsules Returned
June 19th	17
July 3rd	38
July 17th	18
July 31st	33
August 14th	32
August 24th	40

T. Flynn commented when I asked about this that she thought he was forgetful and that he did not take the study medication as he was supposed to. There is no further comment on this record.

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[redacted] was subject number 1008 in this study. He is an [redacted] patient and his date of birth i[redacted] He was on the drug during the study and has opted to go into the open study since. He was hospitalized during the course of the study. His consent form was signed on 5-16-86. He began the study on 6-9-86. However, soon after he was on the study, he went to the emergency room and was admitted to the hospital for treatment of [redacted] He was treated at MGH. He was off the study for four weeks. However, when he returned to the study, records were generated for him almost as though he had not been off the study. So, during the ninth week since he started on the study, Case Report forms were generated for him which said that it was his sixth week on the study. T. Flynn admitted during questioning that this visit should have been identified as Week 10. Another way of explaining this observation is to point to Exhibit D-2 and note that the monitor's listing of the use of the Study Medication indicates that this individual was on the study for 12 consecutive weeks with the possible exception of Week number 3 which was "LOST". When [redacted] was admitted to the emergency ward on 7/7/86, (3 weeks after beginning treatment on the study) he complained of several weeks history of fever, sweats, "HA" (headache), dizziness, nausea, and increased shortness of breath (See Exhibit J-8, page 9). The Case Report form generated that same day does not mention that he went to the hospital. During the course of the study number 1008 had clinical evaluations with numerous symptoms

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listed but never were these included as adverse reactions. Some of the symptoms included moderate: malaise, fatigue, lose of appetite, nausea (week one); plus moderate: headache, diarrhea, shortness of breath, lethargy, abdominal cramps and dizziness (week three); plus moderate: fever, chills, odynophagia. Later in the study he had severe diarrhea (weeks eight and ten). The last case report form generated for number 1008 was for week fourteen. It did not indicate what happened to him at the end of the study.

[redacted] was seen by Dr. [redacted] at MGH on April 28, 1986 (see referral, Exhibit J-8, pages 2 and 3). He complained of a lot of diarrhea since the thirteenth of December of the previous year. Flow cytometry results from May 12 and May 19 were also noted in the background file.

According to the case report form, number 1008 weighed 175 pounds three months earlier. A review of the Hematology values and Lymphocyte panel number two pre-entry showed that different values were used than should have been. The WBC should have been 4.0 and the percent Lymphocytes 36. Instead 4.2% WBC and 33% Lymph were used. It is unclear where these other values came from. The Skin tests were not done at [redacted] hours. They were done after [redacted] T. Flynn said that this was discussed with [redacted] earlier and this was agreed to. [redacted] was on Ludiomil and [redacted]azole as Concurrent Meds (since May 6, 1986; See Exhibit J-8, page 29). He also had the three part form for Infections other than OI which showed he had candida. The same note that had been seen previously on other case records was observed on 6/5/86, "(per sponsor request; seen earlier)." The second page of this three part series showed that it was on the tongue and the last page said that it was ongoing at the end of the study.

The week zero visit was on June 5, 1986. [redacted] weighed 156 pounds. There are numerous out of range [redacted]alues with no comment. The B-12 and folate values were also out of range with no comment. The Lymphocyte panel was not repeated. T. Flynn said that it was too soon to repeat it. The HTLV-III culture result was not listed and the original of this form (CRF page 26) was still in the binder. T. Flynn said that this must have been a late result from the computer and that it had not yet been given to the monitor. I noted that the first visit (week 0) was June 5th but that the Study Medication was not given until June 9th. T. Flynn said that she had to do two neuropsychological examinations and that she was gone at the time and the replacement nurse could not give the exam. Therefore,the subject did not start on the medication until June 9th. There is also an error at this point in that the extra bottle (Week 0) was issued instead of Week 1 as it was supposed to have been done. She said that it was a mistake that he got Week 0 instead of Week 1. I did not ask if she made this error or if the replacement nurse did.

The Week 1 visit was on June 16th. The [redacted] Clinical Lab Printout printed numerous out-of-range values and there was no comment about that. The Clinical Evaluation showed that number 1008 had "moderate": malaise, fatigue, loss of appetite, nausea, and "mild" ataxia, abdominal pain, shortness of breath, and lethargy. At the same time,

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however, he was said to have no adverse reactions (Case Report Form 41). His Concurrent Medicatons were the same as above.

The Week 2 visit was on 6-24-86; the [redacted] Printout of Lab Values ~~was dated 6/30. A number of these values~~ included many that were out-of-range as above and there was no comment explaining that. The Clinical Evaluations were the same as above with no comment and no listing of adverse reactions. Concurrent Medications were also the same as above.

The Week 3 visit was June 30th and the [redacted] Printout of Laboratory Values showed a number of them to be out-of-range and there was no comment made (Exhibit J-8, page 39). The Clinical Evaluation was as above, with numerous notes of moderate symptoms and no comment. All of the above symptoms were included plus "moderate": headache, diarrhea, shortness of breath, lethargy, abdominal cramps, and dizziness. There were no adverse reactions according to Case Report Form page 57. These last two CRFs are pages 40 and 41 of Exhibit J-8.

The Week 4 visit included the three page set of Opportunistic Infection notes showing an onset of July 7th of pneumonia on the first page; lung [redacted] on the second page and ceasing 8-7-86 (Exhibit J-8, pages 42-44;). The brief physical exam on 7-7-86 showed bilateral rales (Exhibit J-8, page 45). The Clinical Evaluation for the same week had all of the above clinical signs and symptoms plus fever, chills, nightsweats and odynophagia that were all "moderate". There was no comment about these numerous symptoms. See Exhibit J-8, page 46. This same visit also noted significant lymphadenopathy (Exhibit J-8, page 47). The Hematology Case Report form for Week 4 was filled out and there was no [redacted] Printout. Ordinarily this means that the tests were run at MGH; this record does not say so but the Clinical Chemistry, page 65 did. The Hematology Record is Exhibit J-8, page 48. The White blood cell count was noted to be 1.5 and Hemoglobin, 12.2. There was no comment about these values. Only the Bilirubin, SGOT, and alkaline phosphatase were filled in on the Clinical Chemistry. The Study Medication Record (Exhibit J-8, page 49) said that none of the Study Medication was dispensed and that the patient had gone from [redacted] The Lymphocyte panel and HTLV III test (CRF pages 67 and 68) were "ND" for not done. Number 1008 was described as having no adverse reactions this week (Exhibit J-8, page 40). For some reason, there were extra copies of Case Report forms for pages 74, and 64 through 66. These were the Study Medication and Hematology, Clinical Chemistry, and Urinalysis Case Report forms. T. Flynn said she could not recall why there were duplicate records. The case reports do not say that this person was sent to the hospital although it does say that he had [redacted] T. Flynn said that not all cases of [redacted] would be hospitalized. The Case Report forms for Week 6 were not completed. All of the blue original forms were left in the binder.

The Week 8 Case Report forms were made by taking apparently a copy of ~~the Week 6 forms and crossing out~~ the number 6 and inserting "8" in ink on the photocopy. Some of the records in this visit are dated 8-7 and some are dated 8-11 so it is not possible to determine exactly when the visit was made. T. Flynn said in response that the monitor, [redacted] wanted the information even though the subject was in the

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hospital. His Clinical Evaluation (Exhibit J-8, page 51) included "moderate": malaise, fatigue, abdominal pain and mild heartburn. Diarrhea was said to be severe. However, page 81 of the Case Report forms (Exhibit J-8, page 52) says that he had no adverse reactions. The [redacted] Printout for this date was as above with no comment. It was dated 8-11-86. There were also [redacted] Laboratories Printouts for number 1008. T. Flynn said that the home care service used [redacted] after [redacted] was in the hospital and went home. She said she thinks they used the 8/11 [redacted] values for the visit but since there had been a July 31st [redacted] Report that they had not repeated it as soon as ordinary (Exhibit J-8, pages 54 and 55). Week 6 Study Medication was dispensed during this visit (CRF page 82). A note on this form says he missed the prior week. This is when T. Flynn said it should have been Week 10 medication that was given. I asked if the monitor told her what to use and my notes only indicate that she said it should have been Week 10. This record also said that he restarted on the drug on 8/7/86 although that does contradict the very first page in the binder for this individual which was a binder divider which says in pencil, "started back on drug Aug 4".

Week 10 visit was 8-21. Some of the records also said 8/22 but T.F. said that was an error. These records had an ink change on the photocopy which alter the records from Week 8 to Week 10. The [redacted] Printout of lab values was as above with no comment (Exhibit J-8, page 58). The brief examination on this visit (Exhibit J-8, page 58) says, [redacted] wheezes with consolidation". The next page, Clinical Evaluation, lists "moderate": malaise, fatigue, heartburn and moderate to severe abdominal pain and severe diarrhea with no additional comment (Exhibit J-8, page 59) and the corresponding adverse reaction form (Case Report form page 100) said there were no adverse reactions. Significant lymphadnopathy was also noted durng this visit (Exhibit J-8, page 60). The T4/T8 values were 48/470 or 0.10 (Exhibit J-8, page 61). Seven of the Study Medication capsules were returned on this visit (Case Report form page 101) and this photocopied record was changed to read that the Week 8 bottle was dispensed and not the Week 10 bottle which was crossed out on the photocopy.

T. Flynn stopped by on the day that I was reviewing this record and said that the week designation should be based on the number of weeks since the first day the subject took the Study Medication. However, if that is the case, the Case Report forms should state clearly when a subject is off the study as opposed to having to determine this by comparing dates of visits.

The next visit was on September 4th and it was identified as the Week 12 visit. In this case the Week 12 Case Report forms were used, not the 10th week visit with a changed week designation. There were numerous out-of-range values for this visit (Exhibit J-8, page 62) including White blood cell count of 1.9 which was asterisked to indicate that it was verified by repeat analysis. No urine sample was received. The Clinical Evaluation Sheet "Case Report Form page 113") noted "moderate": abdominal pain and diarrhea with no comment. There were no adverse reactions according to Case Report Form page 130. Week 14 Study Medications were dispensed during this visit according to

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Exhibit J-8, page 63. However, according to the monitor's tally (Exhibit D-2), the Week 14 bottle was returned to him intact. There is no explanation of this discrepancy on any of the Case Report forms for this individual nor on any other record observed. The only subsequent record was a [redacted] Printout dated 9/22/86 with out-of-range values similar to those cited above. The White blood cell count was 1.2, Hemoglobin, 7.3, and Red blood cells, 2.06. Both the White blood cell count and the Red Blood Cell Counts were verified by repeat analysis. The Study Summary Sheet, the first page in the folder, is Exhibit J-8, page 1. According to information on this record, a telephone call on September 9th indicated that he is stable and taking the dose every four hours.

This record also states that the maximum severity of th[redacted] which started July 7, 1986 (Week 4) was "moderate". It also notes that the ~~succession~~ cessation date was August 7, 1986 (Week 6) and that the Study Medication was discontinued from 7/7 and then restarted. Other records in the Exhibit cover [redacted] visit to Dr. [redacted] at the MGH Internal Medical Associates Primary Care Program (Exhibit J-8, pages 2 and 3). Records from his hospitalization are attached as Exhibit J-8, pages 8 through 23. These include a summary and admit note by Dr. Schooley and a mental health note. His bronchial washings showed [redacted] As of July 13th, his WBC count was 900 so he went from Bactrim to Pentamidine. The infectious disease admit note is written by Dr. [redacted] Exhibit J-8, pages 14 through 17). T. Flynn explained that Dr. [redacted] is an Infectious Disease Fellow. He notes that [redacted] went to the [redacted] for a weekly check of the [redacted] Study and "felt extreme postural lightheadedness and felt close to syncope though did not in fact pass out. He was then transferred to the EW." (Exhibit J-8, page 15). He was given one unit of red cells on July 11th (Exhibit J-8, page 22). There was no mention of having received blood in the Case Report forms for this individual. After he left the hospital, he was treated by [redacted] (Exhibit J-8, page 4). A chest X-ray in mid-August showed that th[redacted] had cleared (Exhibit J-8, page 5).

Was he? See p. 54

Subject 1009, [redacted] was an [redacted] patient who was on placebo during the Study and who died August 20th. His DOB was [redacted] His death was not known until the phone call made September 9th to update the study (See Exhibit J-9, page 1), he had dropped from the study prior to that time. This record also says by Week 4 of the study the patient had increased fevers, extreme fatigue, hallucinations, and ataxia. He quit the study at that point. When I looked at the case report forms for that week (Exhibit J-9, page 27), I noted these symptoms as well as numerous others that were of moderate or mild severity. However, none of it was noted to be an adverse reaction. Number 1009 was a subject who was given four units of Red Blood Cells on 5/22/86 which was one week before he entered the study. There was no medical record covering this. T. Flynn said that Dr. [redacted] would have done it. She said the record might be in his office and that it was in the Emergency Room at MGH.

Was he then on AZT? See p. 54

[redacted] had been treated at the [redacted] in February of 1985. He had pnuemonia, but not [redacted] and was discharged on

Again, the sicker patients were just on placebo,

died 20 Aug.
entered 29 May
Stopped study drug on 26 June
dropped out after 4 weeks
(Did he go back to AZT?)

* 100 g (PCB) - died.

Bactrim and Erythromycin (Exhibit J-9, pages 36 through 38 and 39-42). Then, on April 28, 1986 [redacted] wrote to his [redacted] physician asking him to forward copies of his medical record to himself in [redacted]. On May 5th tongue cultures showed candida (Exhibit J-9, page 44). A MGH Hematology Report on May 19th and 21st shows 8.7 and 8.5 Hemoglobin respectively (Exhibit J-9, page 45). These dates are after [redacted] signed the informed consent, but prior to beginning the study. The four units transfused were given for anemia the date of the second test. The first page of the Case Report form was dated May 29, 1986. I noted that this was also the same date as the Week 0 visit. T. Flynn said usually they are a week apart so that all the preentry information is obtained before beginning the study. I noted also that the Medical history (Case Report Form page 3 Exhibit J-9, page 2) was not dated (It is not an exam but a history). The 2 preentry lymphocyte panels were dated April 28th and May 5th. The first had T4/T8 values of 21/149 and the second had T4/T8 values of 18/52. The subject was taking Tylenol according to Exhibit J-9, page 6. The regimen, route and date started were on the record. The fact that it was "continued" was added to the photocopy. All of the Skin test information for the subject was missing, that is, pages 11, 12 and 14. T. Flynn said she would check with the monitor since he has the originals. At the end of pre-entry testing was the Study Discontinuation Record, CRF page 245 (Exhibit J-9, page 8). This was one of two such records for this subject. This record said that he discontinued the Study Medication on June 26th and in the comments section said the following, "7/3/86 presented to Clinic with increased fevers, extreme fatigue, hallucinations and ataxia. Patient was taking Tylenol every four hours without relief of symptoms. Due to generalized debilitation drug [redacted] was D/C. Patient relocated with family [redacted] The record also included a Clinical Investigator's Statement signed by Dr. Schooley and dated July 30, 1986 closing out the Study record. Note this is before this subject died. There were also Opportunistic Infection pages saying that Candida started on May 29th and ended June 12th, 1986.

Before entry! On AZT and very sick!

The Week 0 visit was May 29, 1986 the Case Report Form covering the Chest X-Ray results was the original form in this binder indicating that the results had not been received or the test had not been conducted. T. Flynn said if they had not received the results of a Chest X-Ray before beginning the Study that they would call over the phone and get the results that way and then perhaps not follow it up. She said that it is also possible that Dr. [redacted] took the results for his files. The [redacted] Printout for this visit included many out of range values with no comment (see Exhibit J-9, page 9). There were numerous out of range values in the [redacted] Printout dated 6/5/86 wich was the Week 1 visit and there were no comments about these values (Exhibit J-9, page 17). The Study medication for this date showed originally that four capsules were returned and this was changed to 17. (Exhibit J-9, page 18) This correction was added to the photocopy. He was still taking Azidothymidine as of this visit; the route, frequency and date of beginning the medication were added to the photocopy (Exhibit J-9, page 19).

The Week 2 visit was on 6/12 and again the comment about the [redacted] Printout was the same as above (Exhibit J-9, page 20). The Alkaline

They missed this! HE WAS ALLEGEDLY ON PLACEBO !!!
He was counted as a placebo patient who died!

#1009 (PCB ???) died!

Phosphatase level at 435 (normal range 20-125) was circled but no comment was made about it. The Study medication return figure was changed from 5 to 13 and this change and T. Flynn's initials were added to the photocopy. The Concomitant Medication added "Trimazole Troches dated 6/5/86". However, that is the date of the first week visit and the information should have been added there. T. Flynn said that he would have started taking this medication after he had seen them in the clinic. As of that previous visit he had been described as having 1-10% Candida and during the Week 2 visit the record said he had 0 Candidiasis (CRF page 45, Exhibit J-9, page 22). T. Flynn said that she could best guess that he is bothered off and on by Thrush and has a prescription to use when he needs it. She said he tried to take nothing; there is no information in his Patient Diary. He did ask to use Tylenol, however. (Still has AZT headaches)

The Week 3 visit was on June 19th; there are numerous out-of-range values in the [redacted] Printout with no comment. No urine was received and the Urinalysis Case Report Form (CRF page 56) says nothing. Returned Study medication count was changed from 6 to 13 and the change and T. Flynn's initials were added to the photocopy (Exhibit J-9, page 25). This record had an addition in pencil "D/C". That note is attached with a line through the date 6/26/86, which is seven days later. However, the Week 4 visit date is July 3, 1986. This is noted in Exhibit J-9, page 26, the brief physical exam. That record notes "massive splenomegaly; scattered erythromatous plaques". There are numerous signs and symtoms during this visit (Exhibit J-9, page 27). There are no raw records of Hematology or Clinical test results. The record of Study Medication Returns shows that ~~the bottle~~ 15 2 capsules ~~in it~~ were returned on 7/2/86 (Exhibite J-9, page 31). The second page 245 that was generated for this subject is attached as Exhibit J-9, page 33. It contains other information than the first which was Exhibit J-9, page 8 as described above. Page 33 of this Exhibit is dated July 3, 1986 and says, [redacted] had massive spleen-capular fevers 102, increased night sweats, generalized weekness with Ataxia-generalized debilitation. [redacted] moved back [redacted] be cared for by family." When I asked T. Flynn why there were two of these she said that one report (the earliest) was completed and then the monitor could not find his original so another had to be generated. I did not ask why a copy was not made of her photocopy. In the meantime she said they found the original and sent that (after the second edition had been generated). She said Dr. Schooley had seen them both so he signed them both. The second addition of this form said that the patient had stopped taking medication on July 3rd. However, T. Flynn maintained that he stopped using the drug on June 26. The last page of the Exhibit for this individual is a Week 6 Hematology listing. I found a MGH printout of this information, however, the date is the date for the week four visit and there is a note written on this record, "already recorded as Week 4". Why these dates conflict as they do, it is not possible to say. T. Flynn said that sometimes she wanted results faster and she would use MGH, or perhaps it was late in the day before the 4th of July and she didn't want the samples to be held for too long before being analysed.

There was no subject 1010; an individual with the initials [redacted] was

May 29 - June 26 = 4 weeks - died Aug, 20

tested and given the code number but did not qualify to be on the Study. He would have been a Placebo patient if he had been entered.

Number 1011, [redacted] (DOB [redacted] had been admitted to the [redacted] Hospital [redacted] in [redacted] in February of 1986. He was a "former IV drug abuser". The Clinical resume says that he had a possible smear for [redacted] and was treated for that at the time. The record also notes that he had not "shot up for six and one half years".

When I reviewed the Case Report Form for this individual I noted that the date given for the [redacted] was January 15, 1986 (CRF) page 3. However, that is 170 plus days or 165 since he was discharged from the hospital until he began the Study. The date of discharge is not clear from the record from [redacted] Hospital. Several of the records in this file have changed study numbers or initials as an example, page 5 the hematology number 1 preentry has a change in the initials. It appears that [redacted] might be ~~the chemical~~ PAS beneath the [redacted] In fact in the clinic file for the subject there was at least one [redacted] printout with the study #1009 which would match the initials [redacted] T. Flynn said that it was an error by the laboratory. However, I did not ask about its possible correlation with page five (5) of the case report form (Exhibit J-11, p. 11).

[redacted] was on Benadryl as a concurrent medication prior to the study (Exhibit J-11, p. 13). He had the set of forms for Opportunistic infections which list Candida beginning 7/14 and ending 8/11 (Exhibit J-11, p. 14-16). The hematology and clinical chemistry case report forms (Exhibit J-11, p. 17 & 18) were [redacted]. There were no initials and no explanation of this. The B12 and Folate test were also not done (Exhibit J-11, p. 19). The urinalysis case report form was blank but a record of its results for June 12th was observed. The lymphocyte panel was not done on this date (case report form 25) and there were no initials or comments. His chart was skimmed briefly and a T4 value of 29 was noted on 6-2-86.

The week one (1) visit was June 23rd. The clinical evaluation notes (as did week 0) that he complained of itching (Exhibit J-11, p. 22 & 23). I asked T. Flynn and she explained that the itching was on his arms and legs and that it was generalized. The B12 and folic acid test were not done previously but were done at the end of the first week. When I asked about this T. Flynn said that they had missed it at first so they had gotten it later. The [redacted] printout dated June 23rd noted that no urine was received. The following week, June 30th, the [redacted] printout showed low Red blood cell counts and Hemoglobin with no comment. The same was true of the week three (3) visit which was July 7th and the week four (4) visit which was July 14th. These [redacted] printouts are Exhibit J-11, p. 24-27. Through week number four [redacted] was concurrently taking Benadryl, and on week four (4) Excedrin (intermittent) was added. The folowing information was added to the photocopy of concurrent medications for that week: "p.o. 7/9/86 (date started), continued". The original CRF of #1011 T4 and T8 values were still in his binder. They were 157/583. I asked why they had not been picked up. T. Flynn said that the monitor was late in getting them or he forgot to follow-up.

During the week six (6) visit, July 28th, the [redacted] white blood cell count, red blood cell count, hemoglobin, and hematocrit were all low with no comment (Exhibit J-11, p. 30). The number of study meds returned was changed from an original entry of 10 capsules to 24 with the initials, [redacted] written on the photocopy with no further explanation (Exhibit J-11, p. 31). The records stated that he was on no concurrent medications although that was contradicted during the next visit (see below, and also see Exhibit J-11, p. 32).

The week eight (8) visit on August 11th, had another [redacted] printout with low hematocrit, hemoglobin, red blood cells and white blood cells and no comment. The T4/T8 value was 98/637. The mitogen testing was not done and there was no comment, initials, or date. The listing of concurrent medication (Exhibit J-11, p. 34) stated that he had been on Benadryl since May 1984 and on Excedrin since July 14th despite the fact that the previous visit's record said he was not taking any concurrent medication. The return study medication record was altered from the original of eight (8) returned to 41 capsules returned with [redacted] initials written on the photocopy. T. Flynn had apparently also written the note, "Slept through noc".

August 25th was the week 10 visit. The same hematolgy values were out of range as described in visits, above along with other out of range values with no comment. The study medication returns were again changed from six (6) capsules to 48 with the same note of have slept through the night. Both of these records are in Exhibit J-11, pp. 36-37. Concurrent medications were the same as in the previous visit. The hematology and blood chemistry and urinalysis tests were performed by MGH for week 12, 9-8-86. There continued to be low hematocrit, hemoglobin, white blood cell count and red cell counts with no comment (Exhibit J-11, p. 38). T. Flynn explained sometimes, especially when she is not in the clinic, that it easier to have MGH run these analyses since the procedures for having [redacted] come to get the samples is too complicated for other people to do. In this case the case report forms were labeled " MGH". Again the study medication returns were changed from an original entry of eight (8) to 30 with the same initials, [redacted] both added to the photocopy (Exhibit J-11, p. 40). For the same visit, several case report forms were not completed including the Hepetitis B form. There was no explanation; however the telephone call that ended the study was the following day, September 9, 1986. The summary form which is Exhibit J-11, p. 1 was supposedly made on September 9th for the subject and it says that he had no OI and was doing well.

Number 1012 [redacted] had some case report forms that were numbered "1058". T. Flynn explained that this happened because she thought she was likely to be in Group B, but his test results showed otherwise and he was then given the study #1012. It is only that a few records and tubes were identified as 1058. He was never on the study as that number. His date of birth is [redacted] he was a [redacted] patient and was on the drug. A review of the hospital record for this subject raises the question of about how many times he had [redacted] before being in the study. He was admitted to MGH's emergency ward on April 11, 1986, and dischared from the hospital on April 18th with a diagnosis of [redacted]

* Open admission that study was not blinded from standpoint of medical personnel? Or, does "study group" refer to diagnosis?

#1012 (AZT)
He was admitted again on May 1, 1986, and discharged on or about May 5th again with a diagnosis of [redacted] T. Flynn said, after looking at the X-ray summary after the first discharge, said that it was not completely resolved as of April 17, 1986. In other words, her interpretation was that it did not represent bouts of [redacted]

[redacted] entered the study on June 12, 1986. He had a chest X-Ray two (2) days prior which said, "Almost but not complete resolution of Bilateral pulmonary infiltration. No new lesions identified." T. Flynn said he did not have to have complete resolution to go on the study. She noted that he was improving and stable. When [redacted] came on the study, the date of diagnosis of [redacted] on the case report form was altered (it's not possible to read the previous entry but the current one is 4/11/86; Exhibit J-12, p. 4). T. Flynn said she would have made such a change although it is not initialled or dated on the record. The printout of [redacted] laboratory values included many out of range results with no comment and no initials. He was taking Ketoconizal as a concurrent mdication (Exhibit J-12, p. 5). His chest X-ray as of June 10th showed, "Almost complete resolution of bilaterial infiltrates." (Exhibit J-12, p. 7). The three (3) page set of Opportunistic infection records is dated June 13, 1986, "(per sponsor's request) (seen earlier)". These records said [redacted] had Candida and that it ended on July 2nd. These records are attached to Exhibit J-12, pp. 8-10.

Patient diary cards had been received by the time this subject's record was reviewed. So a few comments will be made about the diary cards with regard to this individual. There was no diary card for the week zero (0) visit for [redacted] Some records were dated June 12th and others, June 13th for this visit. His [redacted] lab results showed a number of out-of-limit results with no comment (Exhibit J-12, p. 11). The ~~liver~~ lymphocyte ~~site~~ values for this date were found in the file of background material for this individual and had been placed in order in the case report forms in this Exhibit (Exhibit J-12, p. 12). However, the case report form for this date which is the next page of this Exhibit says that these tests were, "ND". The week one (1) visit was on June 19th and the [redacted] hematology values were as above, there was no diary card for this visit. No urine was received and there was no comment on the case report form requesting urinalysis results. T. Flynn said that this was one of the last patients to go on the study and they just did not do all of the tests on him. She said that it was an error that he was missed. The blank CRF for the urinalysis this week is Exhibit J-12, p. 15. The concurrent medication for week one (1) was Ketoconizal. There had been no record of concurrent medication for week zero (0). June 20th, the day after the week 1 visit [redacted] had a Berium swallow X-ray. I asked T. Flynn about this and she said he had some trouble swallowing and some heartburn. Her recollection was that the result was negative. There was no further follow-up in the records.

There is also no diary card for week 2 on June 26th. [redacted] laboratory printout was as above with no comments. The week three (3) visit was dated July 2nd and the same observation about the [redacted] printout was made of this as above (Exhibit J-12, p. 16). The patient's diary card began on July 3rd to July 9th and listed no adverse reactions.

#1012 (AZT)

The week 4 visit was July 10th and the printout of laboratory values again included numerous out-of-range values with no comment. The T4 and T8 lymphocyte panel was "not done" (Exhibit J-12, p. 19). Then one day before the week 6 visit, [redacted] visited [redacted] MD at the [redacted] of MGH on July 23rd. The comments Dr. [redacted] made are attached as Exhibit J-12, pp. 40-41. On the second page of this exhibit is a statement of the "Plan", number 2, "He will return here in approximately 3 months' time to review his past hospital record, and to obtain the [redacted] protocol from Dr. Schooley." I asked T. Flynn what that meant and she said that it meant that the physician wanted to see to protocol, not that it referred to the open study. The week 6 visit was July 24th, the next day, and the [redacted] printout again included out of range values with no comments (Exhibit J-12, p. 20). The study medication entry for this date changed the number of capsules returned from 6 to 17 with [redacted] initials added to the photocopy (Exhibit J-12, p. 21).

The week 8 visit on August 7th showed a rash had developed on 1012's backside, chest, and armpit there was no further comment. T. Flynn said it did go away and that they often have rashes. She agreed that it should have been called an adverse reaction which it was not. Again the [redacted] printout had out of limit values with no comment as above. The first T4/T8 values since the beginning of the study were on this day; 136/310 (Exhibit J-12, p. 25). The number of study medications returned were altered from 7 to 17 with the initials [redacted] all written on the photocopy.

The week 10 visit was on August 21st and had a [redacted] printout of abnormal values as above with no comment. Number 1012 was noted to have a loss of appetite that was "moderate" according to the clinical evaluation but no adverse reactions (Exhibit J-12, p. 28). The number of returned study medication was changed from 7 to 16 as above. The week 12 visit was September 9th, there was no [redacted] printout; there were values from the urinalysis but they were not identified as to their source. There was no hematology other than the reticulocyte count and the erythrocytes sedimentation rate (which are ordinarily done at MGH). These records are in Exhibit J-12, p. 30-31. T Flynn commented that the tests were probably run but not entered in case report forms. On this day the concurrent meds listed for the first time Keflex and noted that it started on August 28th and continues (Exhibit J-12, p. 32). However, there was no statement to explain why he was on this medication.
There had been no concurrent meds from week 4 to the present for this subject.

The week 14 visit was on September 18th and the [redacted] printout again included numerous out of range values with no explanation (Exhibit J-12, p. 35). The white blood cell count was "verified by repeat analysis; result on previous report was entered incorrectly." T. Flynn said this was a reference to a preliminary report that [redacted] supplies before it gives a final copy with each analysis. The "previous report" was therefore not seen. The number of capsules returned on this visit was changed from an original entry of 9 to 16 with the same [redacted] initials and the changes were made on the photocopy (Exhibit J-12, p.

#1012 (AZT)

34). The concurrent medications during this visit included Keflex and added Ketoconazole with no explanation.

At the beginning of the case report form for this individual was a clinical evaluation case report form without a page number, and it was not dated. It noted that the subject (number not identified) had an infection of the right fourth finger. T. Flynn said that yes this subject had such an infection she thought this occurred on or about October 16th however, the record was not so identified. It is possible that this is a record for the open label study, however I did not review those case report forms and can not confirm that.

Three (3) of the diaries for this subject are attached as Exhibit J-12, pp. 36-39. Between September 4th and September 12th I counted either 49 or 52 doses were taken and inbetween September 13th and 18th there were 32 capsules used. That made for a total of 81 or 84 capsules over a 2 week period which meant that 16 or 19 capsules would remain. I asked T. Flynnn if this would account for the number returned during the week 14 visit (9-18-86). She said that this number only came from counting. She said that the subjects often would mark their diary cards as they were waiting to see her in the clinic. She apparently did not put much stock in those cards.

PLEASE NOTE: THE FOLLOWING RECORDS WERE GIVEN THE SAME REVIEW AS THOSE ABOVE (EXCEPTIONS ARE NOTED) BUT THE NARRATIVE THAT FOLLOWS WILL INCLUDE ONLY THE MOST SIGNIFICANT OBSERVATIONS. IF ADDITIONAL INFORMATION IS DESIRED IT IS AVAILABLE IN CSO SPITZIG'S DIARIES.

ARC ?

Number 1051 [redacted] was an [redacted]atient on the drug with the date of birth [redacted] He started on the study on March 20, 1986. For an unknown reason he had 2 informed consents, one dated March 4th and the other March 20, 1986. There was no record or case report form that number 1051 had a history of oral candidiasis. T. Flynn said that he had a negative culture but was positive on physical examination which often happens. In general there were inconsistent and unexplained changes in dates and additions on numerous case report forms for this individual. Some of the them were signed [redacted] was on Clortrimazole throughout the study. During the week 1 visit is SGPT value was noted to be 26. During his week 3 visit on April 10th the SGPT value was 58. That and the fact that malaise and fatigue had changed to "severe" were not listed as possible adverse reactions.

As of the week 4 visit on April 17th number 1051's SGPT value was 57 and 4 weeks later on May 15th it was 20. He complained at that time of mild headaches and neither of these were listed as adverse reactions. When this was mentioned to T. Flynn she said they could have been so listed in retrospect. During that same visit the number of capsules returned was changed from 10 to 16. During the week 10 visit on May 29th Erythromycin was added to the concomitant medication (due to a sinus infection). During the week 12 visit on June 12th, the numnber of capsules returned was changed from 10 to 16.

There were changes in the count of capsules returned during the week 16 and week 18 visits. Each time the original entry was 10 and it was

changed to 16 and 15, respectively. The same kind of changes were made during the next three visits: during the week 20 visit the number of capsules was changed from 5 to 16; week 22 (8/21/86) the number of capsules returned was changed from 5 to 16 and during the week 24 visit the number of capsules returned was originally 7 and it was changed to 17 by adding a "1". Also during the week 24 visit the SGOT was 59 and SGPT was 67 with no comment by the investigator.

Number 1052, [redacted] DO[redacted] was a placebo patient who eventually went on the study open label. He began the study on April 7th and ended on September 25th. His was one of the records which was not reviewed. However his informed consent was dated March 12th, he had a note in his record that he could not account for some of the medication (Exhibit J-14, p. 4).

Subject Number 1053, [redacted] was an [redacted] patient born [redacted] He was on the drug during this study. He received transfusions at least three times during this study and in each case was off the drug from any where from several days to several weeks. However, the case report forms continued to be generated even when [redacted] was not on the study. His inform consent was dated April 4th although the date had been altered with no explanation or initials. He started on the study substance April 10th. As of August 11th, [redacted] was off the study due to low WBC. A month later on September 8th, he was still off the study but it appears that he may have been entered into the open study at that time.

During the preentry visit, Number 1053's T4/T8 was 72/209. During weeks 1-4, 6, 10, 12, 16[redacted] had numerous low Hematology values. During all weeks there were out of range clinical laboratory values. The patient's diary cards were used to compare the subject's statement of use of the study medication versus what was written on the case report forms. However, there was no correlation. Not all diaries for this subject were located. Also adverse reactions according to the subject were noted, as an example, during the week 1 visit[redacted] diary card listed adverse reactions of high temperature, nausea, and marked fatigue. However, none of these were identified as adverse reactions in the case report forms. T. Flynn said that after she had spent time with me that she thought there were reactions that she would identify as possibly adverse reactions and then note whether or not they were believed to be related the study substance.

By the week 4 visit on May 8th, [redacted] WBC was 1.6 and granulocytes were 944. During the same visit his T4/T8 equaled 0.87. This value is accompanied by a question mark which I asked about. T. Flynn said that this seemed to be too high for him. During the same visit identification of the study medication bottle was, "1014201". T. Flynn said that when the other nurse filled in for her she used this number which she believed was a stock number on the bottle. (CRF page 74).

On June 19th Number 1053 received two units of packed cells and was kept off the drug until July 3rd. During the week 10 visit on that date, he complained of fatigue and dyspnea from June 17th. The adverse reaction form stated that these symptoms continued until the day after

#1053 (AZT)

the transfusion. When I asked T. Flynn how this was determined, she said that it was assumed that after two units that his counts would come up. A patient's diary at the time said that his blood counts were too low to take the drug from June 24th to July 8th, which does not coincide with other records or explanations.

On July 2nd the week 12 visit, [redacted] WBC was 1.4 and HGB was 7.5 (MGH results). During this visit he also returned 100 capsules however a note explaining that the return actually occurred on July 7th was crossed out with no explanation. However, none of the records clearly stat that the subject was off the drug during this time and again on July 3rd, the next day, [redacted] received two more units of blood. The same adverse reactions were noted prior to giving the blood. The patient diary beginning July 9th notes that he was on the drug from that day until 7/12 so it appears that he was off the drug during this instance for approximately 5 days. I also noted in the record for the following week, week 14, that there was an additional Hematology report from MGH dated July 7th (which was the same date as the note of return of study medication). During the week 14 visit also the number of study meds returned was changed from 12 to 128. There was no explanation of how this amount could have been returned and this is not the amount noted on the monitor's tally (Exhibit D-2,).

During the following week's visit on July 28th, [redacted] complained of Paresthesia in his toes which had been four weeks. During the same visit the adverse reaction form's original entry of "No" was changed to list Anemia from July 28th to August 15th. All of these additions or changes were added to the photocopy. T. Flynn said she thought that this change on the copy was made because after the monitor picked up the forms he said that anemia is an adverse reaction and this was the only way to pick up this information for the study.

During the week 18 visit on 8/11/86 there was a note that the subject was off the study from this date due to WBC of 600 and later August 15th value of 900. Also the record included a summary of hematology values and when he was given packed cells during the study (Exhibit J-15, p.77). He was then given two units of red cells on August 11th; at the time he had a hemoglobin of 7.5 and a hematocrit of 22. The adverse reaction form for this week (CRF 157) stated that he had anemia from July 28th to August 15th however during the previous weeks visit the adverse reaction form stated that the dates of anemia were August 11th to August 15th. There was no study medication issued during this week 20 visit (August-25-86) nor during the next week 22 visit. During that visit there were no vital signs taken. T. Flynn said this was because the binder was not in the room, not because the subject did not visit. Then on week 24, September 8th, there was a note that appears to say "he has been off drugs since 8/11-OK with you ? (to restart). Do we need to call [redacted] T. Flynn said that the answer was to restart this subject on the open part of the study at 100 milligrams every 4 hours. When I asked to see the record of hospitalization of this subject for the blood transfusions I was told that there was no such record available.

Number 1054 had the initials [redacted] and date of birth of [redacted] He

as an [redacted] patient who was on placebo from April 10, 1986, to September 18, 1986. His consent form was signed two days prior to entering the study. He did opt to into the open label study.

Number 1055, [redacted] was born [redacted] He is an [redacted] patient who was on the drug, [redacted] In the background file for this subject was a business card and letter to Dr. Schooley referring to [redacted] and to the writer's "foundation" to see if they could "help" and a reference to "payment enclosed for your services". Dr. Schooley explained that the writer (a friend of [redacted] was in the catering business in [redacted] and had been frustrated in his attempt to find a laboratory to whom he could give money he had raised for [redacted] He did in fact send a check for $5000 to Dr. Schooley when [redacted] wanted to enter the study. This subject did live in [redacted] but relocated in Boston since it was required that all subjects in the study live locally. Dr. Schooley said there had been a misunderstanding. He thought that the check was for [redacted] so he put it in that fund at the hospital. However, the intention of this money was to provide medical care while [redacted] was here. However, Dr. Schooley later explained to the writer that he did not have a retainer. He said he called and explained the circumstances and eventually the money was left as a donation. [redacted] had been hospitalized in [redacted] the [redacted] Center in late September 1985. He is the subject whose diagnosis at that time was [redacted] but, MGH did not agree. There was a record in the file that referred to shipment of laboratory slides to MGH for their analysis. [redacted] had a record dated February 5, 1986, that showed his T helper/supresser ratio was 0.2 (normal range 1.3-2.9). During his brief time on the study he was hospitalized at MGH. The records said that 5 days prior to his arrival he had fevers up to 103, headaches, rhinitis and occasional chills. He was admitted to MGH on May 20, 1986 and dischared 10 days later. The principal diagnosis was TB with an associated diagnosis of Kaposi's Sarcoma and [redacted] From there after Dr. Hirsch made a note that he found evidence of Herpes simplex virus; he began Acyclovir therapy and was told to hold off on the [redacted] for a while.

The update summary for number 1055 noted that he had stopped the medication at week 2 and had chosen to return to his family in [redacted] and later to his residence in [redacted] He was also found to have KS, MAI (Mycobacterium Avium Intracellulare) and he decided to drop from the study. Note that the date he was said to drop from the study (week 2 or May 7, 1986) conflicts with that noted in the case report forms which is week 5 (May 21, 1986).

When [redacted] entered the study he was taking no medication at all. He signed the consent form on April 9th and began the study on April 17, 1986. His hematology values throughout the study were frequently out of range without any comment by the investigator. On the study visit one week before he entered the hospital was a note that he had fever to 102 degrees at night and nasal congestion for 4 to 5 days. He was said to have "moderate" malaise, fatigue, and nausea, but not adverse reactions.

The week he did enter the hospital which was the week 2 visit, the

#1055 (AZT)

clinical evalution had changes in the values for fatigue, nausea, and loss of appetite. The first of these was increased from mild to moderate and the second two were increased from none to mild with no explanation. There was a note that he had fevers to 105 degrees and he was admitted to the hospital and the drug withheld. However the adverse reaction form (CRF page 49) said there were no adverse reaction. Dr. Schooley said that the reason for this was that none of his reactions were considered related to the drug and they had found acid fast organisms which indicated there was another problem.

The return study medication for this second week visit were "lost" according to the CRF but the hand written tally showing amounts dispensed and returned weekly for the subject said that 5 capsules were returned on this date. Records should be generated for this subject during week 3 and week 4 (dates 5-5 and 5-12, respectively). And records for a fifth week visit, May 19, 1986, were also generated. T. Flynn's comment and response to this was that the subject was off and on the study twice and on or about week 5 or 6 he finally terminated being on the study.

I noted that his SGOT and LDH were elevated at the end which would indicate toxicity. A number of the records used during the week 5 visit for this subject were originally week 18 records. This might help to explain the fact that the week 18 records were missing for subject number 1053 or it may mean that since they were the beginning of the second binder, that it was assumed subjects such as number 1055 would not get that far and therefore it was safe to use that week's record.

PLB → AZT

Number 1056, [redacted] with a DOB [redacted] as an [redacted] patient on placebo. However for two weeks during the study he received number 1057's study medication, which was the active drug. This happened during the week 12 visit for number 1056 (CRF page 131) which says that, "number 1057's week 14 [given] by mistake" with no initials, date, or comments. This is August 7, 1986. Then during the week 14 visit for number 1056 either week 14 or 16 was given to him; the record is not specific (CRF page 139). Then during the week 16 visit the correct study medication is given, week 18. However, there should be an extra bottle of 100 for this subject and it is not identified in the records (see Exhibit D-2). Otherwise the record for number 1056 was not reviewed as a part of this audit.

AZT

Number 1057, [redacted] DOB [redacted] was an [redacted] patient on the drug. Number 1057, a manic depressive, was on lithium throughout the study. On May 12th, four days before he signed the informed consent the hematology series was run on him with a number of low values including a hemoglobin of 8.8, below the protocol exclusion limit. T. Flynn explained that they repeated the analysis and on May 19th, 10 days before he started on the study, [redacted] had a hemoglobin of 10.9. When asked if this was checked with [redacted] she explained that this was closer to the date of the study. She said that they would keep having people with low values come in and she used as an example one woman who came in for 4 weeks and whose values never came up to the level required by the protocol. This subject (No. 1057) had been

#1057 (AZT)

judged amemic and in February had received received 2 units of packed cells (2/16/86-CRF page 16). He started on the study on May 29th and his hematology values were low throughout.

The number of capsules returned during the week 6 and week 8 visits were changed from 10 to zero (0) and 8 to 15, respectively. This is also the subject whose medication was dispensed to number 1056 for one week. He did not recieve number 1056's drug during that time. There was no note explaining what happened to his week 14 medication. And in fact the monitors accountability sheet for number 1057 indicate that he went 16 weeks when in fact it appears that he only went 13 or 14.

Number 1058 was assigned only briefly to the subject who became number 1012. See the text for number 1012 above.

Number 1059 was born [redacted] He was a [redacted]patient on the placebo. He was hospitalized during the course of the study. Ordinarily his records were not planned to be reviewed during this inspection, but the hospitalization records would have been reviewed if they could have been found. However, T. Flynn said they could not be found. The case report forms for number 1059 did not mention that he was hospitalized. He was on the study for approximately 5 weeks from June 16th to July 24th or August 4th. T. Flynn said that he was not hospitalized but was treated as an outpatient: NMR and CT. The background records for number 1059 mention that [redacted] sent him "again" to see T. Flynn on May 22, 1986. He signed a consent form on June 3, 1986. The case report forms for opportunistic infections mentioned that he had the NMR and CAT scan of the head on July 17th, and it was positive for TOXO and encephalitis. There was no clinical evaluation done at the time and T. Flynn explained that [redacted] said he would have to go off the study once they saw the concomitant medication he was taking for the Toxoplasmosis. The background file also included two sheets of medications with the times that the subject was to take them. T. Flynn explained that he had difficulty being compliant with medications and that there were problems communicating since the subject was [redacted] It was T. Flynn's recollection that he was sent to the emergency room from the clinic on or about July 24th, in the middle of a two week stretch for the study. A letter was found in the background file to the house staff dated August 13, 1986. It mentioned that three and a half weeks previously this individual experience voluntary movements of his left arm. That was the reason for the CT and MRI. When I asked T. Flynn if any of his reactions should have been considered adverse reactions she said they were not at the time and perhaps they should have been included.

G. 1. f. The people obtaining raw data that were mentioned above are: Dr. Schooley, Dr. Hirsch, Dr. Ho, Terry Flynn, and her replacement. The laboratory under Dr. Schooley ran the the HTLV III test lab and the B12 and Folate test were run at MGH. Otherwise the routine laboratory tests were run [redacted]

H. Reporting

Ron Beitman

1) The human study subcommittee did review this study prior to its initiation. There were no reports on the progress of the study nor were adverse reactions reported to them.

2) The monitor who is an employee of the sponsor picked up the originals of the CRF's every month or two. The dates of these visits are under the monitor coverage above.

3) The study was discontinued by the sponsor prior to its completion as described above in the "Background" section.

4) The inspection of Dr. Schooley was conducted within 3 months of the completion of the study and therefore it is not possible to say whether or not all the CRF's were submitted to the sponsor within that time.

5) Adverse reactions have occurred as documented above. There was a great deal of confusion at this study center as to what consistituted an adverse reaction and what was expected and not expected.

6) The investigator did not submit a report to the IRB about adverse reaction or subsequent deaths. The sponsor was generally notified of subject reactions, although frequently subject reactions were not deemed to be adverse reactions by the investigator.

7) The adverse reaction reporting to the sponsor is covered in #6 above. The deaths were reported to the sponsor by way of the end of the study summary phone call record. It is referred to as a "Summary" at the beginning of each individual's record.

8) It appears that the investigator did submit information regarding the deaths within 10 days to the sponsor although it is not possible to document that with assurance. The summaries were generated prior to the final meeting of the Data Saftey Monitoring Board. The adverse reactions were generally relayed to the sponsor by way of case report forms which were picked up every month of two. There was no documentation of notification of the sponsor at more frequent intervals for reporting of adverse reactions or deaths.

10) The investigator did not maintain copies all reports submitted to the IRB. He had to refer me to the IRB to review those records. Generally the investigator did keep copies of records he submitted to the sponsor. However there were expections to that which have been noted in the review of records above.

I. 1.) The investigator does maintain custody of his records, however, it was not always possible to see the hospital record for all subjects.

3.) The study has just been completed and therefore it is not possible to say if Dr. Schooley will keep the records the required number of

years. However this was discussed with him briefly.

Laboratory analyses

T. Flynn explained that the HTLV III sample had to have been drawn (to culture) or positive to enroll a study subject. She also explained that the culture did not have to be positive but that if the sample were found to be antibody poisitve and culture negative that sometimes the results changed over. I asked if any of the subjects had given informed consent for the HTLV III testing. She said that it was her understanding that none of the subjects has come into the study without having been tested previously. And it apparently was her interpretation that it was only for the first test that the consent was required. A memo dated December 5th has been written about this to the Director of the Boston Investigations Branch for referral to the State of Massachusetts.

The summary of T4 and T8 values is Ex. D-3. The record of HTLV III test results is Ex. L. I noted that most of this record was incomplete when it was supplied, but the additional pages given me were repeats of what I already had from these dates: 3/24/86; 6/20/86 (p. 1.); and 8/27/86 (p. 1.).

Roy Byington, the Lab Supervisor, showed me the deep freezers where the serum interferon samples and others were being held. I commented that the lab notebook holding the HTLV III results should say in which laboratory they were run, the date, who generated the data, and also a clear reference to the specific study [redacted]

The Elisa test used by this laboratory is manufactured b[redacted] R. Byington said that they did use [redacted] for confirmation in a few cases.

Additional Tests

The Neurotoxicity test was administered by T. Flynn. A copy is attached as Exhibit M to this report. Neither the test nor the results were reviewed during this inspection.

There was also a work questionnaire that was administered as a part of the study. It is attached as Exhibit N to this report. T. Flynn said she attended the all day NIH workshop in January 1986 to explain how to conduct the work questionnaire.

Discussion with Management

Preliminary discussions were held on two occasions once with Dr. Schooley when [redacted] was leaving the inspection, and once with Dr. Hirsch prior to the completion of the inspection, since he did not anticipate being available for the final discussion. At the beginning of the final discussion with Dr. Schooley and T. Flynn on the last day

of the inspection, Dr. Schooley was reminded of his responsibility under the Food, Drug, and Cosmetic Act. I relayed some observations that were not incorporated in the FD 483 prior to issuing it.

Summary

Those observations included: that the research nurse was using an old copy of the protocol; that the clinical investigator did not keep copies of his IRB records; that the research personnel should address returns of study medication that are below or above what is expected. Their comments should be directed to the subject and should be included in the case report forms. In subject 1004's record the adverse reactions were repeated during weeks 14 and 16 but different numbers of packed cells were identified as given. References to the study substance as [redacted]ight might be misleading, especially in the future when it might be unclear what the subject took. Any changes made in records should be lined out such that the original entry can be read with an explanation, date, and initials. I noted that it appeared that they had tried to keep people on the study even though they were no longer taking the study substance e.g. No. 1009.

See p. 39

I noted that pencil is inappropriate to use on any study records including diaries, case report forms, and pharmacy records. Since I had found errors in T4/T8 values I recommended that a second check be made of some such entries. If a sample is lost, etc. the record should say so. It would be preferable to have the subjects list on their diary cards when they did not take the substance so that it would make drug accountability easier. At the present time it is difficult if possible to match up the case report forms with the diary cards. That match should be made and should be addressed in the case report forms. Since the clinical investigator is keeping photocopies, of his records that when they are chopped off (on the Copier) it is impossible to read them (eg. Number 1012, page 86).

Then the FD-483 was issued to Dr. Schooley and a copy was given to T. Flynn. Dr. Schooley made few if any comments in response to the FD-483. The discussion was as follows:

1) Deaths and adverse reactions were not reported to the IRB (Human Studies Committee). There have been two deaths, each after the subject was off the study medication. Adverse reactions have included seizure (thought to be unrealeated), dizziness, severe coughing, etc.

Dr. Schooley had no comment about this observation.

2) There is no documentation to verify that calls were made promptly to notify sponsor of deaths or severe adverse reactions.

Dr. Schooley had no comment about this observation.

3) Deviations from the Protocol were alledgedly approved per telcons.
A. Concurrent Medication

PCB 1001: Cefadroxil, Erythromycin (within 2 wks prior to the study);
ART 1003: Acyclovir, Wacomil, Ranitidine (Zantac);
? 1005: Hydrocortison cream (topical), Benadryl, Dilantin;
ART 1006: Stelazine, Xanax, Halcion, Colace;

1008: Compazine, Tylenol, Lomotil;
1009: Tylenol; and AZT before (clinic) entry into the study!,
1011: Benadryl, Excedrin;
1012: Keflex;
1051: Erythromycin;
1055: Streptomycin, INH (Isoniazid), Ethambutol, Pyridoxine;
1057: Lithium.

B. There is no documentation of "Special permission" received to admit No. 1011 since the timing of [redacted] was outside the protocol requirements.

No. 1055 was diagnosed as having [redacted] but MGH decided it was not. However, clinical investigator did not so document on the CRF's and subject was classified as a[redacted]patient.

C. Tests for the following eleven subjects were not done as frequently as called for in the protocol: 1004, 1005, 1006, 1008, 1009, 1011, 1012, 1051, 1053, 1055, 1057.

Dr. Schooley indicated that he understood Part B (he said, "OK").

4) Adverse reaction of high SGOT is not mentioned on CRF for 1003 (CRF p.73 says "non").

AZT 1004 Severe coughing not addressed if adverse reaction or not in CRF, (wk. 14). AZT AZT

AZT 1004 and (1008 & 1053) were treated in the Emergency Room during the study due to need for blood.

PCP 1005's ataxia and "wobbly-transient" were not reported as adverse reactions, nor explained.

AZT 1008 was hospitalized during the study, which was not stated in CRF's and was said to have no adverse reactions. Wks. 1,2,3,4,8,10,12 had moderate headaches, diarrhea, lethargy, abdominal cramps, dizziness, but no adverse reactions.

AZT 1012 had rash wk 8, but no adverse reaction; wk 10 had moderate loss of appetite, no adverse reaction.

AZT 1051 had SGPT value of 58 during wk 3, and in wk 4, SGPT value of 57, but no adverse reactions.

AZT 1053 wk 2 listed nausea and marked fatigue, but no adverse reactions; wk 3 WBC's were 1.6 and granulocytes were 944, but no adverse reactions. During wks 10 and 12, Pt. diary says blood counts were too low to take the drug, but adverse reaction CRF says patient took drug during part of that time. 14 WBC 1.6; no adverse reaction.

PCP 1059 went to the emergency room during the study and had NMR and CT tests, but this is not stated in the CRF's nor are there any adverse reactions.

Dr. Schooley said he did not agree about the observation of subject no. 1004 (and 1008 and 1053) going to the emergency room. He said they went there only to get blood and that was the only place they could get blood[redacted]

5) Changes that are not dated initialed or explained have been made on

photocopied CRF's (raw records) after the original was taken by the monitor. CRF's rarely state who did the work, or who made the entries on the pages. The research nurse who made many entries was replaced by another nurse for two weeks, but it is not possible to determine that from the records.
Opportunistic infection forms frequently state re: onset date, "(per sponsor's request), (seen earlier)".

Dr. Schooley explained that the note re: opportunistic infections meant that it was seen prior to enrollment in the Study.

6) There is no comment by the clinical investigator re several significant observations (including subject left the study) and abnormal values, eg.:
1003: IgG value out of range (high - 2589, Range 540-1480), wk 12; Note of "neck mass" not explained, initialed, dated at wk 20 (noted on study med record). When it was explained on record 2 wks later, there were no initials and the subject was removed from the study.
1055: "fevers to 105 - admitted to hospital. Drug held", CRF not say why ended study.
1056: a placebo subject, received 1057's medication (AZT drug) for two weeks, this is not explained on his 1056's CRF.
1057's record does not reflect this. There should be an extra bottle of 100 for 1056, but it is not accounted for.
1057: had HGB value below entrance criteria; repeat HGB value was used instead.
1059: not say why ended study.

Dr. Schooley said that in regard to number 1057 that they would repeat the hemoglobin value until it was right. He noted that in the new study that the
hemoglobin test sample was to be taken one week before the subject went on the study. It was made specific for the new study. He also said that individuals can be bled down to "30" and still be OK. He said there was a cushion and that they were really not that sick.

7) Several raw data records (other than CRF's) could not be located to support data in CRF's. The research nurse said if they are missing they were thrown out, eg.
1011: hematology at preentry.

Dr. Schooley indicated that he understood the observation.

8) Records of HTLV-III test esultls from CI's lab do not state where or by whom the tests were done or the record was generated.

Dr. Schooley indicated that he understood this observation.

9) Shipment records do not state clearly what was sent and they were not verified with the shipment. No one recalls one shipment of placebos in envelopes (ordinarily the medicine was in amber bottles). Records are not sufficient to allow-comparison test article useage versus the amount shipped, and as compared to the amount returned to

the sponsor.
To the best of our knowledge, records of shipment indicated 87 more containers (of 50 or 100 capsules each) were shipped than were received by the pharmacy.

Dr. Schooley indicated that he understood the observation.

10) Pharmacy inventory of study medication not kept by #units in bottles; running inventory record was destroyed. A shipment of bottles with a handwritten "50" on the label was not documented.

I mentioned that some of the pharmacy records were kept by the week number identification and under those circumstances it was possible to determine how many units were in a bottle. However, no all pharmacy records were kept this way and were not checked in this manner either.

11) Medication returned by subjects were not counted at the time; estimates of amount returned were changed on many CRF's for 10 subjects.
Returned medication was not always stored in a locked/secured area/cabinet.
Statement of returned study medication is signed by monitor instead of the clinical investigator.

Dr. Schooley made no comment about this.

Dr. Schooley did note as we had discussed during the inspection that in the followup study that there is only one sheet for Concomitant medications and adverse reactions. This reduces the amount of copying and makes it easier for the clinician to turn to one page in the record, especially in an emergency, to get the needed information.

The [redacted] Study

See exhibit O:

O-1 [redacted] of the [redacted] (IRB approval and memo 2pp. and two informed consents, 3pp each).

O-2 Is the [redacted]

The subjects on the current Study who then entered the Open Label Study have been identified in the report above and on Exhibit D-1. That is what is referred to as the followup or "open label" Study. Dr. Schooley commented that the dose has changed several times for this Open Label Study for those individuals who were on the drug and will then be switched to a lower dose. As of the end of this inspection it appeared that all such subjects would be put on [redacted] per dose [redacted] from the Study dosage of [redacted]. When I asked if the bottles received for this Study had been counted so that there could be

a verification of the amount used versus the amount sent and remaining, I was told that the bottles had not been counted. T. Flynn said that she had taken all that they had received to the pharmacy.

In addition to that Study, a [redacted] available to more individuals is being organized. From my discussion with the hospital pharmacist it appeared that there might be some confusion about the Study. Dr. Schooley supplied me with copies of the packet of forms supplied to potential clinical investigators for this Study. It is this packet of information which I recommended to [redacted] be distributed to field investigators and supervisors involved in administering the Bioresearch program (PAS Memo dated 12/15/86).

Patricia A. Spitzig
C.S.O. Bos-DO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 585 Commercial St. Boston, MA. 02109

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED	DATE OF INSPECTION	C. F. NUMBER
TO: Robert T. Schooley, M.D.	10/14-17,20-24,27-30 11/10-12/86	
TITLE OF INDIVIDUAL Clinical Investigator	TYPE ESTABLISHMENT INSPECTED same	
FIRM NAME Mass. General Hospital	NAME OF FIRM, BRANCH OR UNIT INSPECTED Infectious Disease Unit	
STREET ADDRESS Fruit St.	STREET ADDRESS OF PREMISES INSPECTED same	
CITY AND STATE Boston, MA. 02114	CITY AND STATE same	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Records were reviewed for 14 subjects.

1.) Deaths and adverse reactions were not reported to the IRB (Human Studies Committee). There have been two deaths, each after the subject was off the study medication. Adverse reactions have included seizure (thought to be unrelated), dizziness, severe coughing, etc.

2.) There is no documentation to verify that calls were made promptly to notify sponsor of deaths or severe adverse reactions.

3.) Deviations from the Protocol were alledgedly approved per telcons.
These calls were not documented, or noted in the case report forms (CRF's). These deviations from the Protocol were not reported to the IRB:

A. Concurrent Medication
1001: Cefadroxil, Erythromycin (within 2 wks prior to the study);
1003: Acyclovir, Wacomil, Ranitidine (Zantac);
1005: Hydrocortisone Cream (topical),Benadryl, Dilantin;
1006: Stelazine, Xanax, Halcion, Colace;
1008: Compazine, Tylenol, Lomotil;
died — 1009: Tylenol; AZT (prior to and possibly during the study)
1011: Benadryl, Excedrin;
1012: Keflex;
1051: Erythromycin;
1055: Streptomycin, INH (Isoniazid), Ethambutol, Pyridoxine;
1057: Lithium;

B.) There is no documentaion of "Special permission" recieved to admit no. 1011 since the timing o[redacted] was outside the protocol requirements.
No. 1055 was diagnosed as having [redacted] by [redacted] but MGH decided it was not. However clinical investigator did not so document on

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Patricia A. Spitzig	EMPLOYEE(S) NAME AND TITLE (Print or Type) Patricia A. Spitzig Investigator

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 585 Commercial St. Boston, MA. 02109
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Robert T. Schooley, M.D.	DATE OF INSPECTION 10/14-17,20-24,27-30 11/10 12/86
TITLE OF INDIVIDUAL Clinical Investigator	TYPE ESTABLISHMENT INSPECTED same
FIRM NAME Mass. General Hospital	NAME OF FIRM, BRANCH OR UNIT INSPECTED Infectious Disease Unit
STREET ADDRESS Fruit St.	STREET ADDRESS OF PREMISES INSPECTED same
CITY AND STATE Boston, MA. 02114	CITY AND STATE same

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

the CRF's and subject was classified as [redacted]atient.

C.) Tests for the following eleven subjects were not done as frequently as called for in the protocol: 1004, 1005, 1006, 1008, 1009, 1011, 1012, 1051, 1053, 1055, 1057.

Adverse reactions:

4.) Adverse reaction of high SGOT is not mentioned on CRF for A2C1003 (CRF p.73 says "none").

A2C 1004 Severe coughing not addressed if adverse reaction or not in CRF, (wk.14,).

A2C1004 and NOT COMPLETED PAS 11/12/86 were treated in the Emergency Room during the study due to need for blood.

? 1005's ataxia and "wobbly-transient" were not reported as adverse reactions, nor explained.

A2C1008 was hospitalized during the study, which was not stated in CRF's and was said to have no adverse reactions. Wks. 1, 2, 3, 4, 8, 10, 12 had moderate headaches, diarrhea, lethargy, abdominal cramps, dizziness, but no adverse reactions.

A2C1012 had rash wk 8, but no adverse reaction; wk 10 had moderate loss of appetite, no adverse reaction.

A2C1051 had SGPT value of 58 during wk 3, and in wk 4, SGPT value of 57, but no adverse reactions.

A2C1053 wk 2 listed nausea and marked fatigue, but no adverse reactions; wk 3 WBC's were 1.6 and granulocytes were 944, but no adverse reactions. During wks 10 and 12, Pt. diary says blood counts were too low to take the drug, but adverse reaction CRF says patient took drug during part of that time. 14 WBC 1.6; no adverse reaction.

PLCB 1059 went to the emergency room during the study and had NMR and CT tests, but this is not stated in the CRF's, nor are there any adverse reactions.

CRF's

5.) Changes that are not dated initialed or explained have been made on photocopied CRF's (raw records) after the original was

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

taken by the monitor. CRF's rarely state who did the work, or who made the entries on the pages. The research nurse who made many entries was replaced by another nurse for two weeks, but it is not possible to determine that from the records.

Opportunistic infection forms frequently state re: onset date, "(per sponsor's request), (seen earlier)".

6.) There is no comment by the clinical investigator re several significant observations (including sujbect left the study) and abnormal values, eg.:

1003: IgG value out of range (high - 2589, Range 540-1480), wk 12;

Note of "neck mass" not explained, initialed, dated at wk 20 (noted on study med record). When it was explained on record 2 wks later, there were no initials and the subject was removed from the study.

1055: "fevers to 105 - admitted to hospital. Drug held", CRF not say why ended study.

1056: a placebo subject, received 1057's medication [redacted] for two weeks, this is not explained on his 1056's CRF. 1057's record does not reflect this. There should be an extra bottle of 100 for 1056, but it is not accounted for.

1057: had HGB value below entrance criteria; repeat HGB value was used instead.

1059: not say why ended study.

7.) Several raw data records (other than CRF's) could not be located to support data in CRF's. The research nurse said if they are missing they were thrown out, eg.

1011: hematology at preentry.

8.) Recordsof HTLV III test results from CI's lab do not state where or by whom the tests were done or the record was generated.

ACCOUNTABILITY

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)
	Patricia A. Spitzig	Patricia A. Spitzig Investigator

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 585 Commercial St. Boston, MA. 02109

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED	DATE OF INSPECTION	C. F. NUMBER
TO: Robert T. Schooley, M.D.	10/14-17,20-24,27-30 11/10,12/86	
TITLE OF INDIVIDUAL Clinical Investigator	**TYPE ESTABLISHMENT INSPECTED** same	
FIRM NAME Mass. General Hospital	**NAME OF FIRM, BRANCH OR UNIT INSPECTED** Infectious Disease Unit	
STREET ADDRESS Fruit Street	**STREET ADDRESS OF PREMISES INSPECTED** same	
CITY AND STATE Boston, MA. 02114	**CITY AND STATE** same	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

9.) Shipment records do not state clearly what was sent and they were not verified with the shipment. No one recalls one shipment of placebos in envelopes (ordinarily the medicine was in amber bottles). Records are not sufficient to allow-comparison test article useage versus the amount shipped, and as compared to the amount returned to the sponsor.

To the best of our knowledge, records of shipment indiated 87 more containers (of 50 or 100 capsules each) were shipped than were received by the pharmacy.

10.) Pharmacy inventory of study medication not kept by #units in bottles; running inventory record was destroyed. A shipment of bottles with a handwritten "50" on the label was not documented.

11.) Medication returned by subjects were not counted at the time; estimates of amount returned were changed on many CRF's for 10 subjects.
Returned medication was not always stored in a locked/secured area/cabinet.
Statement of returned study medication is signed by monitor instead of the clinical investigator.

AZT	Placebo
1003	1001 (died) (in study for only 1-2 weeks)
1004	1002
1006	1005
1008	1007
1012	1009 (died) (Was on AZT prior to and possibly during the study.)
1051	
1053	1052
1055	1054
	1056
	1057
	1059

? 1011

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)
	Patricia A. Spitzig	Patricia A. Spitzig Investigator

Burroughs Wellcome
Research Triangle Park, NC

UC-SD 534-6708
Med Center
619 453-7500
X 3395

AZT MULTICENTER TRIAL

PRINCIPAL INVESTIGATORS

David Durack, MD
Duke University Medical Center
Durham, NC

Margaret Fischl, MD
University of Miami
Miami, FL 1(305)549-7092

Michael Gottlieb, MD
University of California
Los Angeles, CA

Michael Grieco, MD
St. Luke's-Roosevelt Hospital
New York, NY 554-7194
also 535-2075

Jerome Groopman, MD
Harvard-N.E. Deaconess
Boston, MA

Martin Hirsch, MD
Harvard-Massachusetts General Hospital
Boston, MA

Schooley?

George G. Jackson, MD
University of Illinois at Chicago
Chicago, IL

Oscar Laskin, MD
Cornell Medical Center
New York, NY

John Leedom, MD
LAC-USC Medical Center
Los Angeles, CA

Donna Mildvan, MD
Beth Israel Medical Center
New York, NY 420-4005

Douglas Richman, MD
University of California
San Diego, CA 1(619) 455-[illegible](4)
453-[illegible](4)

Paul Volberding, MD
University of California
San Francisco, CA
1(415) 476-9000 (Cinfo)
476-4378

1(619) 453-7500
X 3395

Dan Brook, MD (212) 500 7th Ave. 246-3610

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Memorandum of Meeting

Date: February 11, 1987

Participants: Dr. Frank Young, Dr. Paul Parkman, Dr. James Bilstad, Dr. Edward Tabor, Dr. Robert O'Neill, Dr. Frances Kelsey Dr. Ellen Cooper, Mr. Sammie Young, Ms. Jackie Knight, Mr. Joe Levitt, Mr. John Taylor, Mr. Antoine El Hage, Ms. Patricia Spitzig, Ms. Mary Gross, Dr. George Lyon Dr. Robert Schooley, Dr. Martin Hirsch, Ms. Terry Flynn, Dr. Dannie King, Dr. David Barry

Subject: Discussion of Inspection Report of a Clinical Trial on Zidovudine (formerly known as Azidothymidine or AZT)

A meeting was held to discuss FDA's investigation of Dr. Schooley's facilities.

Dr. Young summarized the meeting by saying that it was clear from the inspection report that there were some problems in recordkeeping in the study and he impressed upon Dr. Schooley the importance of maintaining good records during these trials in order to help FDA inspectors verify clinical trial activities. However, these procedural discrepancies were judged not to have influenced the validity of the data or the ability to draw conclusions and FDA will include Dr. Schooley's data in the overall analysis of the zidovudine multicenter trial.

Dr. Young thanked everyone for attending the meeting and Dr. Schooley expressed appreciation to FDA for the expeditious review given his data.

Mary Gross

Mary Gross
Policy Analyst
Executive Secretariat
3/5/87

Inference: If the Boston data were accepted, then the other centers must not have been much better,

These minutes are PHONY!