#1315

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Ralph Nader, Founder

December 9, 1993

David Kessler, M.D. J.D.
Commissioner, Food and Drug Administration
5600 Fishers Lane
Rockville, MD
20857

Dear Dr. Kessler:

From our review of the evidence surrounding the recent NIH clinical trial on FIAU, in which 5 patients have died so far from liver toxicity, it is clear that this tragedy could have been prevented but for a cover-up of data on liver toxicity by Eli Lilly, Inc. the licensee of the drug. (see our attached report).

The recent FDA Task Force Report on FIAU pointed out many systemic errors involving NIH and FDA that caused earlier studies on patients not to have been interpreted correctly and made some useful recommendations which may help to avert future disasters. But there are two glaring omissions from the FDA report:

First, there was a clear warning signal about liver toxicity in animal studies done about 10 years ago which were incorrectly interpreted as lacking evidence of liver toxicity (see page 2 of our report).

Second, just prior to the March 24, 1993 initiation by NIH of the last clinical trial in patients infected with hepatitis B virus (HBV), Lilly, at its clinical trials unit in Indianapolis, began a study in 16 normal volunteers--the first study ever in which normal people were given the drug. One of these normal volunteers (Subject 1203) showed a more than 3.5-fold increase in AST and a 7.2-fold increase in ALT after just two 5 mg doses of FIAU and was hospitalized for 4 weeks because of this. Another normal volunteer (subject 508) had a 2.8-fold increase in AST and a 4.7-fold rise in ALT after just one dose of FIAU. The severe liver abnormalities in Subject 1203 were first noted on March 17th and again on March 25th, one week before and one day after the commencement at NIH of the ill-fated trial on March 24th which has killed 5 people to date. Of the 8 participants in the most recent NIH trial who experienced serious liver toxicity--5 of whom have died--5 (including 3 who died) appear to have begun their doses of FIAU ***after*** the normal volunteer was hospitalized in Indianapolis. **There is *no* question that Eli Lilly should have stopped the NIH trial by the end of March or in the first days of**

April, before 3 of the 5 patients who eventually died had gotten any doses of FIAU and at a time when 2 of the others who died had gotten only a fraction of the dose that would eventually kill them. Not only did Eli Lilly fail to get NIH to stop the trial, but the company did not inform NIH in a timely manner that one normal volunteer was hospitalized in Indianapolis because of FIAU liver toxicity after only 2 doses on the drug.

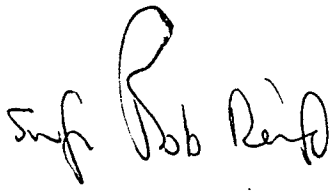
Since no concomitant infections or medications were present in trial H3X-LC-PPPG (as they were in the other trials), there is no possible confusion in ascribing the liver enzyme changes to FIAU toxicity.

We have just learned that, in addition to failing to report the hospitalization of the normal volunteer with liver toxicity to NIH, Eli Lilly also failed, as required by law, to report this hospitalization to the FDA until July 27, 1993, one month after the NIH trial was stopped and after 3 of the 5 deaths in the NIH study had occurred. As you know, according to FDA's IND (investigational new drug) regulations (21 CFR Section 312.32 (a)(c), companies conducting investigational studies on drugs are required to report to the FDA, within 10 days, serious (requiring hospitalization in this case) and unexpected (no previous accepted evidence of liver toxicity) adverse reactions. There are criminal penalties for failure to do so. It is likely, if not certain, that FDA would have ordered NIH to stop the FIAU clinical trial at a time early enough to have spared the lives of at least 3 if not all of the 5 people who died had Lilly not covered up this important data.

We look forward to a prompt response to this urgent matter.

Sincerely,

Sidney M. Wolfe, M.D.
Director, Public Citizen's
Health Research Group



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RESPONSE TO THE FDA TASK FORCE REPORT ON FIALURIDINE

DECEMBER 9, 1993

Public Citizen's Health Research Group

RESPONSE TO THE FDA TASK FORCE REPORT ON FIALURIDNE

An FDA Task Force report[1], released on November 12, 1993, is intended to avert future disasters in human drug experimentation such as the NIH clinical trial which studied the Eli Lilly drug, Fialuridine (FIAU), as a possible treatment for chronic Hepatitis B virus (HBV) infection. In this study of 15 patients (referred to as H3X-MC-PPPC), conducted from March 24 to June 28 1993, 8 patients had serious liver and/or pancreatic damage and 5 have died to date.

In its report, the FDA Task Force examined trial H3X-MC-PPPC, 3 previous clinical trials on patients (with FIAU and a closely related compound, FIAC), 1 human trial on healthy volunteers, and 17 animal trials for evidence of clinical and laboratory abnormalities. The task force reports that, in the 3 previous human trials on patients, an alarming 29.1% of the participants had liver enzyme changes and/or clinical events indicative of liver or pancreatic damage; 5 patients died in these early trials in addition to the 5 in the H3X-MC-PPPC study. In examining the animal trials, however, the Task Force reports that the "FIAU animal pharmacology/toxicology data, either in the literature or submitted by the involved sponsors, are noteworthy because they did not suggest that FIAU was toxic to either the liver or the pancreas." (page 3)

Partly because the task force stated that it did not intend "to determine whether the events in the H3X-MC-PPPC study could have or should have been predicted" and partly because the task force omitted any discussion of the significance of the two findings discussed below, FDA has avoided focussing on exactly how this tragedy could have been prevented.

Our review of the summary data in the FDA Task Force report finds that the animal studies were strongly indicative of liver toxicity. Even though the FDA has refused to make the actual studies and the raw data from either the animal or human studies available for our examination, the limited information which was supplied in the FDA report itself draws into question the FDA's initial approval of FIAU for use in human experimentation. Had the animal toxicity been heeded, it would have averted all the deaths and injuries occurring in all the human studies. Moreover, even though the animal data was falsely interpreted as lacking in liver toxicity, the clear evidence of hepatic and pancreatic toxicity in the 3 early clinical trials on patients should have precluded any further studies.

Our examination of the results of trial H3X-LC-PPPG (a phase I trial in normal healthy volunteers), begun on March 17 1993, reveals that there was ***clear*** evidence of human liver toxicity ***prior*** to the start of trial H3X-MC-PPPC, where 5 people have died to date: Eli Lilly, the sponsor of trial H3X-LC-PPPG in normals, failed to promptly report this evidence to either the NIH or the FDA. Since the results of trial H3X-LC-PPPG on healthy subjects were not clouded by other infections or medications, there is ***no*** question that any further human experimentation should have been halted. When the evidence from the animal studies, the 3 early clinical trials in patients, and trial H3X-LC-PPPG in healthy volunteers, is viewed together,

it is inconceivable that the most recent and most lethal NIH trial was approved and allowed to continue.

I. METHOD

Our analysis of the circumstances surrounding the most recent NIH trial of FIAU is based on the FDA Task Force report, an examination of the informed consent forms for trials H3X-MC-PPPC and R91-010 (which we have obtained), discussions with sources from within the FDA and NIH, and a review of the relevant published scientific literature. Our analysis includes an examination of the summary data for the following studies according to the sequence of events which preceded (or should have preceded) the ill-fated H3X-MC-PPPC trial:

	Dates	Sponsor
a) The Animal Studies		
15 studies	Early 1980s	Bristol-Myers
2 studies	1989	Oclassen
b) The Early Clinical Trials in Patients		
R89-001	11/89 - 05/90	Oclassen
R90-001	10/90 - 06/92	Oclassen
R91-010	04/92 - 09/92	Oclassen
c) A Clinical Trial in Normal Healthy Volunteers		
H3X-LC-PPPG	03/93 - 04/93	Eli Lilly
d) A Clinical Trial in Patients (which ran concurrently with H3X-MC-PPPC)		
H3X-MC-PPPA	05/93 - 06/93	Eli Lilly

II. THE ANIMAL STUDIES

Our analysis of the summary animal data (all studies with positive findings were conducted by Bristol-Myers in the early 1980's) included in the Task Force report shows substantial evidence of liver toxicity in many of the 17 animal studies. The evidence is as follows:

The 4 multiple-dose monkey experiments (involving a total of, we estimate, 56 monkeys):

- 1 monkey had an aspartate aminotransferase (AST) level, a measure of liver toxicity, of approximately 1100 IU/L (normal: 0-35 IU/L in humans and monkeys) or more than **30 times** what it should be.
- 1 monkey had more than a 4-fold rise in alanine aminotransferase (ALT), another measure of liver toxicity.
- An unreported number of monkeys had 2-fold AST rises

The 4 single-dose monkey experiments (involving a total of 16 monkeys):

- 3 monkeys (19%) had AST rises (these are not quantified in the report):

The 10 rodent experiments (including 1 study of both mice and monkeys):

- No mice or rats are reported to have shown hepatotoxicity.

When one examines the AST increases seen in the single and multiple dose monkey experiments in conjunction with the total dose given, the monkeys with a 2-fold or greater AST increase appear to have received higher doses than those which showed no increase. Given this limited information, there appears to be some evidence of a dose-response relationship.

From discussion with sources within the FDA, it is apparent that the FDA staff held a view similar to that taken in the Task Force report and did not believe that the animal studies revealed any evidence of hepatotoxicity.

These animal studies are important for the following reasons:

1. The finding of liver enzyme increases in monkeys should have alerted investigators to potential hepatotoxicity in humans.

2. As the monkeys were not infected with viral hepatitis, it was likely, if not certain, that FIAU toxicity was the sole cause of the observed liver enzyme increases.

Given the apparent FIAU animal hepatotoxicity, the decision to conduct any human trials at all should be seriously questioned. The FDA needs to release immediately all the animal data on FIAU for examination. In addition, the animal data on other closely related nucleoside analogs, such as FIAC and FMAU, should be released (the Task Force report makes no mention of these studies). **We believe that the Task Force conclusion of no animal toxicity is unfounded based on the data in its own report.** Unfortunately, because of the incorrect interpretation of these studies, there were no recommendations in the Task Force report concerning the conduct or interpretation of animal toxicity studies.

III. ELI LILLY'S H3X-LC-PPPG TRIAL ON NORMAL VOLUNTEERS: WHY WAS IT NOT DONE EARLIER? WHY WEREN'T ITS RESULTS USED TO STOP THE NIH TRIAL?

Given that the investigators and the FDA apparently misinterpreted the animal trials, concluding that there was no evidence of animal hepatotoxicity, it is difficult to understand why a trial, intended to evaluate the safety of FIAU in healthy subjects (such as the Eli Lilly's H3X-LC-PPPG study), was not the ***first*** human trial initiated. Instead, trials which were intended to

demonstrate the drug's effectiveness in treating disease, were started on patients with combinations of human immunodeficiency virus (HIV), cytomegalovirus (CMV), and HBV infections (trials R89-001, R90-001, R91-010, H3X-MC-PPPC and H3X-MC-PPPA respectively). It was not until March 1993, 3 years ***after*** the first human trial, that trial H3X-LC-PPPG (a true phase I clinical trial involving normals) was initiated at Eli Lilly's clinical investigation unit in Indianapolis. In this trial, an alarming ***12%*** of healthy participants showed significant liver enzyme changes. One of these normal volunteers (Subject 1203) showed a more than 3.5-fold increase in AST and a 7.2-fold increase in ALT after just two 5 mg doses of FIAU and was hospitalized for 4 weeks because of this. Another normal volunteer had a 2.8-fold increase in AST and a 4.7-fold rise in ALT after just one dose of FIAU. The severe liver abnormalities in Subject 1203 were first noted on March 17th and again on March 25th, one week before and one day after the commencement at NIH of the ill-fated trial on March 24th which has killed 5 people to date. Of the 8 participants in the most recent NIH trial who experienced serious liver toxicity - 5 of whom have died - 5 (including 3 who died) appear to have begun their doses of FIAU ***after*** the normal volunteer was hospitalized in Indianapolis. **There is *no* question that Eli Lilly should have stopped the NIH trial by the end of March or in the first days of April, before 3 of the 5 patients who eventually died had gotten any doses of FIAU and at a time when 2 of the others who died had gotten only a fraction of the dose that would eventually kill them. Not only did Eli Lilly fail to get NIH to stop the trial, but Eli Lilly did not inform the NIH in a timely manner that one normal volunteer was hospitalized in Indianapolis because of FIAU liver toxicity after only 2 doses on the drug.**

NIH's Dr. Dr. Jay Hoofnagle still maintains that, until the patients in H3X-MC-PPPC developed liver damage, he did not believe FIAU was toxic to the liver. Thus, the receipt of timely information on liver toxicity from Eli Lilly could have made a difference in the decision to conduct the final NIH trial.

Since no concomitant infections or medications were present in trial H3X-LC-PPPG (as they were in the other trials), there is no confusion in ascribing the liver enzyme changes to FIAU toxicity. **If this trial had been completed earlier, as it should have been, none of the subsequent 5 clinical trials would have been carried out and the tragedies would have been averted.** Despite this obvious error, the Task Force report makes no mention, in circumstances similar to the ones here, of the problem of not having done Phase I studies in normal people earlier. Even more glaring, there is no mention made of the hospitalization of a patient with liver toxicity in the Eli Lilly trial of normals which occurred ***before*** most of the FIAU had been administered in the most recent NIH trial.

We have just learned that, in addition to failing to report the hospitalization of the normal volunteer with liver toxicity to NIH, Eli Lilly also failed, as required by law, to report this hospitalization to the FDA until July 27, 1993, *after* 3 of the 5 deaths in the NIH study. FDA regualtions rewuire the reporting of such adverse reactions within 10 days. 21 CFR section 312.32 (a) (c)

IV. THE CLINICAL STUDIES ON PATIENTS

Was the FDA Task Force's examination appropriate?

When it examined the evidence for hepatotoxicity in the 3 early clinical trials of FIAU and FIAC (R89-001, R90-001, and R91-010), the FDA Task Force considered what it thought to be appropriate laboratory and clinical endpoints. The only laboratory endpoint which the task force considered significant was a relative 3-fold increase in liver enzymes (AST or ALT). As the Task Force notes, this degree of rise is "arbitrary", intended to dismiss rises associated with HBV infection.

We believe this approach to be incomplete and it may underestimate the laboratory evidence of hepatotoxicity. In addition to relative changes in liver enzymes, the Task Force should have examined the absolute levels; examination of relative values alone may lead to biased interpretations. Moreover, it would have been more appropriate to examine and report on the liver enzyme changes in light of serum markers of HBV activity (including HBeAg, HBV DNA, and HBsAg). Since improvement in these markers of HBV infection was the intermediate objective in the later trials, the results were certainly available to the FDA. It seems obvious that a 2 to 3-fold increase in AST would mean very different things depending on if the HBV markers were improving or deteriorating. Consideration of this information would have made the Task Force's conclusions less "arbitrary". Since the task froce did not report on the examination of any of the HBV markers, FIAU toxicity which caused liver enzyme increases of less than 3-fold was not considered; it is thus likely, if not certain, that the report underestimates the laboratory evidence of hepatotoxicity. Similarly, since the report does not examine any clinical events occurring beyond 6 months or any events which did not result in a clinic or hospital visit, the incidence of hepatic and/or pancreatic clinical events associated with FIAU toxicity may be underestimated.

It is curious that the Task Force did not report on tests of potential pancreatic toxicity (i.e. serum amylase). Since FIAU is toxic to the pancreas, these results are also important. Moreover, it would have been prudent for the Task Force to have reported evidence of other organ toxicities (such as neuropathy and myopathy) in the participants of all the trials. We believe that these toxicities are relevant to any examination of the safety of FIAU. A published study concluded that selective mitochondrial toxicity may be the common mechanism of other delayed toxicities seen with nucleoside analogs (such as peripheral neuropathy)[2]; the presence of delayed toxicity in other organ systems should have alerted investigators to the possibility of simultaneous liver or pancreatic toxicities.

a. TRIAL R89-001 (November 1989 - May 1990) - FIAC

In its report, the FDA states that the data regarding hepatic and pancreatic adverse events obtained from trial R89-001 and the subsequent trials, should have "led to some understanding of FIAU's possible hepatic or pancreatic toxicity by the investigators, the sponsors or the FDA" prior to the start of the H3X-MC-PPPC trial. We conclude that this understanding should have

come much sooner in the research process. The Task Force reports that, in this initial trial conducted with FIAC, 75% of the participants (most of whom were coinfected with HIV and CMV) did not complete the study because of the adverse events. Five of the 12 patients (42%) showed at least 3-fold liver enzyme increases. Since only one of the subjects was coinfected with HBV, the liver enzyme increases could not be attributed to HBV. One of the patients died as a result of liver failure within 6 months of his last dose of FIAC, a rare cause of death in a patient with HIV and CMV infections. Given this disturbing evidence of both increasing liver enzymes and death due to hepatic failure, hepatotoxicity with FIAC and FIAU should have been considered at this early point.

b. TRIAL R90-001 (October 1990 - June 1992) - FIAU

The next R90-001 trial added substantially to the evidence of FIAU's hepatic and pancreatic toxicity. The Task Force reports that this trial, which studied HIV-infected patients, revealed that 12% of the subjects had 3-fold liver enzyme increases (including one patient not coinfected with HBV). The Task Force neglects to state that these rises were evident before the start of the R91-010 trial (see below) and, therefore, this subsequent trial's approval could be questioned.

Even more alarming was the fact that ***100%*** of the patients who were re-treated with FIAU had serious adverse events; 3 (75%) died of liver and/or hepatic failure between May and October 1992. For each of these deaths, an alternate explanation was found even though, as the Task Force reports, there were significant clinical inconsistencies surrounding each of the deaths. The information on the outcomes in these patients who were re-treated was especially pertinent to the investigators of the H3X-MC-PPPC study as this trial also involved re-treatment. Although the Task Force alludes to this fact, we believe that the Task Force did not go far enough and state that these deaths should have precluded approval of the H3X-MC-PPPC study.

c. TRIAL R91-010 (April 1992 - September 1992) - FIAU

Despite the serious warnings of the previous trials, this next trial was approved for the study of FIAU in the treatment of chronic compensated HBV infection. The Task Force makes no mention that, in this trial, the cost-benefit ratio changed significantly from that of the previous trials since these patients were afflicted solely with chronic active Hepatitis B, a disease with a variable clinical course. A previous prospective study of 379 patients with chronic HBV infection revealed a 5-year survival rate of 86% in those patients with chronic active hepatitis.[3] In the R91-010 trial, the Task Force report states that 8 of 24 patients (33%) showed at least 3-fold liver enzyme increases. As with the previous studies, all these increases (which appeared to follow a dose-response relationship) were evident before the start of the H3X-MC-PPPC study. Moreover, by November 1992, 3 patients had significant adverse events and 1 died of liver failure, 4 months ***before*** the start of the H3X-MC-PPPC study. Even though the evidence of FIAU's severe toxicity was apparent in the results of the 2 previous trials, these additional results should have halted any further experimentation.

d. TRIAL H3X-MC-PPPA (June 1993 - July 1993) - FIAU

This trial which ran concurrently with the ill-fated H3X-MC-PPPC trial, is summarized in the Task Force report but is not considered in the conclusions. As with the H3X-MC-PPPC trial, patients with chronic compensated HBV infections participated; 1 of 6 patients (17%) had greater than a 3-fold liver enzyme increase and 1 other had a clinically significant adverse event.

V. WHY WEREN'T ALL THE DATA COMPILED?

The Task Force reports that all the adverse events (including the 5 deaths) as well as the liver enzyme abnormalities in the 3 early trials were looked at individually and attributed to other medications or infections; the results were not compiled and the accumulation of all the evidence alerted no one. If the data had been compiled and systematically analyzed, this tragedy may have been averted. It is inexcusable that the investigators, Eli Lilly, and the FDA did not follow such a comprehensive, common sense policy. It is inconceivable that the FDA is only ***now*** advocating this policy.

VI. THE INFORMED CONSENT FORMS: WERE THEY ADEQUATE?

Neither the H3X-MC-PPPC nor the R91-010 informed consent form (which we have obtained) makes mention of any potential lethal liver and/or pancreatic adverse events. In addition to describing other potential complications, both consent forms state: "FIAU is a new medication, and its side effects have not been completely described. In studies of persons taking FIAU for 4 weeks ['14 days' in the R91-010 consent form], it was very well tolerated".

We believe that these informed consent forms were seriously inadequate for the following reasons:

1. As the Task Force concludes, there was available evidence in the scientific literature of hepatotoxicity associated with other related nucleoside analogs and immune suppressants.

2. Adverse events (including death) were observed in the 3 prior trials on patients, but the informed consent states that FIAU had been "very well tolerated".

3. A normal volunteer (Subject 1203 in the H3X-LC-PPPG trial) had shown evidence of liver toxicity with FIAU ***before*** the commencement of the H3X-MC-PPPC trial.

4. The animal studies revealed evidence indicative of hepatotoxicity.

VII. SUMMARY

It is clear that the investigators, Eli Lilly, and the FDA did not follow the medical profession's overriding ethic to "above all, do no harm". This principle is especially important in the investigation of new drugs since their toxicity has not been clearly established. It is incumbent upon researchers to initially attribute all adverse events, encountered in both animal and human trials, to drug toxicity, ***regardless*** of confounding factors. Moreover, researchers must ***actively*** search for all cases of potential toxicity and when found, interpret them in light of those found in previous animal and human studies. Unfortunately, neither of these common sense principles were followed in the whole history of FIAU experimentation, from the initial animal studies through the final, disastrous NIH trial.

The FDA's Task Force report is inadequate in its response to the tragic experience with FIAU for the following reasons:

1. The FIAU animal studies are indicative of hepatotoxicity even though this is contrary to the Task Force's conclusions. A thorough examination of the raw data is needed. In addition, the results of the additional animal studies on FIAC and FMAU are also of vital importance (even though they are not mentioned in the report). If the animal studies had been interpreted correctly, human trials would not have been done or, at least, the earliest evidence of human liver toxicity would have more likely been attributed to FIAU.

2. Given that the animal studies were interpreted as normal, a trial which examined the toxicity of FIAU in ***healthy subjects*** should have been done before the drug was ever studied in patients with chronic compensated HBV infection, if not earlier. The cost benefit ratio changed significantly from when the drug was tested in HIV-infected patients (who were also infected with other viruses) to when it was tested in patients with HBV-related, chronic active hepatitis, a disease with a much better prognosis which carries a 5-year survival rate of 86%.

3. The Task Force report makes no mention that in the March - April 1993 trial in normal volunteers (H3X-LC-PPPG), one patient was hospitalized for severe liver toxicity ***before*** most of the patients were entered into the recent disastrous NIH trial; this information should have immediately stopped any further FIAU experimentation in patients. It is indefensible that Eli Lilly allowed trial H3X-MC-PPPC to proceed nad that the company dangerously delayed informing NIH and FDA of the results; it is a deficiency in the Task Force report not to have discussed this important piece of information.

4. The laboratory and clinical outcomes, which were used by the Task Force as evidence suggestive of hepatic and/or pancreatic toxicity, are incomplete as they did not include mention examination of:

   a) the viral markers of HBV infection
   b) the absolute levels of the liver enzymes

c) a measure of pancreatic toxicity
d) significant clinical events which occurred beyond 6 months
e) all adverse events which occurred in organs other than the liver and pancreas (such as peripheral neuropathy and myopathy)

5. Although the Task Force states that data from the 3 early clinical trials should have "led to some understanding of FIAU's possible hepatic or pancreatic toxicity" prior to the start of the subsequent NIH-sponsored trial, this early data should have halted approval of trial H3X-MC-PPPC as well as trials R90-001 and R91-010.

The FDA Office of Compliance (which is currently conducting a separate evaluation of whether the sponsors and the investigators complied with FDA regulations governing the conduct of clinical trials) must thoroughly examine the origins of the gross inadequacy of the informed consent forms. The R91-010 and the H3X-MC-PPPC consent forms are misleading and woefully inadequate since they lead participants to believe that FIAU was very well tolerated with no serious liver or pancreatic toxicities in animals or humans.; To the contrary, not only were there publshed reports of human lever and pancreatic toxicity with related drugs, but there was clear, substantial, and early evidence of both animal and human hepatotoxicity with FIAU.

REFERENCES

1. Food and Drug Administration. Fialuridine: Hepatic and Pancreatic Toxicity, Report of an FDA Task Force. Washington, DC: Department of Health and Human Services, November 12, 1993.

2. Chen CH, Vasquez-Pedua M, Cheng YC. Effect of anti-human immunodeficiency virus nucleoside analogs on mitochondrial DNA and its implication for delayed toxicity. *Molecular Pharmacol* 1991;39:625-8.

3. Weissberg JI, Andres LL, Smith CI, et al. Survival in chronic hepatitis B: an analysis of 379 patients. Ann Intern Med 1984;101:613-6.

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