Review of the Fialuridine (FIAU) Clinical Trials

Frederick J. Manning and Morton Swartz, Editors;
Committee to Review the Fialuridine (FIAU/FIAC) Clinical Trials, Institute of Medicine

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Division of Health Sciences Policy
INSTITUTE OF MEDICINE

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

COMMITTEE TO REVIEW THE FIALURIDINE (FIAU/FIAC) CLINICAL TRIALS

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Preface

Approximately 200,000 primary hepatitis B (HBV) infections occur annually in the United States. Symptoms of acute infection include fatigue, loss of appetite, nausea, abdominal pain, and jaundice. Most patients recover completely, but about 5 percent of HBV-infected adults develop persistent infection. It is estimated that there are approximately 400,000 to 800,000 individuals with persistent infection in the United States (more than 200 million carriers worldwide), and as many as 25 percent of these may have chronic active hepatitis. Chronic HBV infection results in scarring of the liver (cirrhosis) with complications of ascites, life-threatening gastrointestinal hemorrhages, increased susceptibility to serious bacterial infections and encephalopathy. Annually, as many as 4,000 patients with HBV-related cirrhosis in the United States may die of their disease, and about 800 succumb to complicating liver cancer. Thus, chronic HBV infection is clearly an important disease in terms of its frequency, associated morbidity, and significant mortality. This explains the continuing attempts over the past two decades to develop effective chemotherapy for chronic HBV disease.

Although spontaneous recovery from chronic HBV infection is occasionally observed, no effective treatment for this disease was known until alpha-interferon (alfa-2b) was licensed for use in the U.S. a few years ago. Because many of the patients treated with alpha-interferon had not benefited from it or could not tolerate its side effects, fialuridine (FIAU) was greeted enthusiastically as a possible alternative for treatment of this disease when it was shown to inhibit HBV replication effectively and, in early trials, appeared to have minimal side effects. FIAU is one of a family of compounds called nucleoside analogues, which includes AIDS drugs such as zidorudine, dideaxyinosine, and dideoxycytidine. The urgency surrounding the development and testing of these nucleoside analogues is understandable, because they are much needed for the treatment of chronically ill patients with progressive diseases. Such drugs still must endure the rigors of careful preclinical and clinical testing, guidelines for which are in place not only to produce major therapeutic gains but also, most importantly, to protect human subjects. As scientists, practitioners, and occasionally patients, the Institute of Medicine (IOM) committee members charged with reviewing this development process were intent on discovering what went wrong in the clinical trial in which five patients ultimately died of FIAU toxicity and whether and how these guidelines failed.

This committee comprised eight individuals with expertise in infectious diseases, clinical research, clinical pharmacology, medical ethics, toxicology, and clinical study design. The committee's purpose was two fold: (1) to perform a thorough analysis of the FIAU clinical trials (and those involving the closely related drug fiacitabine [FIAC] and (2) to focus on recommendations for additional safeguards for the conduct of future clinical trials. In preparing

this report, we performed a thorough analysis of all the FIAU/FIAC clinical trials. The resulting recommendations reflect an intensive review of information provided to us by numerous sources: the FIAU/FIAC clinical study staff, the Food and Drug Administration, the National Institutes of Health, the companies that manufacture the drugs, and several interested parties including patients who formerly received FIAU. This information was culled from volumes of laboratory notes, informed consent documents, study protocols, investigational new drug application (IND) submissions, correspondence, personal interviews, and presentations to the committee. In addition, we were not immune to the pressures of the media and pending lawsuits, and we tried to remain sensitive to the pain of the family members of the deceased patients as we reflected on what recommendations we could make that would prevent such a tragedy from happening again.

As we focused on whether any rules or procedures governing the clinical trials process needed to be changed, detailed knowledge regarding the FIAU clinical trials was of paramount importance to the committee. Several individuals from every phase of the IND process were contacted, to ensure that the committee considered a broad set of views in developing its recommendations. The committee is most grateful to those individuals (Appendix C). The committee also wishes to thank Frederick Manning, the IOM study director, for his tireless efforts in weaving our contributions into a cogent and coherent piece of work in such a short span of time with the assistance of his staff, Carolyn Peters and Thelma Cox. We also wish to thank Kenneth I. Shine, president of IOM, Joseph Cassells, acting executive director of IOM, and Valerie Setlow, Director of the Health Sciences Policy Division for their support and perspective.

MORTON SWARTS, M.D.

CHAIR, COMMITTEE TO REVIEW THE FIAU/FIAC CLINICAL TRIALS

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INTRODUCTION

In June 1993 a clinical trial of a promising new medication for hepatitis B was abruptly terminated when one of the 15 out-patients participating in the National Institutes of Health (NIH) study was suddenly hospitalized with liver failure. Although all the remaining patients were contacted and told to stop taking their medication, six more developed severe toxicity in the next few weeks. Five patients died, and two others were probably saved from death only by liver transplantation.

All of these patients had been taking the experimental drug fialuridine (FIAU) for at least 9 weeks. During the first 8 weeks of therapy, patients had reported only relatively mild side effects—and the levels of hepatitis B virus (HBV) in their blood had dropped precipitously. After the 9-week mark, however, the severity of side effects increased; the dosage of FIAU was decreased in 4 patients and eventually discontinued in three. After thirteen weeks one of these patients, who had stopped taking FIAU 17 days earlier, was admitted to his local hospital with a failing liver, shock, and acidosis. At this point all patients still taking FIAU were told to stop taking it, but this did not prevent serious additional toxicity. In retrospect, we can identify the distinctive characteristics of this severe toxicity: hepatic (liver) failure, despite only mild jaundice and minimal changes in the aminotransferase measures which generally signal liver damage; severe and rapidly progressing accumulation of lactic acid in the blood (lactic acidosis); inflammation of the pancreas to varying degrees (pancreatitis); and a marked accumulation of fat within the cells of the liver (microvesicular steatosis). All seven patients also developed signs of myopathy and/or peripheral neuropathy (damage to the muscles or nerves in the arms and legs). More recent studies indicate that FIAU is incorporated into mitochondrial DNA in the liver and other tissues. In vitro work suggests this may be related to the toxicity seen in the NIH patients, but in vivo studies will be necessary to fully understand the mechanism. An animal model employing the woodchuck shows great promise in this regard.

The Secretary of the Department of Health and Human Services (DHHS) told Congress she would commission an objective and independent study by the National Research Council's Institute of Medicine (IOM), and in June of 1994 a contract for such a study was signed. In it the IOM was tasked to assemble a committee of experts in a variety of fields (clinical research, pharmacology, toxicology, and medical ethics as well as hepatology) to perform a thorough analysis of all the FIAU clinical trials, as well as those of FIAC (a related compound, rapidly converted to FIAU in the human body). The group was to focus on whether any rules

or procedures governing the clinical trials process need to be changed, and what burdens or costs such changes might place on future clinical trials.

CLINICAL TRIALS

Clinical trials are of vital importance in the development of new drugs for use in humans. Preliminary animal experimentation is important in identifying potentially effective interventions in animal models with simulated human diseases and in identifying efficacious and non-toxic amounts of a pharmaceutical to be given. However, no amount of animal testing can substitute for carefully planned and carefully conducted human studies. The process is a lengthy one (4-7 years) and one which involves many study subjects.

One of the things that sets *clinical* trials apart from other scientific experiments is the obligation for care. Investigators undertaking them have obligations to ensure that patients enrolled are adequately cared for, even if doing so conflicts with or is at odds with required data collection and treatment procedures, as set forth in the protocol for the trial.

Evaluation of the treatment is relatively straight forward in randomized controlled trials involving comparison of one or more test treatments vs a control treatment (a placebo, standard medical treatment, or another test treatment). Judging the safety or efficacy of a treatment is much more problematic in the case of trials not involving a designed comparison group often the case in early evaluations of a new drug. In those settings, one is often left in a quandary as to what to make of isolated cases of morbidity indicated by observed clinical events or intimated by changes in specified laboratory tests. Are the changes due to the disease itself or to the drug?

Ethical justification of research involving human subjects requires responsiveness to ethical norms or rules that are embodied in six general behavior-prescribing statements: there should be 1) good research design, 2) competent investigators, 3) a favorable balance of harms and benefits, 4) informed consent, 5) equitable selection of subjects, and 6) in some ethical codes but not in US federal regulations, compensation for research-induced injury. In addition to these six substantive norms there are various procedural rules designed to ensure responsiveness to the substantive rules. Most important for the present considerations are: there should be 1) review and approval by an institutional review board and 2) written documentation of informed consent.

HEPATITIS B AND OTHER VIRAL DISEASES

Viruses, composed of DNA or RNA inside a protein shell or "envelope", include the influenza virus that causes the common "flu," the human immunodeficiency virus (HIV) responsible for AIDS, and the hepatitis B virus (HBV) resulting in a hepatitis infection with variable symptoms. With acute HBV infection patients are frequently fatigued, jaundiced, and complain of abdominal pain. The vast majority of 300,000 persons infected with HBV each year in the U.S. recover completely and only about five percent of infected adults develop chronic liver disease. Although such disease often results in only minor complaints of fatigue,

joint pains, poor appetite and abdominal pain, chronic infection results in scarring of the liver (with consequent impairment of flow of blood through the liver, back-pressure into the veins of the intestine and an increased propensity for life-threatening bleeding episodes). Other complications include retention of fluid in the abdomen (ascites), increased susceptibility to life-threatening bacterial infections, and mental confusion (encephalopathy). Once these complications occur, the life expectancy of the patient is very limited, and liver transplantation the only therapeutic option. HBV infection has also been linked epidemiologically to the development of liver cancer; in males with perinatally acquired infection, life-long risk of development of hepatocellular carcinoma is 40 to 60 percent.

An important feature of chronic HBV infection involves the spontaneous loss of viral replication seen in 2.5 to 25% of patients. Viral clearance is believed to be immune-mediated and is frequently associated with a transient rise in serum aminotransferases (AST, aspartate aminotransferase, and ALT, alanine aminotransferase, enzymes present in liver cells whose appearance in quantity in blood is generally taken to indicate liver damage). This enzyme increase, or so-called "flare" phenomenon, is also seen in patients with a positive response to interferon therapy. It may thus be difficult to distinguish, on the basis of aminotransferase alone, drug-induced hepatotoxicity from a positive response to antiviral therapy. Indeed, because of this flare phenomenon it is easy to understand why investigators like those conducting the FIAU trials might well have been encouraged by a rise in liver enzymes that in other circumstances would have been cause for alarm.

Successful treatment of chronic HBV infection has been limited. Interferon effectively inhibits viral replication in only one third of patients, it must be given by injection, and it is associated with significant toxic effects. Approaches to treatment of viral diseases have generally been either to stimulate the natural host defenses against infection with drugs like interferon or to inhibit the way viruses divide and multiply with nucleoside analogs, molecules which are similar to the building blocks of deoxyribonucleic acid, DNA, and which become incorporated into the viral DNA as the virus divides, inhibiting and interrupting this replicative machinery. Zidovudine (AZT), the commonly used treatment of HIV infection, is an example of this second approach. FIAU was another.

EARLY CLINICAL TRIALS OF FIAC AT MEMORIAL SLOAN-KETTERING CANCER CENTER

Although the toxic effects that led to the formation of this IOM committee were related to the administration of the drug fialuridine (FIAU), our review begins with studies of the parent drug fiacitabine (FIAC) which is metabolized to FIAU. FIAC is a pyrimidine nucleoside analog synthesized by Fox and his colleagues at Memorial Sloan-Kettering Cancer Center (MSKC) in the 1970s. It was found to be highly active, in vitro, against several of the clinically important human herpes viruses and shortly thereafter against hepadnaviruses, inhibiting, in its triphosphate form, the DNA polymerases of human and woodchuck hepatitis viruses. It was studied at MSKC in the early 1980s in the treatment of herpes simplex virus (HSV), varicella-zoster virus (VZV), and cytomegalovirus (CMV). These early trials of FIAC were carried out to a large extent in seriously ill patients suffering from underlying neoplastic

disease or immunosuppressive conditions. These pathogens are frequent and often serious complications in such patients.

FIAC had a beneficial effect in treatment of VZV infections. Its efficacy against CMV was unclear because of the uncertainty of the diagnosis in many patients and the steady downhill course of many of the seriously ill patients. Toxicity appeared to be manifest primarily as hematopoietic suppression, i.e., depressed white blood cell and platelet counts. Whether FIAC may have contributed to any of the many deaths in that study is uncertain from the available information; the underlying disease with disseminated superimposed infections in these very ill patients seems likely to have been the main factor. Since dosing was only for short periods in these trials, the potential for toxicity with long term use would not have been discernible. Further clinical trials of FIAC were not carried out at the time, probably because of the emergence of an effective, relatively non-toxic nucleoside analog (acyclovir) for the treatment of HSV and VZV infections.

Thus, the return to clinical study of FIAC in 1989 under the sponsorship of Oclassen Pharmaceuticals seems to have been reasonable in view of the drug's in vitro activity against CMV (an important viral infection in patients with HIV infection and for which there still was need of effective oral treatment).

OCLASSEN CLINICAL TRIAL R89-001-01

This evaluation of the effects of FIAC for treatment of CMV infection in HIV-positive individuals was developed by Oclassen Pharmaceuticals in conjunction with the AIDS Clinical Trials Group (ACTG) of the National Institutes of Allergy and Infectious Diseases (NIAID). CMV is the most common infectious pathogen in HIV-positive patients, with the most frequent manifestation, chorioretinitis, occurring in 25-30 percent of HIV-positive patients. Other clinical manifestations include fever, malaise, arthralgias, pancytopenia, hepatitis, pneumonitis, and gastrointestinal ulcerations. Disseminated CMV disease is rare (less than 5 percent of CMV infections), but when it occurs it is usually fatal. The need to identify an effective oral drug to treat CMV disease in this patient population was one of the most important scientific priorities of the ACTG.

This trial was conducted at two sites, the University of California at San Diego (Principal Investigator, Douglas D. Richman), and the University of Washington in Seattle (PI, Lawrence Corey). Both are established investigators with extensive experience in the study of antiviral agents in the treatment of other herpes virus infections as well as HIV. Trial R89 was a Phase I/II clinical trial designed to evaluate, simultaneously, the safety and relative anti-CMV activity of FIAC at doses roughly equivalent to the doses the MSKC found effective against VZV. Patients were HIV-infected, had CD4 counts of 500 cells/mm^3 or less, and documented CMV in either their blood or urine. Therapy was limited to 4 weeks, because data from animal toxicity tests of more than 90 days duration were not available, but patients were followed for a total of 3 months.

Gastrointestinal side effects, predominantly nausea and fatigue, were noted in the first dozen study patients, with no demonstrable anti-CMV effect, so the study team recommended discontinuation of the development of FIAC as an anti-CMV drug, and the study was stopped.

Because some later analyses of the FIAU tragedy put great emphasis on the post-trial deaths of patients from the early trials, including this one, the committee paid particular attention to the four participants in this study who died within six months of the termination of FIAC. Three clearly died of HIV-related complications not involving the liver. The fourth patient, 107, suffered liver failure and died 11 weeks after his last dose of FIAC. The 1993 FDA Task Force Report classifies this case as one in which FIAC should be considered a possible cause of death.

The committee judged the trial well designed and conducted. In the case of one patient who died with liver failure 11 weeks after his last FIAC, the committee believes that even in retrospect the confounding variables of CMV infection, hepatitis B infection and continuing treatment of HIV with AZT clearly preclude unequivocal classification of the death as FIAC-related.

OCLASSEN CLINICAL TRIAL R90-001-01

This study, the first involving FIAU, the primary metabolite of FIAC, grew out of the hope that it was responsible for the strong in vitro anti-CMV activity of both compounds, but would not produce the dose-limiting toxicity of FIAC seen in the R89 trial. Richman and Corey planned a traditional Phase I, dose-escalating study of FIAU with the emphasis on safety. During protocol development, several reviewers suggested evaluating the potential role of FIAU in the treatment of hepatitis B virus (HBV) infection, so an amendment was created which allowed investigators to enroll HBV infected patients after an initial cohort of non-HBV infected individuals had been enrolled.

As in the previous trial (R89) there was no evidence of anti-CMV activity even at doses associated with clinically significant gastrointestinal symptoms. The team then turned to patients coinfected with HIV and HBV. A new co-investigator and site, Stephen Straus of the National Institute of Allergy and Infectious Diseases, were recruited for this phase of the study. Like Richman and Corey, Straus had been integrally involved in the development of drugs designed to treat human herpes virus infections, such as vidarabine and acyclovir.

Striking reductions in circulating hepatitis B DNA were noted in most patients, with the majority of patients showing decreases in their circulating HBV DNA values to less than the lower limits of the measurement technology. More importantly, the level of virus remained suppressed for up to 4 to 6 weeks after the drug was discontinued. The experience with other nucleoside analogs had resulted in only a partial reduction of circulating HBV and rapid reversal upon cessation of the drug. Thus, FIAU represented the most potent anti-HBV agent studied to date.

Several patients in the R90 study developed significant elevations in liver function enzyme levels while on treatment. Based on the dramatic fall in HBV DNA and the frequent observation of a "flare" in transaminases associated with successful treatment of hepatitis B, the investigators judged the elevations not to be "serious or unexpected adverse events," but indications of successful therapy. The very modest elevations in the enzymes of the non-HBV patients were consistent with this interpretation. Nevertheless, three patients died within 6 months of receiving FIAU. All three had received a second 14-day course of FIAU treatment

when their HBV DNA levels recovered from the decreases associated with their initial FIAU therapy. One patient died of pancreatitis and two suffered liver failure, but in each case severe underlying disease and/or other more recent medications led the investigators to attribute the two deaths they were told about to causes other than FIAU toxicity.

The committee concluded that this was a carefully performed study which underwent extensive internal and external review, employed a novel real-time data monitoring system and produced convincing evidence of anti-HBV activity at doses of FIAU producing few adverse effects. Although the deaths of three of the four patients receiving two courses of FIAU treatment caused the committee concern, we concluded that even in retrospect underlying disease and/or more recent medications were more plausible causes of death than FIAU toxicity in each case.

OCLASSEN CLINICAL TRIAL R-91-010

The encouraging findings in the R90 study generated plans for instituting an evaluation of more prolonged administration of FIAU. This study was conducted solely at the NIH Clinical Center with Dr. Jay Hoofnagle as the Principal Investigator. Dr. Hoofnagle is a gastroenterologist and hepatologist who is Director of the Division of Digestive Diseases and Nutrition at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the NIH. He was the Principal Investigator on the major studies that established the therapeutic benefit of interferon in patients with chronic active hepatitis B.

It was the opinion of both Hoofnagle and Straus that ultimate control of hepatitis B virus disease would require some degree of prolonged chronic suppression for durable effect. The standard treatment regimen for the only approved drug therapy, interferon, for example, calls for 16 weeks of subcutaneous injections. Therefore, this study was initially designed to evaluate several low doses of FIAU which would be administered over a prolonged period. Duration of therapy was ultimately limited to 28 days because there was only limited animal toxicity data to support longer term courses of treatment. Fatigue, nausea, skin rash, bone marrow suppression, seizures, and "pains in the arms and legs due to irritation of the nerves or the muscles" were all described as potential side effects in the informed consent document. The first patient was dosed in April, 1992 and by February 1993, all 24 subjects had completed therapy and the 6-month followup stipulated by the protocol.

Hepatitis B virus DNA was suppressed 70 to 95 percent in the three highest dosing groups and to a lesser degree in the lowest dose group. Side effects during therapy were mild and transient. No patients developed side effects severe enough to modify dose or interrupt therapy. A total of 9 patients became HBV DNA negative, and AST/ALT "flares" were noted in 8. However, a year later, 6 of the 9 patients showed evidence of circulating HBV DNA.

Several patients in the R91 study experienced significant health problems in the months following their participation in the R91 trial. In each case, a long delay between FIAU and symptom development, preexisting problems and/or inconclusive lab results led the investigators to assign causes other than FIAU. This determination of cause of death was clearly most difficult in the case of patient 4D, a 59-year-old man who died 4 months after completion of his 28-day FIAU therapy. Although interpretation was complicated by an

intervening cholecystectomy, it is now apparent that this patient's experience was very similar to that later seen in the victims of FIAU toxicity in the subsequent six-month trial (H3X-MC-PPPC, or simply PPPC) with systemic lactic acidosis, pancreatitis, and hepatic steatosis. The investigators discussed this death extensively with the sponsor, the NIDDK institutional review board (IRB), NIH Senior Staff, pathologists at the Armed Forces Institute of Pathology, and the FDA before initiating further study of FIAU in trial PPPC. In fact, their acute awareness of the peculiar nature of this patient's presentation was no doubt responsible for their rapid termination of that trial when a patient presented with a similar syndrome on June 26, 1993.

In conclusion, the committee believes this study clearly established FIAU as promising treatment for chronic HBV infection. Although the antiviral effect was most often temporary, the relative absence of serious toxicity during treatment suggested that longer treatment would be possible. Post-treatment health problems in several patients were again difficult to interpret in the context of underlying disease, preexisting conditions, other medication, and long intervals since FIAU therapy. With our current knowledge of FIAU toxicity we can now identify patient 4D in this trial as the first unequivocal FIAU death, but we note that the investigators were suspicious at the time and in our view acted appropriately in incorporating that suspicion into the planning and conduct of the subsequent trial.

ELI LILLY CLINICAL TRIAL H3X-MC-PPPA

This study, one of three begun in late winter or early spring of 1993, was sponsored by Eli Lilly and Company, which entered into a licensing agreement with Oclassen in August of 1992 and assumed responsibility for further development of FIAU. A straightforward followup to trial R91, the study plan called for subjects to receive the drug two or three times per day for 90 days. Patients were entered at 2 study centers: University of Texas Galveston (PI, David Paar) and Tufts New England Medical Center Hospital (PI, Marshall Kaplan). A total of only 5 patients received FIAU before the trial was discontinued promptly upon receipt of information concerning adverse events in subjects in the H3X-MC-PPPC trial at NIH.

The 3 patients in the clinical trial at Galveston took FIAU for periods of 16, 19, and 43 days. The committee feels that no toxicity clearly attributable to FIAU occurred in these 3 patients. At the New England Medical Center Site FIAU was administered to a total of only two patients, for periods of 28 and 55 days. One patient noted leg pain and numbness beginning 3-4 months after stopping FIAU therapy. Evidence of a primary sensory neuropathy was found on neurological consultation, and electrophysiologic studies were confirmatory. The committee feels that although this patient may possibly have been predisposed by virtue of his prior history of alcohol abuse, his documented peripheral neuropathy should be considered a neurotoxic effect of FIAU.

ELI LILLY TRIAL H3X-LC-PPPG

This study, conducted at the Lilly Laboratory for Clinical Research (PI, David Hyslop) in Indianapolis in March and April of 1993, was the only one of those reviewed by this

committee which utilized normal healthy subjects rather than patients infected with HIV and/or HBV. It was also the only one which kept the subjects on-site all day every day during the study. The primary objectives were to determine the relative bioequivalence of a syrup formulation and two tablet formulations of FIAU, and to determine the pharmacokinetic profile of each (i.e. how much of the dose is absorbed, how fast, how quickly is it eliminated, and in what form).

Sixteen subjects each received five doses of FIAU, separated by 3 to 7 day intervals. The study ultimately utilized a newly developed radioimmunoassay (RIA) highly specific for FIAU and far more sensitive than the high-performance liquid chromatography (HPLC) assay that had previously indicated a half-life of 1-4 hours for FIAU. The RIA technique was not perfected until mid-June however, so blood and urine samples from this trial were simply frozen for later analysis. Pharmacokinetic measurements performed on blood and urine samples after the RIA was validated in June revealed more rapid absorption of FIAU in syrup than in tablet form, with food generally decreasing the rate of absorption, and a prolonged elimination phase with a terminal half-life of 28-30 hours.

Adverse events noted included diarrhea, headache, transient myalgia, and in two cases, transaminase elevations. Although both subjects with these elevations were asymptomatic, dosing was discontinued for one (subject 1203) after his serum ALT quadrupled and his AST tripled after the second dose. This subject was encouraged to stay at the lab despite being dropped from his dosage group, while the investigators worked him up for hepatitis and other possible causes of his ALT/AST elevations, which continued to rise to peaks of 137 and 60 respectively a week after his last dose of FIAU. His transaminase levels returned to baseline 5 weeks after his second and last dose of FIAU. The second subject (subject 508), also asymptomatic, showed 3-5 fold increases in ALT and AST after dose 2 as well, but levels of both enzymes decreased on each of the following three days and the subject was continued in the study. AST and ALT measures gradually returned to baseline despite 3 additional 5 mg doses of FIAU.

Since neither of these subjects was infected with hepatitis B, there is no possibility that these rises were "flares" associated with the destruction of infected hepatocytes, a fact given great importance by some critics, who argue that these data should have been sufficient grounds for Lilly to stop not just these patients but all ongoing clinical trials with FIAU, including the PPPC trial at NIH. At the time, however, several pieces of information were available which argued against such an action. The total dose received by each subject, 10 mg, was minuscule compared to the doses apparently well tolerated by the presumably less robust patients in previous trials, whose total doses ranged from 100 to more than 1000 mg. Perhaps more importantly, neither subject with elevated liver enzymes had any clinical signs or symptoms.

We believe it would be a mistake to eliminate clinical judgement from clinical trials, and in this case we believe that dropping subject 1203 from the trial while continuing to observe him carefully was appropriate and sufficient. Similarly, had the revised estimate of FIAU half life been available to the NIH researchers earlier they may have been more wary of the drug accumulating in tissue, but in the absence of any clinical indications it is difficult to imagine halting an apparently successful therapy solely on this basis.

ELI LILLY TRIAL H3X-MC-PPPC (NIH PROTOCOL #93-DK-0031)

This study was conducted at the Liver Diseases Section of the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) at NIH. Principal Investigator was Dr. Jay Hoofnagle. In the previous trial (R91) 4 weeks of FIAU therapy was shown to inhibit HBV replication strongly and consistently, but this inhibition was transient. The rationale for this new trial (PPPC), an open-label, randomized study of FIAU with two treatment groups (0.10 and 0.25 mg/kg/day), was that treatment for 24 weeks would result in short-term inhibition of viral replication, normalization of serum aminotransferases, and potentially long-term viral remission.

Eleven patients previously treated with FIAU in R91-010 met all entry criteria, and were quickly enrolled. Four patients who had never received FIAU were enrolled two months later. Review of the informed consent document by the IOM committee found that it was written clearly in language understandable to the layman and was not misleading in minimizing potential side effects of FIAU. After discussion with the NIDDK IRB, death was not included as a possible adverse event in the consent form itself since at that date the death of patient 4D from the R91 trial was not attributed to FIAU. Nevertheless, patients were informed verbally of the possibility of death, and that the death of patient 4D could have been FIAU-related.

In early June 1993, it became apparent that the ten patients who had been started on FIAU in late March and April were having increasing side effects (mainly nausea, vomiting, diarrhea and abdominal cramps). HBV DNA levels had decreased in all patients and six of ten patients had become HBV DNA negative, but by mid-June three patients were no longer receiving drug because of side effects. When one of these three developed lactic acidosis, hepatic failure and renal failure on June 25th, prior experience with a single puzzling patient from trial R91 (patient 4D) made the investigators consider FIAU a likely cause. The trial was halted on June 26th and all fifteen patients were seen within a few days at the NIH. Seven of the ten patients who had received more than 2 months of FIAU had evidence of FIAU toxicity (lactic acidosis, hepatic failure, pancreatitis, neuropathy and/or myopathy). Despite stopping drug, seven patients had progressive hepatic failure and were transferred to other hospitals for possible liver transplantation.

Although the outcome was tragic, after careful study the IOM committee believes that there was sufficient justification for initiating the PPPC trial, that the protocol and consent form were appropriate, and that the conduct of the trial was equal to or above prevailing standards of care. There is no evidence that there was information available at the initiation of PPPC or at any time during the trial itself that would have or should have reasonably been interpreted to have averted the ultimate disaster.

PATIENT INTERVIEWS

A total of 19 FIAU patients were interviewed over the telephone on issues of informed consent and attention to possible side effects. The subjects were drawn from the three studies testing FIAU in HBV positive subjects without concomitant HIV infection: the 28-day NIH

trial (R-91), the aborted 6-month NIH trial (PPPC), and the 3-month Galveston/Boston trial (PPPA) terminated along with the NIH study.

Perhaps the most important generalization that can be drawn is that the patients' reports of the informed consent process and their satisfaction with their treatment by the study staff are closely associated with their current health. The 3 subjects interviewed who reported currently suffering from peripheral neuropathy, two of whom were in the R-91 trial and the other in PPPA, all felt that the risk of side effects had been minimized in their discussion of the informed consent documents. The pattern of response by the rest of our interview subjects suggests that the studies on the whole were characterized by good to excellent rapport between patient and staff, frank discussion of potential risks, close attention to signs of FIAU toxicity, prompt action when it seemed indicated, and a general feeling by the patients that they had been informed to the best of the investigators' abilities and treated conscientiously throughout.

OVERALL ASSESSMENT OF THE TRIALS

The overall impression of the IOM committee is that the entire series of trials reviewed was an ethically sound clinical research project designed and carried out by highly competent investigators who frequently went beyond the requirements dictated by regulations or imposed by IRBs to respond to the desires and needs of their patient-subjects.

REVIEW OF THE FDA TASK FORCE REPORT

In November, 1993, the Food and Drug Administration (FDA) released a retrospective assessment of three FIAU and FIAC trials by a 3-member internal task force formed "to determine what data and what analyses of data were available to sponsors and the FDA at the start of the H3X-MC-PPPC study, and whether improvement in the rules governing design, analysis and reporting of data from clinical trials is warranted."

The report evaluated preclinical animal studies and three clinical trials (R89, R90, and R91) for information suggestive of hepatic or pancreatic toxicity comparable to that observed in trial PPPC. The IOM committee has serious reservations about the Task Force approaches to both the laboratory data and the clinical events. In summary, we believe the suggested "worst-case" attribution of all possibly adverse laboratory findings and adverse hepatic and pancreatic clinical events to FIAC or FIAU inappropriately ignores other potentially important information.

The FDA Task Force made a series of recommendations on a) clinical design and execution; b) reporting requirements; c) FDA record-keeping; and d) further review of FIAU toxicity. These recommendations have since become the basis for a number of proposed changes to the Code of Federal Regulations (CFR) governing the IND process. The IOM committee agrees in principle with nearly all of the recommendations, although we note that many of the practices they would promote were in fact observed in the FIAU trials and others are likely to make very small contributions to trial safety if they can be implemented at all. We disagree strongly with the Task Force call for worst-case analyses; i.e. assuming that all

adverse health events in trial patients, and more importantly in former trial patients, are drug-related.

REVIEW OF THE NIH REPORT

In April 1994, a seven-member subcommittee of the [NIH] Director's Advisory Committee issued a report on their review of FIAU studies conducted at NIH. The IOM committee agrees with the NIH subcommittee that there was a strong, justifiable, scientific, rational argument for evaluating FIAU for the therapy of hepatitis B. We agree as well with the conclusions of their review of the preclinical toxicology data that the range and duration of testing was appropriate for the proposed studies and that there was no prior evidence to suggest hepatic or pancreatic toxicity. Like the IOM committee, the NIH subcommittee found no evidence that important data were ignored or overlooked in planning for the PPPC trial, nor did they find any evidence to suggest that pressure for fast-track development was a contributing factor to the untoward events of that trial. The subcommittee was satisfied that the two IRBs involved had provided comprehensive, thoughtful and rigorous reviews and were in compliance with the NIH and federal regulations. The subcommittee was also satisfied that patients provided full, informed consent and were impressed by the teamwork between investigators and staff. The IOM committee concurs with these judgments as well as with the favorable review of the NIH subcommittee on the generally high quality of patient care provided during and after the FIAU trials.

FDA-PROPOSED CHANGES TO THE CODE OF FEDERAL REGULATIONS

The FDA has recently issued a series of proposed changes to existing regulations regarding adverse experience reporting. The proposed changes related to INDs are largely derived from and closely follow the recommendations of the FDA Task Force report. We question the wisdom of some of the observations and recommendations contained in the FDA Task Force Report in this report, but there are also elements of the proposed changes that we endorse on general principle. Foremost among them are the desirability of formal ongoing monitoring and use of designed comparison groups in all stages of testing, starting with Phase I and II trials.

We believe that investigators need to abandon the case report form of data collection and plan for real-time monitoring of trials, regardless of size, sponsor, or funding source, preferably in the form of some independent person or group. This is obviously no panacea, since the FIAU studies reviewed here all had formal or informal real-time monitoring systems as well as the mandated case report forms, but it is a change that would help insure that all investigators will be as alert to developing problems as these were.

The use of controls and randomization is also suggested as highly desirable. Although we concur, we are under no illusions as to the power of small trials like the ones reviewed here to detect drug-induced toxicity. Most adverse effects caused by treatments will go undetected

in the typical Phase I or II trial involving 20 to 40 patients and treatment and followup over a short time period.

We also endorse the concept of longer followup on its general merit, but it is difficult enough to determine whether or not morbid or fatal events are treatment related when they occur while patients are under direct observation and being managed according to a specified protocol. Interpretation of such data becomes profoundly more problematic when the events occur long after treatment ends.

The FDA also recommends requiring pre-trial estimates of expected mortality in the patient populations from which the subjects are to be drawn and combined with information from related trials. We tested the likely efficacy of these suggestions by conducting a statistical analysis of available information from the FIAC/FIAU trials of 1989-93. We investigated a range of underlying mortality rates for the analyses (from 10 to 20 percent per year for the HIV patients in the R89 and R90 trials and from 2 to 4 percent per year for the HBV patients in R91 and PPPC). The number of deaths "expected" in each group of patients was calculated and compared to the number of deaths actually observed. The only trial that produced any convincing statistical evidence of drug toxicity is PPPC and all of the deaths in that trial occurred after the investigators had already stopped the trial based on morbidity. To summarize, it is unlikely that the FDA-recommended procedures of estimating expected deaths and following up for 6 months would have resulted in cancellation of trial PPPC.

In regard to the proposed changes requiring a marked increase in safety reporting, we remain skeptical that the benefits from such added efforts will outweigh the increased expense, added time for drug development, delays in access for general use, and so called type II errors—abandoning work on a drug because it is believed to be ineffective or harmful when, in fact, with further testing and development it would have been shown to be both effective and safe.

ANCILLARY ISSUES

Although the committee's focus throughout this review has been on reducing as far as possible the chance of a tragedy like that of trial PPPC ever occurring again in the course of a clinical drug trial, several ancillary issues came to our attention in the course of the review, clearly very secondary in importance to the principal, unfortunate events that form the basis of this report, but bearing directly on regulatory control of clinical trials. Foremost among these were the "warning letters" sent to investigators and sponsors by the FDA in May of 1994. The committee analyzes some misunderstandings surrounding these letters and offers some suggestions on improving the process.

CONCLUSIONS

On review of the FIAU trials, the IOM committee finds no evidence of negligence or carelessness on the part of the investigators or sponsors. The committee is not aware of any preclinical tests available prior to the outcome of this trial that could have been done to

anticipate this unfortunate event. We would nevertheless urge the readers of this report to put this tragedy in a proper perspective as a distinctly rare occurrence, related to a previously unrecognized form of late drug toxicity, in a field with an otherwise exemplary safety record.

On the basis of its review of the FIAU studies, the IOM committee will make some recommendations on the future conduct of early phase drug trials. Although the IOM committee's recommendations are focused on Phase I and Phase II trials, they do not stem from perceived deficiencies in the conduct of the investigators or sponsors in the FIAU studies; as already noted, none were identified. The IOM committee believes that implementation of its recommendations *may* reduce the already very low probability of occurrence of toxicity of the sort there was in the fialuridine studies, particularly when studying drugs that are similar to fialuridine in structure or action. In many instances the effect will be to insure the continued and consistent use of procedures and practices employed in the FIAU trials reviewed here.

RECOMMENDATIONS

Generic Issues

1. Proceed cautiously in revision of the current drug development system. The current system has evolved checks and balances that have benefited new drug development and patient safety, and no single component can undergo a major revision without endangering the system as a whole. The committee is doubtful that any of the changes reviewed above and/or proposed below, had they been in effect prior to the initiation of the FIAC/FIAU trials reviewed here, would have substantially altered the tragic outcome.
2. All clinical researchers engaged in trials should be exposed to explicit training not only on the design and conduct of clinical trials and their ethical obligations to patients but also on their legal and regulatory obligations to both the sponsor and the FDA.
3. We urge the establishment of a system of no-fault compensation for research injury by government, sponsor or some combination of both.

Trial Design

4. Some form of independent safety monitoring would be a valuable component of any clinical trial in which patients are treated for extended periods, but they are especially important for all double-blind trials and in any trial in which there is reason to anticipate that evidence of adverse reactions could be confused with evidence of disease progression or therapeutic response. For other types of trials the sponsor should bear the burden of demonstrating that a monitor is unnecessary.
5. We support in principle the desirability of controls in Phase II studies, even while recognizing that statistical power will generally be inadequate to detect all but the most common of adverse drug effects, and among those, only those that rarely occur in untreated subjects. Nevertheless, particularly in trials involving extended treatment of patients, the use

of some concurrent comparison group should help focus attention on the importance of differentiating drug effects from the underlying disease(s).

6. Research into the development of a database from which to construct historical control groups should also be supported. Such control groups may be needed as comparison groups when suitably matched concurrent control groups are not feasible. The extensive data submitted to the FDA through the IND process are a potentially valuable resource to custom match patients in new drug trials with controls from previous trials, matching not only for entry criteria but also for disease extent and severity, concomitant medications and other confounding variables.
7. Concerted efforts should be made to include in all clinical trial protocols explicit prospective criteria to help distinguish between adverse events related to drug treatment and changes in the underlying disease, for better or worse, whether or not controls are employed.
8. Clinical protocols should also have a section explicitly addressing the determination of the followup period, based on preclinical data and clinical data from other drugs thought to be similar in structure and action. Drugs suspected of modifying DNA or associated macromolecules demand a minimum of 6 months followup.
9. At the outset of extended Phase II trials, consideration should be given as to whether there is sufficient evidence of safety to justify simultaneous enrollment of a substantial group of patients, or whether the patients' disease is so serious that access to the drug seems warranted.

Adverse Event Reporting

10. Data should ideally be analyzed (by the investigators or independent safety monitor in Phase I and Phase II trials, and by data safety monitoring committees or data coordinating centers in multicenter Phase III studies) on a continuing real-time basis rather than only after all case report forms are complete for all patients. This will ensure that the fewest possible patients are exposed to possible hazards, and that rapid intervention will prevent or limit injury to individual patients.
11. We concur with the suggestion of the FDA Task Force that some form of cumulative adverse event reporting should be provided by the sponsor, in a form which includes not only those events previously reported as serious, unexpected and drug related, but also any events judged to have met only the first or the first two of those conditions, along with the sponsor's explanation of the event. A careful analysis of all available information rather than a "worst case" assumption should then determine further actions.
12. We believe that requiring a cumulative and all-encompassing report of the sort referred to in the previous recommendation every six months will prove to be a substantial impediment to development of drugs to combat life-threatening diseases (e.g., cancer) where adverse events are frequent because of the often progressive nature of the underlying disease. Some judgement will always be necessary, by the investigators deciding the most likely cause of adverse events, and by the FDA, in deciding for which drugs and at what intervals a cumulative safety summary is necessary. Ideally the investigators and the FDA would work together in making both of these determinations.

Compliance Audits

13. Given the intense publicity surrounding the issue of FDA "warning letters," regard for due process would seem to require some modifications in procedure. A fairer process, for example, might be for the FDA to refrain from public release of the letters until receipt of the mandated reply from the addressees. Some sort of appeal process, independent of the Office of Compliance, and including scientific peers expert in the area should also be available in the event of intractable disagreement. Where retrospective evaluation by the Office of Compliance is at odds with a prior evaluation by the responsible FDA review division, that fact should at least be acknowledged in the letter.

Further Research Into FIAU Toxicity

14. We urge continued support for research into the mechanism of FIAU toxicity, including development of animal models and other test procedures that could be used to screen drugs with potential to alter DNA prior to clinical trials.
15. Preclinical testing in animals is especially important in the case of FIAU-like drugs with a potential for long-term effects on nuclear or mitochondrial DNA. Toxicology studies in at least two different species, using the route of administration intended for use in patients, with dosing for at least as long as intended for clinical trials, and extended followup on at least a subsample of animals should all be key considerations in preclinical testing. Wherever feasible and reasonable, the preclinical assessment should include testing in an animal model of the disease being targeted.

1

Introduction

GENESIS OF THIS STUDY

In June 1993 a clinical trial of a promising new medication for hepatitis B virus (HBV) infection was abruptly terminated when one of the 15 outpatients participating in the National Institutes of Health (NIH) study was suddenly hospitalized with liver failure. Although all of the remaining patients were contacted and told to stop taking their medication, six more developed severe toxicity in the next few weeks. Five patients died, and two others were probably saved from death only by liver transplantation. The members of the committee wish to express their sadness at the deaths of these individuals and their understanding of the sudden sense of shock and loss that must have been felt at the time and subsequently by family members and friends.

All of these patients had been taking the experimental drug fialuridine (FIAU) for at least 9 weeks (five patients who had received FIAU for less than 4 weeks showed no clinical or biochemical evidence of toxicity). During the first 8 weeks of therapy, patients had reported only relatively mild side effects—some abdominal pain, fatigue, intermittent nausea, and constipation—and assays for the levels of HBV DNA in their blood showed that they had dropped precipitously. In six of them HBV DNA had in fact become undetectable. Neither the side effects, which were quite mild compared with those typical of the only Food and Drug Administration (FDA)-approved therapy (alpha-interferon), nor the antiviral activity was surprising. These same patients had undergone a 4-week course of FIAU treatment 9-12 months earlier, with mild side effects and strong anti-HBV effects. Once they were off the drug, however, their HBV DNA levels rebounded, which was the stimulus for the 6-month trial. After the 9-week mark, however, the severity of side effects increased; the dosage of FIAU was decreased in four patients, and FIAU was eventually discontinued in three. After 13 weeks one of these patients, who had stopped taking FIAU 17 days earlier, was admitted to his local hospital with a failing liver, shock, and acidosis. At this point all patients still taking FIAU were told to stop taking it, but this did not prevent serious additional toxicity. In retrospect, the committee can identify the distinctive characteristics of this severe toxicity: hepatic (liver) failure, despite only mild jaundice and minimal changes in the aminotransferase measures that generally signal liver damage; severe and rapidly progressing accumulation of lactic acid in the blood (lactic acidosis); inflammation of the pancreas to varying degrees (pancreatitis), and a marked accumulation of fat within the cells of the liver (microvesicular steatoses). All seven patients also developed signs of myopathy and/or peripheral neuropathy (damage to the muscles or nerves in the arms and legs). Although liver biopsies on an additional three patients showed the characteristic fatty deposits (steatosis), their only other sign

of toxicity was mild and reversible gastrointestinal discomfort. Many of these toxic effects have been reported to some degree with other antiviral drugs, most notably the anti-human immunodeficiency virus (anti-HIV) agents zidovudine (AZT) dideoxycytidine (ddC), and dideoxyinosine (ddI).

CHARGE TO THE COMMITTEE

In the weeks following the revelation of the FIAU deaths, outcries arose in the popular media, the medical establishment, and the Congress demanding to know what went wrong; how such a disaster could have taken place, especially at NIH, widely regarded as the flagship of U.S. medical research; and why federal regulation and supervision of drug development had failed to prevent a tragedy of this proportion. The FDA quickly began an investigation of whether any FDA regulations were violated and appointed a task force to examine the question of whether some difference in process or behavior on the part of the trial's sponsors, the scientists conducting it, or the FDA itself might have prevented the damage. The director of NIH assembled a committee of medical scientists from around the country and asked them to conduct a fact-finding review of the FIAU studies that took place at NIH. Most relevant to the present document, the secretary of the U.S. Department of Health and Human Services (DHHS), Dr. Donna Shalala, told Congress she would commission an objective and independent study by the National Research Council's Institute of Medicine (IOM). In June of 1994 a contract for such a study was signed. In it IOM was tasked to assemble a committee of experts in a variety of fields (clinical research, pharmacology, toxicology, and medical ethics as well as hepatology) to perform a thorough analysis of all the FIAU clinical trials, as well as those of fiacitabine (FIAC; a related compound that is rapidly converted to FIAU in the human body). The committee was to focus on whether any rules or procedures governing the clinical trials process needed to be changed and what burdens or costs such changes might place on future clinical trials.

More specifically, the committee was asked to review the reports of FDA and NIH and any background documents on the FIAU and FIAC clinical studies, investigational new drug applications (IND) and protocols necessary to determine:

- Whether investigators, sponsors, FDA, and NIH acted appropriately in all phases of the clinical trials of FIAU and FIAC, particularly the H3X-MC-PPPC trial (see glossary) that ended with five deaths. This is to include the development and review of the IND submission; the development and review of the protocols and consent forms, including mechanisms to ensure the ethical design and conduct of the trials regarding risks to research subjects; and the conduct and monitoring of the H3X-MC-PPPC trial (in which the five deaths occurred) and other trials of FIAU or FIAC. The review was to pay particular attention to information available from other clinical and preclinical experience with compounds related to FIAU or FIAC, from clinical trials of FIAU and FIAC prior to the H3X-MC-PPPC trial, and from the H3X-MC-PPPC trial itself.

- Whether the rules or procedures governing the clinical trial process need to be changed to address the problems, if any, identified in the FDA and NIH reports, or problems identified independently by the committee.

METHODS AND PROCEDURE

Although this report touches on a few studies of FIAC done in the early 1980s at Memorial Sloan-Kettering Cancer Center, it focuses on the six clinical trials sponsored by Oclassen Pharmaceuticals or Eli Lilly & Co. listed in Table 1-1. Column 1 of the table shows the trial "names" (e.g. R89-001-01). These designations are those of the drug company sponsors. We have also provided the NIH protocol number for those trials conducted at NIH, since some of the references and documents in the appendices use that terminology. For ease of reading, however, we have attempted to use the following abbreviated "names" in the text: R89, R90, R91, PPPA, PPPG, PPPC. Appendix A is an integrated chronology of the major events involving those trials and the patients who participated in them.

The IOM contract with DHHS provided for access to all documents held by FDA, subject to the same restrictions on disclosure that govern FDA itself. Additional documents were provided by NIH, the drug companies and scientists involved in the trials, and scientific and popular publications. A full list is provided in Appendix B. The committee also questioned representatives of the drug companies, the principal investigators, and various officials from NIH and FDA at two 2-day meetings (Appendix C). Telephone interviews were conducted with all of the surviving patients from the 28-day and 6-month trials at NIH who indicated to the NIH Clinical Center patient representative that they were willing to be interviewed (14 of 22), and all 5 of the patients who participated in the New England/Texas study (H3X-MC-PPPA).

PLAN OF THE REPORT

After an introduction to clinical trials and their role in the drug development process and to hepatitis and chronic viral diseases, the report describes each of the FIAC/FIAU clinical trials, in chronological order covering as objectively as possible the rationale for that trial, the qualifications of the investigator and the facility involved, the conduct of the study from informed consent through reporting to the study's sponsor and FDA, analysis of the results, and long-term follow-up, including continuing investigations into the mechanisms action of FIAU. The subsequent section of the report provides the committee's analysis of the whole series of trials with respect to such issues as informed consent, oversight, reporting of adverse events, and response to the emergency.

Next the report reviews and comments on the patient interviews and the previous professional reviews: the FDA Task Force Report, the NIH Review, the FDA warning letters, and the changes to the Code of Federal Regulations recently proposed by FDA. The report concludes with a section dealing with recommendations for the future regulation and conduct of clinical trials.

TABLE 1-1 Clinical Trials Reviewed in Detail by IOM

Trial No.	Sponsor	Principal Investigator	Location	Patients	Planned Duration	Start	Stop
R89-001-01[a]	Oclassen	Corey	Univ. of Washington	2 HIV+/CMV+	35 days	3/90	5/90
		Richman		10 HIV+/CMV+	35 days	11/89	3/90
			Univ. of California, San Diego				
R90-001	Oclassen	Corey	Univ. of Washington	25 HIV+/HBV+	14 days	10/90	6/92
		Richman		4 HIV+/HBV+	14 days	5/91	5/92
			Univ. of California, San				
		Straus	Diego	14 HIV+/HBV+	14 days[b]	4/91	6/92
			NIH				
R91-010 (NIH protocol 91-DK-AI 213)	Oclassen	Hoofnagle	NIH	24 HBV+	28 days	4/92	9/92
H3X-MC-PPPA	Lilly	Paar	U. of Texas, Galveston	3 HBV+	3 months	5/93	6/93
		Kaplan	New England Medical Center	2 HBV+	3 months	5/93	6/93
H3X-MC-PPPG	Lilly	Hyslop	Lilly Lab. for Clinical Res.	17 healthy males	27 days[c]	3/93	4/93
H3X-MC-PPPC (NIH protocol 93-DK-0031)	Lilly	Hoofnagle	NIH	15 HBV+[d]	6 months	3/93	6/93

NOTE: HIV+, human-immunodeficiency-virus positive; CMV+, cytomegalovirus positive; and HBV+, hepatitis B positive.
[a] FIAC trial; all others FIAU.
[b] Four patients were retreated 45-100 days after the first 2-week treatment.
[c] Five doses at 3- to 7-day intervals.
[d] Ten of these had also participated in the R91-010 trial.

2

Clinical Trials

IMPORTANCE OF CLINICAL TRIALS

A large number of new drugs have been added to the therapeutic armamentarium during the past three decades. They have cured, controlled, or ameliorated a variety of human diseases; their use has saved the lives of numerous individuals and positively affected the quality of life of many others. These drugs have been used successfully to suppress rejection following organ transplantation and to treat a variety of infectious diseases, hypertension, various forms of heart disease, peptic ulcer disease, rheumatoid arthritis, asthma, and prostatic hypertrophy, to mention just a few. Physicians prescribe these medications extensively, and the public gladly accepts the benefits that accrue from their use. However, before they can be approved for use considerable testing for safety and efficacy must be performed.

Clinical trials are of vital importance in the development of new drugs for use in humans. Preliminary experimentation in animals is important in identifying potentially effective interventions in animal models human diseases and in identifying the efficacious and nontoxic amounts of a pharmaceutical to be given. However, no amount of testing in animals can substitute for carefully planned and carefully conducted studies in humans. In clinical studies in humans a particular medication or intervention is administered to individuals with a specific disease under conditions in which beneficial or detrimental effects can be identified during a reasonable period of observation. There are many examples of medications that appear to be effective or ineffective in animal models but have been demonstrated to have the opposite effects in humans. For specific medications or interventions, certain side-effects in humans may apply to humans generally or only to selected individuals. There are always certain risks in the administration of new medications for the first time, since efficacy cannot be assumed and the relevance of side effects can usually be established only on the basis of the human trial. Individuals who agree to participate in clinical trials must be adequately informed about the rationale for the use of a particular drug or intervention and about potential benefits and adverse effects that might occur. Moreover, the individuals should understand that some side effects that occur may not be predictable and may be serious. Unfortunately, there is no alternative to careful evaluation of new medications and interventions in human trials if one is to gain the needed knowledge concerning their efficiencies and possible undesirable effects.

While accepting the benefits from all the new drugs introduced in the past 4 to 5 decades, it is important to recognize what is required in the way of subject participation in the clinical investigation of such new drugs. As an example, consider antimicrobial agents. In Phase I trials (pharmacology; dosage studies) recent practice has involves about 100-300 subjects (Gilbert, 1987). In Phase II trials (controlled clinical trials; relative safety/ efficacy),

300-1,000 subjects have usually been involved. In Phase III trials (expanded trials, both controlled and uncontrolled; effectiveness, specific indications, and precise definition of side effects), recent practice involved 1,000-3,000 subjects. The estimated time to complete such trials is 4 to 7 years (Phase I; 1-2 years; Phase II, 1-2 years; Phase III, 2-3 years). Overall, the total number of new commercial applications submitted to the Food and Drug Administration (FDA) by sponsors each year is large. For example, 371 new applications were submitted in 1992 (FDA, 1993c). Of each 100 drugs for which applications are submitted to the FDA, about 70 successfully complete Phase I trials, about 33 complete Phase II trials, and 25-30 clear Phase III trials. About 20 of the original 100 are ultimately approved for marketing.

In a review of clinical design characteristics in studies of new antimicrobial agents reported in various symposia over the 17-year period from 1969 through 1985, a total of 207 individual trials involving 21 different antimicrobial agents were described (Gilbert, 1987). If one applies the number of subjects commonly studied in each clinical investigation of a new antimicrobial from 1969 to 1985 to the 21 different antimicrobial agents approved by the FDA in that period, then a sizeable number of subjects, somewhere between 29,400 and 90,300, have been involved in the clinical trial process for approval of these new antimicrobial drugs. The process is thus a lengthy one (4-7 years) and one which involves many study subjects. The time involved is lengthy because of the necessary stepwise nature of study progression. The argument can be raised that the trial duration can be too lengthy, particularly when the underlying disease is a life-threatening one for which therapies are limited. This has been raised, for example, in the case of clinical trials of nucleoside analogs and other drugs investigated for therapy of human immunodeficiency virus (HIV) infection. One must balance safety considerations and the need for a particular treatment. Similar considerations must apply as well in defining therapeutic efficacy for a new drug and markers of adverse effects during clinical trials. If too stringent a requirement for efficacy is applied, ultimately useful drugs may be discarded prematurely. Similarly, if adverse effects are defined inappropriately, then introduction of useful drugs may be delayed or proscribed. If the most stringent criteria are applied to adverse events then it may be possible to avert any toxicity. That is certainly an important consideration; some (e.g., Jonas, 1970) would consider it an overriding obligation. However, the other side of the coin must be recognized in tallying up the pros and cons. While avoiding a single serious adverse reaction is an obviously desirable goal, the premature termination of a study for laboratory test abnormalities of uncertain significance may also have undesirable effects by causing the cessation of further development of that drug. The evaluation of this step should consider the potential saving of one life by stopping the further testing of the drug but should also consider the alternative, loss of life by prematurely holting development of a drug that may save many lives. This consideration should necessarily be weighed in the evaluation of adverse events in the course of clinical drug testing for all new drugs, whatever the type (antimicrobial, cardiovascular, psychotropic, etc.)

Thus, there are many precedents in clinical medicine for the urgent need to develop improved therapies for patients with serious illnesses. There are definite risks to such patients as they receive new medications and interventions, and these need to be acknowledged by FDA and involved physician-scientists and to be well understood by the patient. Nevertheless, there have been major clinical gains from improved therapy. These gains have led to reductions in morbidity and mortality on the basis of observations made in clinical trials; they simply could

not have been made without accepting the inherent risks in conducting the necessary clinical trials.

THE RISK-BENEFIT NATURE OF TRIALS

Before the advent of trials, treatments were judged to be safe and effective via personal observation and anecdote. George Washington is reported to have had his demise hastened by blood letting for the treatment of hypertension (Donaldson and Donaldson, 1980; Knox, 1933). The treatment was judged to be beneficial on the basis of logic and clinical impression.

Surgeons in the days of Ambrose Paré treated gunshot wounds with boiling oil. It was his treatment of choice on the field of battle to capture the castle of Vilaine in 1537. Fortunately for those to follow the battle was so heated as to have caused Paré to deplete his supply of boiling oil. He was forced to an alternative—an ointment made of egg yolk, oil of roses, and turpentine. To his great surprise he found that those so treated fared better than those treated with boiling oil. He wrote:

> I raised myself early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament, feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by Arquebuses. (Packard, 1921)

It would have been unthinkable in Paré's day to have subjected the treatment of boiling oil to test in a trial. To have done so almost certainly would have been at odds with the prevailing wisdom of the time and would have likely exposed him to wilting criticisms of his peers. Had he had the vision to want to evaluate it in the context of a trial before the Battle of Vilaine in 1537, he most likely would have been castigated for experimenting on his patients. The fact is, however, that his patients would have been better off had he had the vision and wherewithal to do the evaluation. They would have been exposed to less pain and suffering than by having waited for the events of the minute to cause him to change his treatment approach.

A *trial* is an experiment carried out on human beings for the purpose of determining whether or not a specified treatment regimen is safe or effective. A *clinical trial* is such an experiment performed on people having some defined health condition or disease and that is undertaken to determine whether or not the indicated health condition or disease can be cured, ameliorated, or prevented.

One of the things that sets clinical trials apart from other members of the class of trials is the obligation for care. Investigators undertaking them have obligations to ensure that the patients enrolled in the trial are adequately cared for, even if doing so conflicts with or is at odds with required data collection and treatment procedures set forth in the protocol for the trial. In short, their first responsibility is to the patients who enroll in the trial and in ensuring that the patients has adequate care, even if meeting that responsibility results in violations of

the treatment protocol and discontinuation of the patient's participation in the trial. Indeed, investigators are expected to deviate from the protocol if doing so is considered in the best interest of the patient. The dual responsibility of meeting the requirements of the Hippocratic Oath and a study protocol creates a tension that, of necessity, should settled in favor of individual patients when there is conflict. The goal is to design the study protocol so as to minimize such conflicts by the inclusion of safeguards to allow investigators to meet the requirements of the protocol while also meeting their responsibilities under the Hippocratic Oath.

The protocol specifies details as to the route of administration, dose and dosages, and the points at which treatments are to be suspended or altered, depending on the outcome. The administration may involve a single dose or multiple doses. The period of treatment may consist of a single exposure to the drug or repeated exposures. The exposures may involve use of the same dose administered according to a specified schedule or differing dose administered according to some scheme (e.g., as in a crossover trial in which each person enrolled receives a low or a high dose followed by a high or a low dose).

Only patients judged to be eligible (as determined via defined eligibility criteria) may be enrolled in the trial, and among those, only those who consent can be enrolled or those for whom permission to enroll is obtained from appropriate representatives. Persons are under no obligation to enroll or to continue once they are enrolled. Investigators are required to make these facts known to all who are approached for enrollment prior to enrollment and the start of treatment as part of the consent process.

The amount of data collected on each person enrolled depends on the nature of the drug being tested, the nature of the persons enrolled (i.e., whether or not they themselves have the disease or condition for which the drug is intended), and the period of time that persons are to be under the care and observation of study investigators. Typically, that period is relatively short in the case of Phase I and II drug trials and is usually measured in days or weeks as opposed to months or years. As a rule, it ends when a person is separated from the trial.

All trials involve data collection at various time points over the course of follow-up. The requirement for repeated observation obligates patients to a defined data collection schedule (except for trials done in hospitals or other settings involving resident patients or trials that can be performed in one session) that calls for a series of visits to the site of the trial for observation and treatment. The first visit or series of visits will be for the purpose of determining eligibility, collecting essential baseline data, obtaining consent, and the initiation of treatment. Visits thereafter will be for continued administration of treatment and/or collection of essential follow-up data. The schedule of follow-up visits will be timed from the point of initiation of treatment and will be on a defined time schedule (e.g., once every week), with provisions for interim (unscheduled) visits when they are required or deemed necessary in caring for those enrolled.

Judgments regarding the merits of treatment are made in different ways depending on the design employed and on the kinds of outcome measures used to judge safety or efficacy. All trials, even if they do not involve a control treatment, involve assessment of change for individual patients or the collection of patients by subtraction of a person's baseline value from the value observed at a specified point during the course of follow-up. For example, one

monitors for weight change by comparing a patient's weight on entry with that observed over the course of follow-up.

Evaluation of the treatment is based on results from all patients enrolled in the trial. That evaluation is relatively straightforward in randomized controlled trials involving comparison of one or more test treatments versus a control treatment. The control treatment in the case of drug trials may be a placebo, or it may be a standard medical treatment or another test treatment. Typically, the judgment is based on comparison of the different treatment groups with standard statistical tests on the outcome or outcomes of interest.

Judging the safety or efficacy of a treatment is much more problematic in the case of trials not involving a designed comparison group—usually the case in most early evaluations of a new drug. The problem in those settings is compounded by the fact that those trials are typically of short duration and are small in size. That problem is most acute in cases, such as with fialuridine (FIAU), in which drugs are being tested on people with a life-threatening disease that results in its own morbidity and increased risk of death. In those settings one is often left in a quandary as to what to make of isolated cases of morbidity indicated by observed clinical events or intimated by changes in specified laboratory tests. Are the changes due to the disease itself or to the drug? Even the cause of death becomes difficult to interpret in the presence of a relatively high background death rate from the disease or other characteristics of those enrolled. There is always room for doubt as to cause. Was it the natural outcome of the disease or was it induced by the treatment? The issue is rarely clear until in retrospect sufficient information has accumulated to discount underlying disease as the likely explanation or until one sees an unusual clustering of deaths and morbid events like those in trial H3X-MC-PPPC.

THE DRUG DEVELOPMENT PROCESS

No matter how promising the theory or impassioned the pleas for early use in humans, all potential drugs must go through a series of tests in animals before they can be tested in human beings. The object of these studies is to evaluate the potential toxic properties of the test drug in such a way that possible adverse reactions are identified before introduction of the drug into humans. Consequently, one is interested in (1) as complete an inventory as possible regarding potential toxic events, (2) the exposure conditions that are likely to lead to the appearance of toxicity, (3) the estimated toxic dosage range in laboratory animals, and (4) an estimate of the likelihood that adverse events might occur in human subjects. The testing procedures are designed in such a way that toxicity *will* occur at some dosage level in laboratory animals; relatively large doses are used intentionally in an attempt to elicit the complete inventory of adverse effects as accurately as possible. There are no standard established protocols for preclinical toxicity testing. However, it is essential to have knowledge regarding the possible adverse effects that might occur when the drug is administered acutely (administered once only) or repetitively (multiple treatments over days, weeks, or months). Furthermore, some assessment of potential adverse effects of the test drug on genetic material (DNA) is required, as well as its adverse effects on reproduction (fertility, fetal viability, fetal development, etc.)

It is necessary to establish the various dose-effect relationships that exist when the drug is administered acutely or repetitively (chronically). Toxicologists wish to establish at which dose levels adverse events are observed. One also wishes to determine the dose levels where drugs are unlikely to exert adverse effects (the so-called no-observable-adverse-effect-level). Finally, one wishes to establish dosing regimens for humans that will be devoid of adverse effects.

Since there is no standard series of toxicity studies formally required before going into clinical trials, the final package is determined by the sponsor of the investigational new drug (IND) request and the FDA. The specific requirements for preclinical toxicity testing depend on the type of drug in question and the particular illness for which it is intended. For an antiviral agent like FIAU, it is likely that the FDA would require toxicity information on the test substance when it is administered acutely to at least two species. The route of administration employed in the tests ideally would be the route envisioned for use in the clinical treatment situation. Furthermore, drug effects after multiple-dose treatment of two species would be required. The duration of treatment in these studies in animals would be at least equal to the treatment period envisioned for the clinical trial. They could vary in length from a period of several weeks to a month or up to 6 months. In addition, it is likely that genotoxicity data as well as reproductive studies in laboratory animals would be required.

Compounds considered to lack promise for use in human beings do not come to testing in trials. They are dropped from considerations before reaching that stage. There must be a plausible basis for believing that compound will be useful in the treatment of human beings and sufficient preclinical data to indicate that the compound may be effective and that it is safe relative to the risks associated with the condition or disease of interest.

Testing of new drugs in human beings typically proceeds in three, and sometimes four phases, defined as follows:

Phase I: Usually the first stage in testing performed as part of an IND application to FDA, the trial is done primarily to generate preliminary information on the chemical action and safety of the new drug and is usually not controlled; that is, it is done without the benefit of a concurrently observed comparison group that does not receive the drug. Subjects are most often normal volunteers, but sometimes patients with the target disease.

Phase II: Usually the second stage of testing, the trial is carried out on persons having the disease or condition of interest, and thus provides preliminary information on the efficacy of the drug along with additional information on safety. The design may include a control treatment and random assignment of patients to treatment.

Phase I/II: A trial combining the features of both a Phase I and a Phase II trial, designed to provide preliminary information on both safety and efficacy.

Phase III: Usually the third and final stage of testing, this sort of trial is concerned with assessment of dosage effects, efficacy, and safety. The design usually includes a control treatment and random assignment to treatment. Once this phase is completed (or nearly completed) the drug manufacturer or sponsor may request permission to market the drug for the indication or condition covered in the testing. This is done by submitting a new drug application (NDA) to FDA.

Phase IV: A fourth stage of testing, carried out after approval of NDA, can take a variety of forms, from passive surveillance to carefully planned experimental studies. Goals may be simply examining long-term safety and efficacy, or the utility of the drug for an indication or population not specifically addressed during the IND period. Efficacy and safety are typically measured against a designated control treatment.

After approval drugs remain under surveillance to determine if they cause serious effects not detected during testing. Broadly referred to as postmarketing surveillance, this involves the collection of reports of adverse events via systematic reporting schemes, surveys, and observational studies.

Phase I and II trials by nature tend to be small and are typically performed by one or a few investigators located at the same institution or at a small number of institutions. Typically, the number of people studied in any individual trial will number in the tens as opposed to hundreds. The primary question in a Phase I trial is whether or not the drug can be safely administered to people and in a manner and at a level likely to be beneficial. As a result, trials in this class are generally noncomparative in the usual sense of that term. That is, as a rule they are not randomized trials because all persons enrolled receive the study drug. If there is any randomization it relates to the dosage administered or to the order in which different dosages of the same drug are given (e.g., as in the case of crossover designs). Furthermore, the period of treatment tends to be short, measured in days or weeks as opposed to months or years. As a rule, data collection and follow-up cease on or soon after the last administration of treatment.

The Phase II trial generally includes only slightly more subjects than a Phase I trials, and the period of treatment is only slightly longer than its Phase I counterpart. The main difference is in focus. As the emphasis moves from safety to efficacy, the emphasis also shifts from designs involving dose escalation via some systematic or Bayesian process to designs involving a fixed sample size design (sample size is usually determined by pragmatic considerations as opposed to formal calculations based on type I and II errors) and with each person enrolled receiving the same dosage or with different patients receiving different dosages. The designs are usually parallel treatment designs if more than one treatment regimen or dosage is studied.

The sample size and durations of treatment and follow-up tend to increase as one moves from Phase II to Phases III and IV trials. The latter two phases are likely to have sample sizes numbering in the hundreds. As a rule, they are controlled, have fixed sample size designs, parallel treatment structure, and protocols involving a fixed dosage schedule.

All trials, regardless of phase, are subject to review and approval by a local institutional review board (IRB) before implementation and are subject to periodic review by the IRB of record so long as they remain in force. Investigators undertaking trials have obligations and responsibilities to obtain such reviews and approval before implementation and to seek the review and approval of the responsible IRBs before implementing amendments to the protocol. They have a responsibility, as well, to inform the IRB of any untoward events in the conduct of the trial and to report to such boards any conditions or events believed to be related to the treatment.

All trials of the sort discussed above are done under an IND application held either by a named individual at a performance site or by the sponsor of the drug. The sponsor the is typically a drug company, but in the broader sense of usage of the term it is simply the person or agency holding an IND application regardless of location. Personnel at the performance site or sites are named on the Form 1572 accompanying IND applications. People named are expected to be familiar with FDA regulations in regard to the conduct of trials of an IND and are obliged to comply with those regulations. The regulations, among other demands, make a number of stipulations regarding informed consent by patients. FDA regulations on informed consent are similar, but not identical, to those of the U.S. Department of Health and Human Services and other agencies of the federal government. In addition, FDA regulations are very specific about reporting adverse events.

SAFETY REPORTS

Under an IND application investigators are obliged to file safety reports to FDA for an adverse experience that is both serious and unexpected. The regulations (Code of Federal Regulations [CFR]; 21, parts 300 to 499, Revised 1 April 1992) specify that

> The sponsor shall notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with use of the drug that is both serious and unexpected. Such notification shall be made as soon as possible and in no event later than 10 working days after the sponsor's initial receipt of the information. Each written notification shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA Division of the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which has responsibility for review of the IND. In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.

In regard to telephone reports the regulations specify that:

> The sponsor shall also notify FDA by telephone of any unexpected fatal or life-threatening experience associated with use of the drug in the clinical studies conducted under the IND no later than 3 working days after receipt of the information.

An *unexpected adverse experience* is

> Any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is not required, that is not identified in nature, severity, or frequency in the risk information described in the general investigational plan or elsewhere in the current application, as amended.

A serious adverse experience, as described in the CFR for drugs is

> Any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse drug experience includes any experience that is fatal or life-threatening, is permanently disabling, requires instant hospitalization, or is a congenital anomaly, cancer, or overdose. With respect to results from tests in laboratory animals, a serious adverse drug experience includes any experience suggesting a significant risk for human subjects, including any finding of mutagenicity, teratogenicity, or carcinogenicity.

ETHICAL CONSIDERATIONS

Ethical justification of research involving human subjects requires responsiveness to the ethical norms or rules that are embodied in ethical codes and regulations. The substantive norms presented in ethical codes and regulations consist of various expressions of six general behavior-prescribing statements (Levine, 1986): There should be (1) good research design, (2) competent investigators, (3) a favorable balance of harms and benefits, (4) informed consent, (5) equitable selection of subjects, and, (6) in some ethical Codes but not in U.S. federal regulations, compensation for research-induced injury. In addition to these six substantive norms there are various procedural rules designed to ensure responsiveness to the substantive rules. Most important for the present considerations are that there should be (1) review and approval by an IRB and (2) written documentation of informed consent.

Procedural Requirements

Institutional review board (IRB) review and approval of each protocol for the conduct of research involving human subjects are required by federal regulation for all research sponsored by any agency of the federal government and for all research regulated by FDA. Most institutions that conduct research involving human subjects have voluntarily extended the reach of the requirement for IRB review to all such research in their multiple project assurance MBA—documents filed with the Office for Protection from Research Risks of the National Institutes of Health that provide the details of the institution's plans to comply with federal regulations for the protection of human subjects. The purpose of IRB review is to ensure compliance with all of the other procedural and substantive ethical norms.

Federal regulations set forth a detailed account of the minimum standards for the composition, administration, reporting requirements, and substantive responsibilities of IRBs; most university hospital and research hospital-based IRBs exceed these minimum standards. For example, although federal regulations require at least five members, one of whom must be "primarily concerned" with nonscientific areas, the typical university hospital-based IRB has 20 or more members representing medicine, science, law, ethics, and other professions and other members who are not professionals (Levine, 1986).

Federal regulations also provide detailed requirements for the composition and use of consent forms. The requirement for consent forms is a procedural requirement designed to provide evidence of compliance with the substantive requirement for informed consent. Federal regulations specify circumstances in which the requirement for written documentation of consent may be waived; none are relevant to the FIAU research reviewed by the Institute of Medicine (IOM) Committee.

Substantive Norms

The leading international codes and guidelines in the field of research involving human subjects, *The Nuremberg Code, The Declaration of Helsinki*, and the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (promulgated in 1993 by the Council of International Organizations of Medical Sciences in collaboration with the World Health Organization each clearly presents the requirements for good scientific design and competent investigators as *ethical* requirements (Levine, 1986). This point notwithstanding, it is customary to dissociate the discussion of these matters from discussion of the other substantive ethical norms. This report reflects this customary division; considerations of scientific merit and investigators' competencies are discussed in other sections of this report.

A Favorable Balance of Harms and Benefits

Ethical justification of research requires a determination that the balance of risks and anticipated benefits is —in the words of federal regulations—"favorable" or "reasonable." this determination, which must first be made by the investigators and then ratified by the IRB, must be accomplished at the outset, before the research is begun. All too often, media addressed to the general public look at the results after the research has been completed and challenge the ethical justification on grounds that the "risks" were not justified by the benefits. At this point, what was identified at the outset as "risks"—a statement of probability that harms of a certain type could occur—either have or have not materialized as "injuries."

The process of ethical justification before the research is begun should always include an assumption that there is some statistical probability of injury and should generally include an attempt to calculate that probability. In general, the probability and magnitude of injury should be less than the probability and magnitude of anticipated benefit. It should always be understood, however, that adverse events with a low probability of occurrence will eventually occur if the conditions that create the risk of their occurrence are repeated sufficiently often. Thus, the fact that injury has occurred does not mean that the research project in which it occurred was unethical. Research is justified ethically by the relation of risks to anticipated benefits at the outset, not by the ratio of injuries to actual benefits at the conclusion of the research.

In research designed to evaluate a new drug, the initial estimation of risks must also take into account the possibility of occurrence of novel injuries—harms that cannot be

predicted on the basis of prior clinical or preclinical testing. Fortunately, injuries that are both serious and unanticipated are very unusual (Levine, 1986; Williams, 1990).

Responsiveness to this norm also requires that there be careful monitoring of all events that have a bearing on the assessment of both risks and benefits. It is the joint responsibility of the sponsor and the investigator to see to it that all reasonable measures are put in place to ensure the prompt identification of adverse reactions. With regard to research in the field of drug development, there are two major purposes of such activity: (1) to ensure the timely identification of adverse reactions so that appropriate interventions can be implemented in time to minimize injury to individual subjects; such interventions are exemplified by discontinuation of a subject's participation in the study and by the administration of antidotes to toxic agents; and (2) to ensure accurate estimates of the nature, probability and magnitude of side effects and adverse events (a) to inform subsequent judgments as to whether a drug should be approved for commercial distribution and, if so, (b) to determine what information should be put on the package label. An accurate assessment of benefits also contributes to the effective functioning of the drug approval and labelling process.

Equitable Selection of Subjects

This ethical requirement is usually construed to mean that vulnerable persons should not be enrolled as subjects without suitable justification. "Vulnerable subjects" is a category often equated with those classes identified in federal regulations as the special populations, special in that they have "limited capacities to consent." Populations so identified in regulations are children, fetuses, and prisoners; in addition, regulations were once proposed for the protection of persons with limited capacities to consent by reason of mental infirmity. In general, members of the special populations may not be recruited as research subjects without special justifications. Such justifications include, but are not limited to, the following: the research goals could not be realized by using less vulnerable subjects; the research is designed to develop knowledge or therapeutic products that will be of benefit to the vulnerable class from which the subjects are recruited; the assent of the subject must be obtained (when feasible and appropriate) along with the permission of a parent or other legally authorized person; and interventions or procedures that do not hold out the prospect of direct benefit to the individual and that present more than minimal risk require even more stringent justification.

According to *The Nuremberg Code*, the first international code of research ethics, there are four criteria for valid consent: it must be voluntary, legally competent, informed, and understood. Most commentators on research ethics agree that persons having diminished capacity to understand or to refuse participation should be regarded as at least potentially vulnerable even if they do not have the attributes that define the special populations (*see earlier discussion*). To the extent that such persons are actually vulnerable, careful consideration should be given to applying some or all of the special justifications specified earlier for the recruitment of vulnerable persons as research subjects, even though such justifications are not explicitly required by regulations (Levine, 1986).

Particularly germane to the IOM committee's mandate is a recognition that persons with serious and potentially disabling or deadly diseases are vulnerable in several important respects.

They may lack sufficient voluntariness—in the words of *The Nuremberg Code*, they may not be "so situated as to be able to exercise free power of choice." They may be willing to assume unreasonable risks out of desperation to find a way to prevent or postpone death or disability. They may fear that if they do not cooperate with their doctors or with the health care establishment they might be subjected to some sort of retaliation. Even though they are assured, as required by federal regulations (45 CFR 46.116 (a)(8), that they are free to refuse to participate in research or to withdraw without the loss of any benefits to which they are otherwise entitled, they may fear retaliation. Scientists and IRBs must be alert to these possibilities as they attempt to insure that patients make free and informed choices.

Another condition that undermines the capability of a person to make an unconstrained choice is poverty. Many people with serious chronic diseases are actually or potentially impoverished. Without the free medical care that is commonly made available to research subjects, many would suffer the plight of the medically indigent. Accordingly, one must be especially attentive to avoid what are commonly called "undue inducements." A frequently used guideline calls for limiting cash payments to vulnerable research subjects to the minimum wage for the actual time spent plus reimbursement for out-of-pocket expenses such as parking fees and stipends for baby-sitter (Levine, 1986).

Compensation for Research-Related Injury

Several prestigious groups advisory to the federal government have recommended that there should be "no-fault compensation" for research-induced injury (Levine, 1986). These groups include but are not limited to the U.S. Department of Health, Education, and Welfare Task Force on the Compensation of Injured Research Subjects (1977), the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1976), and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1982). These recommendations notwithstanding, the federal government has limited its involvement in compensation to a requirement that informed consent must include "an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained" (45 CFR 46.116(a)(6).

Informed Consent

The committee has already addressed the procedural standard that requires, in most research protocols, the signing of a consent form. Now attention is turned to the process of informed consent. The process of informed consent is designed to be responsive to the individual's right to self-determination. Through informed consent individuals are empowered to protect their own interests as they are provided with all of the information that is considered "material" to their judgments as to whether to enroll in a research study. The consent form, by contrast, is a document designed primarily to protect the interests of the institution and the investigator. It is, in effect, a signed receipt for the information (Levine, 1986).

The consent form consists of the minimum amount of information that the IRB finds necessary to divulge during the informed consent process. This minimum standard is actually quite comprehensive in that it includes all of the categories identified in the relevant federal regulations. Investigators are permitted to present more information but not less than what is on the document. Commonly, they present additional information in response to questions asked by the subjects.

When subjects are asked to recall what they were told during the process of informed consent, they quite often are unable to repeat many of the details. This is the case even when there is incontrovertible evidence that they have received and acknowledged a comprehensive account of all of the information deemed necessary by the IRB. Some commentators believe that this incomplete recall is due to a loss of memory, particularly of bits of information that subjects consider not worth knowing. This belief is supported by the results of research. For example, in studies in which subjects are given incentives to recall the consent information, their retention of information increases substantially in proportion to the value that they assign to the incentives (Levine, 1986).

Some commentators believe that the subjects' poor performances on tests of recall may reflect a trusting attitude on the part of the subjects. At some point in the encounter between an investigator and a prospective subject, the latter decides whether or not he or she trusts the investigator. If the subject does trust the investigator the subject becomes inattentive to the details of risks and benefits and chooses to participate on the basis of trust. If the subject does not trust the investigator, the prospective subject similarly becomes inattentive, having already decided to refuse on the basis of a lack of trust. Although the committee is not aware of any definitive study on the role of trust in the decision to consent or to refuse to participate in research, members of the committee with experience in recruiting research subjects believe that this is an important factor.

SUMMARY

Clinical trials are of vital importance in the development of new drugs for use in humans. Preliminary animal experimentation is important in identifying potentially effective interventions and eliminating potentially dangerous ones, but no amount of animal testing can substitute for carefully planned and carefully conducted human studies in which a particular medication or intervention is administered to individuals with a specific disease under conditions where beneficial or detrimental effects can be identified during a reasonable period of observation.

Testing of new drugs in human beings typically proceeds in three, and sometimes four phases, beginning with attempts to generate preliminary information on the chemical action and safety of the new drug, generally using normal volunteers, through preliminary studies of efficacy carried out on persons having the disease or condition of interest, to large scale formal studies including a control treatment and random assignment of dozens or hundreds of patients to treatment.

The process is thus a lengthy one (4-7 years) and one which involves many study subjects. The time involved is lengthy because of the necessary stepwise nature of study

progression. The argument has been raised that the trial duration can be too lengthy, particularly when the underlying disease is a life-threatening one for which therapies are limited, e.g., AIDS. One has to balance safety considerations and the need for a particular treatment. If too stringent a requirement for efficacy is applied, ultimately useful drugs may be discarded prematurely. As is now, despite intensive preclinical screening, only about 70 of every 100 drugs for which applications are submitted to the FDA successfully complete phase I trials. About 33 complete phase II trials, and 25-30 clear phase III. About 20 of the original 100 are ultimately approved for marketing.

One of the features of *clinical* trials that distinguishes them from other experimentation with human subjects is the obligation for care. Investigators undertaking them have obligations to ensure that patients enrolled are adequately cared for, even if doing so is at odds with required data collection and treatment procedures set forth in the protocol for the trial. We have therefore include in our overview not only the FDA regulations governing reporting of adverse events, but also an ethical framework which we found useful in evaluating the FIAC\FIAU trials. This framework can be summarized by six substantive imperatives and two procedural norms. There should be 1) good research design, 2) competent investigators, 3) a favorable balance of harms and benefits, 4) informed consent, 5) equitable selection of subjects, and 6) compensation for research-induced injury. In addition to these six substantive norms, there should be 1) review and approval by an institutional review board and 2) written documentation of informed consent.

3

Hepatitis B and Other Viral Diseases

NATURE OF CHRONIC VIRAL DISEASES

Viruses, subcellular organisms that cause both acute self-limited disease in humans and long-term chronic disease, have become the focus of intense research in the last two decades. Composed of DNA or RNA inside a protein shell, these pathogens include the influenza virus that causes the common "flu", and the human immunodeficiency virus (HIV) that is responsible for the many manifestations of AIDS. Some vital infections are eliminated or controlled by the immune system, though often not until the victim suffers through an initial bout of illness. Others are not so easily managed: these viruses often mutate at a high rate in response to the defense mechanisms of the host immune system and cause persistent or chronic disease; viruses can hide in cells in the body or in parts of cells that may not be readily accessible to drugs aimed at killing these organisms; and viruses develop resistance to drugs by changing or mutating with time. Intense research in the last decade has yielded encouraging results in the war against these viruses, but although some persistent vital infections such as HIV and hepatitis C virus (HCV) can be contained with treatment, one can rarely eliminate the virus or completely rid patients of these infectious agents.

Chronic vital diseases such as HCV and hepatitis B virus (HBV) infection are important causes of morbidity and mortality in immunocompromised patients (cancer patients and HIV-positive patients such as those enrolled in the early fiacitabine [FIAC] and fialuridine [FIAU] trials at the National Institutes of Health [NIH] as well as immunocompetent patients (such as those enrolled in the final FIAC trial at NIH). Cytomegalovirus (CMV) is a pathogen that causes chronic disease in immunocompromised but not immunocompetent patients. Infection with HIV is an example of the most lethal of the common vital diseases in human. HIV infection is of particular importance, since the rate of chronicity after acute infection is almost 100 percent and an effective vaccine to prevent infection is lacking. These problems apply equally to HCV, which affects 1-2 percent of the U.S. population. Fortunately, the natural history of chronic HCV infection is much more benign than that of HIV or HBV infection (see below). Nevertheless, HCV disease can result in hepatic failure, hepatocellular carcinoma, and even death, although the length of time to the development of these complications is prolonged (the mean times from transfusion, the presumed time of HCV acquisition, to the development of cirrhosis and hepatocellular carcinoma are 25 and 30 years, respectively).

Infection with HBV differs from that of these other pathogens in that an effective vaccine has been available for more than a decade and the rate of chronicity after acute infection is low. Nevertheless, HBV remains an important global health problem, with a world-wide prevalence of 5 percent, and a U.S. prevalence of 1 percent. Vaccination programs

in the United States targeted at those individuals at greatest risk of infection (health care workers, intravenous drug users, and infants of infected mothers) have failed for two fundamental reasons: difficulty identifying and accessing patients at risk and non-compliance with vaccination regimens once they are instituted. Even in educated population at high risk of infection (e.g., health care workers), compliance with vaccination programs is only 50 percent. Compliance in other risk groups is much lower. Because of these limitations, universal vaccination of all newborns and prepubescent teenagers has been advocated and has begun to be instituted. Proof of the efficacies of these programs is awaited.

FIAC and subsequently FIAU were drugs first tested against CMV and varicella-zoster virus (VZV), which are common pathogens in HIV-positive patients. Little efficacy against these viruses was seen, but marked suppression of HBV infection was observed in patients infected with both HIV and HBV. This led to considerable interest in examining the effects of these drugs in the treatment of chronic HBV infection. To assess the importance of treating patients with chronic HBV infection, an understanding of the prognosis for untreated patients with this disease is necessary.

NATURAL HISTORY OF CHRONIC HBV INFECTION

The risk of chronicity after acute infection is largely determined by the age at which infection is acquired. With perinatal acquisition, chronic infection is almost universal (Stevens, Beasley, Tsui and Lee, 1975). With infection in healthy adults, the rate of chronicity is extremely low (less than 5 percent), but these carriers remain at risk of developing hepatocellular carcinoma (HCC) (Seeff, Beebe, Hoofnagle, Norman, Buskell-Bales, Waggoner, Kaplowitz, Koff, Petrini, Schiff, et al, 1987; Norman, Beebe, Hoofnagle and Seefe, 1993). Since most HBV infections world wide are acquired in the early neonatal period, when the risk of chronicity is high and effective vaccine programs are not yet in place, there remains a large population in whom chronic HBV infection is endemic.

Symptoms of HBV infection are variable. With acute HBV infection, patients are frequently fatigued and jaundiced (i.e., their skin turns yellow) and they complain of abdominal pain. Acute infection in adults rarely results in life-threatening complications; death from acute liver failure occurs in less than 1 percent of adult patients. The vast majority of patients recover completely and develop protective immunity (i.e., they cannot be reinfected with this virus if they are subsequently exposed). Fewer than 5 percent of adults will develop chronic liver disease, often with only minor complaints of fatigue, joint pains, poor appetite and abdominal pain. Children who acquire HBV infection from their mothers are often asymptomatic and develop problems only after prolonged infection. Chronic infection, however, results in scarring of the liver (with consequent impairment of the flow of blood through the liver, back-pressure into the veins of the intestine, and an increased propensity for life-threatening bleeds). Other complications include retention of fluid in the abdomen (ascites), increased susceptibility to life-threatening bacterial infections, and mental confusion (encephalopathy). Once these complications occur, the life expectancy of the patient is very limited and liver transplantation is the only therapeutic option.

HBV infection has been linked epidemiologically to the development of HCC. In males with perinatally acquired infection, the life-long risk of development of HCC is 40 to 60 percent (Beasley, Hwang, Lin and Chien, 1981; Wright, Venock and Millward-Sadler, 1992). Screening programs may detect malignant lesions at a stage when they are still respectable, but they have failed to demonstrate a positive survival benefit. Once patients have symptoms related to liver cancer (abdominal pain or weight loss), the benefit of surgical resection or cancer chemotherapy is limited.

Knowledge of the natural history of disease without therapy is essential when making decisions regarding the need for therapeutic intervention. Many studies have evaluated the long-term consequences of infection. Perhaps that most applicable to the patients included in the H3X-MC-PPPC trial is a study of patients evaluated for antiviral therapy at Stanford University from 1974 to 1981. Three hundred seventy-nine patients were considered for treatment with either interferon or adenine arabinoside (Ara-A; like FIAC and FIAU, Ara-A is a nucleoside analog) (Weissberg, Andres, Smith, Weick, Nichols, Garcia and Robinson 1984). Five-year survival was determined by telephone contact and cause of death was determined by autopsy whenever available. The majority of patients were men (as in the PPPC trial) and histology at the time of entry into the study varied (approximately one-third had chronic persistent hepatitis, one-third had chronic active hepatitis, and one-third had cirrhosis). Five-year survival was 97, 86, and 55 percent in these three histologic groups respectively. Most patients died of liver failure, and only four (8 percent) died of HCC. Since an autopsy was rarely performed, the number of deaths from HCC may have been underestimated. Patients with hepatic decompensation (i.e., patients who have already developed complications because of their infection) were included in this natural history study, though patients with disease this advanced would not have been eligible for the PPPC trial.

The most important conclusion from this and other natural history studies of HBV infection is that when infection becomes chronic, significant liver damage can occur and the risk of progressive liver failure is greater in those with an advanced histologic stage of disease. The morbidity related to chronic infection is hard to determine since subjective end points (fatigue, weight-loss, abdominal pain etc.) are more difficult to assess than objective end-points related to mortality (i.e. rates and causes of deaths). Regardless of the range of morbidity and mortality assessed in different studies, it is clear that liver disease associated with HBV infection may progress to liver failure, the development of HCC, and death.

An important feature noted in studies of the natural history of chronic HBV infection is that of the spontaneous loss of viral replication (indicated by the disappearance from the blood of HBV envelope antigen, a viral protein highly correlated with active infection, and the loss of HBV DNA in serum). This occurs in 2.5 to 25 percent of patients (Hoofnagle, Dusheiko, Seefe, Jones, Waggoner and Bales, 1981; Perrillo, Campbell, Sanders, Regenstein and Bodicky, 1984; Perrillo, 1992). Viral clearance is hypothesized to be mediated by the immune system and is frequently associated with a transient rise in the levels of aminotransferases (aspartate aminotransferas [AST] and alanine aminotransferase [ALT], enzymes that are present in liver cells and are markers of liver injury when they present in quantity in blood). This so-called flare phenomenon is also seen in patients with a positive response to interferon therapy (see below).

NEED FOR ORALLY ACTIVE AGENTS

The first responsibility of an investigator and drug sponsor (usually the pharmaceutical company) assessing the utility of a new drug is to determine whether it is safe. The second duty is to determine whether the drug is efficacious. Finally, the practical realities of everyday patient care come to the fore. Most available antiviral agents have had to be given by injection, either intravenously or subcutaneously, because they are poorly absorbed from the intestine. Approaches to treatment of viral diseases have generally been either to stimulate the natural host defenses against infection (by drugs such as interferon) or to inhibit directly the ways that viruses divide and multiply (by nucleoside analogs, molecules which are similar to the building blocks of DNA and that become incorporated into the viral DNA as the virus divides, inhibiting and interrupting this replicative machinery).

Important advances have been made in the therapy of some viral diseases, notably those belonging to the herpes virus family. Herpes simplex virus is controlled effectively with the oral nucleoside analog acyclovir, and CMV infection is treated effectively with the intravenously administered nucleoside analogs ganciclovir and phosphonoformate (foscarnet). An effective oral agent against CMV disease is still being sought. Long-term administration of nucleoside analogs such as ganciclovir (used against CMV) requires the placement of permanent venous access lines, often utilizing the operating room, and twice-daily home therapy with visiting nurses. These IV lines also carry with them potential complications of systemic and life-threatening bacterial infections. The costs of such parenterally administered antiviral agents have not been examined closely, but it is readily apparent that an orally active agent would have a positive impact on most of the problems outlined above. This brings us to the question of what treatments for chronic HBV were available when the FIAC/FIAU trials were begun.

Interferon, a naturally occurring protein produced by lymphocytes and fibroblasts in response to chronic viral infection, has been tested in the treatment of chronic HBV infection since the mid-1970s (Greenberg, Pollard, Lutwick, Gregory, Robinson and Merigan, 1976). Initially serum-derived and subsequently synthesized interferons have been shown to effectively inhibit viral replication in approximately one-third of treated patients (Greenberg et al., 1976; Perrillo, Schiff, Davis, Bodenheimer, Lindsay, Payne, Dienstag, O'Brien, Tamburro, Jacobsen, et al., 1990). Recombinant interferon alfa-2b is the only treatment for chronic HBV infection in the United States approved by the Food and Drug Administration (FDA), but treatment results in a response rate of only 37 percent (Perrillo et al., 1990). Selection of patients who have HBV DNA levels of less than 100 pg/ml may yield response rates of 50 percent. Nevertheless, a large number of patients either fail to meet the criteria for treatment or do not respond to therapy. Moreover, treatment is expensive (approximately $5,000 for a 16-week course of 5 million units per day), must be given by the parenteral route, and is associated with significant, even if largely reversible, side effects including flu-like symptoms, fatigue, muscle aches, low-grade fevers, and depression. Many of these side effects overlap with the complaints of patients with chronic viral infections and, although not life-threatening, may lead to considerable morbidity and the cessation of therapy. Hence, there is a need for an effective orally available therapy.

Several potential alternatives to interferon in the treatment of chronic HBV infection have been evaluated during the last decade. Ara-A, and its soluble monophosphate, Ara-AMP, as well as nucleoside analogs effective in the treatment of HIV infection (dideoxycytidine [ddC] and dideoxyinosine [ddI]) are agents that have been studied carefully as therapy for chronic HBV infection. All have been found to be only partially effective, must be given intravenously or intramuscularly, and are associated with significant adverse effects, most notably reversible peripheral neuropathy (Ara-A) and pancreatitis (ddI) (Weller, Bassendine, Craxi, Fowler, Monjardino, Thomas and Sherlock, 1982; Bassendine, Chadwick, Salmeron, Shipton, Thomas and Sherlock, 1981; Garcia, Smith, Weissberg, Eisenberg, Bissett, Nair, Mastre, Rosno, Roskamp, Waterman, et al., 1987; Scullard, Pollard, Smith, Sacks, Gregory, Robinson and Merigan, 1981; Kassianides, Hoofnagle, Miller, Doo, Ford, Broder and Mitsuya, 1989). The other drugs examined have been largely ineffective. Ribavirin is an orally available nucleoside analog used in the treatment of respiratory syncytial virus infection. In vivo activity against HBV (Tong, Huang, Lefkowitz, Lee, Co and Lo, in press) is limited and its toxicity is significant (hemolytic anemia, gastrointestinal side effects). Thymosin, an immune modulator, must be administered parenterally, and appears to be safe, but data from a recent randomized controlled clinical trial are still being analyzed for proof of efficacy against HBV. Other drugs such as 3'-thiacytidine are currently under investigation in the treatment of chronic HBV infection. Experience in more than 2,000 patients treated with this nucleoside analog suggests that this drug is safe and that it has at least transient efficacy in inhibiting HBV replication (Dienstag, Perillo, Schiff, Bartholomew, Vicary and Rubin, 1994).

With this background, it is easy to understand the interest generated by FIAU when this drug was shown to inhibit HBV replication and, in early trials, appeared to have minimal side effects.

THE FLARE PHENOMENON

Immunological activation with T-cell destruction of infected hepatocytes has been the postulated explanation for the rise in ALT and/or AST levels; the so-called flare phenomenon, seen in association with spontaneous and therapeutically induced clearance of virus. In either circumstance, this rise in enzyme levels is frequently accompanied by conversion from a replicative state (HBV DNA positive) to a nonreplicative state (HBV DNA negative). A rise in liver enzymes levels may be seen either preceding or concurrent with the inhibition of viral replication (Hoofnagle et al., 1981; Perrillo et al., 1984). In one report, 6 of 23 untreated males experienced this rise (elevations at least twice the average of two previous determinations; mean increase, 4.9-fold) during the spontaneous clearance of HBV (Perrillo et al., 1984). Interferon is believed to act both by immune stimulation and by a direct antiviral mechanism. In patients on interferon therapy, the flare typically occurs between the second and third month of treatment and is associated with a fall in HBV DNA levels. Degree of rise in ALT levels that determines a flare differs in various studies. Retrospective analysis of the U.S. multicenter interferon trial identified a two fold or greater rise in ALT levels in 60 percent of those who responded; this phenomenon was seen in 37 percent of patients overall (Perrillo et al., 1990). In one study from Europe (Alexander, Brahm, Fagan, Smith, Daniels, Eddelston, Williams,

1987), AST levels rose to 10 to 20 times the upper limit of normal accompanied by a "hepatitis-like" illness before the complete normalization of liver enzyme levels. This syndrome was rare in patients who failed to respond to therapy. In a trial at the National Institutes of Health (NIH), a rise in aminotransferase levels (to values at least two fold the pretreatment levels) was noted in the majority of responders to interferon (Hoofnagle, Peters, Mullen, Jones, Rustgi, Di Bisceglie and Hallahan, 1988). Thus, this phenomenon is well-recognized as a positive event either in the course of the natural history of disease or in the course of interferon therapy. The transient rise is typically associated with a fall in HBV DNA levels and heralds a permanent clearance of virus. Most studies define the flare as at least a two fold rise in ALT above baseline values, although the degree of observed elevation may be much greater (Alexander et al., 1987). It is thus difficult to distinguish, on the basis of an elevation in ALT levels alone, drug-induced hepatotoxicity from a positive response to antiviral therapy. Although an FDA task force retrospectively proposed that ALT or AST elevations greater than three times the baseline should be more suggestive of drug-induced hepatic injury than of a flare signaling a positive response to treatment, the task force did acknowledge the difficulty in clearly distinguishing between these two events. It should be emphasized that although the flare is believed to be due to immune-mediated lysis of infected hepatocytes expressing viral antigens on the surface membrane, without confirmation in an animal model of hepatitis B, this remains only a hypothesis.

The pathophysiology of the flare associated with nucleoside analogs such as Ara-A is even less well understood. There appears to be a qualitative difference between the phenomenon occurring with Ara-A and that occurring with interferon, in that the rise in aminotransferase levels in the former case occurs after the drug has been stopped (Weller et al., 1982; Bassendine et al., 1981). Moreover, the information regarding the flare associated with nucleoside analogs is derived from very few cases. Since these drugs have no known immunomodulatory properties, the explanation for the phenomenon occurring in these circumstances is that the drug lowers HBV DNA levels to a point where host immune mechanisms can effectively clear the remaining virus, with associated necrosis of infected hepatocytes. There are no experimental data to support this hypothesis. Regardless, based on knowledge at the time of the PPPC trial, it is understandable that the investigators would interpret the rise in transaminase levels seen in some patients as a positive sign indicative of viral clearance.

A recent trial of another nucleoside analog, 3'-thiacytidine (lamivudine), in the treatment of chronic HBV infection demonstrated a rise in liver enzyme levels (AST and/or ALT) during therapy (greater than two times the baseline level) in 50, 36, and 27 percent of patients treated with 25, 100, and 300 mg per day, respectively (Dienstag, Perillo, Schiff, Bartholomew, Vicary and Rubin, 1994). Elevations in liver enzyme levels three times the baseline level were less frequent (less than 20 percent) (Jules Dienstag, personal communication, November 1994). This rise in liver enzyme levels was associated with a fall in HBV DNA in 8 of the 11 patients. The investigators concluded, that even in the absence of known immunomodulatory effects of this drug, treatment related ALT rises were common (Dienstag et al., 1994). Whether this rise occurs as a consequence of therapeutically induced viral clearance or as a consequence of spontaneous fluctuations during the course of disease is difficult to determine. Regardless of the mechanism, information available subsequent to the PPPC trial suggests that ALT in ALT

levels elevations three times the baseline level may be seen in HBV-infected patients treated with nucleoside analogs other than FIAU.

TOXIC EFFECTS OF OTHER NUCLEOSIDE ANALOGS

Nucleoside agents were initially developed in the 1950s and 1960s as potential anticancer agents. In the late 1960s, the potential use of nucleoside analogs for the treatment of infectious diseases became apparent, with flucytosine, an antifungal agent, being the most prominent example. Other agents which followed, such as adenosine arabinoside, cytosine arabinoside, and iododeoxyuridine, demonstrated antiviral activity against herpes-related viruses, thereby creating an opportunity to treat viral diseases. Since most of these agents were initially developed as anticancer drugs, their major side effect profiles are similar to antineoplastic agents; specifically, they target rapidly dividing cells, such as those in the skin, gut, and bone marrow. Therefore, the most common adverse events noted with antiviral nucleoside agents are nausea, vomiting, diarrhea, cytopenias (low blood counts), and rash.

All of the agents approved by the FDA for use against the human immunodeficiency virus are nucleoside analogs, most of which were originally developed as drugs to potentially treat cancer. Zidovudine, which was developed in 1964, is most commonly associated with nausea, loss of appetite, low blood counts, and muscle aches. Elevation in liver enzymes is seen in a small proportion of patients. Among the other approved antiretroviral agents available for use, didanosine(ddI) is most commonly associated with gastrointestinal disturbances, most notoriously pancreatitis, which may be fatal. The incidence of pancreatitis is dose-related, with a rate of 5 to 9 percent occurring at currently established doses but up to a 30 percent rate at very high doses. Peripheral neuropathy is observed on occasion but hepatotoxicity is uncommon. On the other hand, zalcitabine (ddC) and stavudine (D4T) are most often associated with peripheral neuropathy, in a dose-limiting fashion, and only rarely associated with pancreatitis. Hematologic and hepatic abnormalities are less common in ddC and D4TR recipients than those taking zidovudine.

Microvesicular steatosis, multiple small fat droplets *within* liver cells (hepatocytes), has also been seen in association with nucleoside analogs used in the treatment of AIDS (ddI and azidothymidine [AZT]) (Lai, Gang, Zawacki and Cooley, 1991). Nonspecific fatty changes in the liver (hepatic steatosis) are seen in about 50 percent of all liver biopsy specimens from patients infected with HIV and are common in biopsy specimen from patients with chronic viral hepatitis as well. An observation of microvesicular steatosis, however, is suggestive, although not conclusive proof, of toxic liver injury. Microvesicular steatosis of the liver has been described in association with alcohol, drugs (tetracycline, sodium valproate), Reye's syndrome (a disease of children linked epidemiologically to viral disease in association with salicylate therapy), acute fatty liver of pregnancy, and metabolic disorders of fatty acid metabolism (3-hydroxyacyl-coenzyme A dehydrogenase deficiency) (Treem, Rinaldo, Hale, Stanley, Millington, Hyams, Jackson and Turnbull, 1994). The association with nucleoside analogs was made before the FIAU trials at NIH, and indeed complicates the interpretation of possible FIAU hepatoxicity since many patients in the R89 and R90 trials were on ddI and/or AZT.

Scattered case reports of steatosis and lactic acidosis together have been associated with HIV infection. By January, 1993, 15 cases had been reported in the literature, 3 cases reported as abstracts, and 2 additional cases reported to the FDA. Fourteen (70 percent) of the cases were fatal. Seventeen of the 20 patients had been on zidovudine at the time the acidosis began; the other three had received zidovudine in the past but had not taken the drug for over four weeks prior to the onset of acidosis. The original reports ascribed the syndrome to HIV disease itself, but by 1993, investigators were beginning to ask whether antiretroviral therapy might be the cause of this syndrome, a hypothesis unfortunately not confirmed until the cases of FIAU deaths were reported.

SUMMARY

Viruses, subcellular pathogens composed of DNA or RNA inside a protein shell or "envelope," are the cause of many acute and chronic diseases. Chronic infection by hepatitis-B virus remains an important global health problem despite the availability of an effective vaccine. World-wide prevalence is estimated at 5 percent, including about one million Americans. Acute infection rarely results in life-threatening complications, and most healthy adults resolve acute infection. A small proportion of adults (but a large proportion of neonates) fail to clear the virus and develop chronic liver disease. Symptoms are still relatively mild (fatigue, poor appetite, abdominal pain), but chronic infection gradually impairs liver function and increases the risk of cirrhosis and liver cancer.

Treatment of viral diseases involves either stimulating natural host defenses with substances like interferon, or directly interfering with viral replication with nucleoside analogs such as acyclovir or AZT. Interferon was approved by FDA in 1992 for use against HBV, but it is effective in only about a third of patients, must be given parenterally, and produces significant adverse side effects. Nucleoside analogs tried prior to FIAC and FIAU, all of which required IV administration, were either ineffective or produced unacceptable toxicity. The prospect of an effective oral antiviral drug thus made FIAC and FIAU attractive candidates for development.

Also introduced in this chapter, because it is the center of much post-tragedy discussion about whether liver failure in the PPPC victims should have been anticipated, was the "flare" phenomenon often associated with natural or therapy-induced clearance of HBV. Viral clearance is hypothesized to be immune-mediated and is frequently associated with a transient rise in serum aminotransferases (AST, aspartate aminotransferase, and ALT, alanine aminotransferase). These enzymes are present in liver cells and are generally thought to be indicators of liver injury when present in quantity in blood. Elevations in ALT or AST in patients being treated for HBV infection are thus open to conflicting interpretations - indicating either successful therapy or a toxic effect of the liver.

Finally, we have briefly reviewed what was known about toxic effects produced by nucleoside analogs other than FIAC and FIAU, in part because some have suggested these effects should have provided ample warning that FIAU would produce dangerous effects and in part because many of the subjects in the trials we review here took these drugs before, during or after their FIAU treatment, confounding interpretation of adverse events.

4

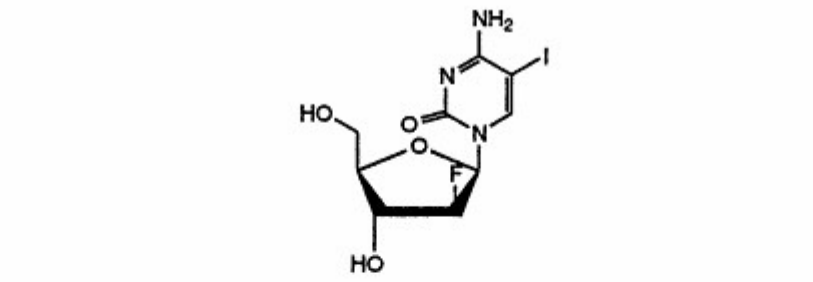
Clinical Trials of FIAC at Memorial Sloan-Kettering Cancer Center

Although the toxic side effects that led to the formation of this Institute of Medicine committee were related to the administration of the drug fialuridine (FIAU), a review of experience with the closely related parent drug fiacitabine (FIAC) is relevant (although it should be emphasized that each of these drugs is a separate chemical entity, and therapeutic efficacy and toxicity need to be studied individually for each). The early trials of FIAC were carried out to a large extent in seriously ill patients suffering from underlying neoplastic disease or immunosuppressive conditions in the early 1980s at the Memorial Sloan-Kettering Cancer Center (MSKC). The following summarizes the available published information and pharmaceutical company summaries on these five trials. This commentary is based solely on the material available in the aforementioned sources; the committee did not review the individual patient records at MSKC.

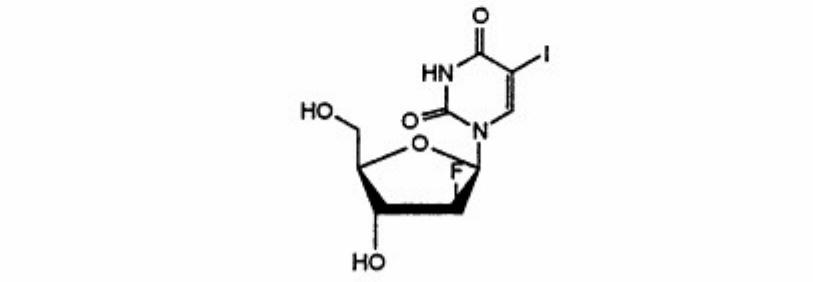
Fiacitabine (FIAC),2'-deoxy-2'-fluoro-l- -D-arabinofuranosyl-5-iodo-cystosine (Figure 1), is a pyrimidine nucleoside analog synthesized by Fox and his colleagues at MSKC in the 1970s. It was found to be highly active in vitro against several of the clinically important human herpes viruses (Lopez, Watanabe and Fox, 1980) and shortly thereafter against hepadnaviruses, inhibiting in its triphosphate form the DNA polymerases of human and woodchuck hepatitis viruses (Hantz, Allaudeen, Ooka, De Clercq and Trepo, 1984). It was studied at MSKC in the early 1980s in the treatment of herpes group (herpes simplex virus [HSV] types 1 and 2, varicella-zoster virus [VZV], and cytomegalovirus [CMV]) infections. Clinical studies were performed under Investigational New Drug application 20,496, and the results were published in several papers in the mid-1980s (Young, Schneider, Leyland-Jones, Armstrong, Tan, Lopez, Watanabe, Fox, and Philips, 1983; Leyland-Jones, Donnelly, Groshen, Myskowski, Donner, Fanucchi, and Fox, 1986) by the MSKC Antiviral Working Group. This group included, among others, a virologist (Carlos Lopez) and the chief of the Infectious Disease Division at MSKC and professor of Medicine at Cornell Medical College (Donald Armstrong).

The rationale for these studies involving compromised hosts was (1) the common and morbidity-producing occurrence of clinically active herpes group viral infections in patients with immunocompromise because of either their underlying disease or immunosuppressive therapy for neoplastic disease and (2) the prior demonstration of potent anti-herpes group virus activity by FIAC in cell culture systems and in mice that had been inoculated with ordinarily lethal doses of HSV-1. Additionally, the availability at the time of only one drug, one with substantial side effects, adenine arabinoside (Ara-A), made these studies of possible therapy

for HSV and VZV infections more cogent. Preclinical toxicological studies indicated that FIAC was well tolerated in short-term dosing experiments in mice; for example, LD50 (the lethal dose for half of the animals) of 1,000 mg/kg/day for 5 days was 10 to 100 times the effective dose range. The antiviral activity was believed to be due to phosphorylation by the pyrimidine nucleoside kinases induced by the virus in infected cells (and then cellular conversion to di-and triphosphates) and subsequent inhibition of virus-encoded DNA polymerases (Lopez et al., 1980).



FIAC: 1-2′deoxy-2′fluoro-1-β-D-arabinofuranosyl 5-iodocytosine



FIAU: 1-2′deoxy-2′fluoro-1-β-D-arabinofuranosyl 5-iodouracil

FIGURE 4-1 Structure of fiacitabine (FIAC) and fialuridine (FIAU).

Pharmacokinetic studies by the mid-1980s (Leyland-Jones, Donnelly, Groshen, Myskowski, Donner, Fanucchi and Fox, 1986) indicated that in humans FIAC was cleared from the blood, after biotransformation in the liver, kidney, and peripheral blood, with a terminal-phase half-life of 1.3 hours after intravenous administration. The principal metabolite is fialuridine (FIAU), 2'-deoxy-2'-fluoro-l- -D-arabinofuranosyl-5-iodo-uracil, which was later shown by high performance liquid chromatography to have a terminal-phase half-life of about 4 hours (Oclassen, 1989). Development of a highly specific and much more sensitive radioimmunoassay for FIAU in 1993 has permitted detection of a very prolonged elimination phase for FIAU in healthy volunteers with a mean elimination half-life of 29.3 hours (Bowsher, Compton, Kirkwood, Place, Jones, Mabry, Hyslop, Hatcher and DeSante, 1994).

After IV administration of FIAC in humans only 12 percent appears unchanged in the urine and 45 percent is excreted as FIAU (Bowsher, Compton, Kirkwood, Place, Jones, Mabry, Hyslop, Hatcher, DeSante, 1994). Small amounts of FAU (1-2'-deoxy-2'-fluoro-l- -D

arabinofuranosyl-5-uracil), FAC (1-2'-deoxy-2'-fluoro-l- -arabinofuranosyl-5-cytosine), and FMAU (1-2'-deoxy-2'-fluoro-1- -arabinofuranosyl-5-methyluracil) have been detected in the urine along with FIAU in other studies, the exact amounts and proportions dependent upon the species. Thus, FIAC and FIAU appear to have a metabolically stable N-glycosyl sugar linkage, leaving deiodination and deamination of the pyrimidine moiety as the major routes of metabolism. Since the termination of clinical trials and the development of the sensitive RIA assay, incorporation of FIAU into DNA, which implies conversion to FIAU-triphosphate, has been observed in spleen, liver, pancreas, jejunum, heart and skeletal muscle, although it was time, species and tissue dependent. Attempts to determine if FMAU and FAU were present in DNA with high concentrations of FIAU have been inconclusive. See Chapter 13 for further information on mechanism of action.

PHASE I EVALUATION OF FIAC IN IMMUNOSUPPRESSED PATIENTS WITH HERPESVIRUS INFECTION

This trial (Young, Schneider, Leyland-Jones, Armstrong, Tan, Lopez, Watanabe, Fox, and Philips, 1983) involved 32 immunocompromised patients (30 with leukemia, lymphoma, or solid tumors and 2 with AIDS) who had active herpes group virus infections (29 were infected with VZV, 3 were infected with HSV) that had shown clinical progression in the previous 48 hours. None of the patients received myelosuppressive therapy concurrently, but 10 percent of them had received cytotoxic chemotherapy or radiation within 21 days prior to entry into the study. Hematologic abnormalities were not considered as exclusionary grounds since herpes group virus infection in such patients with neoplastic disease commonly involves pancytopenia. The institutional review board of MSKC approved the study design and consent procedures, and signed informed consents were obtained from all participants (or a responsible guardian in the case of children). The median performance (Karnofsky) score status of the study patients was only 60 and the principal justifications offered for a clinical trial involving such poorly performing patients were that the study was being carried out before the approval of acyclovir for the treatment of such patients and that FIAC showed minimal toxicity at therapeutic doses in the murine HSV model system.

The design was one of an acute study; dosing of patients was at 60, 120, 240, 400, or 600 mg/m^2/day (two divided doses) IV for 7 days in a dose escalation sequence. Cessation of progression of lesions occurred within 48 to 72 hours (followed promptly by healing) in all 24 patients who entered the FIAC trial without visceral dissemination and who received FIAC at > 120 mg/m^2/day. Spread of disease was not observed in patients with initially localized disease. In patients who had pain before therapy, improvement was noted within 48 to 96 hours. Only two patients developed postherpetic neuralgia, and both had locally advanced zoster with evident sensory nerve involvement before entry into the study. Two patients, both with visceral dissemination of VZV at the time of entry into the study, received the ineffective dose of 60 mg/m^2/day and died of multisystem failure on days 6 and 15 of the trial (autopsy information was not provided). Only one patient had recrudescent zoster after the completion of 7 days of FIAC treatment. The three patients with HSV-1 or HSV-2 infection who entered the study had visceral involvement, and all three patients died. In two patients follow-up viral

cultures became negative within 4 days, but they died of their underlying diseases. The third patient with presumed systemic HSV infection showed no new skin lesions after 96 hours of FIAC therapy but died of respiratory insufficiency on the final day of treatment (an autopsy was not performed). The patients in this trial were severely ill, as indicated by their poor Karnofsky scores. In addition, those patients with visceral involvement were particularly ill, and as a consequence their deaths were not unexpected.

The investigators reported that FIAC was generally well tolerated. At the highest dose levels used, the most common side effects were mild to moderate nausea (10 of 13 patients) and vomiting (7 of 13 patients). The second toxicity was myelosuppression, specifically, decreases in both white blood cell (WBC) and platelet counts under FIAC treatment. Nadirs in the WBC count ranged between 60 and 90 percent of normal, but consistent leukopenia was not seen at any dose. A mild but consistent platelet depression (mean level at a nadir of 42,000) was noted at a dose of 600 mg/m^2/day. These indications of myelodepression were attributed to FIAC since it was observed in patients who had received no other myelosuppressive therapy.

Comment

The rationale and design of the study were reasonable, and the justification for a trial involving immunocompromised patients with VZV (a group at high risk for disseminated infection) deemed acceptable. A therapeutic benefit was shown in the treatment of VZV infections in immunosuppressed cancer patients with FIAC at a dose of 400 mg/m^2/day IV for 7 days. The toxic side effects noted were mild hematopoietic depression (decreases in WBC and platelet counts).

The nature of the trial, with only a short-term follow-up, seems reasonable in view of the short course of infection and what was known at the time about the side effects of this class of drugs. Five deaths occurred among the 24 patients without visceral involvement at the time of entry into the trial. Deaths ascribed to multisystem failure (on the sixth day of treatment and 8 days after completing treatment) occurred in two patients whose VZV infection spread to the viscera and appear likely to have been due to the extensive nature of the viral infections. Two other patients, with HSV infections, died of their underlying diseases after their viral cultures had become negative within 4 days of initiating treatment with FIAC. The fifth death occurred in a patient with presumed systemic VZV infection (skin, esophagus, pulmonary infiltrates) in whom treatment with FIAC was begun on the eighth day of VZV infection. No new skin lesions appeared after 96 hours of therapy, but the patient died of respiratory insufficiency on day 7 of treatment. Autopsies were apparently not performed on any of these patients, and it is not possible to know whether hepatic microsteatosis had developed. From the available limited clinical descriptions it is not possible to ascertain whether lactic acidosis (or an anion gap acidosis) developed terminally. However, it seems to the committee that there were no clear indications in these short-term trials of the type of toxicity that was to develop in 1993 in the trial of chronic dosing with FIAU in the treatment of chronic hepatitis B virus infection.

PHASE I STUDY OF AIDS PATIENTS WITH PRESUMPTIVE OR PROVEN HERPESGROUP VIRUS INFECTION

Eleven patients with AIDS were treated in this study for probable opportunistic herpes group virus infections with FIAC (200-600 mg/m^2/day given IV for up to 7 days)(Oclassen Pharmaceuticals, Inc., 1989; Gold, Leyland-Jones, Urmacher and Armstrong, 1984).

Six very ill patients (Karnofsky scores of 20-50) with a variety of opportunistic infections and one patient with Kaposi's sarcoma (Karnofsky score of 90) and perirectal HSV infection were treated with FIAC. Clinical improvement or resolution was observed during FIAC treatment of several patients with HSV infection and one patient with CMV pneumonia. However, five patients died within 15 days (four patients died within 6 days) of initiating therapy. Confusion, lethargy, tremulousness, myoclonic jerking, and/or seizures were observed after the receipt of 5 to 10 FIAC doses in three patients. These neurologic findings cleared within 2 days of omitting FIAC. Acute hypotension, pulmonary edema or pulmonary infiltrates, and/or renal failure also developed in three patients during therapy (or within 2 days of its completion). At autopsy these three patients had disseminated CMV disease (frequently accompanied by *Pneumocystis and Mycobacterium avium* infections). Two patients developed neutrophil counts of <<1,000/mm^3, and one patient developed thrombocytopenia (20,000/mm^3). Three of the five patients for whom data were available had aspartate aminotransferase (AST) increases of >300 IU/liter.

Another four patients with AIDS and Kaposi's sarcoma were treated with FIAC (600 mg/m^2/day) at a time (1984) when CMV was believed to have a possible direct etiologic role in producing this neoplasm. FIAC was well tolerated without significant leukopenia, thrombocytopenia, or neurologic complications in these patients with Karnofsky scores of 70-90.

Comment

Significant neurologic complications were observed in three patients, and pulmonary complications were observed in five patients. The resolution of the neurologic findings within 2 days of discontinuing FIAC treatment suggests a drug-related side effect. Neurotoxicity had not been observed in any of the 80 other patients with cancer treated previously for HSV, CMV, or VZV infections.

The pulmonary complications or sudden clinical deterioration observed in five patients may have reflected the natural course of their AIDS-associated infections. However, the severity of the deterioration in previously stable patients and the temporal relation of this toxicity with FIAC administration were evident and led the investigators to think that FIAC was responsible. Although several infectious agents (*P. carinii, M. avium-intracellulare*) were responsible for the pneumonias, in all autopsied patients widespread infection with CMV was present. The possibility that FIAC therapy might be associated with worsening of CMV pneumonia was raised by the investigators. They felt that the temporal relationship between FIAC treatment and the neurologic and pulmonary complications noted in this trial warranted caution in undertaking antiviral therapy in patients with AIDS.

As in the other MSKC studies of FIAC, evidence of some marrow suppression, primarily in the sickest patients, was observed. In the sickest patients with systemic opportunistic infections (often multiple), significant elevations in AST levels occurred, but the relative contributions of the infections and of FIAC are difficult to sort out. The committee has found no mention in the publications describing these patients of microvesicular steatosis in the livers of the patients who died. The neurologic and pulmonary complications noted in these patients with AIDS treated with FIAC appear to be different than the hepatotoxicity and pancreatitis later noted in patients with hepatitis B virus infection treated with FIAU.

PHASE I STUDY OF FIAC IN BONE MARROW TRANSPLANT PATIENTS WITH HERPESGROUP VIRUS INFECTIONS

This unpublished study, carried out by members of the Antiviral Working Group of MSKC, involved 15 bone marrow transplant (BMT) recipients who received 60-400 mg of FIAC per m^2 IV daily for complicating VZV or CMV infections (Oclassen Pharmaceuticals, Inc., 1989). Five patients received 120-200 mg/m^2/day for 5 to 7 days for the treatment of cutaneous or visceral disseminated VZV. All five patients had good initial responses. In two of those with VZV, recurrence of lesions occurred immediately posttreatment, and retreatment was successful. The other 10 patients were treated for proven or probable CMV pneumonitis. Two patients were moribund on respirators and died after receiving only one or two doses of FIAC. The remaining patients were very seriously ill (pretreatment Karnofsky scores of 20-40, except for one patient with a score of 70). Modest clinical or radiological improvement was observed for 3 to 5 days in three patients after starting FIAC (120-800 mg/m^2/day for 5-14 days), but the clinical course was progressively downhill; death supervened in 6-20 days following the cessation of treatment in 9 of the 10 patients. Transient improvement in retinitis occurred in one patient, but death was due to disseminated CMV infection. Another patient died on the 12th day after completing therapy and had disseminated CMV disease which included brain involvement. In two patients receiving 300-400 mg of FIAC per m^2/day, sudden hypotension and pulmonary edema occurred after 9 and 14 doses had been administered respectively. In the one surviving patient in the group with CMV infection, urine cultures became negative after treatment, but a lung biopsy showed only adenovirus and *P. carinii* infection, casting doubt on the original diagnosis of CMV infection.

Hematologic and liver function parameters were followed in these 15 study participants. Three VZV patients with well-established grafts (and another treated within 4 weeks of engraftment) did not have clinically significant drops in WBC or platelet counts. Of the eight patients with CMV infections who received more than two doses, six had well-established grafts when they were treated with FIAC. Depression in WBC counts occurred in all of these patients, but in only one of them was the neutropenia <<1,000 cells/mm^3. This patient was one with severe graft-versus-host hepatitis in whom platelets also dropped from 39,000/mm^3 to 3,000/mm^3 eight days after completing 10 doses of FIAC (300 mg/m^2/day). This patient died of a massive gastrointestinal hemorrhage. In four of the remaining five patients platelet counts dropped to less than 20,000/mm^3 from pretreatment levels of 28,000-97,000/mm^3

Increases in AST levels of at least 50 IU/liter occurred in 5 of 13 patients completing treatment (1 with VZV and 4 with CMV), and 8 of 13 patients had bilirubin increases of >1 mg/dl.

Comment

The patients with VZV infection appeared to respond to FIAC at the dosage used, but two patients had relapses and required retreatment. Response to FIAC in patients with CMV infection was more problematic, since these patients were severely ill on entering the trial (Karnofsky scores of 20-40) and only one patient survived beyond 21 days of beginning treatment. The principal side effects noted were drops in WBC and platelet counts, but baseline levels in these BMT recipients were already low. Increases in AST and serum bilirubin levels were noted in more than one-third of the patients, but these were not dose related. It seems likely to this committee that the putative explanations offered for the liver function abnormalities, that is, graft-versus-host disease or CMV hepatitis, were correct in view of the fact that all but the immediate postengraftment patients were already receiving suppressive therapy with steroids for this and in view of the autopsy-confirmed CMV hepatitis in three patients.

PHASE I ORAL DOSE RANGING FIAC STUDY IN IMMUNOCOMPROMISED PATIENTSWITH VZV AND HSV INFECTIONS

This study of oral FIAC therapy in 26 patients with VZV or HSV infections was carried out at MSKC by members of the Antiviral Working Group (Oclassen Pharmaceuticals, Inc., 1989; Fanucchi, Leyland-Jones, Young, Burchenal, Watanabe, and Fox, 1984). All of these patients had underlying neoplastic disease (n = 24), principally hematologic or lymphoproliferative, or AIDS (n = 2). Localized zoster was present in 17 patients, another 7 had cutaneous dissemination, 1 patient had visceral involvement (hepatitis) in the course of disseminated disease, and in 1 patient HSV infection was disseminated on the skin.

Initial dosing was 100 or 1,000 mg/m^2 orally twice daily in 11 patients. Nausea and vomiting followed dosing in 9 of the 11 patients, and this led to decreased but more frequent daily dosing: 11 patients received 30, 90, or 150 mg/m^2/day in aliquots three times daily. Nausea and vomiting occurred in two of five patients taking 150 mg/m^2 daily. Among the six patients taking the lower daily doses only three reported mild nausea and rarely required antiemetics.

The response of VZV infections to oral FIAC therapy was excellent, and no new cutaneous lesions were observed after 72 hours of therapy in 24 of 26 patients. One patient receiving 30 mg/m^2/day continued to have cutaneous progression through the fourth day of therapy.

The toxicity observed in this oral trial, like that in the prior IV trials, primarily involved the hematopoietic system. In 15 patients receiving the higher doses the median WBC count dropped 30-50 percent and the median platelet count dropped 15-40 percent of the baseline

values. One patient with disseminated VZV infection and hepatitis had a baseline AST level of 63 IU/liter, which rose to 395 after 3 days of FIAC at 150 mg/m^2/day given orally, and then rapidly declined while treatment was continued for the rest of the 7-day course of treatment.

Comment

Dosing with FIAC orally was limited to less than 200 mg/m^2/day because of nausea and vomiting. The response of VZV infection to FIAC at 30 to 200 mg/m^2/day was excellent. The main toxicity was mild to moderate, but temporary, leukopenia and thrombocytopenia. In addition, elevated AST levels were observed in one patient who entered the study with VZV hepatitis.

PHASE I/II TRIAL OF FIAC EFFICACY IN IMMUNOSUPPRESSED PATIENTS WITHVZV INFECTION

This trial, the results of which were reported by Leyland-Jones, et al (1986) involved 34 immunosuppressed individuals (advanced malignancy or severe immunodeficiency associated with lymphoproliferative disease or cancer) who developed recurrent infection with VZV and who had shown progression of viral lesions in the 24 hours before entering the study. Study entry required a serum creatinine level of <2.0 mg/dl, but there were no limitations of age, hepatic function, or blood counts. The rationale for this study was the significant incidence of dissemination (7-26 percent in several Series) in patients with such underlying disease and the life-threatening nature of these infections with visceral involvement.

The trial was designed as a randomized, double-blind comparison of FIAC with Ara-A, a drug which had been standard therapy for VZV infections in immunosuppressed patients. Patients were stratified by spread of disease (local, disseminated or visceral) and delay to treatment (≤72 or >72 hours). FIAC was administered for 5 days at a dosage of 400 mg/m^2/day IV, and Ara-A was given IV at a daily dosage of 400 mg/m^2.

Results were evaluable for 31 of the 34 subjects. In those subjects treated with FIAC the clinical response was superior to the response with Ara-A: the median time to formation of the last new vesicle was reduced by approximately 3 days, crusting occurred in a significantly greater proportion of patients within the first 72 hours after the initiation of treatment, the disappearance of pain occurred earlier, and the cutaneous dissemination of zoster occurred less frequently (in 0 of 17 patients receiving FIAC versus 2 of 16 treated with Ara-A).

FIAC produced few toxic reactions in this study, and all were judged to be mild. Fatigue (evaluated on the fourth day of treatment) was noted in 57 percent of those receiving FIAC, and this figure did not differ significantly in those receiving Ara-A. More nausea and vomiting occurred in those receiving FIAC, but the difference was not statistically significant. Hematologic changes observed in the first FIAC trial were again observed, but the median decreases in WBC (37.5 percent) and platelet (42 percent) counts observed did not differ significantly from the decreases observed in the patients receiving Ara-A. Changes in serum

bilirubin, alkaline phosphatase, and creatinine levels also did not differ statistically between the two treatment groups. However, a transient rise in AST levels was observed in 54 percent of those treated with FIAC and in only 14 percent of those receiving Ara-A (P = .046).

Comment

The clinical response of VZV infection to FIAC was better than the response to Ara-A, the available drug therapy at that time. The toxic side effects noted included nausea, vomiting and fatigue, but their frequency in FIAC-treated patients did not differ statistically from that in those receiving Ara-A. However, a transient rise in AST levels was significantly more frequent (P = 046) among those receiving FIAC than those receiving Ara-A. Overall, the toxic reactions were considered mild.

SUMMARY OF ALL THE FIAC CLINICAL STUDIES AT MSKC

FIAC orally given or IV had a beneficial effect in the treatment of VZV infections. Its efficacy against CMV was unclear because of the uncertainty of the diagnosis in many patients and the steady downhill course of many of the seriously ill patients. Toxicity appeared to be manifested primarily as hematopoietic suppression and a mild elevation in AST levels. However, in several severely ill patients with AIDS acute, reversible neurotoxicity developed during FIAC administration. Such toxicity was not observed in treatment groups with underlying neoplastic disease. The pulmonary complications, clinical deterioration, and deaths occurring in the group of patients severely ill with AIDS (and multiple opportunistic infections, including CMV) were temporally related to FIAC therapy. Whether IV administration of FIAC may have contributed to any of the acute deaths in the study cannot be determined from the available information; the underlying disease with disseminated superimposed infections in these ill patients may have been the main factor in the demises. Since dosing was only for short periods in these trials, the potential for toxicity with long-term use would not have been discernible. However the IV doses of FIAC used were very high compared with those used orally in later trials (see the section below on the Oclassen R-89-001 trial). The extremely high dose may be relevant, despite the short course of therapy, in view of what is now known of the long half-life of the principal metabolite, FIAU.

Further clinical trials of FIAC were not carried out at the time, probably because of the emergence of an effective, relatively nontoxic nucleoside analog (acyclovir) for the treatment of HSV and VZV infections. Thus, the return to clinical study of FIAC in 1989 (R89-001-01: Efficacy and Safety of Oral FIAC in AIDS Patients with Cytomegalovirus Infection—A Dose Ranging Study) under the sponsorship of Oclassen Pharmaceuticals seems to have been reasonable in view of the drug's in vitro activity against CMV (an important viral infection in patients with HIV infection and for which there was need of effective oral antiviral drugs).

5

Oclassen Clinical Trial R89-001-01

This study was originally conceived in July 1989 to evaluate the effects of fiacitabine (FIAC), administered orally, for the treatment of cytomegalovirus (CMV) infection in human immunodeficiency virus-positive individuals. The study was developed by Oclassen Pharmaceuticals in conjunction with the AIDS Clinical Trials Group (ACTG) of the National Institute of Allergy and Infectious Diseases (NIAID). CMV is an important pathogen in immunocompromised patients such as those with HIV infection and solid-organ transplant recipients (Chazouilleres and Wright, in press). CMV is the most common infectious pathogen in HIV-positive patients, with the most frequent manifestation being chorioretinitis (occurring in 25-30 percent of patients) (Smith and Brennessel, 1994).

The prevalence of CMV disease following liver transplantation without antiviral prophylaxis is 15-41 percent (Chazouilleres and Wright, in press). Clinical manifestations include fever, malaise, arthralgias, pancytopenia, hepatitis, pneumonitis, gastrointestinal ulcerations, and chorioretinitis. Disseminated CMV disease is rare (occuring in less than 5 percent of those with CMV disease), but is ominous when it occurs since it is usually fatal (Chazouilleres and Wright, in press).

The drugs used to treat established CMV disease in HIV-positive patients include acyclovir, foscarnet, and ganciclovir. Ganciclovir has been used with the most success. Ganciclovir is a synthetic nucleoside analog of deoxyguanosine, which inhibits the replication of herpes virus both in vitro and in vivo (Matthews and Boehme, 1988). In CMV-infected cells, ganciclovir is phosphorylated and the metabolite inhibits viral DNA synthesis by competitive inhibition of viral DNA polymerase with direct incorporation into viral DNA and the resultant termination of viral DNA elongation (Erice, Jordan, Chace, Fletcher, Chinnock and Balfour, 1987). Foscarnet is another drug that has been proven to be effective against CMV (Smith and Brennessel, 1994). At the time that this protocol was developed, ganciclovir, which requires intravenous administration, had just become licensed; foscarnet, another intravenous drug with anti-CMV activity, was just beginning Phase II clinical trials. The need to identify an effective oral drug to treat CMV disease in this patient population was one of the most important scientific priorities of the ACTG.

FIAC was a promising drug. It demonstrated reasonable in vitro activity against CMV and excellent oral bioavailability. In July 1989, draft protocols designed to study the anti-CMV activity of FIAC were developed and circulated through several ACTG committees, including the CMV Pathogen Study Group, the Opportunistic Infection Core Committee, as well as the

NIAID Medical Branch and the Food and Drug Administration (FDA). The final protocol was established in October 1989.

The study was to be conducted at two clinical sites, the University of California at San Diego (Douglas D. Richman, principal investigator), and the University of Washington in Seattle (Lawrence Corey, principal investigator). Richman is an established investigator who has extensive experience in the study of antiviral agents used in the treatment of other herpes virus infections, such as herpes simplex virus types 1 and 2. He also is an established bench virologist with special interest in the pathogenesis of herpes virus infections. Richman was one of the lead investigators in the original studies that demonstrated the benefit of azidothymidine (zidovudine) in advanced HIV disease. On the basis of his experience investigating both herpes-related viruses and HIV, he was well suited to study the effects of a novel nucleoside agent such as FIAC in the treatment of HIV-associated CMV disease. Corey, likewise, is a clinician-scientist who has extensive experience studying herpes-related viruses in the laboratory as well as experience studying the use of nucleoside agents in the treatment of both herpes virus infections and HIV. Corey also had participated in the seminal studies of zidovudine for advanced HIV disease and was one of the lead investigators in studies which evaluated vidarabine and acyclovir for the treatment of herpes virus infections. Early in the HIV epidemic, Corey became established as one of the leading investigators in the treatment of AIDS-related diseases, and at the time that this protocol was being developed, he had assumed the primary leadership position within the ACTG as chair of its Executive Committee, which was responsible for oversight of the group's scientific effort.

FIAC study R89-001 (ACTG 122A) was a Phase I/II clinical trial designed to evaluate, simultaneously, the safety and relative anti-CMV activity of FIAC at doses of 0.6, 1.0, 1.7, 3.0, and 5.0 mg/kg/day given orally (roughly equivalent to the doses that MSKC found to be effective against VZV, assuming an average patient weight of 60 kg and a skin surface area of 1.3 m^2). Patients with documented CMV viremia or viruria were to be entered successively into the treatment groups in an open-label fashion. A total of six patients had to have completed 14 days of therapy, with at least half of them having met protocol-defined tolerance criteria before patients could receive the next dosage level. Patients were of both sexes, but all were HIV infected and had CD4 counts of 500 cells/mm^3 or less and CMV had been documented in either their blood or urine. All patients were followed for a total of 3 months, according to the protocol. The principal end points were the development of a negative CMV culture and tolerability of the drug.

On October 12, 1989, the study investigators, Oclassen Pharmaceuticals (which held the investigational new drug [IND] application), representatives from FDA, and other experienced virologists, including Carl Johnson and Richard Whitley, met to discuss the protocol. It was agreed to limit this study to a total of 4 weeks of therapy on the basis of the fact that data from animal toxicity tests of more than 90 days' duration were not available. The protocol received full institutional review board (IRB) approval at both sites plus a review and approval at the Veterans Administration Hospital at San Diego. Informed consent documents (ICDs) were also reviewed by these IRBs and were judged to be in compliance with national standards. The ICDs included a description of the potential known toxicities of FIAC, including bone marrow dysfunction, gastrointestinal disturbances, neurologic events (such as mental status changes and

seizures), and potential infertility. Appendix D contains copies of these ICDs and the ICDs from all of the FIAU trials.

One of the most striking features of this study was in the implementation of a novel mechanism of data and safety evaluation. On the basis of the experience of the two principal investigators in the development of other HIV-related therapeutic agents, such as zidovudine and zalcitabine, the investigators proposed a real-time data tracking system that employed transmission of laboratory and clinical event safety data to the study sponsor (Oclassen) via fax. Within a week after arrival at Oclassen, updated composite data summary sheets, compiled on a patient-by-patient basis, were faxed to all parties involved in the development of the protocol, including site investigators and coinvestigators, representatives from Oclassen, virology consultants (Johnson and Whitley), the NIAID Medical Officer (Judith Feinberg), and representatives from the FDA (Sandra Kweder and Bob Schnur). These faxed data summaries were followed by conference calls, held every 2 to 3 weeks. During these calls all new data were discussed, trends in the data were reviewed, and potential study changes and amendments were proposed and implemented. This data review process was used for both the R89 and the R90 studies, yielding a total of 92 distributed summaries (see Appendix E for an example) and approximately 30 conference calls. These procedures were not meant to supplant the usual adverse event reporting mechanisms or the 100 percent monitoring of all study charts performed by Oclassen. In addition to the fax data summaries and conference calls, the interim results and protocol amendments were reviewed and approved by the ACTG Viral Pathogen Study Group and the ACTG Opportunistic Infection Core Committee. Therefore, data safety review was conducted both internally among the study team and externally through an independent peer review process for both the R89 and R90 studies. Between October 1989 and March 1990, 10 patients were enrolled at the University of California, San Diego, study site. Several episodes of gastrointestinal side effects, predominantly nausea, as well as fatigue were noted in several patients receiving doses of 1 mg/kg. One patient had an asymptomatic elevation in the levels of creatine phosphokinase (CPK), a muscle enzyme, indicating potential muscle injury. In April 1990, *patient 105* died of bacterial pneumonia 40 days after receiving the last dose of FIAC. Because of the difficulty in distinguishing clinical adverse experiences caused by drug versus those caused by the underlying disease, on April 16, 1990, the protocol team modified the study to allow only patients with CD4 counts of >200 cells/mm^3 to be entered. Two patients, the first of whom developed fatigue and gastrointestinal symptoms, were enrolled at the University of Washington study site. Thereupon it was decided that, should additional patients develop significant symptoms, the study would be stopped. By mid-May, increasing reports of nausea and vomiting among study participants were noted, with no demonstrable anti-CMV effect, even at the 1.7-mg/kg dose level. At this point the study team recommended discontinuation of the development of FIAC as an anti-CMV drug and the study was stopped.

Three other patients died within 6 months of their last FIAC dose. *Patient 103* died of AIDS-related Kaposi's sarcoma, and FIAC was not considered a causative factor. *Patient 110* developed significant peripheral sensory-motor polyneuropathy, attributed to either HIV or CMV infection, shortly after finishing his last FIAC dose. His neurologic abnormalities were

complicated by multiple renal and electrolyte disturbances, and he died approximately 9 weeks after receiving his last dose of FIAC. Neither the investigators nor the 1993 FDA task force believed that this death was related to FIAC. *Patient 107* was an individual with a history of hepatitis B virus infection and previous intravenous drug use. During his treatment with FIAC, he exhibited a minor elevation in transaminase levels and a slight elevation in CPK levels. Seven weeks after completing FIAC dosing, the patient was hospitalized with nausea, vomiting, and fatigue. Clinical chemistry evaluation revealed persistent elevations in AST/ALT levels (five to eight times baseline). He was taking zidovudine, methocarbamol, and amitriptyline, all of which were discontinued upon admission. The patient developed progressive hepatic failure, ascites, intrahepatic cholestasis, and, ultimately, hepatorenal syndrome and death 11 weeks after receiving his last dose of FIAC. Autopsy revealed hepatocellular necrosis, fatty metamorphosis, and cholestasis. The investigators concluded that this patient died of underlying disease or possibly drug-induced hepatitis because of amitriptyline or zidovudine. The 1993 FDA task force concluded that the death of this patient should, in retrospect, possibly be considered attributable to FIAC therapy.

COMMENT

Several features of this study are noteworthy. First, the study was carefully designed, with staggered patient enrollment and classic Phase I dose escalation. Second, the preclinical data and study design were reviewed prospectively and were approved both internally by the investigators and the sponsor and externally by several committees within ACTG and FDA. Most importantly, a real-time data assessment was performed via weekly faxed composite data summaries which were discussed by the investigators and sponsor during frequent conference calls. Although FDA was included on the list of fax recipients, the reviewers apparently found this level of uninterpreted raw data unhelpful (Feigel, 1994). The conference calls enabled the study team, however, to rapidly modify the protocol on the earliest indications of symptoms or possible antiviral activity. This process led to the determination of the maximum tolerated dose in humans after only 12 patients had been enrolled. Although this approach to real-time data assessment was relatively novel at the time that the trial was initiated, it has since been utilized in many Phase I studies and, ironically, is precisely in keeping with the changes to the Code of Federal Regulations recently proposed by the FDA, requiring semiannual reviews of composite safety data. In this study these data were reviewed approximately every 3 weeks.

With regard to patient deaths, three of the four patients who died within 6 months of the termination of FIAC were victims of HIV-related complications. The fourth patient, patient 107, died 11 weeks after receiving his last dose of FIAC. The 1993 FDA task force report classifies this case as one in which FIAC treatment should be considered a possible cause of death, but even in retrospect, although FIAC may have contributed to the observed liver failure, the confounding variables of CMV, hepatitis B and continuing treatment of HIV with zidovudine clearly preclude unequivocal classification of this death.

6

Oclassen Clinical Trial R90-001-01 (NIH Protocol 91-AI-0031)

Once they had determined that the maximum tolerated dose (MTD) of FIAC was without any significant effect on cytomegalovirus (anti-CMV), the investigators hypothesized that minor metabolites of FIAC might be responsible for the toxic effects associated with the drug, particularly the nausea, vomiting, and fatigue. The in vitro anti-CMV activity of the major metabolite, FIAU, was virtually identical to that of FIAC, allowing the possibility of finding a dose of FIAU which would inhibit CMV while producing fewer or less severe adverse effects than FIAC. Acute single-dose animal toxicity data were available demonstrating normal transaminase levels in rats and only minimal elevations in cynomolgus monkeys (see Appendix F for details). Results of multiple-dose studies done in rats (28 days) and dogs (10 days) were available, but long-term dosage studies in animals had not been done as yet. As a result the investigators planned a traditional Phase I, dose-escalating study of FIAU, with the emphasis being placed strictly on safety and not anti-CMV activity. Therefore, patients were no longer required to have CMV in their blood or urine to be eligible for participation in the study. This allowed human immunodeficiency virus (HIV)-infected patients with higher CD4 counts to be entered into the trial.

The development of R90-001-01 was very similar to the development of R89. Multiple meetings and conference calls within the AIDS Clinical Trials Group system reviewed draft protocols, including reviews by representatives from the Medical Branch of the National Institute of Allergy and Infectious Diseases (NIAID) and the Food and Drug Administration (FDA). The protocol was originally designed to establish FIAU as a potential anti-CMV drug. HIV-infected patients were to receive FIAU syrup three times daily at dosages of either 1.0, 1.7, 3.0, or 5.0 mg/kg/day. Cohorts of 10 patients each were to be enrolled successively in each dosage group, beginning at the 1 mg/kg/day dosage.

During protocol development, several reviewers suggested evaluating the potential role of FIAU in the treatment of hepatitis B virus (HBV) infection, citing the potent in vitro activity of both FIAC and FIAU against HBV (Hantz, Allaudeen, Ooka, De Clercq and Trepo, 1984). FIAC also had been shown more effective than Ara-A in reducing circulating viral DNA in woodchucks infected with a HBV closely related to that infecting man (Fourel, Hantz, Watanabe, Jacquet, Chomel and Trepo, 1990). By mid-August, an amendment was created (Amendment 1) which allowed investigators to enroll HBV infected persons after an initial cohort of non-HBV infected individuals had been enrolled. Based on the knowledge that patients with chronic HBV infection often have chronic elevations in their liver enzymes, Amendment 1 also changed the AST entry criterion to allow patients with up to 5 times the

upper limit of normal (from 1.5 times) to be enrolled into the study. The amendment also inserted 1-week and 4-week posttreatment follow-up clinical chemistry evaluations to capture any posttreatment flares that might occur in the HBV-treated patients. These flares are characterized by development of a several fold elevation in transaminase levels concomitant with successful inhibition of HBV DNA and may occur several weeks after termination of drug therapy.

The protocol was reviewed by the IRBs at the University of Washington and the University of California, San Diego and was approved by both. During this review the ICD was evaluated and judged to be in compliance with national standards. The possibility of gastrointestinal disturbances, bone marrow toxicity, neurologic toxicity (including confusion and seizures), and cardiac toxicity, which was noted in animal studies, were all mentioned in the ICD (Appendix D). The possible development of polymyositis, an issue not raised in the FIAC (R89) ICD, was explicitly mentioned in the R90 ICD on the basis of the reversible myositis seen in the FIAC study. Faxed weekly summary data and interim conference calls (every 2 to 3 weeks) were used throughout the R90 study. In addition, as with the R89 study, Oclassen periodically visited the study site to review the charts of study patients.

The first 10 patients in this study were enrolled at the University of Washington site (initial dosage 1 mg/kg/day), with the first patient receiving drug in October 1990. These patients completed treatment without significant clinical adverse experiences. Therefore on the basis of the protocol, the dose was escalated to 1.7 mg/kg/day. The first patient receiving this higher dose experienced nausea and fatigue. The next patient who received this dose also developed significant gastrointestinal symptoms and fatigue. This information was shared with the rest of the study team via fax memorandum, and a conference call was convened to discuss these issues. It was determined that, should a third patient experience similar symptoms at this dosage level, further enrollment in this study at dosages higher than 1 mg/kg/day would cease. Patient 214, who was enrolled on April 19, 1991, became the third patient to develop gastrointestinal intolerance, and it was determined that no further patients should be enrolled in this study. As a result of this close monitoring system, the MTD of FIAU was determined with only 13 patients enrolled in the study.

It was now clear that neither FIAC nor FIAU would ever be developed as an effective anti-CMV drug. There was no evidence of anti-CMV activity even at doses associated with clinically significant gastrointestinal symptoms. However, on the basis of the known in vitro anti-HBV activity of the compound, the team decided to further pursue the role of FIAU in patients coinfected with HIV and HBV.

During the months that the first 13 patients were being accrued into the R90 study, Stephen Straus at the Intramural Research Division of NIAID had submitted the R90 protocol to the NIAID IRB. The IRB carefully reviewed the protocol, and in November 1990, after Straus responded in writing to all of the board's stipulations, the NIAID IRB approved the protocol for implementation at the National Institutes of Health.

Stephen Straus is Chief of the Laboratory of Clinical Investigation, Medical Virology Section of NIAID at the Bethesda, Maryland, campus of NIH. Like Douglas Richman and Lawrence Corey, Straus had been integrally involved in the development of drugs designed to treat human herpes virus infections, such as vidarabine and acyclovir. Straus is also a bench research scientist with special interest in the pathogenesis of herpes simplex virus disease. As

a member of the NIH staff, he has participated in dozens of clinical studies and was well qualified to lead the R90 study at the NIH.

With the new focus on potential anti-HBV activity and reduced dosage of FIAU (a maximum of 1 mg/kg daily), the first patient enrolled at NIH (patient 401) began treatment on April 16, 1991. In less than 2 weeks, a marked decrease in the patient's serum HBV DNA polymerase level was noted. This information was reported to all other investigators via fax. At this dose the drug showed similar activity in three additional patients. When the results were reviewed during the conference call, the investigators agreed that this was the most striking effect on HBV they had ever seen. On the basis of the anticipated need to administer prolonged therapy to patients with chronic HBV infection and the knowledge that the 1 mg/kg dose was close to the MTD, the investigators decided to convert the trial into a dose de-escalating study, to find the lowest dose still effective against HBV. Therefore, the next cohort entered into the study would receive a dose of 0.5 mg/kg and the final group would receive a dose of 0.1 mg/kg, 1/10th of the original dose. It was anticipated that cohorts of approximately 10 to 12 patients per dose group would be enrolled. All of the early HBV data and the decision to convert the study into a dose deescalation design was reviewed by the Viral Pathogen Study Group of ACTG and by the Antiviral Drug Division of the Food and Drug Administration. Both concurred with the decision to continue studying the drug as an anti-HBV agent in this fashion.

Throughout the remainder of 1991 and into the spring of 1992, several interim reviews were undertaken by the IRBs at all three participating institutions via requisite status reports submitted for routine review as well as through review of the amendments required to establish the dose deescalation component of the study. By June 15, 1992, the last HIV-positive, HBV-positive patient was entered into the 0.1 mg/kg dose cohort, and by June 29 the last dose of FIAU in study R90 was administered. In total, 4 of the 43 patients were enrolled at UCSD, 25 patients were enrolled at the University of Washington (12 non-HBV infected and 13 HBV-infected), and 14 (all HBV-infected) patients were enrolled at the NIH Clinical Center. Striking reductions in circulating HBV DNA levels were noted in most patients, with the majority of patients showing decreases in their circulating HBV DNA levels to less than the lower limits of the measurement technology. More importantly, the level of virus remained suppressed for up to 4 to 6 weeks after the drug was discontinued. The experience with other nucleoside analogs such as vidarabine resulted in only a partial reduction in circulating HBV DNA levels and rapid reversal upon cessation of the drug. As such, FIAU represented the most potent anti-HBV agent studied to date.

On the basis of these findings, the protocol was modified to allow retreatment, for an additional 14 days, of four patients who displayed recrudescence of DNA polymerase levels following their initial treatment. The length of follow-up after drug was stopped was 4 weeks.

Several patients in the R90 study developed elevations in liver function enzyme levels while on treatment. Most notably, *patients 216, 221,* and *224* exhibited two- to three-fold elevations in transaminase values in the second or third week of the study. All three of these HIV-positive individuals had coinfection with HBV; two of the patients (patients 221 and 224) had received the lowest dose of drug (0.1 mg/kg/day), while the third patient (patient 216) received an intermediate dose of 0.5 mg/kg/day. In each of these individuals, no clinical signs

of hepatic dysfunction were noted and the increases in transaminase levels in liver function tests were interpreted as flares associated with the clearance of HBV.

Three patients died within 6 months of receiving their last dose of FIAU. All three patients had received a second course of FIAU treatment for their chronic HBV disease.

Patient 401 was an individual with underlying HIV, HBV, hepatitis C virus, and hepatitis D virus infections. He was initially dosed from April 16 to April 30, 1991, and was assigned to receive 1 mg of FIAU per kg daily in three equal doses. Through an error in dosing, the subject actually received 10 times the scheduled initial dose on the first study day (i.e., 3.3 mg/kg rather than 0.33 mg/kg). He suffered no apparent ill effects from this round of dosing and approximately 13 months later was retreated for 13 days, from May 23 to June 4, 1992 (bringing his total dose to 2,437 mg). Three months after his last FIAU dose, he was hospitalized with jaundice, ascites, and hepatic encephalopathy. His AST and ALT levels were 203 and 216 units/liter, respectively, his bilirubin level was 6.3 mg/dl (ultimately rising to 31 mg/dl), and his CD4 count was 669 cells/mm^3 The patient continued on a downhill course, ultimately dying on October 18, 1992, approximately 5 months after receiving his last FIAU dose. At autopsy, the liver exhibited cirrhosis with bridging fibrosis, regenerative nodules, periportal inflammation, cholangiolitis, and cholestasis. There was no evidence of steatosis and no lactic acidosis was observed during the terminal phases of his disease. The patient was judged by the investigators to have died from his underlying diseases.

Patient 406 was a 45-year-old HIV-infected male with concomitant HBV disease who had participated in previous clinical trials of interferon, ribivarin, and ampligen. In addition he had received several therapies for HIV between 1988 and June 1991, including AZT and ddC. He received 1 mg of FIAU per kg/day for 14 days, from June 4 to June 17, 1991, before and after which his personal physician prescribed ddC for his HIV infection, although ddC was replaced by AZT in the fall of 1991 because of peripheral neuropathy. The patient was retreated with FIAU approximately 1 year later (June 1992) for 17 days at a dose of 0.5 mg/kg/day (total dose, 1,718 mg). Treatment was discontinued because of pain in the feet. After 2 weeks of follow-up the patient missed all further appointments at NIH. The patient's HIV medication was switched from AZT to ddI in July by his local physician, and 6 weeks later he developed fulminant hemorrhagic pancreatitis, ascribed to the ddI in combination with his HBV and HIV infections. He was admitted to a local hospital with an amylase level of 1,166 and a lipase level of >4,000. Despite discontinuation of ddI and aggressive therapy, he died secondary to severe hemorrhagic pancreatitis. NIH investigators were informed of his death 2 weeks later. On autopsy, the entire pancreas was involved with necrosis and hemorrhage extending into the retroperitoneum. Importantly, the liver demonstrated only minimal steatosis with fibrosis around the portal triads. There was no report of lactic acidosis in this patient.

The third death was *patient 408*, a 38-year-old HIV- and HBV-infected male with cirrhosis documented by liver biopsy in 1988 who received 1 mg of FIAU per kg/day for 12 days beginning on November 3, 1991. Approximately 2 months later he received a second course of FIAU at the same dosage level (total dose, 2,534 mg). Within a week after stopping FIAU, the patient was started on a combination of ddI and AZT and he continued to take them for approximately 2 months of therapy (until March 15, 1992), at which time the drugs were stopped in response to abdominal bloating and discomfort. In April 1992, the patient was

diagnosed as having hepatic failure on the basis of the physical findings of jaundice and ascites. In early May he suffered an acute upper gastrointestinal hemorrhage secondary to cirrhosis and associated esophageal varices and coagulopathy. Despite aggressive resuscitative measures, the patient died on May 16, 1992. Autopsy showed micro-and macronodular cirrhosis, pancreatic fibrosis, and esophageal varices. Microscopic examination showed marked obstruction of hepatocytes but no evidence of steatosis. The patient did not develop any lactic acidosis throughout the course of his illness, and his peak AST and ALT levels were 284 and 154 units/liters, respectively. The investigators were not aware of this patient's death until July 1993, at the time that the patients in the PPPC study were being diagnosed with hepatic failure.

An additional patient, *patient 409*, developed pancreatitis within 6 months of being dosed with FIAU and survived the episode. The patient is a 36-year-old male coinfected with HIV and HBV who received 0.5 mg of FIAU per kg for 2 weeks in December 1991. In late April he received the drug at the same dose another 14 days (total dose, 1,663 mg). In late May the patient was started on ddI therapy. In late July he developed abdominal pain and subsequent volume depletion. On August 10, 1992, he was admitted to the hospital and a diagnosis of pancreatitis was established. His pancreatitis resolved after ddI was discontinued. The investigators concluded that the pancreatitis was most likely due to the ddI therapy.

COMMENT

Like the R89 trial, this was a carefully performed Phase I clinical study that underwent extensive internal and external peer review prior to initiation. The real-time data and safety assessments via fax and conference calls once again resulted in remarkably efficient identification of an MTD and modification of the protocol into a dose-deescalating study, with a shift in focus from the study of CMV disease to one of HBV infection.

A unique aspect of this study is the availability of a relative "control" group of non-HBV-infected individuals, all of whom received the highest dosages of drug (1.0 to 1.7 mg/kg/day). None of the individuals in this non-HBV-infected control group experienced any elevation in transaminase levels >3 times the upper limit of normal at any time, and none of these patients had elevations of >1.7 times the upper limit of normal at the end of the study (day 14) (Table 6-1).

On the basis of the dramatic fall in HBV DNA levels and the anticipation of a flare in transaminase levels associated with successful treatment of HBV, the investigators judged the elevations in transaminase levels not to be "serious or unexpected adverse events" that require immediate formal reporting to the sponsor as such. In retrospect, with the additional perspective of the control group, this judgment appears sound and appropriate. Even if one judged these elevations in liver enzyme levels to be a serious or unexpected adverse event, from a functional standpoint the sponsor and FDA were kept fully informed of all laboratory values the laboratory reports faxed to them. Moreover, discussion of abnormal laboratory values occurred during conference calls in which the investigators, the sponsor, the NIAID Program Office, and FDA participated.

With regard to the patients who died, *patient 401* showed no evidence of steatosis or lactic acidosis at the time of death and had extensive cirrhosis consistent with advanced viral

TABLE 6-1 Liver Function Test Results of non-HBV-Infected Patients in Trial R90-001-01

Patient No.	Peak/Base ALT Level	Peak ALT Level	Peak/Base AST Level	Peak AST
201	3.0	135	2.7	72
202	1.5	10	1.2	36
203	2.8[a]	27	1.3	21
204	1.2	91	1.3	57
205	1.7	53	1.5	40
206	1.7	23	1.2	29
207	1.3	28	0.7	25
208	2.6	46	1.7	33
209	1.9	32	1.9	26
210	2.0	86	1.8	51
211	2.0	41	1.4	29
212	1.0	10	1.4	17
214	0.9	31	0.9	22

[a] Highest value was within normal reference level
SOURCE: Corey, 1994

hepatitis. Therefore he could quite appropriately be judged as having died as a result of his underlying hepatic disease, which was a result of hepatitis C and D virus infections as well as HBV infection. *Patient 406* clearly died from severe pancreatitis. However, on the basis of the recent institution of ddI therapy and the known association of pancreatitis with ddI therapy, the investigators attributed the pancreatitis as being secondary to ddI therapy. It is difficult even in retrospect to argue with this assessment. It is well known that ddI causes pancreatitis, which may result in a fatal outcome. Whether FIAU aggravated or accentuated the development or course of the pancreatitis in this patient will never be known. *Patient 408* died of progressive liver disease 4 months after his second course of FIAU therapy. He had a long-standing history of cirrhosis, and it is plausible that his death was due to progression of his underlying disease. In support of this assessment is the histologic finding at autopsy of advanced cirrhosis without evidence of microvesicular steatosis. In any case, investigators were not informed of this death until July of 1993, after trial PPPC was terminated.

7

Oclassen Clinical Trial R91-001-10 (NIH Protocol 91-DK-AI-213)

On the basis of the encouraging findings in the R90 dose-deescalation study, much enthusiasm was generated for instituting a study that evaluated more prolonged administration of fialuridine (FIAU) in patients with chronic HBV infection who were not coinfected with HIV. This study was conducted solely at the NIH Clinical Center, with Jay Hoofnagle as the principal investigator. Hoofnagle is a very experienced gastroenterologist and hepatologist who has developed a special interest in therapeutic approaches for viral hepatitis, especially hepatitis B and hepatitis C viruses. He is Director of the Division of Digestive Diseases and Nutrition at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at NIH. He was integrally involved in the early trials of vidarabine as a potential treatment of HBV infection and was the principal investigator on the major studies that established the therapeutic benefit of interferon in patients with chronic active HBV infection. He was one of the first investigators to describe the flare in transaminase levels associated with the successful clearance of HBV from the blood and has established a large group of patients with chronic active HBV whom he follows at the NIH Clinical Center.

In conjunction with Oclassen Pharmaceuticals, Hoofnagle and Stephen Straus developed a protocol entitled "A Four Week Course of FIAU for Chronic Hepatitis-B" that was submitted to the NIDDK IRB in August 1991. This study was initially designed to evaluate several doses of FIAU that would be administered over a prolonged period of time; however, the duration of therapy was ultimately limited to 28 days because there was only limited animal toxicity data to support longer-term courses of treatment. The rationale behind the desire for more prolonged courses of treatment was based on the understanding that HBV disease is a persistent infection associated with chronic viral replication. It was the opinion of both Hoofnagle and Straus that ultimate control of HBV disease would require some degree of prolonged chronic suppression for a durable effect. The standard treatment regimen for the only approved drug therapy, interferon, for example, calls for 16 weeks of daily subcutaneous injections. The promise of an orally bioavailable drug that was more potent than any previous anti-HBV therapy and that was associated with relatively few side effects at the lower doses generated much enthusiasm for this protocol. The protocol received approval, after compliance with a number of stipulations, by the NIDDK IRB and by the acting director of the Clinical Center. As part of their review, the IRB evaluated the informed consent document and found it to be in keeping with NIH standards. In the Risks and Discomforts section, fatigue, nausea, skin rash, bone marrow suppression, seizures, and "pains in the arms and legs due to irritation of the nerves or the muscles" were all described as potential side effects (Appendix D).

In February 1992 the protocol was submitted to FDA. During the time of the FDA review, information became available from the R90 study that suggested that lower dosing levels (e.g., 0.1 to 0.5 mg/kg/day) would be effective. As such, the protocol was amended to utilize four doses, 0.05, 0.1, 0.25, and 0.5 mg/kg, to be taken every day for 4 weeks. It was anticipated that six patients would be enrolled in each dosing cohort. This protocol was reviewed and approved by the NIH Clinical Center, and the first patient was dosed on April 18, 1992. By August 15, 1992, all 24 subjects had been enrolled in the protocol and all but 6 subjects had completed therapy. The length of clinical follow-up as stipulated by the protocol was 6 months. All patients ultimately completed therapy and followup. All patients returned for all study visits and were intensively monitored during and after therapy, including evaluation with a pretreatment liver biopsy (a posttherapy biopsy was considered but rejected as providing too little unique information to justify the known risks).

HBV DNA was suppressed 70 to 95 percent in the three groups receiving the highest dosage and to a lesser degree in the groups receiving the lowest dosage (0.05 mg/kg/day). Side effects during therapy were mild and transient. No patients developed side effects severe enough to modify the dose or interrupt therapy. In nine patients (patients 2A, 4A, 6A, 1B, 3B, 5B, 4D, 5D, 6D) HBV DNA levels decreased markedly, and two of these (patients 1B and 5B) eliminated HBV envelope antigen (HBeAg). Among the nine patients who became HBV DNA negative, flares in AST and ALT were noted in eight patients as the HBV DNA levels fell. Transaminase levels fell into the normal range in six of nine individuals and into the near normal range (45 to 61 units/liter) in the remaining three patients. With more than 1 year of follow-up, six of the nine patients have evidence of reactivated HBV disease with a return of HBV DNA; however, three patients have become HBeAg negative and have normal transaminase levels.

One patient (*patient 4D*) died within 6 months of receiving FIAU. This 59-year-old man with chronic HBV infection died on January 6, 1993, 2 months after laparoscopic cholecystectomy and 4 months after completion of his 28-day FIAU therapy. He had previously been treated in a 1989 interferon protocol at NIH (a pretreatment liver biopsy in 1989 revealed mild chronic active hepatitis with bridging fibrosis). He was subsequently enrolled in a prednisone/interferon trial at NIH, but he failed to have a sustained response to treatment.

In August 1992 he began FIAU as part of the R91 trial. A pretreatment liver biopsy in July 1992 showed chronic active hepatitis with fibrosis. His pre-treatment ALT level was 72 units/liter and his bilirubin level was 0.6 mg/dl. He received 28 days of FIAU until September 2, 1992 (total dose, 1,756 mg). During the last 2 weeks of treatment he developed mild nausea, fatigue, and myalgias. With treatment his HBV DNA levels fell from 52 to 1.9 pg/ml.

He was seen at NIH during a follow-up visit in September 1992 and was asymptomatic. However, in October 1992 he developed fatigue, nausea, and epigastric discomfort for which he was seen by his local physician. An upper gastrointestinal series and ultrasound were normal. A HIDA scan showed decreased gallbladder contraction after cholecystokinin. He was seen at NIH on October 25, 1992. His ALT level was two- to fourfold above baseline, he was HBV surface antigen (HBsAg) and HBeAg positive, but HBV DNA was low. Ultrasound and computed tomography scan again showed no evidence of gallstones and a heterogeneous liver. He was believed to be having a flare of hepatitis in response to FIAU. He complained of numbness in the feet and had clinical evidence of a neuropathy. Against the advice of the NIH

physicians, he underwent laparoscopic cholecystectomy in November 1992. No gallstones were present. An intraoperative liver biopsy showed chronic active hepatitis with fibrosis with a small amount of fat. Stains for HBV antigens were positive, but their levels were markedly reduced compared with those at the previous biopsy.

He was seen at NIH 1 week later, at which time he had developed ascites. A peripheral neuropathy was documented by nerve conduction studies. He continued to have ascites despite the use of diuretics and paracenteses. He was transferred from North Carolina to NIH on December 20, 1992, 4 months after completion of his FIAU treatment, at which time he had massive ascites and intravascular volume depletion. Hepatic function was preserved (bilirubin, 0.8 mg/dl; albumin, 3.5 g/dl; prothrombin time, normal). Refractory ascites was ascribed to complications of the cholecystectomy. He had also developed lactic acidosis of unknown etiology and had biochemical evidence of pancreatitis (normal amylase levels but high lipase levels) but no abdominal pain. Despite normal serum bilirubin and near normal liver enzyme levels, he was encephalopathic and was believed to be in hepatic failure. He was therefore transferred to Pittsburgh for liver transplant evaluation. He died of multisystem organ failure and lactic acidosis prior to transplantation. An autopsy performed at NIH revealed inactive cirrhosis of the liver with marked microvesicular steatosis, but rare hepatocyte staining for HBV antigens. The pancreas was autolyzed but had histologic evidence of pancreatitis.

The etiology of this patient's syndrome was puzzling, but was not thought to be related to FIAU at the time since the patient was no longer on the drug and hepatic decompensation appeared to be temporally related to cholecystectomy. Nevertheless, a description of this death was included in the Clinical Investigator's Brochure from Eli Lilly dated February 1993 which was central to the preparation of the ill-fated 6-month protocol (PPPC)(Lilly Research Laboratories, 1993). The death was ascribed to complications of surgery in that document, although a simple "cause unknown" would probably have been a better reflection of reality. It was also discussed by medical staff fellows with every patient who participated in the PPPC trial.

Several other patients in the R91 study developed evidence of hepatic or pancreatic damage within 6 months after receiving their last dose of FIAU. *Patient 006B* was a 59-year-old, HBV-infected male who received 0.25 mg of FIAU per kg/day for 28 days starting in late May 1992. Approximately 4 months after the discontinuation of FIAU therapy, the patient was hospitalized for severe abdominal pain. The pain was not associated with an increased ALT level or any abnormalities of amylase, lipase, or acidosis, and no diagnosis was established. This patient still experiences bouts of similar pain without explanation. The hospitalization was reported to the study sponsor in a routine fashion, but the investigators did not feel that this abdominal pain was related to the FIAU therapy.

Two additional patients experienced significant health problems in the months following their participation in the R91 trial. *Patient 1C* is a 56-year-old HBV-infected male who received 0.05 mg of FIAU per kg/day in June 1992. He was admitted to the hospital in October 1992 with right upper quadrant pain, at which time a cholecystectomy was performed. A liver biopsy obtained perioperatively showed moderately active micronodular cirrhosis; a stone was found in the cystic duct. In the opinion of the investigators, the hospitalization appeared to be due to a preexisting problem (cholelithiasis that was known before his FIAU therapy) and unrelated to FIAU.

Patient 1A is a 52-year-old man who received 28 days of FIAU therapy beginning on April 13, 1992, but he developed sensations of numbness and tingling in late September 1992 (4 months after receiving his last FIAU). Because of progressive pain, he underwent nerve conduction studies at NIH in January 1993. These were compatible with a peripheral neuropathy. Symptoms were similar to those experienced 5 years previously when he had been consuming significant amounts of alcohol. Because of this prior history and because the neuropathy was believed to be atypical for a nucleoside analog in that it began 4 months after FIAU treatment was stopped and persisted (Ara-A induced neuropathies, for example, are usually transient), the investigators could not draw a clear relationship between drug and toxicity. In retrospect it is likely that this neuropathy was FIAU related. At the time this was considered to be a possibility by the investigators, and the appropriate precautions were taken to monitor subsequent patients. Because of this patient and the unequivocal peripheral neuropathy of patient 4D (above), peripheral neuropathy was included as a potential complication of FIAU in the PPPC trial and all patients were monitored with nerve conduction studies.

COMMENT

This study clearly established the clinical utility of FIAU in the treatment of chronic HBV infection. All patients responded with reductions in circulating HBV DNA levels, and many in the groups receiving the three highest doses became HBV DNA negative. Unfortunately, this antiviral effect was not maintained for an extended period after the cessation of drug therapy. This lack of permanence and the relative absence of dose-modifying toxicities while the patients were being treated strongly suggested the need for a longer duration of FIAU treatment, which was the rationale for the 6-month PPPC trial.

As with the previous R89 and R90 studies, several patients developed clinical problems after finishing their courses of treatment. In the cases of patients 6B and 1C, it is most likely that their clinical problems were due to preexisting disorders and were not related to FIAU.

Patient 4D, on the other hand, presented with a more complicated clinical picture. In retrospect it is apparent that this patient died of what would later be termed the *FIAU syndrome* with systemic lactic acidosis and hepatic steatosis. On the basis of the unchanged liver biopsy findings at the time of the patient's cholecystectomy, the investigators concluded that his subsequent liver failure and death were due to complications of the cholecystectomy, possibly related to the anesthetic agent, rather than to delayed toxicity of FIAU. Since the syndrome of FIAU toxicity was undescribed at the time, the investigators cannot be strongly criticized for coming to this conclusion. Indeed, it is obvious that the investigators took this death very seriously. The progress and course of this patient were fully described to the sponsor via telephone. The death was reported to the NIDDK IRB, was discussed at NIH senior staff meetings, reviewed by pathologists at the Armed Forces Institute of Pathology, and described in the subsequent PPPC protocol. After discussion with the NIDDK IRB, the death was not described in the consent form given to participants in the PPPC trial, but it was nevertheless discussed with each patient before they signed that form. Furthermore, this patient's clinical course, along with a detailed review of four other known deaths of former FIAU- or FIAC-

treated patients, were reviewed at a pre-PPPC protocol meeting with FDA in April 1993. FDA approved the initiation of the PPPC trial after those discussions.

The attention paid to this patient's death by the investigators and their acute awareness of the peculiar nature of his presentation were no doubt responsible for their increased vigilance throughout the conduct of the ensuing PPPC study and the rapid termination of that trial when a patient presented with a similar syndrome on June 26, 1993.

8

Eli Lilly Trial H3X-MC-PPPA

This study, under the sponsorship of Eli Lilly and Company, was carried out under investigational new drug (IND) application 34,973 after Lilly assumed IND responsibilities as part of a licensing agreement with Oclassen Pharmaceuticals. It involved a "pharmacokinetic/pharmacodynamic dosing regimen" to determine the safety and efficacy of FIAU in patients with compensated HBV disease. The study was planned to include 36 subjects and employ oral dosing of 0.10 or 0.25 mg/kg/day for 90 days. Half of the subjects in each dosage group were to receive the drug in two equal portions each day and half were to receive it in three equal doses. Patients were entered at two study centers: the University of Texas, Galveston, and Tufts New England Medical Center Hospital. A total of only five patients received FIAU between May 3 and June 26, 1993, when the trial was discontinued promptly upon receipt of information concerning adverse events in subjects in the H3X-MC-PPPC study that had commenced at the NIH in March 1993.

UNIVERSITY OF TEXAS, GALVESTON SITE

The principal investigator for this study was David P. Paar. He is a 1984 graduate of West Virginia University Medical School and, following residency in internal medicine at West Virginia University Hospitals, served an infectious disease fellowship in the Medical Virology Section of the Laboratory of Clinical Investigation at the National Institute of Allergy and Infectious Diseases (NIAID) from 1988 to 1991. Following an additional year (1991-1992) as a medical officer at the NIAID AIDS Research Clinic at NIH, he served as assistant professor of medicine/chief resident in the Department of Internal Medicine at West Virginia University Hospital. Currently he has an appointment as an assistant professor of medicine in the Infectious Disease Division at the Medical Branch, University of Texas, Galveston. He is board certified both in internal medicine (1987) and in the subspecialty of infectious diseases (1992). His publications deal with a variety of viral infections or their treatment or complications, coauthored with Stephen Straus, and several abstracts which concerned the effects of FIAC in HIV-infected patients and FIAU in patients chronic with HBV infection.

The three patients in the clinical trial at Galveston (see Appendix G for patient summaries) showed declines in serum HBV DNA levels to 2-33 percent of the levels observed at the time of study entry. FIAU was administered orally at doses of 0.05 or 0.125 mg/kg twice daily for periods of 16, 19, or 43 days. In one patient the AST and ALT levels remained

normal throughout the study; in a second patient, the levels were slightly elevated at baseline and did not change significantly during treatment, but they declined to normal during follow-up; in the third patient, the AST and ALT levels had almost doubled from the baseline values when FIAU treatment was discontinued after 16 days, and 3 months later they were 2-2.6 times higher than the baseline.

One patient, who had a preexisting seizure disorder, had several seizures on his 21st day of FIAU therapy. The seizures were associated with subtherapeutic phenytoin levels, and no further seizures occurred after adequate phenytoin levels were obtained. In the second patient there was no clinical or laboratory evidence of hepatic or pancreatic toxicity or neurotoxicity related to FIAU administration during the short course of therapy or for 1 year after discontinuation of treatment with the drug. In the third patient an increase in his nausea over his baseline and lower-extremity weakness raised the investigator's suspicion of possible FIAU toxicity. However, these symptoms subsided after 1 day of hospitalization, there was no lactic acidosis, and a muscle biopsy showed no evidence of mitochondrial abnormalities—all of which were not supportive of the diagnosis of FIAU toxicity. Three months after discontinuation of FIAU liver treatment transaminase and serum HBV DNA levels began to rise; the investigator reasonably attributed these to reactivation of the chronic HBV-related hepatitis. An episode of hepatic decompensation occurring 6 months after receiving his last dose of FIAU was attributed to progression of the underlying active HBV-related hepatitis rather than to FIAU toxicity on the basis of the following: (1) a liver biopsy showed active inflammation and cirrhosis and only minimal microvesicular fat, (2) and there was no lactic acidosis. The committee feels that this interpretation is the most reasonable one considering the accumulated evidence. Thus, no toxicity clearly attributable to FIAU occurred in this clinical trial involving three patients.

The informed consent document employed in this investigation (Appendix D) explained the details of the study and the known side effects of FIAU. Peripheral neuropathy was, however, not included as a known side-effect. Only one of the three study subjects interviewed 15 months later recalled being told about numbness or tingling of the toes and feet as a possible side effect. All three noted that Paar had personally talked to them about the informed consent form and had taken time to walk them through its contents. When interviewed, all three had expressed the opinion that Paar and staff had provided excellent care, and two stated that they would volunteer again for studies of new anti-HBV drugs. One of the three indicated that he was disappointed that he had not been informed of the deaths of prior patients and of the occurrence of neuropathy as a toxic side effect. For that reason he felt he would probably not consider volunteering for further studies of new anti-HBV drugs at Galveston or elsewhere.

TUFTS NEW ENGLAND MEDICAL CENTER SITE

The principal investigator was Marshall M. Kaplan, and coinvestigators were D. Greenblatt, Y. M. Lee, M. Nguyen, T. Sepe, G. Dickstein, A. Fribush, and D. Pratt. The principal investigator graduated from Harvard Medical School in 1960. He is board certified in internal medicine and gastroenterology. He is a professor of medicine at Tufts Medical School and is chief of Gastroenterology there and an associate editor of the *New England*

Journal of Medicine. In the area of gastroenterology his interest is particularly in hepatology. His publications have dealt with various forms of liver disease, and he has been involved in multicenter clinical drug trials, especially in the treatment of primary biliary cirrhosis.

Ten patients entered the screening phase of this trial. Four were subsequently excluded because they did not meet the entrance requirements. Four had not yet begun treatment when the study was discontinued on June 28, 1993, and two patients actually received FIAU. Both of these patients (see Appendix G for details) showed declines in serum HBV DNA levels to less than 5 percent of the levels observed at the time of entry in to the study. This represents a clear response of the infection and, in view of its coincidence with FIAU treatment, is unlikely to have represented a spontaneous fluctuation in HBV infection. FIAU was administered at dosages of 0.05 or 0.125 mg/kg twice daily for periods of 28 or 55 days. In one patient, the ALT levels rose to 1.9-fold the baseline levels at the end of 4 weeks of therapy; it then peaked at 3.2-fold the baseline level 1 week later, dropping to 35 percent of the baseline level at 5 months after starting treatment and then rising to 3.2-fold the baseline level at the end of 7 months. In the second patient, ALT levels rose to 1.8-fold the baseline at the time of cessation of FIAU therapy, peaked at 2.7-fold the baseline level 2.5 weeks later, and then gradually fell to below the baseline level of 88 units/liter at 8 months after the start of therapy. The rises in ALT level may have represented a flare in ALT levels associated with a reduction in circulating HBV DNA levels or may have been a fluctuation in the course of the underlying hepatitis. Although this may have represented a manifestation of FIAU hepatotoxicity, the committee believes that this is less likely in view of the type of hepatotoxicity associated with FIAU and in view of the fluctuations in ALT levels observed over the 6-month period of observation.

One patient noted leg pain and numbness beginning 3-4 months after stopping FIAU therapy. Evidence of a primary sensory neuropathy was found on neurologic consultation, and electrophysiologic studies identified the presence of an axonal neuropathy, primarily sensory, but some motor involvement as well. Unfortunately, there are no antecedent nerve conduction studies that can be used to objectively evaluate whether this condition predated the administration of FIAU, and it may have been related to his previous alcohol and parenteral drug abuse. Over the next 8 months there were no significant changes on neurologic examination or on nerve conduction studies, but subjectively the patient felt that his symptoms had worsened. His total dose of FIAU was two-thirds that of a patient in another study who also had a past history of alcohol abuse and who developed peripheral neuropathy 4 months after stopping FIAU therapy in a 28-day trial. The committee feels that although this patient may possibly have been predisposed by virtue of his prior history of alcohol abuse, his documented peripheral neuropathy should be considered a neurotoxic effect of FIAU.

The informed consent document (Appendix D) explained the details of the study and the known side effects of FIAU. Peripheral neuropathy (numbness, tingling) was, however, not included as a possible side effect, although mention of possible muscle aches was mentioned. A statement to the effect that "other unpredictable bad effects due to the study drug may occur" was included in the consent form. Neither of the two subjects interviewed 14 months later recalled being told about numbness or tingling of the toes and feet. Both recalled being counseled about the informed consent forms by study nurses, and one of the two subjects remembered the study nurse walking him through its contents. The committee has reviewed

the informed consent form and finds it to be of generally high quality, but noted that it did not include specific reference to the clinical manifestations of peripheral neuropathy. The patient who developed peripheral neuropathy recalled that during the last or penultimate scheduled visit he happened to mention to the study nurse numbness in his toes, which he attributed to wearing "flip-flops." She insisted on setting up an appointment with a neurologist to evaluate this symptom. Neither subject would consider volunteering for further studies of new hepatitis drugs, but one indicated that it was because he could not take time off from work.

9

Eli Lilly Trial H3X-MC-PPPG

This study, conducted at the Lilly Laboratory for Clinical Research in Indianapolis, Indiana, in March and April 1993, was the only one of those reviewed by this committee which utilized healthy subjects rather than patients infected with HIV or HBV. The primary objectives, as stated in the protocol, were to determine the relative bioequivalence of a syrup formulation and two tablet formulations of FIAU, and to determine the pharmacokinetic profile of each (i.e. how much of the dose is absorbed, how fast it is absorbed, how quickly is it eliminated, and in what form is it eliminated). A secondary objective was to determine the influence of food on these processes.

The principal investigator for the study was David L. Hyslop, and Benito J. Cerimele and Karl A. DeSante, were listed as scientific collaborators. All three are Lilly employees; the first is a clinical research physician assigned to the Lilly Laboratory for Clinical Research, the second is a mathematician assigned to the Statistical and Mathematical Sciences Division at Lilly Corporate Center, and the third is head of the Bioavailability and Pharmacokinetics Department and the Clinical Analytical Group at the Lilly Laboratory for Clinical Research. Hyslop, a 1978 graduate of Indiana University School of Medicine, is board certified in internal medicine (1981) and infectious disease (1986), and was Assistant Professor at the University of Missouri-Columbia before joining Lilly in 1987. Although none of his professional publications have dealt with hepatitis, he appears to have been qualified to run this study on healthy volunteers. His more senior collaborators are both established scientists who have published extensively in their fields.

Sixteen subjects each received five doses of FIAU, separated by 3-to 7-day intervals. On three of these occasions the subject received the drug after an overnight fast and continued to fast for 4 hours after taking the drug. The FIAU was provided once as a single 5-mg tablet (between 0.06 and 0.08 mg/kg), once as five 1-mg tablets, and once as 5 ml of 1 mg per ml of syrup. On a fourth occasion subjects were given a 5-mg tablet immediately before a standard meal. Subjects were randomly assigned to one of four groups, balancing the order in which the various formulations were received. The last dose for every subject, however, was a 5-mg tablet, given 30 minutes or an hour before or after the meal. The study ultimately utilized a newly developed radioimmunoassay (RIA) highly specific for FIAU and 250 times more sensitive than the high-performance liquid chromatography (HPLC) assay that had previously been used to estimate a half-life of 1 to 4 hours for FIAU. The RIA technique was not perfected until mid-June, however; so blood and urine samples from this trial were simply frozen for later analysis.

Unlike any of the other FIAU studies reviewed in this report, the volunteers remained at the laboratory for the duration of the study. The laboratory is adjacent to the Wishard Memorial Hospital of the Indiana University Medical Center, where acute medical care is provided to any Lilly subjects who require it. The protocol was reviewed and approved by the Indiana University Medical Center IRB. According to Lilly, this inpatient arrangement not only facilitates control of diet and close monitoring of protocol compliance but also ensures complete data collection and follow-up on frequently unemployed and transient subjects.

Risks to subjects were described in the informed consent document (Appendix D) as including stomach pain, diarrhea, nausea, vomiting, headache, and muscle aches or fatigue. There was no mention of peripheral neuropathy, nor was there any description of symptoms like numbness or tingling in the arms and legs that might imply peripheral neuropathy. The form did note that changes in laboratory test values that measure liver, kidney, and muscle functions, and anemia (low blood count) had also occurred in prior studies. Decreases in sperm production and heart muscle damage "in animals given 3,500 to 14,000 times the dose planned for this study" were also reported, and subjects were warned that FIAU or the procedures used in the study might have other unknown effects. An extensive battery of hematology, blood and urine chemistry, and microscopic clinical laboratory tests was conducted 24 hours after the administration of each dose, but no explicit provision for grading toxicity or discontinuing subjects in the study was included in the protocol.

Pharmacokinetic measurements performed on blood and urine samples after the RIA were validated in June revealed more rapid absorption of FIAU in syrup than in tablet form, with food generally decreasing the rate of absorption, rapid distribution with all forms, and a very prolonged elimination phase with a terminal half-life of 28-30 hours (10 times the half-life previously estimated with the less sensitive HPLC method).

The adverse events that were noted included diarrhea, headache, transient myalgia, and in two cases, elevations in transaminase levels. Although both subjects with these elevations were asymptomatic, dosing was discontinued for one (subject 1203) after his serum ALT level rose to 92 units/liter (from 19 units/liter) and his AST level rose to 56 units/liter (from 17 units/liter) after dose 2. This subject was encouraged to stay at the laboratory despite being dropped from his dosage group, while the investigators worked him up for hepatitis and other possible causes of his ALT and AST elevations, which continued to rise to peaks of 137 and 60 units/liter, respectively, 1 week after receiving his last dose of FIAU. Lilly was later criticized for not promptly reporting this "hospitalization" to the FDA within the 10-day limit for serious adverse events. Lilly's records indicate that he was neither admitted (since he was already staying at the laboratory) nor given any acute medical treatment (since he remained asymptomatic). His transaminase levels returned to the baseline 5 weeks after receiving his second and last dose of FIAU.

The second subject (subject 508), who was also asymptomatic, also showed three- to five-fold increases in ALT and AST levels after receiving dose 2, but the levels of both enzymes decreased on each of the following 3 days and the subject was continued in the study. AST and ALT levels gradually returned to the baseline levels, despite the administration of three additional 5-mg doses of FIAU.

Subjects were called back for follow-up blood work and questioning about symptoms of possible FIAU toxicity in July and August 1993, after the emergency cessation of the 6-month trial at NIH. No symptoms or indications of toxicity were detected in the 12 subjects that could be located. There has been no further follow-up except for that for a 13th subject (subject 1203), who reappeared in June 1994 inquiring about studies for which he could volunteer. He was also free of any indication of FIAU toxicity.

COMMENT

This study, the only one of which the committee is aware conducted with healthy subjects free of viral disease, is noteworthy in two respects. First, the newly developed RIA for FIAU revealed (when it became available in June, about the time the trial PPPC investigators were beginning to doubt whether their patients could take the drug for a full six months) a half-life for FIAU in blood 10 times as long as previous estimates. Although all drugs reveal longer half-lives when more sensitive analytical methods are developed, since it is then possible to see concentrations reflective of the diffusion of drugs from pools outside the blood, and this longer half-life does not necessarily indicate that a significant accumulation will occur with repeated dosing, it is certainly consistent with potential accumulation and attendant toxicity at a peripheral site.

A second aspect of this trial in need of some commentary was the elevations in the AST and ALT liver enzyme levels in 2 of 17 subjects. Since neither subject was infected with HBV, there is no possibility that these rises were flares associated with the destruction of infected hepatocytes, a fact given great importance by some critics of Lilly (Wolfe and Reid, 1993), who argue that these data should have been sufficient grounds not just for Lilly to stop the trials with these patients but for all ongoing clinical trials with FIAU, including the H3X-MC-PPPC trial at NIH, to be stopped. In retrospect there is no denying that such an action would have prevented a disaster. At the time however, several pieces of information that argued against such an action were available. The total dose received by each subject, 10 mg, was miniscule compared with the doses apparently well tolerated by the presumably less robust patients in previous trials, whose total doses ranged from 100 to more than 1,000 mg. Perhaps more importantly, neither subject with elevated liver enzyme levels had any clinical signs or symptoms. Although the elevations in serum AST and ALT levels occurred after administration of the second dose of FIAU in 2 of the 17 subjects, a drug hypersensitivity reaction caused by intermittent dosing is not likely to be the explanation, since despite receiving three additional intermittent doses, AST and ALT levels in one subject continued to gradually return to baseline levels. Some well-established drugs produce an initial elevation in AST or ALT levels (isoniazid, for example, the most common therapy for tuberculosis, produces a significant rise in about 10 percent of patients, but enzyme levels generally return to normal, despite continued treatment). The committee believes that it would be a mistake to eliminate clinical judgment from clinical trials, and in this case the committee believes that dropping subject 1203 from the trial while continuing to observe him carefully was appropriate and sufficient.

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Eli Lilly Trial H3X-MC-PPPC (NIH Protocol 93-DK-0031)

This study was conducted at the Liver Diseases Section of the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) at NIH. This open-label randomized study of FIAU used two treatment groups (0.1 and 0.25 mg/kg/day given orally in three divided doses). Duration of treatment was to be 6 months, in the hope of prolonging the temporary inhibition of HBV DNA seen in the previous NIH study (R91). The subjects in fact were largely drawn from patients who had participated in that earlier trial.

Principal investigator was Jay Hoofnagle, a staff scientist in the section from 1978 to 1986. In 1986, Hoofnagle became Acting Clinical Director of NIDDK and subsequently Director of the Division of Digestive Diseases and Nutrition. Adrian DiBisceglie assumed the responsibilities of senior investigator in the Liver Diseases Section in 1988, and in 1991 he became Chief of the Hepatitis Study Section, supervising four medical staff fellows. The day-by-day conduct of clinical studies was the responsibility of DiBisceglie and the medical fellows. Michael Fried was the fellow primarily assigned to the PPPC trial and it was the responsibility of Fried and DiBisceglie to recruit patients for the study, discuss the protocol with the patients, obtain informed consent, and see patients during subsequent visits. NIH attracts first-rate fellows, the majority of whom have already completed internal medicine residencies and 2 years of gastroenterology training before coming to NIH. Graduates of this fellowship program rank among the finest hepatologists not only in the United States but in the world (D. Shafer, M. Peters, A. DiBisceglie, P. Martin, G. Davis, G. Dusheiko, to mention but a few). Hoofnagle is internationally recognized for his contribution to clinical research in the treatment of chronic viral hepatitis. Testimony to his stature in the field of hepatology is that he is recent Past-President of the American Association for the Study of Liver Diseases, the foremost hepatology association in the world.

Rationale for the study came from the lack of available effective therapy for chronic HBV infection, the lack of major toxicity of FIAU in preclinical animal toxicology studies, and the promise of this compound as an anti-HBV drug in earlier human trials. Interferon has been approved by the FDA for treatment of this disease, but therapy inhibits viral replication in the minority of patients (approximately one-third), the drug must be given parenterally (subcutaneously), and side effects, although rarely leading to the discontinuation of treatment, are frequently significant.

Phase I/II trials of FIAU (R90-001-01) by the AIDS Clinical Trials Group (ACTG) showed that FIAU has no significant anti-CMV activity, but showed a clear suggestion that it has significant anti-HBV activity. FIAU was readily bioavailable by the oral route of

administration, and it appeared to be well-tolerated without major side effects. Marked reductions in serum HBV DNA levels were noted in the majority of patients in that trial, with clearance of HBeAg from two of the patients. In some this inhibition was sustained, but in others HBV DNA levels returned to the pretreatment baseline levels. Some of these patients had complex medical problems and were also receiving other antiviral drugs with potential side effects, complicating subsequent interpretation of possible FIAU-associated toxic effects. In addition, since HIV infected patients are immunocompromised and as such may be less likely to have a sustained response to therapy, treatment in nonimmunocompromised patients seemed the logical next step.

Given the lack of effective orally available antiviral agents for the treatment of HBV infection and the promising nature of these early studies, a 1-month study was conducted at NIH to look at the safety and efficacy of this drug in patients with HBV infection alone. In NIH trial 91-DK-AI-123 (Lilly Trial R91-010), FIAU was shown to inhibit HBV replication effectively. However, this inhibition was transient, with viral reactivation in most patients. The rationale behind the final NIH FIAU study was that retreatment of approximately 20 patients with chronic HBV infection for 24 weeks would result in short-term inhibition of viral replication, normalization of serum aminotransferase levels, and potentially long-term virologic remission. The protocol was written in September 1992, before completion of the R91 study. Submission of the retreatment protocol to FDA was delayed because of the lack of long-term animal toxicity data. Six-month toxicity data from studies in animals or humans were not yet available. Appendix F summarizes the preclinical toxicity data available when the PPPC trial was finally begun in March 1993. These included a 6-month study in mice, and similar studies in rats, dogs, and monkeys were under way.

AVAILABLE CLINICAL DATA REGARDING POTENTIAL TOXICITY

At the time of initiation of the PPPC trial in March 1993, there was knowledge of eight deaths of patients who had participated in previous FIAC/FIAU trials: patients 107 (hepatic failure), 105 (bacterial pneumonia), 103 (AIDS), and 110 (AIDS) from R89; patients 101 (*Pneumocystis* pneumonia), 401R (hepatic failure), and 406R (pancreatitis) from R90; and patient 4D in protocol R91 (hepatic failure). Patient 408R in trial R90 also died of liver failure, but his death occurred after the follow-up period and investigators did not learn of the death until July 1993. These deaths have been reviewed in previous sections. Concern about patient 4D and recognition of a similar spectrum of signs and symptoms when it arose in patient 2 in the PPPC trial led to prompt and appropriate termination of this study in late June 1993.

A variety of other potential toxic effects had been identified from earlier trials (R89 and R90) in HIV-positive patients. Nausea, vomiting, and abdominal discomfort were side effects of FIAC/FIAU and were dose limiting. Peripheral neuropathy was also considered to be a possible adverse event associated with FIAU therapy. One of the patients from trial R91 (patient 1A) had a clear-cut neuropathy. This 52-year-old man received 28 days of FIAU therapy in March and April 1992, but sensations of numbness and tingling were not noted until late September 1992 (5 months after receiving his last dose of FIAU). Because of progressive pain, he underwent nerve conduction studies at NIH in January 1993. These were consistent

with a peripheral neuropathy. Symptoms were similar to those that the patient had experienced 5 years previously. Because of this prior history and because the onset of symptoms was fully 5 months after FIAU treatment was stopped, the investigators were not convinced of a clear relationship between drug and toxicity. However, given the known neurotoxicities of other nucleoside analogs, the investigators were sufficiently concerned to include careful neurologic assessment and nerve conduction studies in the next protocol, H3X-MC-PPPC. *In retrospect, it is almost certain that this neuropathy was FIAU related* . A second patient in the R91 study (patient 4D) also complained of numbness and tingling in the lower extremities several months after stopping study drug. Peripheral neuropathy was confirmed by nerve conduction studies. This patient subsequently died following a cholecystectomy. Although both of these neuropathies were believed to be atypical for that seen with nucleoside analogs in that they occurred after the drug was stopped, and persisted (Ara-A induced neuropathies are usually transient), peripheral neuropathy was included as a potential complication of FIAU in the PPPC protocol, and nerve conduction studies were included in the study design.

Pancreatitis was another potential side effect of FIAU. In the R90 study, patient 409R developed mild pancreatitis while on ddI, requiring hospitalization 3 months after discontinuation of FIAU (total dose received, 1,662.5 mg spread over 2 weeks). The pancreatitis resolved after the discontinuation of ddI treatment. Pancreatitis was therefore attributed to ddI, although ddI treatment was subsequently reinstituted at a lower dose. *In retrospect, it is unclear even now whether this pancreatitis was FIAU related, given the known association of pancreatitis and ddI. The investigators cannot be criticized for failing to recognize a possible association at the time*.

The potential for myopathy was included in the consent form for the PPPC trial. Previous experience with nucleoside analogs had highlighted the difficulty in determining whether pain and numbness in the arms and legs was due to a neuropathy or a myopathy, or both. Myoclonic jerks, confusion, and/or seizures had been seen in three HIV-positive patients after they had received 5-10 doses of FIAC. These occurred only in critically ill patients with AIDS treated in the FIAC trial and were not seen in any patient on FIAU. Nevertheless, the possibility that seizures could be due to treatment was included in the informed consent document for the PPPC trial. In the R91 trial, a rise in CPK levels was noted in patient 2A as clinically significant.

Hepatotoxicity was not believed to be a toxic effect of FIAU. In the R91 trial, a rise in liver enzyme levels associated with the loss of HBV DNA was interpreted as a positive event. Inhibition of HBV replication occurred in 9 of the 24 patients. This was associated with a rise in liver enzyme levels in eight of the nine patients. Subsequently, ALT levels returned to normal or near normal in all patients. The rise in liver enzyme levels associated with the loss of HBV DNA was interpreted as a flare associated with the resolution of infection. This was well documented in the patients charts at NIH. Patients 6A and 1B, for example, ALT levels rose to 722 and 733 IU/1 respectively. In contrast to earlier FIAC trials for CMV, an elevation in the ALT level was deliberately not included as an adverse event because of the expected flare seen in drug-induced inhibition of viral replication. This flare was unusual in these two patients in that it occurred after the completion of therapy, but in both patients it was associated with the loss of HBV DNA. Importantly, there was no other evidence of hepatic decompensation in association with this rise in ALT level (increased serum bilirubin or

prolongation of prothrombin time). A liver biopsy performed during the flare showed acute or chronic hepatitis with less HBV core antigen (HBcAg) staining than in the pretreatment biopsy specimens. Neither liver biopsy was interpreted at the time as showing microvesicular steatosis (which was later identified as a hallmark of FIAU hepatotoxicity). Hyman Zimmermann of the Armed Forces Institute of Pathology subsequently reviewed the posttreatment liver biopsy in patient 006A and also found no evidence of microvesicular or macrovesicular steatosis.

Patients 6A and 1B subsequently became HBeAg negative, with normalization or near normalization of ALT levels, suggesting that the investigators' interpretation was indeed correct and that the ALT elevations were indicative of a positive response to treatment rather than FIAU toxicity. Even with hindsight, these changes in ALT levels cannot be ascribed to FIAU toxicity, particularly in view of the minimal ALT elevations (less than two-fold elevations) characteristic of the fatal hepatic failure ultimately seen in the PPPC trial, and the recognized flare phenomenon that occurs with a positive response to antiviral therapy.

AVAILABLE SAFETY DATA

At the initiation of the PPPC trial there was considerable information regarding the safety of FIAU. In the R90 trial, the first patients coinfected with HIV and HBV treated at NIH received FIAU at 1 mg/kg/day and marked inhibition of viral replication was noted. The protocol was amended to evaluate the anti-HBV activity of lower doses of FIAU (0.5 and 0.1 mg/kg/day). Treatment duration was 14 days, with 28 days of follow-up.

In the R91 trial, 24 patients with chronic HBV infection received four different doses of FIAU for 28 days (0.05, 0.1, 0.25, and 0.5 mg/kg/day), with six patients in each dosing group. Enrollment in this study was staggered to allow evaluation of the safety and efficacy of each dose before testing the next dose. All patients completed therapy without dose modification, and all patients completed follow-up. The side effects were mild and were seen mainly in those who had received the highest dose. It must be emphasized that although the planned duration of treatment in the PPPC trial was longer than those in previous trials, the doses used in the PPPC trial (0.1 and 0.25 mg/kg/day) were 4- to 10-fold lower than those used in early trials.

DEVELOPMENT OF PROTOCOL AND FDA REVIEW

On September 16, 1992, Hoofnagle submitted the PPPC protocol to the NIDDK IRB. The protocol was initially designed as a retreatment for patients who had not responded to therapy in the R91 study. The PPPC protocol was discussed extensively with the FDA's Division of the Antiviral Drug Products in late October 1992. Present at this meeting were the NIH investigators and representatives of both Lilly and Oclassen. Included in the protocol was discussion of peripheral neuropathy and the death of patient 4D from protocol R91. Other adverse events summarized included the elevations in ALT level seen in protocol R91 (patients 6A and 3B seen in association with the inhibition of vital replication and interpreted as a delayed flare of hepatitis). Concerns of hepatotoxicity were not raised by FDA either then or

at any later date until the toxicity of FIAU became readily apparent. The consent form for the PPPC trial was reviewed by FDA, which asked for the inclusion of the possible teratogenicity of FIAU in mice. After the review of the data, FDA approved the six month treatment study.

On October 24, 1992, Hoofnagle responded to issues regarding the protocol raised by the chair of the NIDDK IRB, and the protocol was approved on October 30. In February 1993, two amendments to the protocol were submitted to the NIDDK IRB, to include (1) patients who had not previously received FIAU and (2) nerve conduction studies before and during therapy. The amended protocol was approved by the NIDDK IRB on March 5, 1993.

PATIENT SELECTION AND ENROLLMENT

All patients in the PPPC trial had chronic HBV infection with active viral replication (HBeAg and HBV DNA positive). Eleven patients (patients 1-10, and 15) had previously been treated with FIAU in trial R91, and four patients (patients 11-14) had never received FIAU. This was an open-label, randomized study of FIAU with two treatment groups (0.10 and 0.25 mg/kg/day given orally in three divided doses). Other patients from the R91 trial were ineligible for retreatment because of the loss of HBV DNA with initial therapy (n = 9), side effects from previous treatment (n = 1), need for interferon (n = 1), and inconvenience (n = 2). Thus, only 11 patients were suitable for retreatment, and the protocol was amended to include patients who had never received FIAU.

Inclusion Criteria

The following criteria were used for the inclusion of patients in the PPPC trial: (1) male or female patients age 18 years and older who had been included in 91-DK-AI-123 as well as additional new patients to bring the study total number of subjects to 24; (2) HBsAg positive with active viral replication (HBeAg positive and HBV DNA or HBV DNA polymerase positive for at least 6 months; (3) compensated liver disease (prothrombin time less than 3 seconds prolonged, serum albumin greater than 3 g/dl, serum bilirubin less than 4 mg/dl, no history of ascites, encephalopathy, or bleeding esophageal varices); (4) elevated serum ALT levels (average of three determinations of more than 50 IU/1); and (5) provision of written informed consent.

Exclusion Criteria

The following were evaluation criteria for the PPPC trial: (1) seropositivity for HIV, hepatitis C virus (HCV), or hepatitis D virus (HDV); (2) significant cytopenia (hematocrit less than 30 percent, white blood cell count less than 2,500/mm^3, and platelet count less than 50,000/mm^3); (3) compromised renal function; (4) substance abuse within the preceding 6 months; (5) pregnancy; (6) significant systemic illness; and (7) preexisting peripheral neuropathy.

Re-enrollment

The protocol stipulated that patients enrolled in the R91 study were eligible for retreatment 5 months after completion of a 28-day course of FIAU. Since the majority of patients from the previous FIAU study at NIH met this criterion and were already well known to the NIH investigators, enrollment of the first 10 patients was rapid (from March 23, 1993 to April 21, 1993). This resulted in a "bolus" of patients admitted into the study without the usual built-in delay for the observation of toxicity. Although the trial was halted after the recognition of major toxicity in only one patient in the study (patient 2), major toxicity in six other patients was unavoidable because they had already had prolonged exposure to the drug.

Entry of the last retreatment patient (patient 15) was delayed 2 months while a skin lesion was investigated and a flare of hepatitis resolved. After the initial 10 patients had been treated for 2 months, four additional patients (patients 11-14) and the single delayed patent (patient 15) were begun on FIAU in June 1993.

Possible Adverse Effects

Side effects discussed in the protocol included (1) irritability; (2) gastrointestinal upset at the highest dose; (3) transient CPK elevations; (4) potential severe side effects that were not clearly related to FIAU, including one patient who died following laparoscopic cholecystectomy and two patients who developed a peripheral neuropathy after FIAU was stopped; mention was made of a single patient with an elevated CPK level that resolved on therapy and two additional patients with fatigue and irritability that resolved after FIAU was stopped; (5) Possible toxic effects, which included neuromuscular damage and bone marrow suppression; and (6) that no patient previously developed serious side effects while on treatment.

Toxic events graded as mild, moderate, or severe for dose reduction or cessation included nausea, diarrhea, fatigue, muscle aches, fall in hematocrit, neutrophil and platelet counts, and rise in creatinine and CPK levels. The discussion of potential toxic effects of FIAU, the frequency of monitoring, the methods used for patient monitoring, and the parameters used for dose adjustment appeared to be appropriate for what was understood at the time about FIAU. Most notable was the lack of dosing guidelines for changes in ALT levels. This was specifically not included (after intense discussion between the investigators, sponsors and FDA), to prevent premature cessation of FIAU treatment in patients having a positive response to therapy.

Informed Consent

There were several submissions and modifications of the protocol and consent form, which took place in late 1992, and early 1993. The final consent form explains clearly to patients the rationale for the study (Appendix D).

Each patient was briefed on the study by a medical staff fellow at NIH. The informed consent process included discussion of the possibility of peripheral neuropathy. After discussion

with the NIDDK IRB, death was not included as a possible adverse event in the consent form itself since the death of patient 4D from the R91 trial was not attributed to FIAU. Nevertheless, patients were informed verbally of the possibility of death and that the death of patient 4D could have been FIAU related. The majority of the patients in the PPPC trial had previously been treated with FIAU in the R91 trial and had tolerated FIAU with minimal side effects. Risks and discomforts of FIAU included in the ICD were (1) Fatigue, irritability, and insomnia; (2) nausea and upset stomach; (3) skin rashes; (4) bone marrow suppression; (5) seizures; and (6) pains in the arms and legs. Review of the informed consent document by the IOM committee found that it was written clearly in language understandable to the layperson and was not misleading in minimizing the potential side effects of FIAU.

CONDUCT OF STUDY

Weekly staff meetings were held at NIH to discuss the status of research protocols. These meetings were regularly attended by both Hoofnagle and DiBisceglie. Present were the fellows and staff nurses. The original protocol had patient visits scheduled at weeks 1, 2, 4, 8, and 12, but NIH investigators asked patients to come in on two occasions between scheduled visits to monitor them more closely. In addition to these added clinic visits there was frequent telephone contact with the patients. Compliance with clinic visits was 100 percent for all 15 patients. The investigators kept flow sheets on all of the patients. These flow sheets were used for day-by-day monitoring and were separate from the charts which were kept in the medical records department at NIH. They were important for weekly meetings as well as for facilitating communication with patients.

Given the attention to details, the close supervision of the junior medical staff, and the qualifications of these junior staff, the IOM committee finds no evidence to suggest that the monitoring of the patients by senior investigators was inadequate or that a different monitoring system would have averted the FIAU tragedy.

Thorough review of the conduct of this study by the IOM committee has shown that the physician and nursing staff at the NIH were both compassionate and meticulous in the care of these patients. Documentation of the quality of care is apparent from the frequent patient monitoring visits and the frequent telephone contacts. There is no evidence of errors in clinical judgment related to interpretation of clinical or biochemical adverse events that would have predicted the fatal toxic events that occurred. Moreover, there is no evidence that the patients were coerced to remain within the trial or that the investigators overlooked significant adverse events that should have led to a dose reduction or dose cessation according to predetermined definitions of adverse events. In several instances the apparent lack of documentation of adverse events in case report forms (CRFs) resulted from a change in protocol to increase the frequency of visits without a concomitant change in the CRFs. If an event occurred at one of these additional visits, it was recorded in the clinic chart and the investigators and nurse coordinators were instructed to record the event on the page in the CRF at the subsequent clinic visit. In some instances, if the complaint had resolved before this subsequent visit, the event was recorded only in the clinic chart, not the CRF. Hence, the perception of protocol violations during the FDA audit.

STUDY OUTCOME

In early June 1993, it became apparent to the investigators at NIH that the 10 patients who had been started on FIAU in late March and April were having increasing side effects (mainly gastrointestinal, with nausea, vomiting, diarrhea, and abdominal cramps). These were reviewed by Hoofnagle, DiBisceglie, Fried, Straus, and McKenzie, and although the doses were reduced for two patients, adverse events were not thought to be of sufficient severity to discontinue treatment. After a meeting on June 22 to review the status of the trial and to discuss these adverse events with representatives of Lilly (Jennifer Stotka), the NIH investigators elected to continue the trial for an additional week. HBV DNA levels had decreased in all patients, and 6 of 10 patients had become HBV DNA negative. Because of this marked therapeutic benefit, the trial was continued.

At this point three patients were no longer receiving drug because of side effects. When one of these three developed lactic acidosis, hepatic failure, and renal failure on June 25, prior experience with a single puzzling patient (patient 4D) from the R91 trial made the investigators consider FIAU a likely cause. A decision was made to halt the trial on June 26. All 15 patients were seen at NIH within a few days. Seven of 10 patients who had received more than 2 months of FIAU treatment had evidence of FIAU toxicity (lactic acidosis, hepatic failure, pancreatitis, neuropathy, and/or myopathy). Despite stopping drug, seven patients had progressive hepatic failure and were transferred to other hospitals for possible liver transplantation. The other eight patients (three of whom had received FIAU for more than 2 months) had either minor toxicity or no adverse events.

Deaths

Patient 2

This 42-year-old man was diagnosed with HBV infection in 1981. A liver biopsy in 1984 revealed chronic active hepatitis. He was first evaluated at NIH in April 1985, when his only complaint was of fatigue. In March 1987 he was diagnosed with HBV-related membranoproliferative glomerulonephritis. A liver biopsy showed chronic persistent hepatitis. He was enrolled in an interferon protocol at the NIH in 1987 and then subsequently in the prednisolone/interferon protocol. Active HBV infection persisted. In June 1990 he was treated in the NIH ddI protocol, and a liver biopsy at that time showed chronic active hepatitis. Fatigue persisted on therapy and he continued to have active HBV replication.

In April 1992 he began the 28-day FIAU protocol. A pretreatment liver biopsy again showed chronic active hepatitis. He received FIAU at 0.25 mg/kg/day (total dose, 476 mg) and tolerated treatment other than for mild and transient irritability. HBV DNA levels fell markedly with treatment, but he remained positive for HBsAg and HBeAg.

In March 1993 he was retreated with FIAU (0.25 mg/kg/day; total dose, 1,218 mg; cumulative dose, 1,694 mg). He had side effects of fatigue and nausea, and after 4 weeks of therapy, he developed tingling and numbness of the feet. Nerve conduction studies were normal, but the dose of FIAU was decreased on June 2, 1993, and was stopped on June 8. He

continued to complain of pain in the feet. The total bilirubin level remained within the normal range while he was on FIAU. The patient's pretreatment ALT level was approximately 140 IU/liter and rose to a peak of approximately 160 IU/liter 10 weeks after starting FIAU. A serum albumin level of 2.8 g/dl on June 14 was attributed to hepatic decompensation in the subsequent FDA task force report, but for several reasons we believe it is likely that this was not related to FIAU-induced liver damage because (1) hypoalbuminemia was present before the patient began FIAU; (2) the patient had membranoproliferative glomerulonephritis with significant proteinuria; and (3) a pretreatment liver biopsy did not show cirrhosis or even fibrosis, which would be necessary if the hypoalbuminemia were secondary to hepatic decompensation.

On June 25 the patient contacted NIH complaining of nausea for 2 days. He did not wish to be seen at NIH, but an antiemetic was prescribed. Because of progressive nausea and weakness, he went to an emergency room in Virginia and was found to be markedly hypotensive and acidotic. The patient was seen by DiBisceglie that evening and was transferred to NIH.

Evaluation at NIH revealed hepatic and renal failure, severe peripheral neuropathy, and rhabdomyolysis (CPK elevations). The CPK elevation was likely related to muscle necrosis associated with hypotension. On June 30, he was transferred to the University of Virginia for consideration of liver transplantation. He developed worsening liver failure, renal failure, and acidosis. He was treated with an experimental hepatic assist device and underwent emergency liver transplantation on July 4, 1993. There was primary nonfunction of the liver, and the patient died on July 6 of circulatory failure and progressive acidosis.

Autopsy revealed hemorrhagic pancreatitis, glomerulonephritis, esophageal varices, and pneumonia. Histology of the liver explant showed micro-and macrovesicular steatosis, chronic active hepatitis with fibrosis, and cholestasis. Electron microscopy showed mitochondrial changes and fat accumulation.

Patient 1

This 35-year-old man was found to have HBV infection in April 1988 when he was evaluated for jaundice. He was first seen at NIH in August 1988, when he was noted to have a predominantly indirect hyperbilirubinemia and was given the concomitant diagnosis of Gilbert's syndrome. A liver biopsy in December 1988 showed chronic active hepatitis.

He was treated in a controlled trial of interferon at NIH in December 1988, initially receiving placebo and then 10 MU three times weekly. Although his HBV DNA levels fell, he remained HBsAg and HBeAg positive. In 1990, he was enrolled in a ddI trial at NIH. A repeat liver biopsy showed chronic active hepatitis. He was subsequently enrolled in the ribavirin trial at NIH in April 1991.

In April 1992 he was started on FIAU (0.1 mg/kg/day) as part of the R91 study (total dose, 247 mg). While on drug therapy, his ALT level peaked at three times the baseline level, but his HBV DNA fell from 308 to 78 pg/ml. He remained HBsAg and HBeAg positive. His only side effects while on FIAU therapy were headaches.

He was enrolled in the final FIAU study in March 1993 (at a dose of 0.25 mg/kg/day, total dose, 1,366 mg; cumulative dose, 1,613 mg). He complained of nausea (rated as moderate on the CRF at week 1 and mild during subsequent visits). The patient also had some mild anorexia and moderate abdominal pain at week 4. Appropriate tests were scheduled to evaluate the pain. The dose of FIAU was reduced by the investigators on May 27, 1993. Abdominal pain had resolved at a visit 2 days after reducing the dose, but the patient eventually stopped taking FIAU on his own on June 10 because of abdominal cramps. HBV DNA had become undetectable, but he remained positive for HBsAg and HBeAg. Hyperbilirubinemia, which was predominantly indirect, was noted on several occasions while he was on FIAU therapy and was likely due to Gilbert's syndrome. His pretreatment serum bilirubin level was 3.0 mg/dl and it rose to 4.4 mg/dl. His ALT level rose from a pretreatment value of approximately 60 IU/liter to approximately 120 IU/liter. The IOM committee finds no clear-cut evidence of drug-related hepatotoxicity during FIAU treatment in this patient. Attribution of hyperbilirubinemia to Gilbert's syndrome appears reasonable even with current knowledge of the FIAU syndrome.

There is documentation of frequent telephone contact as well as clinic visits throughout this period and no evidence that the patient was coerced into continuation of FIAU. Many attempts were made to try to reach him from June 26 to 28. Finally, he was contacted on the evening of June 28 and was admitted to NIH on the following day when he was noted to be jaundiced. Examination revealed a peripheral neuropathy. Over the ensuing days, he developed progressive hepatic failure and lactic acidosis. He was treated with glucose infusions. A computed tomography (CT) scan showed normal liver and pancreas, but ascites. Because of progressive liver failure, he was transferred to Pittsburgh for evaluation for liver transplantation. He became progressively acidotic and hypotensive and died on July 30, 1993. Autopsy revealed hemorrhagic pancreatitis, myocardial infarction, and pulmonary congestion. Liver histology revealed fibrosis, cholestasis, and severe micro-and macrovesicular steatosis.

Patient 4

This 52-year-old man was diagnosed with chronic HBV infection in May 1989, at which time a liver biopsy showed chronic active hepatitis with cirrhosis. He was initially seen at NIH in December 1989 and was subsequently enrolled in an interferon protocol (randomly assigned to the control group), a ribavirin protocol, and then the R91 FIAU protocol. A pretreatment liver biopsy for the R91 trial showed chronic active hepatitis with cirrhosis. He received a total of 134 mg of FIAU in the initial trial, and his HBV DNA levels fell from 75 to 6 pg/ml. The levels remained low for 5 months following therapy, but then returned to pretreatment levels. He tolerated FIAU well, with minor symptoms of abdominal cramps, fatigue, and irritability. He was retreated with FIAU from April 1993 until he was told to stop taking the drug on June 26, 1993 (total dose, 628 mg; cumulative dose, 762 mg).

During the second course of FIAU treatment, he developed cough, fever, muscle cramps, anorexia, fatigue, insomnia, and mild nausea. His dose of FIAU was reduced and he was treated with clarithromycin for a pneumonia documented on chest radiograph. Pretreatment serum bilirubin was 1.6 mg/dl and remained in the normal range while he was on FIAU therapy (1.7 mg/dl when FIAU therapy was stopped). His ALT level never rose

above the pretreatment value of approximately 140 IU/liter and was 59 IU/liter when FIAU treatment was stopped.

The patient was evaluated at NIH on June 26, 1993 at which time he had no new complaints. Hepatic synthetic function was well-preserved, and he was treated with oral carnitine, uridine, diuretics, and intravenous thymidine and glucose. However, over the ensuing 2 weeks he had progressive hepatic failure (serum bilirubin, 10.3 mg/dl, prothrombin time, 20 seconds) and lactic acidosis. His serum lipase level was elevated but his amylase level was normal. He was transferred to the University of Virginia on July 12, 1993, for liver transplant evaluation. Acidosis and hepatic failure worsened, and he became comatose and hypotensive and died on July 16 awaiting liver transplantation. Autopsy revealed active cirrhosis of the liver with marked macro- and microvesicular steatosis. Electron microscopy showed diffuse mitochondrial damage. There was hemorrhagic pancreatitis.

Patient 6

This 37-year-old woman was diagnosed with HBV infection in March 1990, and a liver biopsy in October 1990 showed chronic active hepatitis. She was first seen at NIH in July 1991, at which time a repeat liver biopsy showed mild to moderate chronic active hepatitis. She was enrolled in the ribavirin protocol and then the R91 FIAU protocol, in which she received 115 mg of FIAU. With this first course she noted a mild increase in fatigue. HBV DNA levels fell but never became negative, and she also remained positive for HBsAg and HBeAg. Pretreatment serum ALT level was 66 IU/liter and rose to a peak value of three times the baseline level. These returned to baseline levels after stopping FIAU.

In the PPPC protocol she received a total of 551 mg of FIAU (cumulative dose, 666 mg). She complained of right upper quadrant pain at the week 8 visit. She had tenderness but no complaints of pain at a previous visit (week 6). She had also had right upper quadrant pain before starting FIAU treatment, likely related to her hepatitis. The pain experienced while on FIAU occurred approximately three times per week, lasted only a few minutes, and was not of sufficient severity to require a dose reduction. Before retreatment her serum ALT level was 96 IU/liter, and this rose to three times the baseline level by week 8. She reported myalgias (rated as mild), which occurred on a single day and for which no medication was taken. These myalgias did not meet the protocol criterion for dose reduction. When the patient told an associate investigator of nausea, vomiting, headaches and dizziness on June 15, 1993, she was instructed to stop taking the drug.

She was admitted to NIH Clinical Center on June 17 with nausea, vomiting, diarrhea, and fatigue. Hepatic synthetic function and amylase were normal; here ALT level was 221 IU/liter. Over the subsequent weeks she continued to have nausea and deteriorating hepatic function (ALT levels, 554 IU/liter, bilirubin levels, 8.2 mg/dl). The diagnosis of FIAU hepatotoxicity was made when patient 2 presented in liver failure. She was treated with thymidine and glucose, but on June 28 she developed severe abdominal pain and biochemical evidence of pancreatitis.

On June 29 she was transferred to the University of Virginia for evaluation for liver transplantation. She had progressive lactic acidosis and hepatic failure. She was treated with

an experimental hepatic assist device and underwent liver transplantation on July 9. Lactic acidosis and hepatic function improved but pancreatitis continued. A CT scan revealed infarction of the left lobe of the liver, and an angiogram diagnosed hepatic artery thrombosis. She underwent repeat liver transplantation on August 14, but died of complications of pancreatitis and renal and respiratory failure on August 31. The first liver explant showed chronic active hepatitis with fibrosis, microvesicular steatosis, and cholestasis; electron microscopy revealed mitochondrial degeneration. The second liver explant showed subtotal hepatic necrosis. Autopsy revealed multisystem failure with acute and chronic pancreatitis.

Patient 7

This 44-year-old man with chronic HBV infection was first diagnosed in 1990 and was first seen at NIH for evaluation for possible therapy in March 1991. A liver biopsy in May 1991 showed mild chronic active hepatitis. He was enrolled in the ribavirin protocol in June 1991 without response and was therefore evaluated for and enrolled in the R91 FIAU protocol. He received 0.5 mg/kg/day for 28 days in August 1992 (total dose, 1,353 mg) which he tolerated well other than mild nausea and one episode of muscle cramps. His serum ALT level rose on therapy to three times the baseline levels, and HBV DNA levels decreased but did not become negative.

He began the PPPC protocol in April 1993. His pretreatment ALT level was 58 IU/liter, serum bilirubin was 0.6 mg/dl, and albumin level and prothrombin time were normal. He received FIAU at a dose of 0.25 mg/kg/day for 75 days (total dose, 1,753 mg; cumulative dose, 3,106 mg). On therapy he developed increased fatigue, irritability, and mild nausea. He complained of slight bilateral abdominal pain, documented in the NIH chart on May 26, which had resolved by a follow-up visit on June 10. Given the mild and transient nature of the pain, there was no indication for a dose reduction since protocol criteria were not met. He also had occasional pains in the hands and feet, but nerve conduction studies were normal other than demonstrating carpal tunnel syndrome, which had been present on prior studies. On therapy his ALT level rose to approximately 140 IU/liter from a pretreatment level of 60 IU/liter and his HBV DNA level fell (from 249 to 4 pg/ml). His serum bilirubin level remained within the normal range on therapy. Echogenicity consistent with fatty infiltration of the liver was seen on an ultrasound performed on May 26 in a routine screening for hepatocellular carcinoma. These findings are nonspecific and poorly predictive of fatty liver, which is best documented by a liver biopsy.

Repeated attempts to contact the patient were made on June 26 and 27. He was traveling and returned home late on the 28. He had noted increasing fatigue, anorexia, nausea, vomiting, abdominal pain, numbness, and tingling of the feet. Upon admission to NIH on June 29 examination revealed jaundice, hepatomegaly, and a peripheral neuropathy. His serum bilirubin level was 10.5 mg/dl, ALT was 121 IU/liter, prothrombin time was 15.1 seconds, and lactate was 8.3 mmol. Over the subsequent 2 days, he developed progressive liver failure, lactic acidosis, and renal failure. On June 30 he was transferred to Pittsburgh for liver transplant evaluation. Temporarily supported by an artificial hepatic assist device, he was HBsAg and HBeAg positive but HBV DNA negative. He underwent emergency liver transplantation on

July 4, but was hypotensive and severely acidotic and the graft failed to function. The patient died of hepatic failure, acidosis, and circulatory collapse on July 5, 1993. Autopsy revealed hemorrhagic pancreatitis, severe pulmonary fibrosis, renal necrosis, and ischemic colitis. Liver explant showed chronic active hepatitis, marked cholestasis, and a mixed micro- and macrovesicular steatosis. Stains for HBsAg and HBcAg were positive.

Liver Transplantation

Of the five patients who underwent liver transplantation, only two patients survived (patient 3 at Emory University and patient 10 at the University of Virginia). Three patients who died following liver transplantation are described above (patients 6, 2, and 7).

Patient 3

This 57-year-old man with chronic HBV infection had previously been enrolled in a ribavirin protocol at NIH. A liver biopsy before therapy reportedly showed chronic active hepatitis. A repeat biopsy prior to the R91 protocol showed chronic active hepatitis with fibrosis. As patient 1C in trial R91, he received 28 days of FIAU treatment in June 1992, with side effects of mild fatigue, irritability, and muscle cramps. During follow-up he had right upper quadrant pain. A laparoscopic cholecystectomy on October 29, 1992, revealed a single gallstone and gallbladder pathology showed cholecystitis. An intraoperative liver biopsy showed severe chronic active hepatitis with fibrosis. He was retreated with FIAU in the PPPC trial at a dose of 0.1 mg/kg/day from March 1993 until he was told to stop taking the drug on June 26, 1993 (doses of 121 mg in the R91 trial, and 678 mg in the PPPC trial, total dose, 799 mg). His serum bilirubin level remained within the normal range while he was on FIAU. His serum ALT level went from 163 IU/liter pretreatment to a maximum of 244 IU/liter. He developed symptoms of a peripheral neuropathy, but nerve conduction studies were inconclusive. He complained of cramps in his arms and legs on June 21, 1993.

The patient underwent a full evaluation at the NIH Clinical Center on June 28. Initially, he had only mild hepatic impairment, but in the subsequent 2 weeks he had progressive jaundice and hypoprothrombinemia (serum bilirubin levels, 11.2 mg/dl; prothrombin time, 18.3 seconds) with lactic acidosis, although there were only minor changes in his serum ALT levels. His serum lipase level rose, but his amylase level remained normal. He was treated with oral vitamins, carnitine, and uridine, and intravenous thymidine and glucose. He was transferred to Emory University for liver transplant evaluation. His hepatic function continued to deteriorate and he underwent liver transplantation on August 4. Immediately pretransplant he was HBsAg and HBeAg positive but HBV DNA negative. He received perioperative and postoperative high dose hepatitis B immune globulin prophylaxis to prevent posttransplant HBV infection. He did well postoperatively and was discharged 17 days later. Pathology of the liver explant revealed chronic active hepatitis with cirrhosis, positive staining for HBsAg and HBcAg, cholangitis, cholestasis, and micro- and macrovesicular steatosis. He had persistent neuropathy following liver transplantation.

Patient 10

This 63-year-old man with chronic HBV infection had been followed at NIH since 1988. A liver biopsy at that time showed mild chronic active hepatitis with fibrosis. He had been a subject in interferon, prednisone/ interferon, and ribavirin trials at NIH and received a total of 154 mg of FIAU in the R91 study in June and July 1992. His only side effects were mild fatigue and irritability. Although his HBV DNA levels decreased with treatment, he continued to have active viral replication and was thus enrolled in the PPPC trial in April 1993. He received a total of 1,716 mg of FIAU between April 21 and June 26, when he was told to stop taking the drug (cumulative dose for both studies, 1,870 mg). Side effects during the second course of therapy included moderate fatigue, mild muscle weakness, and decreased libido. Before retreatment his serum ALT level was 42 IU/liter and serum bilirubin level was 1 mg/dl.

He was admitted to NIH Clinical Center on June 28 complaining of fatigue, nausea, and weakness. His serum bilirubin level on admission was 3.9 mg/dl; his prothrombin time was normal, and his ALT level was 111 IU/liter. He was treated with oral carnitine and uridine, and intravenous glucose and thymidine. His hepatic function continued to deteriorate, with the development of jaundice (bilirubin, 35.7 mg/dl), ascites, hypoprothrombinemia (19.3 seconds), mild encephalopathy, and progressive lactic acidosis.

On July 11 he was transferred to the University of Virginia for evaluation for liver transplantation. Because of deteriorating hepatic function and progressive encephalopathy, he required intracranial pressure monitoring and underwent successful liver transplantation on July 19. He had a complicated postoperative course but was eventually discharged 92 days following the transplantation. He received peri-and postoperative hepatitis B immunoprophylaxis and immunosuppressive therapy with cyclosporine and prednisone. The liver explant demonstrated cirrhosis with cholestasis, cholangitis, and marked microvesicular steatosis. He had persistent neuropathy following liver transplantation.

Other Nonlethal Adverse Events

In early June 1993 it became apparent that the 10 retreatment patients were having significant side effects, particularly nausea and peripheral neuropathy.

Gastrointestinal side effects/pancreatitis

The majority of patients (patients 1, 3, 4, 5, 6, and 7) had gastrointestinal complaints. Patient 3 complained of mild abdominal pain prior to retreatment with FIAU in March 1993. On therapy he complained of mild nausea and constipation. Patient 5 had abdominal discomfort and persistent hyperamylasemia.

Hepatoxicity

The mean rise in ALT levels in the seven patients who developed severe systemic toxicity was less than twice the pretreatment levels. In contrast, mean serum bilirubin levels

in these same patients rose from within the normal range (less than 1.5 mg/dl) to greater than 15 mg/dl. *Thus, hyperbilirubinemia, not marked aminotransferase elevation, is a feature of FIAU hepatotoxicity* . Three surviving patients (patients 5, 8, and 9) who had received more than 2 months of FIAU treatment and who did not undergo liver transplantation had mild FIAU toxicity. ALT levels fell in patient 8, from a pretreatment level of 110 IU/liter to 80 IU/liter. The ALT level fell in patient 9, from a pretreatment level of approximately 360 IU/liter to less than 50 IU/liter. The ALT level remained less than 50 IU/liter throughout therapy in patient 5. Despite the mean fall in ALT levels in these patients while they were on therapy, microvesicular steatosis indicative of FIAU toxicity was present on liver biopsies performed subsequent to June 1993 in all three.

Peripheral Neuropathy/Myopathy

Several patients developed symptoms of a peripheral neuropathy while on FIAU therapy, but nerve conduction studies were normal or near normal.

Fatigue

Several patients (patients 6, 2, 3, 10, and 4) complained of fatigue, but given the nature of chronic HBV infection and the existence of fatigue before starting FIAU therapy in these patients, assignment of this symptom to FIAU therapy was and is problematic. The protocol specified a dose reduction for "fatigue moderately affecting activity," but although fatigue in these patients was on occasion rated as moderate, there is no evidence that the fatigue "moderately affected activity."

No Adverse Events

All five patients who received FIAU for less than 1 month of FIAU (patients 11-15) were asymptomatic.

RESPONSE TO THE EMERGENCY

There is clear evidence that the investigators, medical staff fellows, and nurses at NIH were very involved in the care of the patients in this trial. Careful documentation of patient visits in CRFs, clinic charts, and flow sheets attests to the attention that was given to these patients. This was no more apparent than on June 25, 1993. After NIH was notified that patient 2 was hospitalized in Virginia with lactic acidosis, DiBisceglie drove to the hospital that evening (a trip of about 80 miles each way). Admittedly, this was an unusual, catastrophic event. Nevertheless, it would be erroneous to assume that all physicians, be they clinical researchers or community physicians, would respond in this manner. Hoofnagle was notified

at home at 1:30 a.m. on June 26, 1993. He had the patients' updated flow sheets on hand to try to understand what was happening. Again, the fact that he had this information with him at home attests to his close involvement with the study and the patients. Hoofnagle and Straus met at NIH on the morning of June 26 and attempted to call all of the patients to instruct them to stop taking FIAU and to return to NIH for evaluation. All 15 patients in the trial were seen within a few days.

The IOM committee would like to emphasize that the investigators promptly recognized the syndrome of FIAU toxicity in the second patient (patient 2), with patient 4D from R91 being the index patient, and that their subsequent response to the crisis was exemplary. The committee has only minor criticisms of the conduct of the trial at NIH. These would include patient 1A from R91, in whom the peripheral neuropathy was ascribed to alcohol rather than FIAU. It is likely that the difficult nature of the patient-physician interactions had a negative impact on the care of this patient.

Following the termination of the PPPC trial, ACTG investigators involved in prior FIAC/FIAU trials were informed, and they attempted to contact all previously treated patients. Only then was the death of patient 408R in the R90 trial discovered. Even with hindsight and full knowledge of the syndrome of FIAU toxicity, only one of the deaths that had occurred before the PPPC trial was *clearly* FIAU related (patient 4D from the R91 trial). Three deaths were *possibly* FIAC/FIAU related (patient 107 from the R89 trial, patients 406 and 409 from the R90 trial) and two deaths were *probably not* FIAU related (patients 401 and 408 from the R90 trial). The principal investigators at NIH, Hoofnagle and Straus, concluded that the deaths in the PPPC trial were due to previously undescribed and unique toxicity which was progressive and irreversible despite the discontinuation of therapy. A difficult feature of this syndrome, which included hepatic failure, lactic acidosis, pancreatitis, neuropathy and myopathy, was that it became manifest even after the drug treatment was stopped. Neither the nature nor the severity of the toxicity was predicted by preclinical toxicology studies in animals. Accurate association between the drug and the toxic events was confounded by liver abnormalities associated with chronic HBV infection, rises in liver enzyme levels that were interpreted as a positive response to the drug (the flare), and confounding variables including treatment in previous FIAU/FIAC trials and with other nucleoside analogs known to cause neuropathies and pancreatitis (ddC and ddI).

LONG-TERM FOLLOW-UP

The 10 surviving patients (including two liver transplant recipients) are still being followed at NIH every 1 to 3 months. Those patients who have not previously been treated with interferon have been offered this therapy. Ongoing studies of these patients with nuclear magnetic resonance spectroscopy are attempting to elucidate the mechanism of toxicity of FIAU. Two patients who survived after liver transplantation have evidence of peripheral neuropathy and one patient has muscle weakness (myopathy). The other eight patients have no clinical evidence of FIAU toxicity.

One patient (patient 9) became HBV DNA and HBeAg negative while on FIAU therapy and has remained negative, with normal ALT levels in follow-up examinations. Patients

5, 8, and 11-15 have evidence of ongoing HBV infection (HBsAg, HBeAg, and HBV DNA positive, with elevated liver enzyme levels).

Patient 3, who underwent liver transplantation, is doing well on cyclosporine, azathioprine, and prednisone. He is receiving long-term hepatitis B immunoprophylaxis and remains HBsAg and HBV DNA negative. He has physical signs of an ongoing peripheral neuropathy, confirmed by nerve conduction studies. He continues to be followed at Emory University and NIH every 3 to 6 months. Liver function is now normal, and a recent liver biopsy showed only nonspecific changes.

Patient 10 continues to be followed closely at NIH following liver transplantation. He has both clinical and electrophysiologic evidence of a peripheral neuropathy. His liver function is normal, and he remains HBsAg and HBV DNA negative on hepatitis B immunoprophylaxis. His immunosuppression consists of cyclosporine and prednisone treatment. He continues to be weak and to have difficulty walking, although he can drive a car. A follow-up liver biopsy has shown only nonspecific changes. He will continue to be followed at NIH and the University of Virginia on a regular basis.

CONCLUSIONS

Although the outcome was tragic, the IOM committee believes that there was sufficient justification for initiating the PPPC trial, that the protocol and consent form were appropriate, and that the conduct of the trial was equal to or better than the prevailing standards of care. There is no evidence that there was information available at the initiation of the PPPC trial or at any time during the trial itself that would have or should have averted the ultimate disaster.

11

Summary of Patient Interviews

A total of 19 patients who received FIAU were interviewed over the telephone by the IOM committee study director. The focus of the interview was on issues of informed consent and attention to possible side effects. The subjects were drawn from the three studies testing FIAU in hepatitis B virus-positive subjects without concomitant HIV infection: the 28-day NIH study (R91), the aborted 6-month NIH study (PPPC), and the 3-month study in Galveston and Boston (PPPA) were terminated along with the NIH study. All five subjects enrolled in the PPPA trial were contacted by the principal investigators and were asked if they were willing to participate in a telephone interview for the IOM committee reviewing all of the FIAU trials. All agreed and consented to provision of their names and phone numbers to IOM, although they were given the option of calling the IOM study director if they preferred to remain anonymous. A similar procedure was followed with the NIH patients, except that the NIH Clinical Center's patient representative, rather than the principal investigators, made the initial contact with the patients. Since 10 of the 24 patients in the 28-day trial (R-91) subsequently became subjects in the 6-month trial (PPPC), and 5 of the 15 patients in the PPPC trial died, only 24 NIH patients were potentially available for interview (24 + 15 - 10 - 5). Of these, 15 indicated that they were willing to be interviewed, and 14 were successfully contacted and interviewed. Eight of these 14 participated only in the R91 trial, four were subjects in both the R91 and PPPC trials, and 2 participated only in the PPPC trial.

Although the numbers of patients from each study are far too small to allow any meaningful quantitative analysis, the committee felt that some firsthand information from the patients themselves was necessary to properly evaluate both the possibly self-serving accounts of the scientists and drug companies on the one hand and the often sensational media accounts charging or implying systematic negligence, indifference, or even willful misrepresentation on the other hand.

Several generalizations are in fact possible from an examination of the answers of the group as a whole to a few of the questions. For example, only 3 of the 19 subjects reported that their current health was worse than that before their exposure to FIAU. This is at least partially a result of bias in the sample. Five subjects died, of course, and it is quite possible that others who might have reported poor health declined to be interviewed for that reason or because of concern about pending legal action against the government and the drug companies. Nevertheless, all of those interviewed reported that they had been encouraged to read the ICD carefully and had done so. Some had been given a copy of the protocol as well. All of the subjects interviewed reported being fully aware that participation was entirely voluntary and

that they were free to withdraw at any time (although two subjects also reported that it was made clear that they were lucky to be accepted and should be very grateful; no one interviewed ever considered dropping out of the study). Surprising, only four subjects sought advice from another physician once they had the consent form or protocol in hand (all four were encouraged, to a greater or lesser degree, to sign the form).

All of the interview subjects reported that the study staff had been very attentive to their reports of side effects at every appointment, pointing out that they were always quizzed not only on the symptoms from a long written list but about any other changes in their health of any sort. When they reported new symptoms or increased severity of previously reported symptoms to nonphysician staff, the latter were quick to call in a physician. Four of the 19 patients (3 with current injuries they attribute to FIAU) interviewed reported that they would not consider volunteering for further drug trials with their previous investigators under any circumstances.

An important commonality among the six patients in the PPPC trial was their universal recall of discussion during the informed consent process about the death of one of the patients in the PPPC trial 4 months after completing FIAU therapy, following surgical removal of his gallbladder. Although the PPPC protocol discussed the death in some detail, along with the rationale behind the investigators' judgment that the death was not FIAU related, the ICD actually given to the subjects for signature contained none of this information. All of the subjects interviewed recalled being told about this patient, as well as another patient in the R91 trial who developed peripheral neuropathy some months after his course of FIAU treatment. All of them also recalled, in varying detail, that the investigators did not believe that FIAU was responsible for the death and that nerve conduction tests had been added to detect neuropathies. The Boston/Galveston (PPPA) trial, which began at roughly the same time as the PPPC trial, did not include such a discussion, and as a result one of the patients from that trial, who was otherwise quite satisfied with his treatment by the study staff expressed disappointment that he "didn't get full disclosure." As he put it, "Even if they thought it was irrelevant it should have been my call." This patient was one of the four who told the interviewer that they would not volunteer for another drug trial (in this subjects' case, "anywhere").

Perhaps the most important generalization that can be deduced from this small sample of 19 interviews is that the subject's reports of the informed consent process and their satisfaction with their treatment by the study staff are closely associated with their current health. The three subjects interviewed who reported currently suffering from peripheral neuropathy, although two were in the R91 trial and the other was in the PPPA trial, were insistent that the risk of side effects had been minimized in their discussion of the ICD. One reported being satisfied with the answers to his many questions at the time, but he now feels that significant pieces of information were withheld or denied; the second reports that his only question, directed at one of the associate principal investigators sometime after signing the ICD, earned him a scolding for his lack of faith. The third patient reported a painful neuropathy that developed, like that of the others, sometime after halting FIAU and complained of indifference or disbelief by the study staff (see chapter 7 above). Although NIH continued to provide evaluation and consultation to the patient's private physician (the patient had moved to the Far West in the interim), relations became increasingly adversarial. Difficulties initially centered upon the apparent reluctance or inability of NIH to provide for pain treatment, but

escalated sharply when the tragic events of the PPPC trial unfolded. The patient felt that the trial should never have been undertaken in view of his neuropathy and adverse effects noted in other patients during and after the previous trials. The doctor-patient relationship finally ruptured with the patient's very strongly worded testimony to this effect to the FDA Antiviral Advisory Committee in September of 1993 and a subsequent letter to him from Hoofnagle informing him that in view of those remarks he did not think it appropriate for NIH to continue providing medical care or advice. Upon appeal to the Acting Director of NIH the patient was extended a formal apology, assured that he would receive the same opportunities for assistance as other former trial participants, and given a new point of contact at NIH, the Clinical Director of NIDDK. He subsequently received a thorough clinical evaluation which included assays for FIAU in blood and urine (negative). He has declined to participate in a formal long-term study of FIAU patients at NIH.

The committee cannot and does not see it within its charge to make judgments on the veracity of every patient's complaint. Accordingly, the unhappiness of these three patients may be completely justifiable. The overall pattern of response by the interview subjects, however, suggests that the studies on the whole were characterized by good to excellent rapport between patients and staff, frank discussion of potential risks, close attention to signs of FIAU toxicity, prompt action when it seemed indicated (leaving aside the question of whether the investigators should have known more than they did about toxicity at the time), and a general feeling by the patients that although they would certainly never have volunteered for a study that they believed involved a serious risk of death or permanent injury, they felt that they had been informed to the best of the investigators' abilities and had been treated conscientiously throughout the trials.

12

Overall Assessment of the Trials

Although the committee has offered comments throughout the reviews of the individual trials, it will be useful to try to summarize the committee's overall impression of the conduct of these trials. In doing so the committee will return to the rules and norms for ethical research with human subjects described above in the section describing clinical trials.

PROCEDURAL REQUIREMENTS

The IOM Committee reviewed the various documents related to review and approval by the IRBs; it also interviewed the chairs of these committees. The IOM committee also reviewed the sample consent forms that were used in these studies. It is always possible to second-guess such documents, particularly the consent forms. It is rare that an IRB reviews a consent form that has already been reviewed and approved by another IRB without finding some way to improve it (Lipsett, Fletcher and Secundy, 1983). The IOM committee found these documents to be of generally very high quality.

In the opinion of the IOM committee, there were no clear departures from the requirements of relevant federal regulations. One omission detected by the IOM committee could be considered a possible deviation from the regulatory requirements, but members of the committee are uncertain about whether it should be so considered because earlier trials had not clearly established a cause-effect relationship between FIAU and peripheral neuropathy. The consent form for protocols PPPA and PPPG did not mention peripheral neuropathy or anything else that would enable a prospective subject to anticipate this adverse effect. It did mention muscle aches, but this does not suffice as disclosure of the possibility of peripheral neuropathy.

Both of these studies were initiated roughly contemporaneously with the 6-month PPPC trial at NIH, and the protocols were very likely written well after the PPPC protocol, which included not only a discussion of peripheral neuropathy, albeit somewhat atypical in its delayed onset in two patients who had participated in trial R91, but also included a provision for nerve conduction tests to help assess developing neuropathy.

SUBSTANTIVE NORMS

The IOM Committee provides no comment in this section on compliance with the ethical norms calling for good research design and competence of investigators because these matters are discussed at length in other parts of this report.

Favorable Balance of Harms and Benefits

As discussed earlier, the ethical justification of research requires a determination that the balance of risks and anticipated benefits is—in the words of federal regulations—"favorable" or "reasonable." This determination, which must first be made by the investigators and then ratified by the IRB, must be accomplished at the outset, before the research is begun. These estimates of risk and anticipated benefits may turn out to be badly mistaken when the results are in, and all involved may regret doing the research, but the work should not be deemed unethical solely on that basis.

In this case there were reasonable grounds for great optimism about FIAU. It often inhibited hepatitis B virus DNA replication very promptly and virtually completely; no other therapeutic agent that could accomplish this salutary objective so efficiently was (or is) known. Moreover, it was an easily administered oral medication, and there was no advance indication of any serious adverse events.

In all research activities designed to evaluate a new drug, the initial estimation of risks must take into account the possibility of occurrence of novel injuries—harms that cannot be predicted on the basis of prior clinical or preclinical testing. Fortunately, injuries that are both serious and unanticipated are very unusual. In this case there occurred an injury that was both serious and unanticipated. This occurrence does not indicate that the research was ethically deficient. The IOM committee cannot—even in retrospect—suggest any tests that might have been done to anticipate this serious toxicity.

Responsiveness to this norm also requires that there be careful monitoring of all events that have a bearing on the assessment of both risks and benefits. In this case there have been allegations that the monitoring of safety data may have been faulty and that findings of adverse events did not result in indicated changes either in the protocol or in the risk information divulged to subjects. On review of this matter, the IOM committee finds that the monitoring of such data was not merely adequate; when considered in the light of prevailing practices in the field, the monitoring activities of these research groups and the sponsors were exemplary. Interpretation of such data, particularly data indicating either damage to the liver or diminishing liver function, was not recognized promptly as indicating drug toxicity for at least three reasons. (1) Since the patients had chronic hepatitis some fluctuation in the results of liver function test results is expected as the activity of the disease waxes and wanes. (2) Some of the patients in whom changes in liver function tests were detected had other factors that could have contributed to such changes. (3) Some, although not all, experts believe that improvement in patients with chronic hepatitis is often heralded by flare responses during which laboratory test results that most commonly indicate damage to the liver (elevated serum aminotransferase) may be observed.

It should also be noticed that the PPPC trial (and the PPPA trial running concurrently in Boston and Galveston) was discontinued almost immediately after the sponsors and investigators became aware of the second instance of hepatic failure in a subject who had participated in the FIAU studies. Under the circumstances, this was a remarkably prompt response.

Equitable Selection of Subjects

These studies did not involve as subjects any members of the so-called special populations that have been identified in federal regulations or proposed regulations as requiring special protection. And yet, as discussed earlier, there are reasons to consider as vulnerable in relevant respects persons with serious and potentially disabling or deadly diseases. Such persons may not be "so situated as to be able to exercise free power of choice." The subjects of the FIAU studies can certainly be considered vulnerable in this regard.

Ethical justification of the involvement of such persons requires determinations that the research goals are important and that they could not be realized with less vulnerable subjects and that the research is designed to develop knowledge or therapeutic products that (one reasonably expects) will be of benefit to the vulnerable class from which the subjects are recruited. Moreover, it is generally accepted that investigators should recruit subjects who have the capacity to consent for themselves before turning to those who cannot (Levine, 1986). These conditions seem to us to have been met by the studies under review.

In consideration of the possibility that at least some of the subjects might have been relatively impoverished in that they would be unable to secure medical services of high quality without participation in these studies, there was a need to be especially careful to avoid offering "undue" material inducements in the form of cash payments. The IOM committee found no evidence of undue inducements. It must be acknowledged that the offering of excellent medical care and promising new therapies free of charge is a very substantial material inducement. Although many commentators in the field of medical ethics have identified and described the problems associated with this fact (Levine, 1986), the IOM committee is aware of none who have recommended a satisfactory resolution of these problems.

It must be acknowledged that some persons with serious chronic diseases may enroll as research subjects as a consequence of desperation or in fear of retaliation for not cooperating. Investigators can respond to the fear of retaliation by informing prospective subjects of their right to refuse to participate or to withdraw at any time without the loss of any benefits to which they are otherwise entitled. Such advice is required by federal regulations and was provided to subjects of the FIAU studies. But, as noticed earlier, such information will not alleviate all fears of retaliation in all prospective subjects.

The most constructive way that investigators can respond to the desperation and fears of some prospective subjects is to be sensitive to such feelings and to try to avoid exploiting those who experience them. The IOM committee, on the basis of its interviews with investigators, research nurses, and patients, found that most of them reported that the investigators were sensitive to such matters. This topic will be discussed in more detail in the section on informed consent.

In some respects, many of the subjects of these studies may be considered less vulnerable (more capable of informed consent) than typical subjects in early-phase drug trials in that many of them were experienced as research subjects, having previously served as subjects in other drug trials.

Compensation for Research-Related Injury

The consent documents for each of the protocols reviewed by the IOM committee were in compliance with the regulatory requirement to provide "an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained."

There is no question that all possible steps were taken by the NIH investigators and Eli Lilly to insure that the patients injured in trial PPPC received whatever medical care was necessary. Eli Lilly in fact has spent over $2 million to date for services to these patients and their families. Obviously these efforts were largely in vain, and a number of victims or their families have turned to the legal system in search of compensation.

As noted earlier in this report, several prestigious national advisory bodies have recommended to the federal government that it establish a no-fault system for compensation for injured research subjects. The IOM committee believes that the availability of such a system would have been very helpful in the aftermath of the FIAU studies. Among other things, it would have made possible an appropriate response to the just claims of injured patient-subjects and their families without the need for litigation with its attendant vexation, delay, and added financial burdens. Moreover, it would have made it unnecessary for the investigators and the patient-subjects who had grown accustomed to cooperation and mutual support in the pursuit of a common goal to become wary of one another and guarded in their communications as is customary in potential adversary proceedings. For these and other reasons, the IOM committee supports the development of a no-fault system of compensation for research-related injury.

Informed Consent

As noted earlier, the IOM committee found that the informed consent documents were of high quality and thoroughly responsive to the requirements of federal regulations. Now the report addresses the process of informed consent.

The committee was presented with persuasive evidence that each of these investigators went beyond the requirements set forth by the IRBs. For one notable example, the IRB decided that it would not be necessary to divulge the fact that one subject had died following participation in an early trial of FIAU. The circumstances of that death were such that one could not state confidently that FIAU played any role in the unfortunate outcome. That point notwithstanding, investigators and subjects recalled that the investigators had, in fact, informed prospective subjects of that death and spoke candidly about their concern that it might be related to FIAU.

SUMMARY

The overall impression of the IOM committee is that these trials were ethically sound clinical research projects designed and carried out by highly competent investigators who frequently went beyond the requirements dictated by regulations or imposed by IRBs to respond to the desires and needs of their patient-subjects. Indeed, with rare exceptions, their relationships with the patient-subjects appeared to have elements of the depth and sensitivity to which good primary care physicians aspire in their relationships with their patients.

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Recent Studies of FIAU Toxicity

Since the tragic events associated with the (PPPC) clinical trial, Lilly and NIH have conducted and sponsored extensive additional research into the characteristics and mechanism of the FIAU toxicity described in humans and into the development of a possible animal model for this toxicity. The investigators involved gathered in April and December 1994 to provide progress reports to each other and their sponsors, who kindly agreed to allow the IOM committee access (Lilly-NIH FIAU meeting, 1994).

MECHANISMS

Among several studies utilizing tissue from FIAU-treated patients was work on mitochondrial (mt) enzymology by Douglas Kerr of Case Western Reserve University, which suggested that the liver toxicity from FIAU was related to injury to enzymes of the electron transport chain encoded in part by mt DNA. These liver samples showed relatively normal levels of mt enzymes of pyruvate metabolism, which are encoded largely from nuclear DNA.

Cecil Fox of Molecular Histology Laboratories and Richard Sallie of NIDDK used in situ hybridization with patient tissue to demonstrate widespread DNA injury in patients with severe FIAU toxicity, with associated apoptosis (cell death). Their studies also suggest that the relatively small decrease in total mt DNA measured in homogenized tissue may result in part from no change or even an increase in mt DNA from non-parenchymal cells in the liver.

Frank Richardson of Eli Lilly has been conducting studies in a variety of animal species, looking at FIAU incorporation into DNA, finding concentrations in some rat liver tissue as high as 1 molecule per 90 molecules of thymidine. Timed hydrolysis of rat liver DNA indicated a continual rise in the FIAU concentration, suggesting that FIAU was not chain terminating, that is, that it could continue to be incorporated (Richardson, Engelhardt and Bowsher, in press).

Inhibition of mt DNA replication has been proposed as the mechanism of FIAU clinical toxicity, and William Lewis and colleagues at the University of Cincinnati have shown in vitro that FIAU-triphosphate is a potent inhibitor of DNA polymerase gamma (which is responsible for mt DNA replication) (Lewis, Meyer, Simpson, Colacino and Perrino, in press). Colacino and colleagues (Colacino, Malcolm, and Jaskunas, 1994), however, demonstrated, also in vitro, that FIAU (and ddC) can increase lactic acid levels at doses and durations that do not inhibit mt DNA replication. Therefore, simply screening nucleoside analogs for their abilities to

inhibit mt DNA replication during a short exposure in a cell culture will be inadequate to predict serious problems in a clinical setting.

ANIMAL MODELS

Lilly Rat Studies

Despite failing to produce any significant histological or biochemical abnormalities in dogs given FIAU at 3 mg/kg/day for 90 days or in monkeys given 25 mg/kg/day for 30 days, Eli Lilly completed a report in July 1994 describing a study conducted from September 23 through December 2, 1993, in which they set out to produce in rats the toxic syndrome seen in the PPPC clinical trial. Rats (five rats of each sex receiving each dose) were treated with FIAU three times per day, with total daily dosages of 255 or 510 mg/kg/day (a dosage 1,000 times greater than that administered to humans) for a period of 10 weeks. Originally, the study was designed to last only 2 weeks, but since the animals tolerated the high doses better than expected, the study was extended first to 1 month and finally to 10 weeks. The FIAU was administered by gavage as an aqueous acacia suspension.

All rats survived the 10-week period, but clinical signs started to appear during the last 4 weeks. Significant differences in body weight gain and food utilization efficiency were seen in all animals, but the male rats were more severely affected than the females. Decreased body weight gain was attributed primarily to the decreased efficiency of food utilization. Hematologic parameters were assessed on days 27 and 70. Slight to moderate decreases in erythrocytes, lymphocytes, and leukocytes were observed in both male and female rats treated with the higher dose; lymphocytes and erythrocytes were also decreased in male rats treated with the lower dose. Regarding clinical chemistry parameters, blood urea nitrogen values were increased slightly in both dosage groups, but not in a dose-dependent manner; there was a slight increase in total plasma bilirubin concentration in males at both dose levels, but only at the higher dose in females. gamma-glutamyltransferase activity was increased (about 33 percent) in both males and females at the higher dose level. It is noteworthy, however, that no significant increases in ALT or AST were observed in either test group. Dose-related decreases in glucose (both doses, both sexes), total protein (both doses, males; high dose, females), and albumin (both doses, males; high dose, females) were recorded. There were moderate increases in plasma lactate (≈ 67 versus 16 mg/dl) in animals of both sexes at both dose levels.

Mitochondrial parameters were assessed from liver samples obtained at day 70. Citrate synthase activity was significantly higher than that of control rats in both males (≈ 165 percent of the control at both doses) and females (≈ 187 percent of the control at the lower dose; ≈ 161 percent of the control at the higher dose) treated with FIAU. On the other hand, cytochrome oxidase activity was significantly lower than that of control rats, in both males (≈ 44 percent of the control at both doses) and females (≈ 44 percent of the control at the lower dose; ≈ 62 percent of the control at the higher dose) treated with FIAU.

DNA was isolated from liver, heart, spleen, jejunum, and epididymal sperm about 24 hours following the last treatment with FIAU. The FIAU concentration in cellular DNA was assessed by radioimmunoassay and was normalized to the thymidine concentration in each

sample. FIAU was found in nuclear DNA from all tissues; the highest concentration was found in liver (about 1 FIAU molecule/90 thymidine molecules); incorporation in males was twice that seen in females. DNA isolated from hepatic nuclei was reported to contain essentially all of the FIAU-DNA found in the cell. Nuclear FIAU-DNA was also observed in the jejunum and spleen, with lesser concentrations found in the sperm and heart.

Nephropathy was observed in all rats receiving the higher doses. Regenerative myopathy (three of five males, two of five females) was observed in animals receiving the high dose. Changes in hematopoietic tissue were unremarkable in the treated groups.

The liver was affected in all FIAU-treated rats. Histologic evaluation of liver tissue indicated slightly increased apoptosis and increased numbers of multinucleated hepatocytes; mitotic figures were also increased, with some mitoses having atypical morphologies; dose-related nuclear atypia and cytoplasmic hyaline droplet accumulation were also observed. Hepatic lobular architecture was generally normal even in animals most affected by cytologic alterations. By electron microscopy, enlarged mitochondria and increased numbers of secondary lysosomes were observed in rats treated with the higher dose of FIAU. The cytoplasmic droplets seen histologically were attributed to the megamitochondria observed by electron microscopy.

Comments

This new study performed by Lilly indicates that hepatic involvement can be observed in laboratory animals under specific treatment conditions. This is an important contribution, since previous animal studies included in the FIAU preclinical toxicology assessment did not show hepatic dysfunction or hepatotoxicity. Although the changes are important, it should be noted that the morphologic and biochemical descriptions do not mimic exactly what was observed in humans during the tragic clinical trials. Elevations in plasma aminotransferase activity were not observed in the rats treated with FIAU for 10 weeks. Histologically, no mention was made of microsteatosis in rat liver at either dose level, although this was a major finding in humans. Finally, the morphologic evidence does not indicate an onset of liver failure. On the other hand, the finding that megamitochondria are observed in FIAU-treated rats is important and relevant. Furthermore, changes in serum lactate levels suggest changes in mitochondrial intermediary metabolism. There are suggestions in the literature, based on in vitro studies, that FIAU may affect mitochondrial function and that this event could be related to some of the toxic effects of the agent. The rat findings in vivo are supportive of the hypothesis; the data indicate that mitochondrial involvement in toxic manifestations of FIAU must be pursued in vivo to test the validity of the hypothesis. The incorporation of FIAU into liver nuclear DNA is also an important finding. Its relationship, however, to undesirable events remains to be established.

Cornell Woodchuck Studies

An entirely different animal model has been utilized in two studies with FIAU conducted by Bud C. Tennant at Cornell University College of Veterinary Medicine. The Eastern U.S. woodchuck (*Marmota monax*) harbors an hepadnavirus, woodchuck hepatitis virus (WHV), that is similar to human hepatitis B virus. Tennant provided the IOM committee with a brief written summary of the results of two experiments performed with FIAU-treated woodchucks (Tennant, 1994; Tennant and Gerin, 1994). For both of these studies, laboratory-born and reared woodchucks were inoculated shortly after birth with WHV-positive serum; 95 percent or more became infected and 65-70 percent became chronic carriers with progressively worsening hepatitis. Infected woodchucks generally die of liver cancer during the second or third year of life (the lifetime risk of liver cancer for these animals approaches 100 percent).

The first study was started on December 9, 1992 and was completed on March 30, 1993. Three groups (six animals per group) of woodchucks with chronic WHV infection were treated with daily injections of FIAU (0.0, 0.3, or 1.5 mg/kg) directly into the abdomen (intraperitoneally) for a total of 28 days. On the basis of the metabolic size of woodchucks compared with that of humans, the 1.5-mg/kg/day dose of FIAU was estimated to be equivalent to a human dose of 0.5 mg/kg/day, whereas the 0.3-mg/kg/day dose was estimated to be equivalent to a human dose of 0.1 mg/kg/day. A 12-week observation period following FIAU treatment was included in the design of the experiment. Although the antiviral effect of FIAU at the lower dose (0.3 mg/kg/day) was equivocal, FIAU appeared to have a strong antiviral effect at 1.5 mg/kg/day.

Accumulation of lipid in the liver of one of six animals receiving 1.5 mg/kg/day was observed at the end of the FIAU treatment period and again in a liver biopsy specimen 4 weeks after the end of the treatment. The animal died 3 days after the liver sample was obtained by biopsy, but the death was attributed to complications of the liver biopsy. Another woodchuck receiving FIAU at the same dose level exhibited a milder accumulation of liver lipid at 4 and 12 weeks; this animal also died, but the death was considered to be due to the anesthetic agent. One of six woodchucks treated only with a placebo (no FIAU treatment) also exhibited an accumulation of lipid in the liver at 4 and 12 weeks following treatment. Because lipid accumulation was observed in one placebo-treated animal, the investigators found it impossible to conclude that FIAU was the cause of the liver lipid change in the FIAU-treated woodchucks. On July 2, 1993, the group at Cornell, who had been advised of the adverse effects seen in patients treated with FIAU in the PPPC clinical trial, reinitiated posttreatment observations on the surviving woodchucks; the observations were continued until February 1994, when the remaining animals were euthanized and postmortem evaluations were performed. A significant difference in body weights between the group treated with FIAU at a high dose and the placebo-treated animals was observed; the groups receiving FIAU weighed less (3.4 versus 3.8 kg), but the meaning of this finding is not evident.

The second study in woodchucks was initiated in February 1994 and was completed in May. One objective of the second study was to see if the presence of a chronic HBV infection was a factor of importance in the liver injury observed in humans following treatment with FIAU. Furthermore, the route of administration of FIAU was oral rather than direct abdominal injection. Eighteen woodchucks were infected with virus (WHV) at 3 days of age and were

reared as adult chronic WHV carriers; 18 other woodchucks were reared to be virus-free. Before initiating the daily FIAU treatments (duration, 12 weeks), clinical tests as well as serologic tests for the presence of WHV were performed. There were four separate groups of woodchucks in the 12-week treatment study. Nine animals with chronic WHV infection were given FIAU orally (1.5 mg/kg/day); nine other animals with chronic WHV infection received only the placebo orally. These 18 infected animals were compared with two other groups of uninfected woodchucks (nine animals treated with FIAU at 1.5 mg/kg/day and nine animals receiving only the placebo). All of the data from the study have yet to be completely analyzed. Some preliminary results are available, however. After 4 weeks of treatment, no treatment-related findings were observed in any of the groups. Accumulation of liver lipids was observed at this time. After 8 weeks, the mean body weights of the FIAU-treated woodchucks (both WHV carriers and uninfected animals) were lower than those observed in the placebo groups (receiving no FIAU). Anorexia accompanied the weight loss; the effects persisted in surviving woodchucks during the posttreatment period. The effects were attributed to the FIAU treatment and were similar in WHV carriers and uninfected animals; the toxicity was not dependent on the presence of a persistent WHV infection or underlying hepatitis. Biochemical signs of liver injury were observed in woodchucks treated with FIAU. Furthermore, both WHV infected and uninfected animals receiving FIAU are reported by the investigator as exhibiting elevations in transaminase activity, particularly AST as the animals became moribund. Kidney insufficiency was also observed in FIAU-treated animals; elevations in blood lactic acid concentrations were found in the final stages of FIAU toxicity. Changes were observed in the pancreases of some woodchucks, but the role of FIAU treatment is not yet established. Evidence of liver injury, including increases in liver lipids, was observed in all but one FIAU-treated woodchuck. Similar changes in placebo-treated animals (WHV positive or uninfected) were not observed. Finally, at the dose level of 1.5 mg/kg/day, it was reported that all FIAU-treated woodchucks "either died or were euthanized because of multiorgan failure 78-111 days after beginning drug treatment."

Comments

The results of the first woodchuck study do not allow one to draw any firm conclusions, since the changes seen in the livers of some of the FIAU-treated animals were also observed in the control placebo-treated woodchucks. Furthermore, the deaths observed could be attributed to the sampling procedures used to obtain tissue specimens rather than to then FIAU treatment. In terms of the chronology of the study, it is important to note that although this study actually preceded the PPPC clinical trial, there really were no indications of remarkable untoward effects caused by FIAU.

The second study was initiated after the PPPC clinical trial. Although the data have not been completely analyzed, the preliminary findings reported by the investigator indicate that with extended treatment, FIAU does exert toxic effects in woodchucks. The study also indicates that the presence of a chronic viral infection is not a necessary factor for the toxic effects observed. In this experiment, there is a much stronger indication that FIAU can effect liver toxicity in woodchucks. One striking point is the presence of toxic signs in this species of

animal at doses of FIAU that are quite small compared with those utilized in previous toxicity testing with mice, rats, dogs, and monkeys. The first doses in fact were just sufficient for an antiviral effect. A burning question is how closely this woodchuck model resembles FIAU toxicity in humans. The incompleteness of the data, particularly the lack of specifics on the numbers of FIAU-attributable deaths (no numbers were supplied to the committee), undermines significantly the interpretation one can make of the results. The situation should undoubtedly be clarified when the final evaluations are available for scientific scrutiny.

It is important to note that the woodchuck is an uncommon animal species for toxicity testing. They were used in the present instance only after the toxicity of FIAU in patients with liver disease was clear. It is highly unlikely that the woodchuck could become a routine species for the preclinical testing of FIAU-like chemicals. To the committee's knowledge these animals are difficult to obtain; the animals used at Cornell University were born and reared in the local facilities, since those trapped in the wild are often rabid. The reproductive capacity of the woodchuck (one breeding cycle annually yielding one or two offspring) unfortunately precludes its use as a routine species for animal toxicity testing, but the data to date suggest that it might be a powerful addition to preclinical testing for anti-HBV drugs.

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Review of the FDA Task Force Report "Fialuridine: Hepatic and Pancreatic Toxicity

On November 12, 1993, the Food and Drug Administration (FDA) released a report "Fialuridine: Hepatic and Pancreatic Toxicity" that had been prepared by a special task force. This report was presented together with an oral report by the authors to the Institute of Medicine (IOM) Committee to Review the Fialuridine (FIAU/FIAC) Clinical Trials on July 25th, 1994 (FDA, 1993a).

OBJECTIVE OF FDA REVIEW

The deaths of 5 of 15 participants in the clinical trial H3X-MC-PPPC, evaluating the safety and efficacy of FIAU in patients with hepatitis B virus (HBV) infection, raised the question of whether differences in process could have averted the disaster. A special Task Force of FDA undertook a retrospective assessment of FIAU and FIAC with the stated objective "to determine what data and what analyses of data were available to sponsors and the FDA at the start of the H3X-MC-PPPC study, and whether improvement in the rules governing design, analysis and reporting of data from clinical trials is warranted."

From the outset the FDA Task Force recognized and prefaced their presentation with the recognition that this was a retrospective review initiated in response to the deaths and restricted to the three clinical studies undertaken before the PPPC study. The focus was therefore an evaluation of possible changes in process and design and not a determination of whether or not the outcome of the PPPC trial could have or should have been predicted.

TASK FORCE COMPOSITION

The Task Force was comprised of the following individuals: Ann Witt, Special Assistant to Deputy Commissioner for Operations, Office of Commissioner; Roger Williams, M.D., Associate Director, Science and Medical Affairs, Center for Drug Evaluation and Research; and Leland Pierce, M.D., Clinical Investigations Branch, Office of Compliance, Center for Drug Evaluation and Research. One external advisor, Willis Maddrey, M.D., a hepatologist from the University of Texas Southwestern Medical Center in Dallas, Texas, aided the Task Force.

This was a small internal FDA Task Force that operated independently of the major clinical researchers in HBV disease. Its membership was intentionally restricted to avoid

introducing bias; however, its relative isolation from other components of the medical scientific community meant that only a portion of available expertise and background information was utilized.

METHODOLOGY

The report evaluated preclinical animal studies submitted as part of the FIAU IND and three clinical trials (R89, R90, and R91) for information suggestive of hepatic or pancreatic toxicity comparable to that observed in the PPPC trial.

Animal pharmacology and toxicology assessments were based on existing guidelines for 14-day, 28-day and 6-month human studies in nonexpedited drug development. A focus of the assessment was to look for evidence of hepatic or pancreatic toxicity in animal models. The methods of using pre-existing criteria for animal toxicology and pharmacology data seem appropriate to this IOM committee.

The clinical study review was based on "selected laboratory observations" and "clinical events."

Selected Laboratory Observations

The Task Force defined a selected laboratory observation as any instance of an elevation in serum levels of the hepatic enzymes aspartate aminotransferase (AST) or alanine aminotransferase (ALT), greater than three times the baseline level. Although the Task Force acknowledged that investigators and sponsors often considered such changes indicative of a beneficial drug effect in patients with hepatitis B infection, for the purposes of the Task Force analysis, all observations meeting this definition were instead assumed to be evidence of drug-induced liver inflammation. The definition was constructed following discussions with Willis Maddrey, a hepatologist with expertise in drug-induced hepatotoxicity, with the statement: "Although arbitrary, the ratio appears reasonable based on the natural history of chronic hepatitis associated with HBV infection."

Clinical Events

These were defined as any events "suggestive or indicative of hepatic or pancreatic damage within 6 months of the final dose of FIAC or FIAU that required inpatient or outpatient evaluation by a health professional." The Task Force clearly states that this definition did not require a causal attribution to the drug and could be related to the underlying disease. This analysis thus involved a worst-case assessment that presupposes that all untoward events are attributable to drug effects.

The IOM committee has several major objections to the definition of a rise of AST or ALT to $\geq$ 3.0 times baseline at any point in a 6-month period as an adverse drug related hepatic event.

1. The Task Force has used the principle of percentage change from baseline as their prime measure and criticized the investigators for looking at and presenting absolute values. This approach is certainly not the recognized, conventional approach. From a conceptual perspective, it suffers from being numerically biased to subjects with low baseline levels. As a generalization any scientific comparison of percentage change from a different baseline is open to criticism and introduces this bias.
2. Increases in ALT or AST were considered in isolation and not in conjunction with DNA markers of HBV disease. The concept of a flare as a marker of therapeutic response was dismissed in this worst-case analysis. Given the complexity of this disease process, no single piece of information should be considered in isolation, and when possible, all alternative explanations, both good and bad, should be considered. It was notable that the Task Force interpretation was not in accordance with inferences drawn not only by investigators and sponsors but also by the Antiviral Drug Division of FDA that was charged with monitoring the FIAU trials.
3. The focus on changes in ALT and AST appears to be inappropriate as a marker of FIAU hepatic toxicity. On examination of the hepatic enzyme data in those subjects who died of this toxicity, a unique feature was that despite the presence of extensive metabolic acidosis, encephalopathy, and coagulopathy, changes in AST and ALT were unremarkable and there was a lack of temporal association between rises in these enzyme markers of hepatic necrosis and other evidence of acutely progressive liver dysfunction. In the opinion of the IOM committee, a rise in ALT or AST did not provide a useful marker of the FIAU hepatotoxicity responsible for the deaths in the PPPC trial. It is important to note that if decisions to alter trial design or stop the PPPC study had been made based on elevated ALT or AST levels in prior studies, they would have been made on an erroneous inference.

The committee also finds problematic the approach of using a worst-case interpretation of all clinical events within 6 months of an investigational drug exposure. Application of this approach has major implications for all drug development, particularly those drugs that are being developed for life threatening diseases which have their own natural history of progression. For example, the FDA report advocates considering as drug-induced any negative change in health while taking the drug or during the 6 months after stopping it. This definition should be evaluated from the perspective that most instances of acute hepatocellular damage occur at the time of taking a drug. In this instance, patients with a chronic viral hepatic infection are being evaluated over a prolonged period off this investigational drug and often while receiving other therapy. With a variable disease process, the longer the follow-up, the higher will be the frequency of cases meeting this definition. Most approved medications for any serious disease would fare very badly in this sort of analysis. Before accepting such arbitrary criteria, it is essential to evaluate this methodologic approach in subjects with similar entry criteria but not receiving an investigational new drug.

At the present time, there is no methodologic approach that adequately takes into account the inherent variability of the natural history of the disease and allows discrimination of superimposed drug-related events or separate events owing to different drugs. The danger of accepting a worst-case analysis and extending the time of observation to 6 months is that all new drug development for rapidly progressing diseases (e.g., cancer, AIDS, progressive

neurological disorders) is likely to be compromised by the inappropriate assignation of disease progression to drug toxicity. Each drug trial must be evaluated in the context of the disease it is meant to treat.

In the present case, the IOM committee believes that despite the usual difficulty in ascribing causal relationships to adverse events, the remarkable reproducibility of major FIAU-induced hepatic and pancreatic toxicity in those patients in the PPPC trial, the known ability of ddI to induce pancreatitis, and the natural history of HBV infection progressing to chronic liver failure does permit attribution of causation to the observed toxic events. In the committee's view, attribution of all adverse hepatic and pancreatic clinical events to FIAC or FIAU as proposed by the FDA Task Force would inappropriately ignore potentially important information.

RESULTS

Animal Pharmacology and Toxicology Studies

The FDA Task Force concluded, and the IOM committee agrees, that the animal studies were comprehensive, with the use of appropriate numbers of species, routes of administration, and in certain studies, measures of drug levels in blood. There was no evidence from studies in animals from which hepatic or pancreatic toxicity might have been anticipated.

Although we are aware that the FIAU experience is stimulating efforts to model the toxic effects of FIAU on the pancreas and liver in animal models and that new animal model criteria may be developed, it is clear that, the basis of known animal toxicity models available prior to the PPPC trial, there was no way of anticipating the major human toxicity subsequently observed.

Overview of Laboratory Events in Studies Prior to H3X-MC-PPPC

In the three studies analyzed by the Task Force, R89-001-01 with FIAC, R90-001-01 with FIAU and R91-010-01 with FIAU, 79 patients received one of these investigational drugs. Of those, 24 (29 percent) had an increase in AST or ALT peak-to-baseline ratio of >3.0 at some point during therapy or follow-up. The implication of the report, if not the explicit conclusion, was that if these data had been collected and analyzed in this fashion at the time of the trials they would likely have led FDA, if not the investigators, to view FIAU as a liver toxin. As indicated previously, the IOM committee did not consider this variable a valid measure of drug-induced hepatotoxicity and considers inferences and recommendations based on it to be inappropriate.

In this section of the report, the Task Force authors also noted that many of the subjects who developed the unequivocal hepatic and pancreatic adverse effects of FIAU had a history of drug challenge and then rechallenge. The FDA Task Force concluded that "readministration was likely to be associated with severe hepatic and/or pancreatic damage and death." It is unequivocal that most subjects who had the major FIAU toxicity syndrome had a reexposure

to the drug and cumulative toxicity might have occurred. However, a minor degree of microvesicular steatosis occurred in at least one subject without reexposure. The numbers of subjects with or without reexposure are too small to discriminate between the alternative hypotheses of a total cumulative dose and first exposure sensitizing a subject to later exposure.

In considering the cumulative dose explanation, it is relevant that the investigators considered the implications of extending the duration of drug treatment by reducing the daily drug dosage so that the overall total dosage was not unduly increased in transitioning between one study and the next. Despite these changes in administration, total dosage and duration of dosing are highly correlated, making it difficult to discriminate between them as possible causes of toxicity. There was one example of an individual who erroneously received 3.3 times the normal dose on the first day without immediate ill effects, and still had 13 additional days of protocol treatment. Identification of the mechanism of toxicity and the role of FIAU incorporation into nuclear and mitochondrial DNA may in the future lead to a better understanding of the role of total dose, dose duration, and reexposure to dose to the risk of toxicity.

Attribution of Toxicity to Adverse Clinical Events

The FDA Task Force observed that none of the 10 adverse clinical events they identified in patients from the trials conducted prior to the PPPC trial were attributed to FIAU toxicity by the investigators or sponsors. The report offers a number of reasons for that:

1. The drug effect might mimic the disease process or the effect of another drug. There was "no prior stated expectation as to the likely incidence of mortality."
2. There was no stated prior expectation of liver enzyme increases in the test population.
3. Because there was a delay in the adverse response, it was reasonable to attribute the adverse response to other, more temporally proximal factors.
4. Changes in liver enzymes levels were ascribed to a "flare."
5. Each adverse effect appeared to have been considered separately. The Task Force noted that "under current rules governing design, analysis and reporting of data from clinical trials, the sponsor is not required to conduct a cumulative analysis." The FDA Task Force goes on to state the need for a worst-case analysis, assuming all adverse effects are drug related.

Phase II efficacy and toxicity studies of drugs used to treat complex diseases like AIDS, HBV and cancer are inherently difficult, due to the need to use small numbers of subjects from highly heterogeneous populations. Despite defined entry criteria, it is exceptionally difficult to anticipate the natural history of the disease. If the investigational drug targets the diseased organ, it can be exceedingly difficult to discriminate disease from toxicity of the drug. Any recommendations based on the experience of FIAU must be viewed from the broad perspective of drug discovery. A worst-case analysis as proposed by the Task Force would have the potential to severely compromise future drug development for all diseases with high morbidity and mortality, since the adverse effects of the disease will necessarily be attributed to the drug instead.

Investigators, sponsors, and the Antiviral Drug Division of FDA were working with the hypothesis that an increase of AST or ALT level followed by a fall in DNA markers of HBV was associated with therapeutic response. Presumably, a rise in enzyme level without change in HBV DNA would be attributed to adverse hepatic drug effects. However, this combined analysis was not done by the FDA Task Force. In more general terms, the ability of the disease process to influence measures of drug effect creates a confounding variable for all Phase II studies. At the present time, there is no appropriate methodology that can be used to anticipate the extent of variability in disease states seen in studies with small sample sizes.

The uniqueness of FIAU toxicity is in providing the first example of a drug that induces progressive multiorgan failure that occurs at long intervals after stopping drug administration. The fact that it has now been identified means that surveillance for delayed organ toxicity must be incorporated into study designs for drug development in the future. It should, however, be appreciated that correct attribution of delayed-onset toxicity is increasingly difficult the longer the follow-up and the sicker the patient group initially studied.

In the opinion of the IOM committee, there is a need for cumulative collection of data on adverse events by the sponsor, but that a worst-case analysis is inappropriate. Each case should be interpreted to the full extent of the available information (e.g., pathology reports and autopsy reports), and the cumulative data should be systematically reviewed for unexpected trends. Events reasonably attributed to the underlying disease or other concomitant therapy should not be automatically attributed to the investigational drug. It is recognized that attribution of cause requires judgment. It is the opinion of the IOM committee that the clinicians directly responsible for patient care are those most likely to exercise appropriate judgement.

We now turn to another section of the FDA Task Force Report, in which the authors review adverse clinical events associated with the studies immediately preceding the disastrous PPPC trial. In the following sections, we summarize the Task Force review and comment where it differs from our own.

Review of Adverse Clinical Events in Trial R89-001-01

This study was sponsored by Oclassen and conducted at the University of California, San Diego (n = 10) and the University of Washington (n = 2) between November 1989 and May 1990. It was a dose ranging Phase I trial of FIAC in patients who were seropositive for both HIV and cytomegalovirus (CMV). The study only used the two lower doses of the four doses originally proposed, and was stopped due to lack of activity against CMV.

As noted in Chapter 6, four subjects from this study died in the 6 months following the trial. One developed a severe axonal neuropathy followed by a terminal pneumonia, one died of Kaposi's sarcoma, and the third died of AIDS dementia. These three were not attributed to FIAU toxicity by either the investigators or the Task Force. The fourth case, patient 107, was a 32-year-old drug abuser who was also positive for HBV. He received FIAC at 1 mg/kg/day for 36 days. His serum AST at the start was 43 IU/liter, which rose to 93 after 14 days of therapy. Serum ALT was 44 IU/liter at baseline and rose to 135 after 14 days of therapy. Seven weeks later, when the patient was on zidovudine (AZT), methocarbamol, and

amitriptyline, he was admitted with nausea, vomiting, and coagulopathy. The patient deteriorated, with development of jaundice and ascites preceding death. An autopsy showed intrahepatic cholestasis, pancreatitis, and fat necrosis. The study investigators concluded that the patient died of underlying disease or possibly of AZT- or amitriptyline-induced hepatic failure.

The FDA Task Force designated this a drug-associated clinical event and considered it relevant because FIAC is predominantly metabolized to FIAU. It is possible that this attribution is correct, but two cardinal features of FIAU toxicity, namely, lactic acidosis and microvesicular steatosis, were not described. The later histological review by Dr. Hyman Zimmermann, who described hepatocellular necrosis with fatty metamorphosis, is described as equivocal. The IOM committee reviewed the available information and designated the probability of causation by FIAC as uncertain.

Review of Adverse Clinical Events in Trial R90-001-01

This study was sponsored by Oclassen and was conducted as a Phase I safety study of FIAU at the University of California, San Diego, the University of Washington, and the National Institute of Health (NIH). The study population consisted of patients with serologic evidence of HIV and herpes virus infections; some, but not all, also showed serologic evidence of hepatitis B virus infection. The design was a 14-day, parallel group, dose-ranging study (0.1 to 1.7 mg/kg/day). After the trial had begun approval was obtained for a second course of treatment for those patients whose DNA polymerase markers for HBV fell during the first 14 days of treatment but subsequently recovered. Of the 43 subjects studied, 30 were infected with both HIV and HBV. Thirty-four completed the study and four had repeat therapy. Three of those four who had repeat therapy died within 6 months of their last dose of FIAU, and one was hospitalized with pancreatitis. The study was terminated at the fourth dose level (1.7 mg/kg/day) because of patients' complaints of fatigue. Several cases were reviewed in depth:

Subject 401

This 33-year-old patient was a drug abuser who was infected not only with HIV and HBV but also with hepatitis C and D viruses. This patient took FIAU at 1 mg/kg/day for 13 days in April and completed the study in May. He developed progressive liver failure and was readmitted to the hospital 91 days after receiving his last dose of drug with coagulopathy, encephalopathy, and low blood glucose. There was no evidence of lactic acidosis or pancreatitis. Liver histology at autopsy revealed end-stage liver disease with bridging fibrosis. A coincidental autopsy finding was a left renal carcinoma.

This patient was identified as a clinical event by the FDA Task Force. In the opinion of the IOM committee, a more reasonable explanation is end-stage liver disease secondary to multiple hepatitis viral infections. There was no evidence of lactic acidosis, pancreatic dysfunction or microvesicular steatosis. Inclusion of this subject among those with drug-related adverse events is unjustified.

Subject 406

This 45-year-old patient was HIV and HBV positive and had a prior peripheral neuropathy attributed to treatment of his HIV infection with ddC. He received FIAU at 1.0 mg/kg/day for 14 days in June 1991 and again at 0.5 mg/kg/day for 17 days in June 1992. Before and after taking FIAU, the patient also received AZT, ddI, famotidine, desipramine, and naproxen. In August 1992, he was admitted to his local hospital with abdominal pain and serum amylase of 1,166 and lipase of > 4,000. An autopsy following his death indicated hemorrhagic pancreatitis. Liver histology indicated minimal steatosis with bridging fibrosis.

The FDA Task Force describes this as a clinical adverse event potentially related to FIAU therapy. The study investigators attributed the pancreatitis to the patient's current ddI therapy rather than the more distant FIAU trial. In the opinion of the investigators and the IOM committee, it is not possible to confidently assign a single drug a causative role. It is possible that FIAU contributed to the pancreatic toxicity, but the undoubted association of ddI therapy and fulminant pancreatitis, together with the absence of lactic acidosis, microvesicular steatosis, and fulminant liver failure make this a less likely attribution.

Subject 408

This patient was a 38-year-old patient with HIV and HBV infections, allergies, eczema and hypertension. A cirrhotic liver was observed when the patient had a splenectomy in 1988. He received FIAU at 1.0 mg/kg/day for 12 days in November 1991 and for 14 days in January 1992. After the FIAU study, he received ddI and fluconazole in addition to AZT, enalapril, and beclomethasone. In April 1992, he developed liver failure, ascites, jaundice, and coagulopathy. He had bleeding esophageal varices and died of liver failure. At autopsy he was found to have advanced micro- and macronodular cirrhosis with active destruction of hepatocytes, fibrosis, cholestasis, and bile duct proliferation. There was no acute pancreatitis or evidence of microvesicular steatosis.

The FDA Task Force identified this death as a clinical event potentially related to FIAU. The clinical investigators and the IOM committee consider a more likely explanation to be progressive end-stage liver disease related to longstanding hepatitis B infection.

Subject 101

This 31-year-old patient with HIV and HBV infections received FIAU at 1.0 mg/kg/day for 13 days in May 1991. In October 1991, the patient was found to have a peripheral neuropathy requiring narcotic pain control. He subsequently died of *Pneumocystis carinii* pneumonia in September 1992.

This patient was considered not to have a hepatic or pancreatic event by the FDA Task Force. The IOM committee concurs.

Subject 409

This 36-year-old HIV- and HBV-positive patient received FIAU at 0.5 mg/kg/day for 14 days in December 1991 and again in April 1992. In August 1992, while the patient was being treated with ddI for his HIV infection, he was admitted to the hospital with right upper abdominal pain and elevated serum amylase levels. The patient improved after ddI treatment was stopped.

The FDA Task Force identifies this subject as having a hepatic or pancreatic clinical event that could be related to FIAU. In the opinion of the IOM committee, a more plausible relationship is to ddI, a well-known pancreatic toxicant. It is feasible that FIAU produces pancreatic toxicity, but this patient did not have any other evidence of the FIAU toxicity syndrome.

To summarize the adverse events in the R90 trial, none of the 5 patients who had major adverse events had unequivocal evidence of the FIAU toxicity syndrome, even in retrospect. The implication that these were early examples of the toxicity that ultimately killed 5 patients in trial PPPC stretches the facts too far.

Review of Adverse Clinical Events in Trial R91-010-01

This study was a dose-ranging study of FIAU in patients infected with HBV free of HIV. The objective was to progress from the previous study by extending the treatment duration from 14 to 28 days and using a smaller daily dose ranging from 0.05 mg/kg/day up to a ceiling of 0.5 mg/kg/day. With the longer treatment, follow-up was extended to 6 months.

All 24 subjects enrolled were at NIH and completed drug therapy without incident, but in the following 6 months one patient died and three others had clinical events that were reviewed.

Subject 4D

This was a 59-year-old patient with chronic HBV infection who received FIAU at 0.5 mg/kg/day for 28 days in August 1992. In October 1992 the patient was admitted to the hospital with abdominal bloating and a peripheral neuropathy. Following right upper quadrant pain, the patient underwent laparoscopic cholecystectomy without finding gallstones. The patient subsequently developed ascites and a persistent severe metabolic acidosis, despite normal hepatic enzyme and bilirubin levels. The patient developed coagulopathy, encephalopathy, and renal failure and died in January 1993. At autopsy there was a nodular architecture, focal bile duct proliferation, lymphocyte infiltration, hepatocyte necrosis, and marked microvesicular steatosis. The pancreas was inflamed.

The FDA Task Force identifies this patient as having hepatic and pancreatic toxicity attributable to FIAU. The IOM committee concurs and suggests retrospectively that this is the index patient, i.e. the first clear case of FIAU toxicity as it is now understood. At the time that these events were taking place, the investigators were acutely aware that they were observing

a novel and confusing situation. Despite discussions with other senior staff at NIH and with the IRB of record, causation remained uncertain and the lack of a close temporal relationship to FIAU therapy put it low on their list of potential causative mechanisms.

Compelling evidence to suggest a late hepatotoxin-induced syndrome unrelated to FIAU was provided by comparison of liver biopsies obtained at the time of the patient's laparoscopic surgery with prior biopsies and with that obtained at autopsy. The biopsy specimen obtained laparoscopically two months after completing FIAU therapy was reported in the investigators' detailed report to the IOM committee to show "chronic active hepatitis with marked bridging hepatic fibrosis. There were small amounts of fat similar in extent to those in biopsies obtained before therapy" (Hoofnagle, 1994b). In contrast, at the autopsy at NIH the findings were described as "micronodular cirrhosis with mild inflammatory activity and with moderate to marked microvesicular fat." This represented a marked change in hepatic morphology occurring long after exposure to FIAU but almost immediately after exposure to anesthesia and numerous other therapeutic agents over the intervening time. It did, however, increase their awareness of this unusual syndrome, so that when it was next seen, it was immediately recognized and a correct association was identified.

Subject 6B

This 59-year-old patient with HBV infection received FIAU at 0.25 mg/kg/day in May 1992. Four months later, the patient had an episode of right upper abdominal pain. No cause was found and the patient recovered.

The FDA Task Force identifies this subject as having a clinical event which should be attributed to FIAU in a worst case analysis. In the opinion of the IOM committee, there is insufficient evidence to causally ascribe these symptoms.

Subject 1C

This 56-year-old patient with HBV infection received FIAU at 0.05 mg/kg/day for 28 days in June 1992. In October 1992 the patient developed right upper quadrant pain and had a biliary stone removed from the cystic duct. A liver biopsy showed a moderately active micronodular cirrhosis.

The Task Force identified this subject as having a significant clinical event related to FIAU therapy, but acknowledged that interpretation was difficult because of the cholelithiasis. The IOM committee considered the gallstone the more plausible explanation for the abdominal pain, since other features of FIAU hepatic and pancreatic toxicity were not present.

Subject 6A

This 27-year-old male with HBV infection received FIAU at 0.1 mg/kg/day for 28 days in April 1992. By January 1993, he had an elevation in his hepatic enzymes (94 IU/liter to 235

for AST, 244 to 730 for ALT), and a liver biopsy in February 1993 showed moderate active hepatitis with lobular inflammation and bridging fibrosis but no evidence of microvesicular steatosis, which was confirmed in an independent histology review by Zimmermann subsequent to trial PPPC.

The FDA Task Force identifies this subject as having probable evidence of an adverse clinical event related to FIAU therapy. In the opinion of the IOM committee and the investigator, the more likely explanation is that this patient's underlying hepatitis had become more active. The relationship of this change in activity to FIAU therapy is uncertain.

Subject 3B

This 23-year-old woman with HBV infection had a liver biopsy in April 1992 which demonstrated chronic persistent hepatitis without fibrosis. In May 1992 she received 28 days of FIAU at 0.25 mg/kg/day. Following this, her serum liver enzymes rose from 48 IU/liter to 156 for AST and 69 to 191 for ALT. Subsequently, in November 1992, she had peak levels of 1326 and 934 respectively and her serum bilirubin level peaked at 3.6 mg/dl. A liver biopsy at that time showed severe chronic active hepatitis with bridging fibrosis and lobular inflammation. By July 1993, her liver enzymes levels had returned to normal.

The FDA Task Force identifies this patient as one having an adverse clinical event occurring within 6 months of taking FIAU. In the opinion of the IOM committee, the more likely explanation is that this patient had a flareup of her hepatitis or a flare reaction indicative of viral clearing. There was no evidence of lactic acidosis or pancreatic involvement to indicate a full FIAU toxicity syndrome. Identification of FIAU in the liver might provide further information.

In summary, in trial R91, the index case of FIAU toxicity was first retrospectively identified. All other clinical events identified by the Task Force have more plausible explanations than FIAU toxicity.

RECOMMENDATIONS

The FDA Task Force has made a series of recommendations on (1) clinical design and execution, (2) reporting requirements, (3) FDA record-keeping, and (4) further review of FIAU toxicity. These recommendations have since become the basis for a number of proposed changes to the Code of Federal Regulations (CFR) governing the IND process. These deserve review and discussion before being implemented as a unilateral decision.

Clinical Trial Design and Execution

The FDA Task Force recommends greater attention in the design of clinical trials to the possibility that drug toxicity could mimic the underlying disease process or effect of other drugs. Specifically, they recommend

1. Strong consideration of control groups.
2. Prospective evaluation of endpoints.
3. Assessment of the expected incidence of death or serious events in the study population in the absence of the investigational drug.
4. Inclusion of observed effects on identified end points in the investigator brochure with presumption of drug-related toxicity.

Consideration of Control Groups

The IOM committee agrees that there is a major need to develop methodology for creating appropriate control groups for Phase I and Phase II clinical trials.

The combination of the variable natural history of diseases and small sample sizes make the design of control groups for evaluation of drug response extremely difficult in the early stages of drug development. Essentially two alternatives are used, each with major limitations. One option is to randomize subjects to either placebo or standard therapy or to the investigational drug. In an ideal world this remains the "gold standard." However, the major objection to this approach is that the natural history of the disease is too variable to permit valid inferences to be drawn from studies with small samples, so that the number of subjects required for this approach to be valid is usually large. This approach is optimal for larger Phase III comparative trials, but it is generally not considered practical for Phase I and Phase II trials. The alternative approach is to use historical controls from previous studies, groups of untreated patients, or patients given conventional therapy. In the majority of instances, however, the size of the control group is small, the selection criteria are subtly different, the location and timing of the study are different, and the effect of standard drug therapy is hard to dissociate from the underlying disease process.

The IOM committee recommends funding research to explore new methodologic approaches to the design of appropriate comparative patient groups with which to compare new information from Phase I and Phase II trials. A major focus could be to develop techniques enabling the use of historical data from previous trials to match patients and events with study participants, thus allowing for more accurate and objective attribution of adverse events to an investigational drug or other causes. Matching of subjects should not be confined to consideration of entry criteria, but should also include personal demographics, disease extent, disease complications, concomitant therapy, or any other relevant dimension. There is now a substantial body of data that in essence is a national repository and resource. This information is provided in Phase I, II, and III drug trials with stringent quality control to the FDA through the IND process. It has the potential to be integrated to provide large series of subjects that could be matched not only for entry criteria but also for disease extent and severity assessment and other potential confounding variables. In recent years, substantial advances have been made in multivariate analysis and in determining the probabilities of associations within complex data sets. It is therefore conceivable that a more sophisticated individualized basis of selecting comparative groups from an expanded, documented prior series of patients could be developed to incorporate not only entry criteria but estimates of disease pathology at the time of the study. It is contemplated that recent advances in multivariate methods for the detection of associations

between variables could be coupled with Bayesian approaches to provide a more systematic, dynamic, objective, and accurate attributions of events than those provided by current approaches.

Prospective Evaluation of End Points

The IOM committee agrees that protocol design should define prospective end point measures in study design and should also define the rules for stopping a study. These should be individualized to the study context and not be rigidly defined to embrace all study designs.

Assess Expected Incidence of Death or Serious Events in The Study Population in The Absence of The Investigational Drug

The IOM committee agrees with the principle that observed events should be compared with the expected events in the study population, but we wish to emphasize our prior comments that selection of comparison groups is difficult. A subsequent section of this report demonstrates how little such an assessment would have added to the conduct of the FIAU trials. This topic is one that requires the development and validation of new methodologic approaches.

Observed Effects on Identified End Points Should Be Included in The Investigator Brochure and Presumed to Be Drug-Related Toxicity.

The IOM committee does not agree that all observed events in a clinical trial should be included in the investigator brochure and presumed to be related to the investigational drug. This worst-case analysis has the potential to be counterproductive to drug discovery by trivializing event analysis and constitutes an overreaction to the FIAU tragedy. The current approach of informed interaction and discussion between the sponsor and FDA on a case by case basis is considered to be an effective and appropriate mechanism. In the PPPC trial, the investigator did inform all study participants of the death of the previous trial's patient 4D, and stopped the study within 12 hours of their recognizing a similar pattern of severe hepatotoxicity in a second patient. This was an appropriate and rapid response. The fact that other patients had already been exposed to the drug and subsequently developed complications, even though the drug was discontinued, was surprising and unfortunate, but not a failure of the decisionmaking process.

Extent of Follow-Up

The FDA Task Force recommends that greater attention be given to establishing adequate follow-up periods for subjects in clinical trials after the conclusion of the study.

Specifically, the protocol submitted to FDA should include the length and type of follow-up. The IOM committee agrees that the experience of delayed severe hepatic and pancreatic toxicity caused by FIAU indicates the need for greater consideration of extended follow-up. However, it must be realized that the longer the follow-up the greater the chance that non-drug-related events are confounding variables in drawing causal inferences. The IOM committee recommends flexibility in study design in terms of requirements of end point measures, the use of independent review committees, and the development of new methodologic approaches as described above to integrate and anticipate adverse events to be expected in the absence of the investigational drug.

Given the current inability to predict outcome, the statement of the Task Force that "Sponsors should, therefore, be responsible for developing and evaluating an adequate data base for any investigational drug to help assess whether adverse events are likely to occur at protracted intervals after cessation of drug administration" is outside the current state of knowledge and the current ability of sponsors. In the absence of new approaches, it is an unrealistic expectation.

Adequate Safety Monitoring

The FDA Task Force recommends that "sponsors describe their safety monitoring and evaluation program and if inadequate, require them to develop extramural resources for this purpose." The IOM committee wishes to comment that an irony of the FIAU experience is that the safety monitoring in place in all studies reviewed was of exceptionally high quality, and lack of it was not the cause for the disaster. The IOM committee endorses the general concept of routine evaluation of events occurring to trial subjects by independent safety monitoring committees. This has been proven effective in the management of multicenter studies and provides a mechanism for reducing bias from investigator or regulatory authority. A broader application of this mechanism is strongly advocated; however, its presence in the FIAU studies seems unlikely to have altered their outcomes.

Reporting Requirements

The FDA Task Force recommends that there should be "full, complete and timely reports of all deaths and serious adverse experiences and safety discontinuations during the IND/NDA process". Specifically they wish to establish the following requirements:

1. To receive information, on a semiannual basis, regardless of attribution of cause, of all serious adverse events that occur within 6 months or the prescribed follow-up period (whichever is longer), including both U.S. and non-U.S. experiences, along with a reasonable analysis by the sponsor. The FDA Task Force recommends that a worst-case scenario be assumed by the sponsor, whose analysis should then focus on refuting this assumption of drug toxicity. They acknowledge that reports of data from double-blind studies should not be unblinded for this reporting purpose.

2. Autopsy reports should be provided when available.
3. Any toxicity detected or suggested should be acknowledged in each new study protocol and in the updated investigators' brochure.

The IOM committee strongly endorses the effective reporting of information during new drug discovery to FDA. The committee wishes to point out that implementation of the above recommendations will not only double the FDA workload (i.e., change from annual to semiannual reports) but will exponentially increase the amount of information presented by requiring the cumulative, worldwide experience to be reported. This has the potential to create an administrative nightmare without guaranteeing enhanced patient safety. The IOM committee also agrees that all serious events observed should be reported and that the sponsor and investigators should provide a reasonable analysis of each, using all available information. The current requirements for 3- and 10-day safety reports when an event is ascribed to a drug-related event are considered appropriate (even though the time frames are short) and events considered not related to the study drug should be included in the periodic IND reports. The IOM committee also agrees that the sponsor should provide a cumulative report of all known adverse events to date at the time of each annual report to facilitate critical analysis.

The IOM committee does not agree that a worst-case analysis should be performed for all routine reports or that all adverse events should automatically be incorporated into new protocol description and drug information brochures. This process would essentially be unduly restrictive to the search for new drugs for the treatment of life-threatening diseases. It is recognized that the current working model in which an investigator working with a sponsor presents information for FDA review creates a situation in which two groups address the same information with opposite biases. As pointed out in the FDA Task Force report, an "unavoidable feature of clinical trials is that investigators and sponsors are optimistic about the safety and effectiveness of the drug they are testing." It is equally valid that FDA review provides a pessimistic counterbalance. In the opinion of the IOM committee, the adoption of a worst-case analysis as a routine requirement would tip the balance too far in a pessimistic direction. In our view, all available information should be routinely screened by an independent data monitoring system developed by the sponsor and investigator in agreement with FDA. Such a monitoring group could also take advantage of new input if new methods are developed for collating prior experience in Phase I and Phase II studies and anticipating patient outcome in the absence of an investigational drug.

A major concern identified by the IOM committee is that adoption of reporting requirements would decrease the signal-to-noise ratio in interpretation of clinical studies. A further consideration that is relevant not only to what data should be included in the investigators' brochure but to what information should be made available to institutional review boards and prospective patients via consent form is that relevant adverse event information will be at risk of being trivialized if judgment is not exercised in data evaluation.

Summarization of All Existing Safety Data

"The FDA Task Force recommends that sponsors be required to prepare and submit summaries of all safety data generated during the IND process." They explain that the timing of such overviews should be negotiated with FDA, that such overviews should extend to related classes of drugs and be linked to semiannual reports and that sponsors be required to submit a final report of an IND within 90 days if it is requested by the FDA.

As previously indicated, the IOM committee endorses full cumulative data reporting to FDA on all events by the sponsor. It agrees that FDA should have the option of requesting an interim report if new information becomes available within 90 days of a request. However, the nature of information being provided to FDA reviewers by the sponsor (e.g., the definition of end point measures) needs to be agreed upon before the study begins and not on a post hoc basis. Furthermore, because an increasing number of events are going to be considered, the division of FDA working concurrently with the sponsor should also be responsive to causal attribution by independent safety monitoring boards and should not rely solely on a worst-case scenario analysis.

FDA Record Keeping

The FDA Task Force noted that its current systems for collecting and retrieving data in an IND are largely manual. Because the review of safety data is a critical element in the evaluation of a new drug, they recommend that FDA "assess the feasibility of and resource requirements for updating its tools and systems."

The IOM committee acknowledges that implementation of this recommendation will require significant infusion of new resources. It strongly endorses this investment. One possible avenue that should be explored is a joint funding venture with other organizations, both public and private, to explore new approaches to patient safety management in Phase I and Phase II drug trials. The organization of and access to available information from previous studies could be a major resource for such an approach, but the only way to have this information readily available would be through a computerized relational data base.

Further Review of Fiau Toxicity

The FDA Task Force recommends that "the Public Health Service appoint a panel of qualified experts in relevant fields to evaluate the pathophysiology of FIAU toxicity."

The IOM committee strongly endorses this opinion and recommends that research resources be identified and targeted at complementary studies to current research in this area. It is clear that a delayed drug-specific toxicity first identified in humans was the primary cause of this disaster. Other drugs may induce similar adverse effects. The role of a newly identified mechanism causing cumulative changes in mitochondrial or nuclear DNA in disease pathophysiology is still uncertain. A clearer understanding of the mechanism of this process is a pre-requisite to preventing similar tragedies in the future. Many current antiviral drugs and

cancer chemotherapeutic strategies, as well as the introduction of gene therapy, have the potential to induce changes in nuclear and nonnuclear DNA. There is therefore an urgent need to develop model systems that predict clinical outcomes if we are to see development of drugs free of this toxicity in the future.

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Review Of "Report To The Advisory Committee To The Director, National Institutes Of Health"

On April 29, 1994, a subcommittee of the Advisory Committee to the Director of the NIH presented its report on review of the FIAU studies to the Director of the NIH, Harold Varmus. This report was presented to the IOM Committee to Review the Fialuridine (FIAU/FIAC) Clinical Trials on July 26, 1994, with an oral briefing by the subcommittee's co-chairs, David Challoner, Vice President for Health Affairs at the University of Florida, and David Kipnis, Distinguished University Professor at Washington University of St. Louis School of Medicine (NIH, 1994b).

OBJECTIVE OF THE NIH REVIEW

In October 1993, the then Acting Director of NIH asked a subset of his standing advisory committee of outside experts to conduct an independent, fact-finding review of the FIAU studies conducted at NIH. The charge to the committee was "to conduct a fact-finding review of all aspects of the FIAU studies carried out at the NIH, from concept to protocol development and implementation ... to consider whether the FIAU studies were conducted in full conformance to NIH policies." The subcommittee's task was further specified by four questions:

1. Why were the FIAU studies conducted?
2. How well were the FIAU studies conducted?
3. How well were the adverse events in the FIAU studies handled?
4. Could the adverse events have been avoided, particularly in the last study?

The subcommittee was asked to formulate recommendations for changes in regulations and procedures to enhance the intramural NIH conduct of clinical research.

The focus of the study was the design and execution of the NIDDK protocol 93-DK-0031 (Lilly study H3X-MC-PPPC [PPPC trial]) entitled "A Six-Month Course of FIAU for Chronic Hepatitis." In addition, the committee reviewed NIAID protocol 91-AI-0031 (Oclassen study R90-001-01) entitled "The Tolerance of HIV Infected Patients to Oral Doses of FIAU" and the joint NIAID-NIDDK protocol 91-DK-AI-0213 (Oclassen study R91-010-01) entitled "A Four-Week Course of FIAU for Chronic Hepatitis B."

In addition to the co-chairs, the members included Richard Corlin, Physician and Vice Speaker of the Delegates Committee of the American Medical Association, Santa Monica, Calif.; Suzanne Oparil, Director, Vascular Biology and Hypertension Program, University of Alabama, Birmingham; Robert E. Handschumacher, Professor of Pharmacology, Yale University, New Haven, Conn.; Rudi Schmid, Dean Emeritus, University of California, San Francisco; and Marguerite Kinney, Professor of Nursing University of Alabama, Birmingham. An expert consultant to the committee was Paul S. Lietman, Wellcome Professor of Clinical Pharmacology, Johns Hopkins University, Baltimore, Md.

The committee held three meetings in closed session on December 20, 1993, and January 4 and 5 and February 16, 1994. An extensive list of documents and information from personal interviews was made available to the subcommittee and are listed in the report.

Question 1—Why Were The Fiau Studies Conducted?

Was The Scientific Rationale For The Studies Sufficiently Strong?

The IOM committee agrees with the NIH subcommittee that there was a strong, justifiable, scientific, rational argument for evaluating FIAU for the therapy of HBV infection. The sequence of drug protocol development was logical and rational and occurred at an appropriate pace with an appropriate transfer in focus from AIDS to HBV infection. There was an appropriate interaction between the NIDDK IRB and investigators as new information became available, and the protocol was modified appropriately.

The IOM committee also agrees with the concurrent review by NIH staff and the later subcommittee review that the critical evaluation of the death of the patient (patient 4D) from study R91 was rigorously undertaken using all of the information then available and can only retrospectively be assigned to a novel, delayed adverse reaction to FIAU. The decision to proceed with the 6-month study despite this death was not unreasonable at that stage of knowledge.

Were the Patients with Hbv Infections Appropriate Candidates for the Second and Third Nih Trials of Fiau?

The IOM committee agrees with the subcommittee's conclusion that the justification for developing Phase I/II studies directly with patients with HBV infection was appropriate. Furthermore, the entry criteria of including only patients with compensated liver disease was appropriate, because a temporary flare-up of acute transient deterioration in liver function, even if it was associated with the clearance of the virus, could be dangerous for a patient with decompensated liver disease. A further consideration is that failure to metabolize FIAU because of impaired liver function might make such patients more susceptible to other toxicities such as neuropathy. Thus, an appropriate consideration and review of the entry criteria were made.

Were the Preclinical Toxicology, Kinetic, and Safety Data Adequate?

The subcommittee reviewed the preclinical toxicology data available to FDA and Eli Lilly from studies performed with FIAU in animals before protocol 93-DK-0031 was conducted to determine whether there was an indication of potential hepatic or pancreatic toxicity. An extensive review concluded that the range and duration of testing were appropriate for the proposed studies and that there was no prior evidence to suggest targeted hepatic or pancreatic toxicity. In a subsequent study reported by Eli Lilly on January 14, 1994, a three-times-daily, oral gavage dosing study with 100 times the human dose in Fischer rats provided the first evidence of hepatotoxicity associated with lactic acidosis in a nonhuman test subject, but no elevations in AST or ALT levels were noted. The histopathology of this model was different from that in humans and the model was not replicated in the mouse. There was also a suggestion of diffuse fatty infiltration of the liver obtained in 1992 in the woodchuck hepatitis model. The subcommittee gave emphasis to the fact that animal models at the time did not raise cautions about hepatic toxicity.

The subcommittee received information pertaining to FIAU incorporation into DNA. They noted that analytical techniques were not available to the sponsor to permit investigation of this hypothesis which, at the time of the report, still remained to be confirmed.

The subcommittee reviewed information on the kinetics of FIAU obtained with high-performance liquid chromatography (HPLC) methodology and concluded that the early kinetic studies did not indicate a deep pool suggestive of DNA binding.

The IOM committee concurs with the NIH subcommittee that a detailed review of preclinical toxicity data available at the start of the third study complied with existing regulations and provided no indication of the liver and pancreatic toxicity later observed in humans. The subsequent and ongoing research on FIAU integration into nuclear and mitochondrial DNA is critical to understanding the mechanism of toxicity and predicting the potential of new chemical entities to pose a similar risk in the future. Once models have been validated, they will become part of an elective screen. However, this information was not available before the onset of the third study and is still only suggestive. It can be anticipated that novel drug toxicity appearing for the first time in humans and not predicted by animal models will occur again in the future because it is an inherent risk of all new drug development programs. An appropriate response to such an event is to learn the mechanism of the toxicity and devise new predictive models.

Should the Deaths That Occurred After the First and Second Trials Have Precluded the Use of Fiau in the Third Hepatitis B Trial?

Clinical problems were identified in four of 14 HIV-positive patients subsequent to their participation in the first NIH trial (R90); These problems led to three deaths and one case of pancreatitis that resolved. One of the 24 patients in trial R91 also died within a few months of completing the study. The subcommittee provided an in-depth review of clinical information provided by the principal investigator's in both studies, Stephen Straus for the first study and

Jay Hoofnagle for the second study. Information available only to the FDA was not made available to the committee.

The IOM committee concurs with the subcommittee's review of the deaths of trial R-90 subjects 401,406, and 408, well after completion of their FIAU treatment and their conclusion that "even in retrospect, these deaths could not be attributed to FIAU." A fourth death (patient 4D) from the R91 trial was problematic for both the investigators and the NIH subcommittee.

Patient 4D received FIAU for 28 days in August 1992. In November 1992 the patient had a laparoscopic removal of his gallbladder in response to persistent abdominal pain. No stones were found, and the patient developed intractable ascites and lactic acidosis. On evaluation by NIH investigators in December 1992, his liver enzyme levels were normal, but he was in liver failure. He died while awaiting a liver transplantation. Microvesicular steatosis was identified at autopsy.

At the time of death, the cause of his syndrome was unknown, but it was not attributed to FIAU because of the long delay between the end of therapy and the onset of his syndrome. There were, however, in-depth internal discussions of possible underlying pathophysiology. The syndrome of metabolic acidosis, normal serum liver enzyme levels, and microvesicular steatosis that would later characterize the syndrome in the victims of FIAU toxicity in the PPPC trial was identified. In retrospect, the NIH subcommittee and the IOM committee consider this patient (patient 4D in trial R91) to be the first real case of the delayed FIAU toxicity syndrome responsible for the five deaths in the PPPC trial (93-DK-0031).

Did the Investigators Adequately Consider All Data Available to Them in the Design and Conduct of the Protocols, or Were Important Data Ignored?

The IOM committee concurs with the subcommittee's report that the study design was carefully considered and that all steps of the study had been appropriately revised. There is no evidence that any information was overlooked. The death of patient 4D was discussed, but there was insufficient information to ascribe the syndrome to any one cause. Hoofnagle was enthusiastic about the potential of FIAU providing an effective therapy for HBV infection. However, his approach was careful. There was evidence that information available in the investigator's brochure and from preclinical studies had been reviewed and discussed with both the sponsors and FDA. Clinical events in patients from the second trial (e.g., neuropathy) were incorporated into the trial design and information provided at the time of obtaining informed consent.

Was The Third Study Prematurely Implemented or Put on A "Fast-Track"?

The NIH subcommittee raised the question of whether transferring the focus of drug development from HIV- to HBV-infected patients led to an inappropriate fast-track initiation of clinical studies before full conventional animal toxicology studies were performed. In reviewing the sequence of events for the IOM committee, FDA officials (Feigal, 1994) indicated that the time frame for the development of FIAU was within the normal range for

an antiviral drug (being on the conservative side). It was noted that the second (R91) and third (PPPC) protocols were delayed to permit completion of studies in animals and safety evaluation.

The IOM committee concurs with the NIH subcommittee that the sequence of development of FIAU was within existing guidelines and there is no evidence to suggest that fast-track development was a contributing factor to the untoward events induced by FIAU.

Was The Third Study Accelerated By Pressure From Eli Lilly & Company?

The subcommittee noted that the impetus for the third drug trial was investigator initiated and driven. There was every indication of close and full collaboration between the investigators and the sponsor and between the sponsor and the Antiviral Drug Division of FDA.

The IOM committee concurs with the subcommittee that there was no evidence of undue haste or coercion from Eli Lilly.

Question 2—How Well Were The Fiau Studies Conducted?

The subcommittee further subdivided this issue to address the following specific aspects.

Compliance With Nih Multiple Project Assurance And The Quality and Thoroughness of Irb Review of Protocols

The subcommittee reviewed each protocol in depth and found each had received prior clearance from respective clinical directors of NIH. All IRB stipulations and reviews were met, including incorporation of amendments. The minutes of the IRB review accurately reflected the review proceedings, and the principal investigator promptly reported adverse events to the IRB. The subcommittee was satisfied that the two IRBs had provided a comprehensive, thoughtful and rigorous review and were in compliance with NIH and federal regulations.

The Design of Clinical Studies with Particular Reference To The Third Protocol (Lilly Pppc/Nih 93-Dk-0031 Trial)

The rationale, design, entry criteria, study measurements, safety monitoring, definition of stop points if toxicity occurred, and duration of follow-up of the third protocol were reviewed and were considered to be not only appropriate but of exceptionally high quality. In the words of the subcommittee report, the protocols were "meticulously prepared and implemented." The IOM committee concurs with the subcommittee critique.

Quality and Content of The Consent Process

The subcommittee undertook an exhaustive review of the process of enrolling subjects in FIAU studies. This included review of patient records and direct interviews with all 10 surviving patients, the investigators, the research nurses, the chairs of the two involved IRBs, the institute directors, and the acting director of the Clinical Center. The subcommittee was satisfied that the patients were provided full, informed consent and were impressed by the teamwork between investigators and staff. There was no evidence to suggest that pressure was exerted on the patients to enroll in the study.

The IOM committee concurs with the subcommittee's report that all appropriate reviews and protections for human subjects were followed. One of the more unusual features of the third protocol was the close relationship between the patient volunteer group and the investigators at NIH. The patients tended to be well educated, well informed and highly motivated to participate, in many instances, in more than one study.

Reporting to The IND Sponsor and FDA

The subcommittee did not have the results of the investigations of the Compliance Office of FDA at the time of presentation of their report. The subcommittee was informed of a review of case report forms submitted by NIH investigators to Eli Lilly. On the basis of that and other reports, the subcommittee saw "no reason to believe that compliance reporting was not in order."

The NIH subcommittee's task was not to provide a detailed audit of compliance with regulatory authorities, and it did not have all of the information available to FDA. It would therefore be inappropriate to relate their conclusions to the FDA audit process or review. It was clear, however, that the subcommittee, like the IOM committee, considered the investigator-sponsor relationship and the exchange of information to be of high quality.

Clinical Care of Patients

The NIH subcommittee reviewed the objectives and procedures of the NIH Clinical Center. Several specific points were raised:

- Patients attend the NIH Clinical Center only as participants in clinical research.
- The caliber of physicians and nurses is first rate.
- There was an exceptional, interactive, and well-informed relationship between staff and patients.
- Routine patient data and symptoms were carefully monitored and accurately reported.
- Side effects were given serious attention, and patients were carefully evaluated to ensure that anticipated and unanticipated events were properly addressed.

- Excellent concordance was observed in a comparison symptom reports prepared by the patients with the reports in the charts prepared by staff.
- In reviewing the files of 10 surviving patients, there was no single instance in which recorded complaints from the patients were not addressed.

The IOM committee concurs with the favorable review of the NIH subcommittee on the quality of patient care provided by Hoofnagle and staff in the FIAU studies. A publicized incident between one patient in the study and Dr. Hoofnagle was addressed in the subcommittee report, in which it was considered to be a patient-specific incident. In the opinion of the IOM committee, there is no evidence that a lack of quality of patient care contributed in any way to the events that took place in patients receiving FIAU.

Question 3—How Well Were The Adverse Events in The Fiau Studies Handled?

As stated above, in the opinion of the subcommittee the three deaths in the R90 trial were thought to be unrelated to FIAU, and the death of a subject in the R91 trial "was considered but could not be proved to be drug related." The subcommittee therefore focused on the investigator responses to events occurring in subjects in the third protocol (PPPC trial), particularly in June 1993.

On June 25, 1993, a patient was admitted in an emergency to a Virginia hospital with lactic acidosis. The clinical picture was identified as being similar to that of the patient from the previous protocol who had died with lactic acidosis and liver failure. Within 12 hours of recognition of an FIAU-related severe hepatotoxicity, the trial was terminated and the patients in the trial were urgently admitted to a hospital for evaluation.

It was noted that Eli Lilly paid the expenses for transplantations, and all surviving patients continue to be followed on a regular basis at the NIH Clinical Center.

The NIH subcommittee noted that the presentation of the patient with acute liver decompensation with lactic acidosis was immediately recognized as probable FIAU toxicity. This terminated the administration of FIAU and led to intensive efforts involved in managing the care of patients who still developed evidence of toxicity, despite discontinuation of the drug. Even in retrospect there was no time before this hospital admission, when evidence of adverse effects was sufficiently compelling, to warrant stopping this study of a very promising and sorely needed therapy. The IOM committee is in agreement with the conclusions drawn by the NIH subcommittee.

Question 4—Could The Adverse Events Have Been Avoided, Particularly in The Last Study?

The subcommittee considered it unlikely that changes in the research protocol or additional testing in animals or humans would have provided signals that would have delayed or prevented use of FIAU in patients with chronic HBV infection.

Could The New, Highly Sensitive Ria Method Have Alerted The Attending Physicians to The Possibility of Hepatic and Pancreatic Failures?

The initial HPLC assay lacked sensitivity in defining the terminal half-life of FIAU in humans. Following licensure to Eli Lilly, a 100-fold more sensitive assay, the RIA, was developed in June 1993 and was used to estimate a half-life of 29 hours rather than the 1-4 hours estimated previously.

The IOM committee concurs with the NIH subcommittee that even if information from the RIA had been available before implementation of the final protocol, it would not have changed the study design or focused attention on hepatic or pancreatic toxicity. The information needed to anticipate this delayed selective toxicity would have been evidence of either differential uptake into liver and pancreatic tissue or differential effects on these two organs. It should be noted that neuronal, not hepato-pancreatic, toxicity was the primary danger anticipated.

Could Damage to Mitochondria Be Responsible for The Delayed Toxicity Seen in The Extended Fiau Trial?

The subcommittee reviewed what was known and speculated on the potential for FIAU to be incorporated into mitochondrial and nuclear DNA, particularly the incorporation into mitochondrial DNA in cell culture preparations. They concluded that too little information was available to influence study design on the basis of these considerations. At the time of review by the IOM committee substantial progress had been made, but there is still insufficient information to influence study design of drug development or even to recommend one strategy in preference over another.

There is an intensive investigative effort being made by researchers at Eli Lilly and other laboratories to understand the mechanism of FIAU toxicity, learn the structure-activity relationships of different molecules to induce similar events, and develop a predictive in vitro model to anticipate and prevent similar toxicity in the future. There is a clear imperative to more clearly understand the pathophysiology of this syndrome.

Would New Knowledge Concerning The Delayed Clearance of Fiau Have Changed The Daily Regimen Used in The Third Trial?

Modification of the dosing interval in the third protocol in light of the longer half-life was discussed by the subcommittee. Specifically, was there a potential for drug accumulation during chronic therapy? It is evident that the kinetics of incorporation of FIAU into DNA are still unclear; just as importantly, the functional consequences of incorporation are also unknown.

The IOM committee agrees that too little information is known relating the kinetics of FIAU to any dynamic effect, and knowledge of the longer half-life per se does not provide sufficient information to influence the study design.

What Effect Might An HBV Infection Have on The Hepatic Toxicity of FIAU?

The subcommittee report speculates on the potential additional variable of the presence of HBV in the hepatocytes of the treated patients.

The IOM committee agrees that there is a potential for a disease-specific contribution to the adverse effect profile of a drug. For example, a modification caused by a virus in a target cell might induce changes only in infected cells. As indicated in Chapter 13 of this report, to the extent that the woodchuck hepadnavirus model allows hypothesis to human HBV infection, this extrapolation seems unlikely with FIAU. In any case, insistence on developing a convincing animal model for each human disease before attempting human drug trials would drastically impede the development of new drug therapies.

Would A Different Accrual Pattern of Recruitment in The Final Protocol Have Affected The Outcome?

In some clinical trials, the rate of accrual is defined and staggered for safety concerns. In most studies with small sample sizes, staggering of accrual is not preplanned but tends to occur naturally because of the limited availability of subjects. In the PPPC protocol, a 6-month delay in implementing the study led to the identification of most candidates from a previous trial. Furthermore, the initial study design was planned as a retreatment program. Thus, when the study started, 10 of the 15 subjects (all of the ones with prior FIAU exposure) were entered into the study within 1 month and had already received prolonged FIAU therapy when the first toxicity was noted. The subcommittee recommended that when short-term trials are extended to 6 months or more that accrual should be staggered (for example, only 20 percent to 25 percent of the patients started each month) to reduce the incidence of unexpected long-term or delayed toxicity.

The IOM committee concurs with this recommendation to avoid the simultaneous enrollment of large groups of patients, at least in Phase I and II trials.

SUMMARY AND RECOMMENDATIONS

The NIH subcommittee concluded: "The FIAU studies represent the best of current practice in clinical investigations and exceeded regulatory requirements ... and that Dr. Hoofnagle and Dr. Straus were among the leading researchers in their fields and well qualified to conduct this research." An unfortunate sequence of events does not constitute the failure of a system. Conversely, if the studies had proceeded along less rigorously controlled conditions, it is probable that a major disaster involving large numbers of subjects would have occurred in the Phase III studies that were about to be implemented. "Delayed, fatal human toxicity due to FIAU represents a novel type of toxic reaction not previously encountered."

The subcommittee could find no example of either clinical judgment or research process in which a change could have been expected to influence the outcome. In the words of the subcommittee, "It could not see itself having concluded or acted differently from the

investigative team or the patients, given the information available at each step." The IOM committee concurs with this assessment.

Recommendations from The Nih Subcommittee

Mechanisms of Toxicity

1. It was recommended that all drugs that have potential for entering or modifying DNA should be considered for their abilities to damage not only nuclear DNA but also mitochondrial DNA. They recommended support of research to provide new and early measures of mitochondrial DNA damage.

   The IOM committee strongly endorses the need for further research to more clearly understand the mechanisms involved in FIAU toxicity. This is clearly vital not only for antiviral drug development but also for gene transfer studies. There is an urgent need to define drug incorporation into DNA (a pharmacokinetic description) and relate such changes to changes in function (i.e. a pharmacodynamic response). This issue merits financial support for research and given the high profile of AIDS and gene transfer research, it should have a high priority.
2. The potential for extended reutilization or recycling of a nucleoside analog in and out of DNA must be considered. Support for further research in this area would be valuable.

   The IOM committee strongly endorses this recommendation. The identification of a new type of drug-induced toxicity in which prolonged therapy is associated with late-onset toxicity but rapidly progressive and fatal toxicity suggests long-term drug incorporation into DNA. Recent reports now suggest that a similar syndrome may also be induced on rare occasions by other nucleoside analogs, including those, like AZT, used extensively in the treatment of HIV infection. If this occurs for a variety of drugs, this mechanism has major implications in drugs with acute, delayed, mutagenic, and carcinogenic toxicity, and the factors involved are currently unknown. This underscores the urgent need to take advantage of this adverse sequence of events to positively identify currently unknown pharmacologic mechanisms of drug action.

Preclinical Tests in Animals

1. The subcommittee recommended that preclinical testing in animals should mimic as nearly as possible the route and dosage regimen proposed for use in humans and the disease state that occurs in humans. This is particularly important for orally administered drugs if first-pass clearance occurs in the liver.

   The IOM committee endorses the approach, but emphasizes that the current lack of knowledge makes it difficult to implement this recommendation. There are substantial differences in the activities and specificities between related drug-metabolizing enzymes in different species. Thus, experiments in animals must be shown to relate to human drug metabolism in humans before drawing inferences of relevance to toxicity and disease in

humans. There will always be the possibility of unexpected adverse events that are identified only in or that are identified first in humans.

The comment on the need for models of disease is an appropriate plea for more research. However, there needs to be clear recognition that it is extraordinarily difficult to develop models of disease in animals truly analogous to disease in humans. At present there is insufficient evidence to justify the regulatory requirement of a model of disease in animals. FDA should not hold up drug development in the absence of such models. Conversely, FDA should encourage the positive development of such models to facilitate decisionmaking.

2. The subcommittee recommended that vigorous preclinical screening is indicated for a suitable time period, particularly in patient populations whose lives are not imminently threatened by this disease.

   The IOM committee is concerned that translation of this recommendation into restrictive regulatory requirements would be counterproductive to the intent of this statement and would place an inappropriately heavy burden on the investigator. It does not in any way address the major difficulties of Phase I and Phase II trials with small sample sizes: differences in the extent or severity of disease process or the presence of confounding variables. The IOM committee recommends exploration of new approaches to comparative control groups for Phase I and Phase II studies. A variety of alternative approaches are available, and large amounts of potentially useful information have already been provided to FDA. The IOM committee recommends that the development of new methods be sponsored independently of FDA, to emphasize the research nature of such matters. It is recognized that issues of confidentiality would have to be addressed to permit full access to information.

Patient Enrollment

As noted previously, the subcommittee recommended that when patients were entered into Phase I or Phase II clinical trials of drugs with the potential for entering or modifying nuclear or mitochondrial DNA, there should be a delay between recruitment of each cohort to minimize the chance that many patients would be at risk of delayed toxicity if it should occur.

The IOM committee suggests extending this recommendation of staggered entry to any study that involves prolonged therapy (i.e., 6 months or more) to humans. This should not be restricted to drugs that have a potential to modify DNA, because the mechanism of FIAU toxicity remains uncertain. The IOM committee does not recommend an inflexible rate of staggering, but suggests that a stipulated maximal rate of accrual should take into account the available information about the drug and the clinical context of its use. In retrospect, in the third FIAU trial, an entry criterion of 25 percent of the projected study group per month would have reduced the duration of exposure in half of those patients who suffered FIAU toxicity, although this half would still have had substantial, albeit 1 month less, exposure.

Patient Follow-Up

One of the recommendations of the FDA Task Force is that all patients in Phase I or II trials of any new drugs should be monitored for 6 to 9 months after the cessation of therapy. The NIH subcommittee recommended that this recommendation should apply only when there are scientific reasons for suspecting the possibility of long-term or delayed toxicity.

The differences between the two sets of recommendations reflect a somewhat predictable difference in the relative weighing of risk and benefit by the two groups. A 6- to 9-month detailed follow-up on every patient in a Phase I study of an anti-cancer or anti-HIV drug will substantially increase the time and cost of new drug discovery. It will also very substantially increase the difficulty in establishing causal relationships. The net result is likely to be a trade-off in which a few drugs with dangerous toxicities are uncovered at the cost of stopping the development of at least some safe drugs that would have benefited large numbers of patients. The IOM committee recommends that the duration of follow-up be stated explicitly in each protocol along with a rationale. The IOM committee anticipates that because of the FIAU case, the potential for the delayed onset of toxicity after stopping therapy will influence follow-up protocol designs. There is a need to maintain flexibility in study design and tailor protocols for specific drugs to specific clinical situations.

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FDA-Proposed Changes To The Code Of Federal Regulations

FDA has recently issued a series of proposed changes to existing regulations regarding adverse experience reporting in the wake of the FIAU tragedy (FDA, 1994a). The proposed changes in relation to premarketing studies are largely derived from the recommendations of the FDA Task Force report reviewed above and are described below:

STUDY DESIGN AND PROTOCOL

- Specification of the cut-points for measures and events to be considered indicative of an adverse reaction.
- Specification of procedures for distinguishing between drug toxicity and underlying disease process.
- Specification of measures or events to be used to trigger actions regarding a trial (reduce dose, stop treating the patient, terminate the trial, etc).
- Summary of safety data at regular intervals under the supposition that all adverse events observed are drug related.
- Protocols to contain list of clinical events and laboratory measures to be reported to the sponsor; list to include events and outcome measures attributable to underlying disease or concomitant medications.
- Immediately reportable events should trigger remeasurement or challenge procedures, or interrupt treatment.
- Control groups should be used in safety studies when underlying disease likely to mimic drug toxicity.
- Sponsors required to provide estimates of underlying mortality and morbidity rates for diseased populations.
- Follow-up beyond the period of dosing or treatment (3 months suggested for Phase I and Phase II trials).
- Procedures for ongoing safety monitoring in the form of a formal monitoring committee or acceptable alternative.

REPORTS

Safety Reports

- Periods for submission of written and telephone reports extended to 15 and 7 calendar days respectively; faxes acceptable in lieu of telephone reports.
- Form 3500A (same as proposed form for postmarketing reports) allowed.
- Disclaimer to apply to all safety information so as not to constitute a statement or admission of a causal link between drug and a subsequent adverse event.

Semiannual Reports

- Current annual death and serious adverse experiences report to be supplemented by semiannual reports; semiannual report not to take place of annual report.
- Report all deaths, serious adverse experiences, and study discontinuations due to adverse experiences, whether or not unexpected, and whether or not caused by the study drug.
- Data required from IND studies, worldwide premarketing studies, and foreign postmarketing trials or reporting systems.
- Data to be presented cumulatively as well as for a 6-month period.
- Worst case analysis of data required—presumption against drug then attempt to refute presumption.
- Submission of all available autopsy reports and medical reports of deaths required; sponsor to clarify inconsistencies between reports and cause of death reported to FDA by the sponsor.
- FDA may modify reporting requirements, e.g., when it would interfere with a blinded (masked) study, in which neither patients nor study staff are aware of which patients are receiving control treatment until the end of the trial.

Special Safety Summary

- Data on events not defined as serious adverse reactions.
- Agency to determine when it is needed and the information required.
- Should contain results of cumulative analyses in other reports as well as analyses of lesser events.
- Generally, 30 days from request to comply.

Final Clinical Study Report

- FDA may require a final report or study summary of a study at its discretion.

CLINICAL HOLDS

- FDA may suspend ongoing study of an IND or closely related drug under investigation by the same sponsor for failure to submit a special safety summary or final study report.

TERMINATION

- IND may be terminated for failure to submit a semiannual report — nonsubmission of an annual report is currently grounds for the same.
- Failure to implement adequate safety monitoring to be grounds for clinical hold or termination of an IND.

REVIEW OF ONGOING INVESTIGATIONS

- Investigators required to submit safety data to sponsors to allow sponsors to comply with safety reporting requirements, i.e., semiannual reports.

IOM COMMITTEE COMMENT

The time schedule of our review does not permit detailed comment on each of the proposed changes, in part because they were promulgated just prior to the committee's final meeting. The timing of the promulgation is unfortunate, if for no other reason other than that there is much in this report that bears on the regulations being proposed. The period for written comment on the proposed rule changes closed (January 25, 1995) prior to the release of this report. We find ourselves agreeing with David Challoner and David Kipnis (co-chairs of the NIH special review subcommittee) in wishing that the "FDA had waited for another investigation [namely the present one] of the deaths to be completed before promulgating new rules" (Hilts, 1994).

The committee has questioned elsewhere in this report the wisdom of some of the observations and recommendations contained in the FDA Task Force report. Those reservations are germane to the proposed rule changes in that many of those changes have their origins in that report. There are also elements of the proposed changes that we endorse on general principle and have so indicated elsewhere in this report. Foremost among them are the desirability of formal ongoing monitoring and the use of designed comparison groups in all stages of testing, starting with Phase I and Phase II trials.

Formal Real Time Monitoring

The IOM committee believes that IRBs need to be more vigilant in ensuring that investigators have adequate plans for ongoing monitoring of trials, regardless of their size, the sponsor, or the funding source. Although the review and approval process should include assurances from the investigators of a commitment to publish the results of the trial regardless of its outcome, IRBs should insist, as well, on some form of ongoing monitoring, preferably in the form of some independent person or group, and should be satisfied that the investigator or study has an adequate system for data flow and follow-up to make such real-time monitoring practical and useful.

The committee notes in this regard that the usual case report form of data collection and reporting is not amenable to such monitoring. In that approach, investigators are given a booklet containing a set of forms to be completed for a particular patient. The entire package is retained at the data collection site until the patient has completed the study, died, or dropped out of the study. The data contained in a case report are not entered at the data center until the entire package has been completed and sent to the sponsor or data center. As a result, there is a lag of weeks or months in the flow of information to the sponsor or data center and in the conversion of the data to electronic form for processing and analysis. A real-time form of monitoring and analysis requires real-time data flow and abandoning the case report form of data collection in favor of a contact or visit-driven form of data collection and flow. This is obviously no panacea, since the FIAU studies reviewed here all had formal or informal real-time monitoring systems as well as the mandated case report forms, but it is a change that would help insure that all investigators are as alert to developing problems as these FIAU investigators were.

Controls

Among the recommendations in the FDA report, the one having the greatest intellectual appeal is their recommendation having to do with the need for controls. The use of controls and randomization in this case would have, at the very least, provided a better framework for evaluating background morbidity and mortality. It would have provided another benefit in that, assuming the same rate of recruitment as achieved but with only half of the patients being assigned to the test treatment, only half of the patients would have been exposed to a bad treatment, and the slower rate of enrollment to the test treatment would have increased the chance of detecting the late complications, with fewer patients being exposed.

These things said, however, the IOM committee is also under no illusions as to the power of such trials for detecting untoward events. The typical Phase I or Phase II trial involves 20 to 40 patients and treatment and follow-up over a short time period. Most adverse effects caused by treatments will go undetected in such settings. Hence, although there are lots of reasons to favor the notion, it would be a mistake to assume that such a provision will significantly reduce the risks of exposure in phase I and II trials, especially when those effects are heretofore unknown and unanticipated.

The absence of appropriate comparison groups in the Phase I or Phase II setting leaves those doing such trials in a quandary as to the interpretation to be given to morbid and fatal events observed during or shortly after the course of a trial. The problem of interpretation is most acute when the trial involves sick people with an increased background morbidity and mortality. One can expect, in such cases, for some patients enrolled in the trial to have morbid events or to die during or soon after the trial and for those events to be unrelated to the experimental treatment. The interpretation given to any single event in such cases is much more difficult than when the trial involves healthy subjects without any apparent risk of morbidity or mortality.

Follow-Up

The IOM committee concurs with the view expressed in both the FDA and NIH reports arguing for follow-up beyond the formal close of a trial, especially for trials involving new compounds. It is reasonable to expect sponsors and investigators to maintain some minimal form of contact with patients (e.g., via mail or telephone and for a period of weeks or months) following separation from phase I and II trials involving new compounds. The follow-up would provide data on mortality and gross morbidity that *may* serve to alert to possible problems, with emphasis on *may*. The reason for the equivocation is that it is difficult enough to determine whether or not morbid or fatal events are treatment related when they occur while patients are under direct observation and being managed according to a specified protocol. Interpretation of such data becomes profoundly more problematic when the events occur after the patient's separation from the trial, and especially in the absence of a corresponding control group for comparison. One is forever uncertain as to whether such events are or are not related to something done weeks or months before the event in question.

The committee endorses the concept of longer follow-up on its general merit. However, we doubt that such a practice would have averted the disaster of the PPPC trial. In reality, at least one of the 3 trials done before the PPPC trial was in fact designed to provide such follow-up as a routine part of the study protocol (R91; 4 weeks of treatment and 20 weeks of follow-up), and the PPPC trial, had it gone to completion, would have provided such follow-up. Hence, only two out of the four trials in question did not make some provision for extended follow-up: R89 (FIAC; 4 weeks follow-up; n = 12) and R90 ([FIAU; 4 weeks follow-up; n = 43). The period of treatment and follow-up combined was 5 weeks for the R89 trial and 6 weeks for the R90 trial. See Table 1 of Appendix H for details.

All nine of the deaths noted in the FDA report occurred after the completion of treatment of those patients. If one assumes that the FDA report represents a full accounting of deaths up to the time of compilation of the report then the follow-up system proposed (6 months following the last administration of treatment) would have yielded just four of the nine deaths occurring before all studies of FIAU were stopped on June 28, 1993 (patients 105, 110, and 107 in trial R89 and patient 4D in trial R91).

The committee also believes that it is prudent to view all events as possibly related to the treatment, but we recognize the need for judgment in this regard. We find it unfortunate and puzzling in this regard that so much is made, in retrospect, of AST and ALT elevations that, in the actual course of activities, investigators had legitimate grounds to view as positive

indicators of treatment success. Given the grounds for that belief it is difficult to view something considered to be beneficial as an "adverse" event as well. Furthermore, the fact that they so regarded them was known to the FDA's Antiviral Drug Division, and if for no other reason than the absence of objection, investigators and sponsors had good reason to believe that their interpretation of such flares was also accepted by the FDA.

Stopping Rules

The IOM committee views the recommendations regarding stopping rules with skepticism for the following reasons. First and foremost, Phase I and Phase II trials are not large enough to be amenable to the use of statistically based stopping rules. Second, most Phase I and Phase II trials that use patients as subjects are conducted without concurrent control groups, and hence, there is no statistical basis for comparison. Third, it is virtually impossible to construct operational decision rules for the entire constellation of conditions or circumstances that one may encounter in a trial when one is dealing with events on a real-time basis. The main value in stopping rules would be in the thought processes used to focus on actions that might be taken in the presence of certain conditions or events and not in the algorithm itself.

There is merit to the process of specifying events that will trigger changes in a trial, to the extent that it serves to cause investigators to focus on the nature of results that might be expected. However, the resulting calculations are not likely to represent much more than educated guesses as to background morbidity or mortality, given the varied nature of the patients involved and their underlying disease states and medical histories. (See the following section on statistical analysis of mortality for several educated guesses about mortality in the patient population from which the FIAU/FIAC trials drew their subjects, and the predictive utility of those guesses).

Both the FDA and the NIH reports speak to the need for doing trials in sequence, with thorough analysis at each step before proceeding. The need or desirability of staging, however, must be balanced against the need for speed in trying to find and develop new treatments for existing diseases. That need, as well as pressure from the public (AIDS activists in particular) for increased efficiency in bringing drugs to approval, makes it difficult to justify a strict sequential approach for serious life-threatening or life-limiting diseases.

A Statistical Analysis of Mortality in The Fiau/Fiac Trials

Both the FDA and NIH reports speak of the desirability of following persons enrolled for a period of 6 months or longer following enrollment. The FDA report speaks, in addition, to the desirability of pretrial estimates of expected mortality in the patient populations from which the subjects are to be drawn, and combining information from related trials in deciding whether or not to continue development of a drug. That being the case, it is instructive to reanalyze the available information from the FIAC/FIAU trials of 1989-1993, assuming that

each person enrolled is followed for a period of 26 weeks following enrollment and that the FDA report contains a full accounting of the deaths that occurred in that time interval.

The question of interest is whether there was sufficient death data available before the start of the PPPC trial to have caused prudent investigators not to have started that trial. The question is addressed by looking at each trial individually and by a form of ongoing reanalysis at the point of each death using all available data at that point in time for three trials (R89, R90, and R91). The analyses are performed assuming 26 weeks of follow-up for each person enrolled with censoring at that point (i.e., deaths occurring after the 26th week are not counted in the analysis) and assuming a control treated group of the same size as the number enrolled in the individual trials. For example, the R89 trial is assumed to have been done with a total of 24 patients, half of whom were assigned to treatment with FIAC and the other half of whom were assigned to ordinary medical care without FIAC.

The staging or sequencing suggested in the two reports prevailed in this case by virtue of when the trials were done. Trial R90 started 23 weeks after the last dose was given in trial R89 and, hence, all patients in trial R89 would have had at least 26 weeks of follow-up at the start of trial R90. Similarly, trial R91 allowed for at least 26 weeks of follow-up for all patients enrolled in that trial before the start of trial PPPC. The only overlap is for R90 and R91. Trial R91 started 185 days after the start of R90 and 77 days prior to the close of recruitment for R90. However, even if the start of trial PPPC would have been delayed to allow for the last person enrolled in R91 to have been followed for 26 weeks following enrollment, the staging would not have changed the information available for the start of PPPC (the reason being that the single death noted in the FDA report for trial R91 occurred in the 27th week following enrollment and would not have been noted or counted in an analysis with censoring after the 26th week of study). Hence, the information available at the start of PPPC was the same as if staging had taken place.

None of the trials was controlled, so it is necessary to hypothesize underlying mortality rates for the analyses (i.e., the rates that would have been likely in an untreated control group). Since there is no way of knowing those rates exactly, the best that can be done is to investigate a range of values (see Appendix H for details). Using hypothetical mortality rates ranging from 10 to 20 percent per year for the HIV-infected patients in the R89 trial and from 2 to 4 percent per year in the R91 and PPPC trials, the number of deaths "expected" in each group of patients was calculated and compared to the number of deaths actually observed.

The statistical evidence for harm is weak (see Tables 3, 4, 5, and 6 in Appendix H). In fact, depending on the assumed underlying mortality rate, some of the analyses actually suggest a beneficial treatment effect (i.e., death was less likely than expected). The only trial that produces any convincing evidence of harm is the PPPC trial, and all of that information accumulated after the investigators had already stopped the trial because of morbidity.

To summarize, it is unlikely that the FDA-recommended procedures of estimating expected deaths and following up for 6 months would have resulted in cancellation of trial PPPC, and might even have led the investigators to persist longer than they did when patient 2 was hospitalized.

Reporting

In regard to the proposed changes requiring a marked increase in safety reporting, we remain skeptical that the benefits from such added efforts will outweigh the risks. The risks must be measured in increased costs, in terms of added time for drug development, in terms of delays in access for general use, and in terms of so-called type II errors — abandoning work on a drug because it is believed to be ineffective or harmful when, in fact, with further testing and development it would have been shown to be both effective and safe. Perhaps we would be less skeptical concerning the wisdom of proposed refinements and expansions of the existing safety reporting system had the proposal been supported with detailed analysis of the current reporting systems and its strengths and failings and with a detailed accounting of its product in terms of public safety and well-being.

A major impact of the proposed changes is likely to be in relation to the number of safety reports generated (see discussion of safety reports in Chapter 2 for current definitions and regulations). The proposed revised definition for *serious adverse drug experience* is

> An adverse drug experience occurring at any dose that is fatal or life-threatening, results in persistent or significant disability/incapacity; requires or prolongs inpatient hospitalization, necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure, or is a congenital anomaly.

The thrust of the revision is to reduce the amount of discretion left to investigators and to broaden the scope of events to be considered reportable. That expansion is likely to lead to a flood of "safety" reports without any real increase in safety as seen from a societal perspective. Indeed, there is reason to fear the reverse. There is already anecdotal evidence suggesting that the paper flow to IRBs in regard to presumed adverse events has increased markedly in the wake of the FIAU experience. The increase is almost certainly the result, in part, of an increased defensive posture on the part of investigators that is related to their desire to avoid being faulted by FDA for having failed to report some event later judged by auditors to have been important, but not reported.

The increased flow of such reports to IRBs has consequences above and beyond the added administrative burden involved in review and written communications. The change will almost certainly result in a marked increase in false-negative reports. The long-term consequence of such a change will depend on the "personalities" of individual IRBs. One effect may be to reduce the sensitivity of an IRB to all safety reports, if the majority are viewed as unrelated to treatment. That effect will be similar to that observed by the "little boy who cried 'wolf' once too often." The other effect, more likely perhaps with inexperienced IRBs, is to make IRBs consider all reports as serious and, hence, end studies that should have been allowed to continue:

The possibility for confusion of IRBs with a flood of reports is real. As it is now, investigators are obligated to forward any safety reports received from a sponsor in relation to the IND covering their trial even if the reports relate to other trials done elsewhere and under

protocols different from their own. Each such report can result, in the case of multicenter trials, in dozens of individual communications with local IRBs.

Another impact will be the frequency of summary reports to FDA (from annual to semiannual). If there is merit at all to the increase, it should be the exception rather than the rule and should be related only to those compounds that are truly new and for which little is known regarding mode of action or safety.

There is another sort of "reporting," however, that the IOM committee would strongly endorse, even if, as seems likely, it would not have saved any lives in the present case. Trials represent a form of public trust that exists regardless of the drug being evaluated and regardless of how they are funded or sponsored. It can be argued that maintaining that trust carries an obligation on the part of sponsors and investigators to facilitate a free and open exchange of information and to do so even if at the risk of divulging trade secrets or arming would-be competitors with information on compounds under study.

The best way to maintain that trust is via free and open exchanges in regard to the design, conduct, and analysis of individual trials, to be able to do so at all stages of testing, and to do so via recognized routes of presentation and publication. We note, in this regard, that the medical community still awaits a detailed accounting in the peer reviewed literature of the events of the trials in question. Although the committee understands that such a publication is being prepared, we also note that the events in question transpired some time ago. The best defense against repeating the mistakes of the past is via publication in the medical literature.

The committee also notes, in passing, that existing regulations in regard to trials done under INDs work against free and open exchanges. The only obligation on the part of sponsors is to report to FDA. Data submitted to FDA, by law, constitute privileged communications and may not be divulged or released by FDA prior to approval of a new drug application (NDA). Even after approval, the amount of information available to the public is limited to that which can be obtained under the Freedom of Information Act (FOIA). As a result, failing publication, there is no reliable way for sponsors or investigators to obtain data on related compounds being tested under INDs held by other sponsors.

Even after a drug is approved, access to results of individual trials done under INDs supporting an NDA is problematic. Requests for the information must be made under the FOIA and, even if successful, may not result in information amenable to any reliable form of analysis or review. Fortunately, in this case all trials were done under linked INDs so the sponsor and investigators had the means of linking and combining data without constraint.

The solution to information access is not straightforward nor is it likely to be forthcoming soon, since it requires changes to existing laws. That said, however, there is nothing, so far as the committee can ascertain, to stop a sponsor from waiving its right to confidentiality of data sets supplied to FDA or of making them available themselves to interested parties on an as needed basis. Furthermore, there is nothing to stop investigators undertaking trials from publishing their results and, in the case of multicenter trials, insisting that the combined results be published as a condition for participation. In addition, there is nothing to stop IRBs from ensuring that such assurances are provided before approving a clinical trial.

Various people and groups have called for real-time systems of registration of trials as they are undertaken (Dickersin, 1988; Meinert, 1988; Chalmers, Hetherington, Newdick,

Mutch, Grant, Enkin, and Enkin, 1986; Simes, 1986). The means to do so exist. All that is needed is the collective will. Virtually all trials performed at major research institutions, regardless of the funding source, are subject to IRB review before implementation. The establishment of a system for registering trials at that point of review, along with a nationwide system for harvesting such information, would provide a means for sponsors and investigators alike to identify trials done or underway on the compound of interest or on related compounds. At present they are in the dark. At least with such a system they would have a vehicle for the identification of related investigations. Even if this did not lead to data sharing, it would at least have the potential of informing of hidden disasters.

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Ancillary Issues Raised During The Period Following The H3x-Mc-Pppc Trial

The tragic events that occurred in June to September 1993 in the group of ambulatory patients participating in the NIH trial (H3X-MC-PPPC) of FIAU therapy of chronic hepatitis B virus infection has been the principal focus of this committee's review. The tragedy that occurred, in which 7 of the 15 study participants developed sudden, rapidly progressive liver failure and 5 died (2 other lives were saved by liver transplantation), is heartbreaking. Our feelings go out for these patients and to the families and friends who suffered these irreparable losses, although we recognize that no amount of sympathy can compensate for the lives lost and for the shock and grief that these events induced. The committee is also cognizant of the sadness felt and expressed by the physicians and nurses who cared for these patients during this trial (and, in many instances, during earlier drug trials). Accordingly, the primary concern in this report has been to determine (1) whether investigators, sponsors, FDA, and NIH acted appropriately in the clinical trials of FIAC and FIAU, and (2) whether the rules or procedures governing the clinical trial process need to be changed to address problems identified in the FDA and NIH reports and in the review of all the FIAU/FIAC trials carried out by this committee. These have been considered in the earlier sections of this report. In many instances we agree with changes recommended by the FDA Task Force report or the report of the Advisory Committee to the Director of NIH. In other instances we have disagreed with some of the recommendations and have stated why (see Chapters 14 to 16). Our overall conclusions and recommendations are summarized in Chapter 18. In all instances the committee's concern has been to reduce as far as possible the chance of such an unanticipated misfortune ever occurring again in the course of a clinical drug trial. This is done with the acknowledgment of the benefits that can accrue to society as a whole by the performance of clinical trials in the drug discovery process, and with the recognition that the measures recommended here cannot provide absolute assurance against the appearance of an unanticipated type of toxicity during the course of early clinical trials of some yet untested class of promising drugs in the future.

In the course of the committee's review and deliberations several ancillary issues came to our attention, represented by events transpiring over the year subsequent to the catastrophic events that immediately followed termination of the PPPC trial at NIH. The committee considers these issues to be clearly very secondary in importance to the principal, unfortunate events that form the basis of this report. However, since these issues bear directly on the regulatory control of clinical trials, the committee believes that it would be reasonable to acknowledge these issues and add a commentary on them in the following paragraphs.

Officials in the Office of Compliance in the Center for Drug Evaluation and Research of FDA began an investigation of the FIAU and FIAC trials within a month of the deaths of the PPPC trial subjects. The investigation apparently continues to this day, although it has already resulted in the public censure of four scientists and two drug companies (Schwartz, 1993; Hilts, 1994).

Part of the mission of the Division of Scientific Investigations of the Office of Compliance is to perform on-site audits of sponsors and investigators performing research under INDs. The division carries out hundreds of such audits every year. Most of them are routine and performed as part of the ongoing activities of the Division in relation to its general mission of assuring compliance with federal guidelines for research performed under INDs. A small fraction of them are performed because of suspected problems, because of complaints from investigators or patients as to possible wrongdoing, or because of publicity surrounding a study. The audits in the case of the FIAU trials were prompted via the last of these and were initiated by the division after publicity in the media and the threat of hearings in Congress.

Most audits conclude with an oral briefing of the findings and the provision of a list of problems or violations to the investigator or sponsor being audited. On other occasions this is followed up with letters notifying investigators or sponsors of problems or violations noted in the audit. Letters conveying such information are broadly referred to as warning letters and in terms of action indicated are classified as no action indicated (NAI), voluntary action indicated (VAI), or official action indicated (OAI). Letters of the first type, as implied by the name, do not require a response from the recipient. VAI letters request a response within 30 days of receipt with a proposal for correcting or preventing the cited problems or deviations in the future. OAI letters are intended to warn of an impending action such as disqualification from future drug research or even criminal prosecution and require a response within 15 working days. The committee was unable to determine exactly how the decision on what type of letter to send is reached, but it would appear to be a subjective decision based on some combination of the number of violations and their perceived seriousness.

The division has issued a total of 3,731 such letters since beginning the practice in 1977 (20 percent NAI, 74 percent VAI, and 6 percent OAI). The number issued in fiscal year 94 was 187 (31 NAI, 91 VAI, and 8 OAI, with 57 remaining to be classified at the time of the testimony [July 25, 1994]).

Letters were sent by the division pursuant to FIAC and FIAU trials to four scientists and two sponsors: Stephen E. Straus, Douglas Richman, Lawrence Corey, Jay Hoofnagle, Oclassen Pharmaceuticals, Inc. (Terry L. Johnson addressee), and Eli Lilly & Company (Randall Tobias addressee). These letters were generated as a result of on-site audits carried. out in the latter half of 1993 (all were started in August or early September). All letters were dated May 11, 1994 and were sent out by fax and overnight mail on May 13. The letters to Richman, Corey, Hoofnagle, Oclassen, and Lilly were OAI letters. The letter to Straus was a VAI letter.

Technically, the letters are intended simply to note violations of protocol or procedure, devoid of judgment as to the relevance of the citations to patient care or treatment, as indicated below in testimony before the Committee:

> But I want to emphasis to all of you very strongly that the letters issued by the Office of Compliance were issued primarily based upon violations, documented failures by the clinical investigators and/or the sponsors/monitors to comply to the regulations. There is no place in our letters, nor should there have been, and we did not allude to or present any insinuation that was a direct criticism of patient care or of lack of concern or that in any way the ultimate unfortunate results of the deaths of those patients should have been prevented. That never entered our review. (Richardson, 1994b)

That intent was certainly not obvious to many readers of the letters, illustrated best perhaps by a news release from the Chairman of the House Government Operations Subcommittee on Human Resources and Intergovernmental Relations issued Friday, May 13, 1994 (before actual receipt of the warning letters by the letters' addressees). Over a headline alleging "lethal science fiction used in the death of FIAU patients," it reads, in part, as follows:

> the Food and Drug Administration (FDA) warning letters to the two drug companies and three clinical investigators involved in the flawed fialuridine (FIAU) experiments confirm that the patients involved were neglected and mistreated. FDA's letters document that the clinical investigators and the drug companies consistently misinformed and misled the patients.

It goes on to say:

> FDA's warning letters show that the drug companies and the investigators repeatedly and flagrantly violated FDA regulations, study protocols and good medical practice. In view of the death and suffering their negligence caused innocent victims their behavior and actions are reprehensible, unconscionable and inexcusable. In their self-serving rush to bring this drug to market, the overzealous researchers and drug companies lost sight of their primary duty to "do no harm" to their patients. (Congress of the United States, 1994)

The communique concludes: "It appears this whole tragedy could and should have been prevented."

The actual citations in the letters fall in four general categories: (1) protocol violations (e.g., You failed to reduce the dosage and/or stop FIAU in subjects when they demonstrated moderate toxicity); (2) informed consent document violations (e.g., You failed to state in the ICD that a purpose of the study was a determination of the safety of FIAU); (3) recordkeeping violations (e.g., You failed to complete several case report forms by not identifying significant clinical and laboratory experiences); and (4) reporting violations (e.g., You failed to assure that all safety reports of severe, unexpected laboratory adverse experiences [elevations in liver enzyme values and others] in subjects were promptly reported to the sponsor or IRB).

The number of violations cited in the letters ranged from 5 to 25, and many were indeed "devoid of judgment about patient care." A number of very serious sounding charges however revolved around the issue of elevated liver enzyme levels in the blood (AST or ALT). As we

have discussed in earlier sections, the investigators and sponsors, with at least the tacit approval of the FDA's Antiviral Drug Division, considered such elevations evidence of a successful effect of FIAU therapy and therefore did not include such elevations in their protocols as a basis for stopping therapy or changing dose. The Office of Compliance, however, decided that the elevations should have instead been viewed as serious and unexpected adverse events and reported as such in writing within 10 days of their occurrence.

The committee believes that the NIH investigators' view was a legitimate one, and is supported by the minimal enzyme elevations which characterized the toxic syndrome of the PPPC victims. The committee recognizes nonetheless that there is room for reasonable persons to disagree with that position. In contrast, a problematic pattern in the warning letters has to do with their declarative nature in matters of judgment and opinion. Nowhere is this more apparent than in citations regarding the content of consent statements used by Richman. The letter to him, in the section on informed consent documents (ICDs) used in the R89 study, indicates that:

> You failed to describe adequately and clearly foreseeable risks of central nervous system toxicity, myasthenia, myopathy, rhabdomyolysis, and liver toxicity in ICDs.
>
> You failed to provide in the ICDs complete and clear information regarding who to contact for answers to questions regarding research subjects' rights, information regarding compensation, and information on whether any medical treatments are available if injury occurs.

The question is what is adequate and clear? According to Richman's response, the statements provided to patients included the following (see Appendix D for a copy of the statement):

> Some other side effects that I may experience include nausea and perhaps vomiting. It is also possible that confusion, jerking, and even seizures may occur while I am taking this medication, although this is unlikely on the doses I will receive. In animal studies there was evidence of heart damage in those animals receiving very high doses of FIAC.

That statement was considered adequate and appropriate by Richman's institutional review board (IRB) when the trial was undertaken. That it no longer seems so, 3 years after the trial was done, is not, in our opinion, grounds for censure.

The second of the two citations also raises questions as to what is to be considered complete and clear. Richman's response in regard to injury and compensation indicates that the consent statements used included the following:

> If I am injured as a result of participation in this research, the University of California will provide any medical care that I may need to treat those injuries—except when they are the consequence of research designed to benefit

> me directly. The University will not provide any other form of compensation to me if I am injured. I may call (619) 534-4520 for more information about this.
>
> Participation in research is entirely voluntary. I may refuse to take part or withdraw at any time without jeopardy to my medical care at this institution.
>
> I have received a copy of this consent document to keep and a copy of "The Experimental Subject's Bill of Rights."

The above mentioned Bill of Rights includes the following:

> If you have any questions regarding a research study, the researcher or his/her assistant will be glad to answer them. You may seek information from Human Subjects Committee—established for the protection of volunteers in research projects—by calling (619) 534-4520 from 8 am to 5 pm, Monday through Friday, or by writing to the above address.

A additional flaw in the letter process, at least as practiced in this case, has to do with the absence of any appeal, or independent review process, for resolution of differences of opinion or of interpretation of fact. Seemingly, the only recourse open to an investigator or sponsor on receipt of an OAI letter is to suggest "remedies" until they are considered "adequate," and to do so without recourse. Furthermore, there are no guidelines as to the length of time an investigator or sponsor remains under the cloud of a warning letter once one is received. As of the committee's last meeting on November 17, 1994, none of the original addressees had received any response from FDA to their rapidly crafted responses of the previous Spring.

The review process carried out by the FDA and culminating in warning letters leaves much to be desired. The nature of the review, with emphasis on mechanics rather than substance, is troubling, especially since there is a tendency on the part of the media and the public, including lawmakers, to equate mechanical faults with faults of substance. At the very least, if the focus in future reviews is to remain on mechanics, the warning letters in which they are summarized should also include some qualitative judgment as to their importance in regard to conclusions about safety and efficacy. For example, the issue in regard to consent is not whether there is evidence in the file that an investigator witnessed and dated a subject's signature on a consent statement but rather whether the subject was adequately informed.

We believe, as well, that the compliance audit was not as informed or balanced as it should have been as a result of the decision to exclude from participation those at FDA in the best position to judge the conduct of the trial, namely, the Antiviral Drug Division. The view of the investigators in regard to ALT and AST flares, for example, was well known to the reviewers in that division assigned to the FIAU IND. In fact, the Antiviral Drug Division was a well-informed participant in the planning and evaluation of each of the Oclassen-and Lilly-sponsored studies, offering suggestions to the protocols and consent forms orally (by phone and in meetings with the sponsors and principal investigators) and in writing, and giving explicit or implicit approval of each study in turn. The fact that at times they were not informed of the

death of a former subject within 10 days of its occurrence or discovery in no way meant that they were not informed of the death well in advance of subsequent trials. If the Antiviral Drug Division was consulted by the Office of Compliance in the course of their investigation it is surprising that there is no acknowledgment in the warning letters that communication among investigators, sponsors, and the Antiviral Drug Division had been frequent and extensive. The Office of Compliance should at least acknowledge that there was a basis for inferring FDA approval on the part of investigators, even when the office later disagrees with actions subsequently taken by the investigators.

The committee is troubled, as well, by a system of communication in regard to warning letters that makes them available to the media and others before their receipt by the parties being cited. There were newspaper accounts of the letter to Richman that appeared before he received it. We recognize and respect the need of the public to be informed and we recognize that the FDA is obligated to respond to requests for information under the Freedom of Information Act. In cases involving drugs already on the market, alerting the public should be the primary concern. That said, the committee nonetheless believes that it is well beyond the requirements of that act to release letters like those in this case to the public before the addressees have received the communications.

The committee also believes that review of existing procedures for the preparation, release, and resolution of OAI letters would be appropriate. The review should be undertaken with the aim of providing a written description of the processes used for generating such letters and to ensure that they are fair and accurate. It should also outline due process procedures for sponsors or investigators wishing to challenge citations. Those processes might reasonably include provision for a hearing before parties independent of FDA.

The rules and regulations regarding INDs are many and complex and are open, in many cases, to various interpretations. It seems apparent that investigators undertaking trials under INDs would benefit from courses or workshops having to do with their responsibilities and with procedures for complying with the guidelines. Ideally, every person engaged in such trials should be required to show proficiency before being allowed to proceed.

Institutions have been required of late to set up courses on research ethics to qualify for training grants. The same should apply for investigators engaged in IND work. A reduction in the perceptual gap between investigators and FDA compliance personnel may be accomplished by a continuing dialogue between interested parties, perhaps in the form of an annual workshop jointly sponsored by FDA, the pharmaceutical industry, and members of the academic community.

Expectations regarding the usefulness of the treatment protocol as a blueprint for a trial are viewed from differing perspectives. Investigators responsible for caring for patients in the context of a treatment trial know that their protocol, in spite of their best efforts, of necessity leaves room for judgment. They know that it has the potential of being viewed as "flawed" by themselves or others with the perspective of hindsight and that it is likely to be found lacking as a detailed blueprint. The personnel in the FDA responsible for assessing compliance, on the other hand, desire something more akin to a blueprint, used much as a building inspector uses a building plan to determine whether or not a builder is guilty of code violations.

Testimony offered by representatives of the Office of Compliance of FDA suggests that the view from that vantage point is that a protocol submitted in a specified IND for a particular

trial is, in effect, a contract with FDA, and that violations of it are violations of FDA regulations and, hence, of federal law, and, ergo, are criminal offenses (Richardson, 1994). This view is disturbing from the perspective of an investigator, if for no other reason than that it seems apparent that given variation in patient needs there is no trial, regardless of how meticulously performed, capable of passing muster if it is subjected to sufficient retrospective scrutiny.

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Conclusions and Recommendations

Anyone apprised of the disastrous events that occurred in the PPPC trial at NIH can only have been shocked and saddened by the suffering of the seven patients who developed sudden and severe FIAU toxicity (lactic acidosis, liver failure, pancreatitis). The Institute of Medicine committee understands the grief that must have been felt at the time by the families and close friends of the 5 individuals who died, all volunteers for a clinical trial for which hopes were high for clinical benefit; and the committee recognizes that their families undoubtedly continue to carry a heavy emotional burden. The recommendations of this IOM committee, as the earlier recommendations of the NIH subcommittee and the FDA, have the goal of reducing to a minimum the possible occurrence of such a calamity in any future clinical drug trials, but their implementation cannot render the process absolutely risk free. At the same time we believe that the recommendations are not so stringent or onerous as to restrict the benefits to the ill that can accrue from successful new drug development.

The deaths and morbid events related to the PPPC trial of FIAU have, as with other tragedies, resulted in private and public soul searching as to their cause and as to whether they were preventable. There have been efforts to affix blame. There have been calls for new safeguards and procedures to protect against future tragedies of the kind described here without full consideration as to whether those recommendations are adequately supported by an analysis of the costs and benefits of such safeguards. Although the history of drug regulation has been driven, in part, by disasters that have prompted new legislation (Hutt, 1994), that tendency should be resisted in this case because there is no evidence that anything could have been done to protect against the previously unknown and unanticipated late toxicity of FIAU.

The United States is a culture in which an event perceived by the public as evil, tragic, or unjust evokes often the response, "There ought to be a law!" (Toulmin, 1981). It may be useful to consider such "evils" or "tragedies" as falling into two classes. The first is the kind of evil that can be remedied or prevented by human action. In such cases it is appropriate (and sometimes morally obligatory) to consider the development of public policy designed to remedy or prevent the evil in question. A good case in point was the finding in September 1937 that more than 100 people died of diethylene glycol poisoning following the use of sulfanilamide elixir, a preparation in which the antibacterial drug sulfanilamide was dissolved in diethylene glycol for pediatric use. This solvent had been marketed without any prior safety testing (Hutt, 1994). In response to this, Congress added to the Federal Food, Drug, and Cosmetic Act of 1938 a requirement that new drugs be tested for safety in humans before being licensed for commercial distribution.

The second category of evil consists of tragic or unfortunate events that cannot be remedied or prevented by any reasonable human behavior. The appropriate response to such events is to acknowledge their existence and to view them with fear and trembling, but to refrain from a regulatory reaction until an action that can prevent their future occurrence is clear. A good case in point is the lethal reaction to FIAU. At the time of this writing the IOM committee is aware of no test that could be done to anticipate such lethal reactions. Among the actions we recommend is the conduct of careful studies aimed at developing a test or series of tests that would identify other agents that could produce such reactions. If and when such a test becomes available, it should be considered a part of routine preclinical testing of new drugs.

The public's frequent tendency to rely on a regulatory response to tragedies of this type may be grounded in some incorrect assumptions. Some individuals appear to assume that all calamities are preventable. Therefore, when they occur it is further assumed that somebody must have been careless, negligent, or exploitative. Favorite targets for such accusations are the industrial sponsors, the investigators, and the regulatory agency. Such behavior by the sponsors is usually attributed to their presumed willingness to override all other values in the single-minded pursuit of corporate profit. Investigators are similarly accused of negligent behavior owing to their presumed overly-zealous pursuit of financial or academic rewards such as tenure and prestige (e.g., Twentieth Century Fund Task Force, 1984). Regulatory agencies are portrayed as inept or out of touch with the needs of the people, and individuals within the agencies are accused or suspected of conflicts of interest.

The committee wishes to call attention to two dangerous consequences of these assumptions. The tendency to "close the book" by indicating blame has the effect of reinforcing the erroneous public perception that new treatments can be developed and tested free of risks if only enough care is taken. As a result, once society is satisfied that it has identified the individual or group responsible for the tragic event and removed this danger from the drug development system, we can all feel free to return to business as usual.

A second danger is even more insidious. The failure of the public to appreciate the risks of research in the field of drug development compounded with a strong tendency to affix blame on those who carry out the trials when something goes wrong creates a risk for the future of clinical research. Young medical scientists cannot fail to notice that this situation presents grave risks to their personal reputations and careers. Skilled clinical investigators in the field of drug development are a valuable national resource who can reduce the burden of pain, illness, and premature death.

The committee has found nothing in its review to suggest that the tragedy was preventable given the heretofore unobserved and unanticipated late complication of the treatment. Furthermore, we find nothing to suggest that investigators were negligent in the conduct of the trials under review or that they were calloused or insensitive to the needs and conditions of the patients whom they studied.

The fact that we cannot at this time recommend a regulatory action that would absolutely prevent a recurrence of a tragic event of the sort caused by FIAU should not be a source of intimidation with respect to new drug development. Examination of the past record of experience with Phase I testing of new drugs shows that, in fields other than oncology,

lethal or disabling adverse events are exceedingly rare. For example, Zarafonetis, Riley, Willis, Power, Werbelow, Farhat, Beckwith and Marks (1978) found that in Phase I drug testing in prisoners a "clinically significant medical event" occurred once every 26.3 years of individual subject exposure. In 805 protocols involving 29,162 prisoner subjects over 614,534 days, there were 58 adverse drug reactions, of which none produced death or permanent disability. The only subject who died did so while receiving a placebo.

Cardon, Dommel and Trumble (1976) reported the results of their large scale survey of investigators designed to determine the incidence of injuries to research subjects. They found that the risk of either disability (temporary or permanent) or of fatality was substantially less than the risk of similar unfortunate outcomes in similar medical settings involving no research. Further examples illustrating the safety of being a research subject can be found in Levine (1986) and Williams(1990).

To summarize, on review of the fialuridine tragedy, the IOM committee finds no evidence of negligence or carelessness on the part of the investigators or sponsors. The committee is not aware of any preclinical tests that could have been done to anticipate this unfortunate outcome. This should not be a source of great alarm to the public, since there has been an excellent record of safety in early phases of research in the field of drug development in the United States. Against this background, the FIAU tragedy can be put in proper perspective as a painful but distinctly rare occurrence.

As part of this review of the fialuridine studies, the IOM committee will make some recommendations on the future conduct of early-phase drug trials. These are recommendations for the "fine- tuning" of rather than for making major changes in the drug development process. Although the IOM committee's recommendations are focused on Phase I and Phase II trials, they do not stem from perceived deficiencies in the conduct of the investigators or sponsors in the FIAU studies (on the basis of the current knowledge); as already noted, no deficiencies were identified. The IOM committee believes that implementation of its recommendations *may* reduce the already very low probability of occurrence of toxicity of the sort that occurred in the FIAU trials, particularly when studying drugs that are similar to FIAU in structure or action. In many instances the effect will be to insure the continued and consistent use of procedures and practices employed in the FIAU trials reviewed here.

RECOMMENDATIONS

Generic Issues

1. Proceed cautiously in revision of the current drug development system. The current system has evolved checks and balances that have benefited new drug development, and no single component can undergo a major revision without endangering the system as a whole. The committee is doubtful that any of the changes reviewed above and/or proposed below, had they been in effect before the initiation of the FIAC and FIAU trials reviewed here, would have substantially altered the tragic outcome.

2. All clinical researchers engaged in trials should be exposed to explicit training not only on the design and conduct of clinical trials and their ethical obligations to patients but also on their legal and regulatory obligations to both the sponsor and the FDA.
3. We urge the establishment of a system of no-fault compensation for research injury by government, sponsors, or some combination of both.

Trial Design

4. Some form of independent safety monitoring would be a valuable component of any clinical trial in which patients are treated for extended periods, but they are especially important for all double-blind trials and in any trial in which there is reason to anticipate that evidence of adverse reactions could be confused with evidence of disease progression or therapeutic response. For other types of trials the sponsor should bear the burden of demonstrating that a monitor is unnecessary.
5. We support in principle the desirability of controls in Phase II studies, even while recognizing that statistical power will generally be inadequate to detect all but the most common of adverse drug effects, and among those, only those that rarely occur in untreated subjects. Nevertheless, particularly in trials involving extended treatment of patients, the use of some concurrent comparison group should help focus attention on the importance of differentiating drug effects from the underlying disease(s).
6. Research into the development of a database from which to construct historical control groups should be supported. Such control groups may be needed for comparisons when suitably matched concurrent control groups are not feasible. The extensive data submitted to FDA through the IND process are a potentially valuable resource for custom matching patients in new drug trials with controls from previous trials, matching not only for entry criteria but also for disease extent and severity, concomitant medications and other confounding variables.
7. Concerted efforts should be made to include in all clinical trial protocols explicit prospective criteria to help distinguish between adverse events related to drug treatment and changes in the underlying disease, for better or worse, whether or not controls are employed.
8. Clinical protocols should also have a section explicitly addressing the determination of the followup period, based on preclinical data and clinical data from other drugs thought to be similar in structure and action. Drugs suspected of modifying nucleic acids or associated macromolecules demand a minimum of 6 months of followup.
9. At the outset of extended Phase II trials, consideration should be given as to whether there is sufficient evidence of safety to justify simultaneous enrollment of a substantial group of patients, or whether the patients' disease is so serious that access to the drug seems warranted.

Adverse Event Reporting

10. Data should ideally be analyzed (by the investigators or independent safety monitor in Phase I and Phase II trials and by data safety monitoring committees or data coordinating

centers in multicenter Phase III studies) on a continuing real-time basis rather than only after all case report forms are complete for all patients. This will ensure that the fewest possible patients are exposed to possible hazards and that rapid intervention will prevent or limit injury to individual patients.

11. We concur with the suggestion of the FDA Task Force that some form of cumulative adverse event reporting should be provided by the sponsor in a form that includes not only those events previously reported as serious, unexpected, and drug related but also any events judged to have met only the first or the first two of those conditions, along with the sponsor's explanation of the event. A careful analysis of all available information rather than a worst-case assumption should then determine further actions.
12. The committee believes that requiring a cumulative and all-encompassing report of the sort referred to in the previous recommendation every 6 months will prove to be a substantial impediment to development of drugs to combat life-threatening diseases (e.g., cancer) in which adverse events are frequent because of the often progressive nature of the underlying disease. Some judgment will always be necessary, by the investigators in deciding the most likely cause of adverse events, and by the FDA in deciding for which drugs and at what intervals a cumulative safety summary is necessary. Ideally, the investigators and FDA would work together in making both of these determinations.

Compliance Audits

13. Given the intense publicity surrounding the issue of FDA warning letters, regard for due process would seem to demand some modifications in procedure. A fairer process, for example, might be for FDA to refrain from public release of the letters until receipt of the mandated reply from the addressees. Some sort of appeal process, independent of the FDA Office of Compliance, and including scientific peers expert in the area, should also be available in the event of intractable disagreement, and when retrospective evaluation by the Office of Compliance is at odds with the prior evaluation of the responsible review division, that fact should at least be acknowledged in the letter.

Further Research Into Fiau Toxicity

14. We urge continued support for research into the mechanism of FIAU toxicity, including development of animal models and other test procedures that could be used to screen drugs with potential to alter DNA before performing clinical trials.
15. Preclinical testing in animals is especially important in the case of FIAU-like drugs with a potential for long-term effects on nuclear or mitochondrial DNA. Toxicology studies in at least two different species, using the route of administration intended for use in patients and a duration of treatment at least as long as that intended for clinical trials, and extended follow-up on at least a subsample of animals should all be key considerations in preclinical testing. Whenever feasible and reasonable, the preclinical assessment should include testing in an animal model of the disease being targeted.

Appendixes

A

Chronology of FIAU/FIAC Clinical Trails

1989

July

R89 Corey and Richman approached by Oclassen Pharmaceuticals about use of FIAC for treatment of CMV infection in HIV-positive persons.

August-October

R89 Protocol modified, approved by ACTG committees, CMV Study Group, Opportunistic Infection Committee, NIAID Medical Branch and University of Washington and UCSD's IRBs.

October

R89 12- Meeting between Oclassen and FDA. Decision to limit trial to 4 weeks, due to lack of 90-day toxological support studies. 31-FIAC protocol open to accrual. 10 patients enrolled at UCSD.

1990

February

R89 8-Conference call between UCSD site, Oclassen, and FDA to review results to date.

April

R89 15- First patient (subject 105) dies 40 days after last dose of FIAC. Death attributed to bacterial pneumonia, unrelated to FIAC.

R89 16- Protocol modified to include only patients with CD4 counts >200.

May

R89 18- Second patient (subject 110) dies 58 days after last dose of FIAC. Death attributed to underlying disease.

R89 30- FIAC protocol discontinued due to lack of efficacy against CMV.

R90 Drs. Richman, Corey, and Straus, and Dr. Johnson from Oclassen draft an FIAU protocol, a two-week tolerance and pharmacokinetic study.

1990

June

R89 2- Third patient (subject 107), dies 63 days after last dose of FIAC. Death attributed to underlying disease. The PI concludes that demyelinating polyradiculoneuropathy was caused by progressive HIV infection (the patient's family did not permit an autopsy). (FDA 1993 Task Force identifies this death as possibly FIAC-related.)

R90 Draft protocol revised through multiple correspondence both written and via telephone between UW, UCSD, NIH (Straus), Oclassen, ACTG members, and FDA.

July

R90 Protocol presented to UW: Human Subjects Research Committee (HSRC).

August

R90 10- Amendment No. 1 sent to PIs by Oclassen. This amendment calls for enrolling HBV infected persons after initial cohort of non-HBV infected persons recruited. It also changes AST criteria to up to five times normal, from one and a half to three times normal and calls for one- and four-week port-treatment follow-ups to look for post-treatment "flare".

September

R90 10- The protocol is submitted to the NIAID IRB, after approval by the Chief, Laboratory of Clinical Investigations (LCI) and the Acting Clinical Director, NIAID.

R90 19-UW HSRC application approved, "Tolerance of HIV Infected Patients to Oral Doses of FIAU".

October

R90 1- First patient enters study at UW (1 mg/kg/day).

R90 31- The NIAID IRB approves the protocol after PI responds to 23 stipulations.

November

R90 26- The Acting Director, NIH Clinical Center approves of protocol.

1991

February

R90 25- First patient enters study, at dose of 1.7 mg/kg/day. Fatigue and nausea are documented with this dose of FIAU.

March

R89 11- Fourth patient (subject 103) dies 13 months after last dose of FIAC. Death attributed to AIDS, CMV, and Kaposi's sarcoma.

R90 18/19- When 3rd of 3 patients dosed at 1.7 mg/kg develops gastrointestinal symptoms etc., it is decided to enroll no more subjects at this dose or higher.

1991

April

R90 16- NIH enrolls their first HBV-infected patient at 1 mg/kg. Investigators feel that the 1.0 mg/kg 14-day dose is being well tolerated at other sites, with marked anti-HBV activity. Protocol reviewed by FDA and ACTG Viral Pathogens Working Group. It is agreed that the results deserve continued study. Amendment No. 2 initiates dose de-escalation to 0.5 mg/kg (1/2 the dose) to determine if drug active at lower doses.

R90 19- First HBV-infected subject enrolled at UW site at 1.0 mg/kg dose.

July-August

R91 1- Drs. Hoofnagle and Straus submit a protocol entitled "A 4-week course of FIAU for chronic Hepatitis B" to the NIDDK IRB. This study would use different doses of FIAU (0.25, .50, or 1.0 mg/kg/day) in patients with HBV without HIV-infection. Oclassen would not agree to therapy for more than 28 days because animal toxicology data available only in support of short-term courses of treatment. This study was written to include a staggered entry of patients so efficacy and tolerance could be assessed before increasing dosage.

R91 28- The NIDDK IRB reviewed the protocol, and approval was granted pending compliance with a number of stipulations.

August

R904- UW IRB approves Amendment No. 2—lowering dose to 0.5 mg/kg.

R90 5- The NIAID IRB recommends approval pending compliance with 8 stipulations.

R90 27-UW IRB approves revised consent form.

September

R89 2- Fifth patient (subject 101) dies months after last dose of FIAC. Death attributed to P. carinii pneumonia.

R91 9- Protocol approved by the Acting Chair, NIDDK IRB and the Clinical Director, NIDDK as well as by the Acting Director, Clinical Center.

R90 19- UW renewal application submitted to HSRC. Reports adverse reactions seen in FIAU among the 13 UW patients (gastrointestinal complications in 11, fatigue in 6, and elevated SGOT and CPK in 2).

October

R90 27- Amendment No. 3 proposed—to continue dose de-escalation to 0.1 mg/kg-as anti-HBV activity is present at both the 0.5 mg and 1 mg/kg. Detailed pharmacokinetic work is added.

R90 31- The Chair of the IRB and the Clinical Director, NIAID approve continuation of the protocol.

1991

November

R90 14- Dr. Straus requests approval from the Chair, NIAID IRB of annual report to the FDA on protocol 91-I-31 (R90-001). The report notes that one subject had received an overdose of FIAU, without adverse effect (NIH).

R90 18- The NIAID IRB votes to recommend approval of the report to the FDA.

R90 27- Dr. Straus writes the IRB Chair requesting approval of Amendment 3—lowering dose to 0.1 mg/kg.

December

R90 5- Investigators meet to discuss efficacy and toxicity data with initial HBV-infected enrollees.

10- Switch to 1 mg/ml syrup formulation. UW IRB notified.

15- Approved consent to Amendment No. 3 from UW IRB.

23- Approved consent to Amendment No. 3 from NIAID IRB, pending clarification of amount of blood drawn.

1992

February

R91 Protocol R91-010 submitted to FDA.

March

R91 26- Approval received from the FDA subject to changes in consent form language, use of DNA polymerase activity rather than just HBV DNA as a means of monitoring therapy, and a change in doses. While waiting for FDA approval, more information becomes available from the study (R90-010) and the protocol is amended to use four lower dose levels (.05, 0.1, 0.25 and .50 mg/kg/day). Also, in the case of moderate toxicity, the drug would be stopped rather than reduced in dose.

April

R91 18-First patient dosed in study R91-010.

May

R90 16- Patient 408 (R90-001) dies of an esophageal hemorrhage and cirrhosis of the liver secondary to hepatitis B, C, and D, 6 months after completing a second 2 week course of FIAU. His death is not discovered by investigators until July 1993. (FDA 1993 Task Force identifies this death as possibly FIAU-related.)

June

R90 15- Last HIV+/HBV+ patient entered into 0.1 mg/kg dosage.

R90 29- In total, 4 HIV+ patients enrolled at UCSD, 25 HIV+ at UW (12 non-HBV+ and 13 HBV+) and 14 HIV+ (all HBV+) at NIH clinical Center.

R91 30- The Chair, NIDDK IRB approves continuation of protocol 91-DK-AI-213 (R91 study) for a second year.

July

R90 30- Patient 409 (R90 study) hospitalized with pancreatitis, 3 months after completing second 2-week course of FIAU. Pancreatitis attributed to current ddI use.

1992

August

R90 11- Patient 406 (R90 study) dies 2 months after completing 2nd 2-week course of FIAU. Death attributed to ddI-induced pancreatitis. (FDA 1993 Task Force suggests this death FIAU related, although interpretation of FIAU toxicity is complicated by concurrent administration of ddI).

R91 15- Status report on 24 subjects shows FIAU administration led to an immediate and profound inhibition of serum hepatitis B virus levels. All dose levels were well tolerated and the only toxicities reported were minor degrees of irritability and gastrointestinal upset at the highest dose level, with no patients requiring modification of dosage.

September

R91 10- Last R91-010 patient receives last does of FIAU.

PPPC 16- Dr. Hoofnagle submits a 6-month course of FIAU protocol (PPPC) to the NIDDK IRB. The protocol is initially designed as a retreatment for patients who had not responded to therapy in the 28-day study. They would be eligible for enrollment five months after completion of the 28-day course.

October

R90 18- Patient 401 (R90 study) dies 4 months after completing second 2-week course of FIAU. Death attributed to liver failure due to cirrhosis. (FDA 1993 Task Force suggests this death possibly FIAU related, but notes that the presence of multiple hepatitis virus infections limits possible conclusions about FIAU toxicity.)

PPPC 21- Lilly summarizes results of R90, R91 trials at meeting with FDA, lays out future plans.

PPPC 24- Dr. Hoofnagle writes to the Chair, NIDDK IRB responding to the stipulations required by the NIDDK IRB.

PPPC30- The Chair of the NIDDK IRB approves the protocol.

November-December

R90 Last of 4 patients retreated at NIH, finishes study. One of the 4 developed neuropathy. Protocol terminated.

1993

January

R91 7- Death of patient 004D from this FIAU study (R91 study), 4 months after completing 1 month course of FIAU. Death was attributed to post-surgical complications of gall bladder removal (against the advice of PIs). In retrospect, the presence of lactic acidosis and the absence of elevated liver enzymes raise real suspicion that this patient may have had FIAU toxicity. (FDA 1993 Task Force suggests this death FIAU toxicity related.)

1993

February

PPPC 12- Dr. Hoofnagle writes to the Chair, NIDDK IRB requesting two amendments to 93-DK-0031 (PPPC): 1) provision to include additional patients who have not previously received FIAU and 2) provision to do nerve conduction tests on patients before starting therapy and again after 3 months of therapy. The memo includes a discussion of the death of a subject and the appearance of peripheral neuropathies in two subjects who had participated in R91-010 (28 days).

PPPC 19- Lilly provides Dr. Hoofnagle a copy of the newly revised FIAU Clinical Investigators's Brochure that includes the FDA's modifications in the informed consent documents.

March

PPPC 5- After the PI responds to the IRB's stipulations, the Chair, NIDDK IRB approves the amended protocol.

PPPG 19- Sixteen healthy volunteers begin series of 5 doses of FIAU in different formulations at Lilly Laboratory of Clinical Research in Indianapolis, where subjects reside for duration of study.

PPPC 24- First patient dosed in PPPC protocol.

PPPG 25- Subject 1203 dropped from Indianapolis study due to elevated AST/ALT measures after 2nd dose of FIAU.

April

PPPG 12- Fifteen subjects receive fifth and last doses of FIAU.

May

PPPA 3- First patient dosed in PPPA trial at New England Medical Center.

PPPG 5- Sixteenth subject receives final dose at Indianapolis.

PPPA 14- First patient dosed in PPPA trial at Galveston.

June

PPPC 7- The PI writes to the Chair, NIDDK requesting approval of an amendment permitting the dosing of subjects twice daily rather than three times per day as specified in the protocol.

PPPC 8- The Chair, NIDDK IRB approves the amendment—dosing two times daily rather than three.

PPPC 15- Patient #6C telephones to report symptoms of nausea, vomiting, diarrhea, and fatigue.

PPPC 25- Patient #2B admitted to a Virginia emergency room with lactic acidosis.

PPPC 26- All subjects who ha received FIAU in either the 28 day or the 6 month study were recalled to NIH for examination and possible treatment of FIAU toxicity.

PPPA 26- Last patient (total of 3) dosed in PPPA trial at Galveston.

1993

June *cont.*

PPPC 28- Dr. Hoofnagle calls the Acting Director, Clinical Center to report that two subjects receiving FIAU on protocol 93-DK-31 had been admitted with catastrophic illness and that all subjects had been contacted and told to stop taking FIAU on June 26.

PPPA 28- Last patient dosed (total of 2) at New England Medical Center.

PPPC 29- The PI writes to the Chair, NIDDK IRB reporting the complications during the protocol with two subjects. At a regularly scheduled meeting of the NIDDK IRB, Dr. Hoofnagle provides patient updates and reports on the death of the subject who had participated in protocol 91-DK-213. The IRB minutes reflect discussion of attempts to "rescue" subjects from the toxic effects of FIAU. The IRB approves a consent document to be used for their treatment.

PPPC 30- A meeting on FIAU toxicity is held at NIH. Attendees include staff from NIDDK, NIAID, the NIH Clinical Center, FDA, Lilly, Yale University, University of Alabama at Birmingham, Tufts University (Clinical Investigator on FIAU) and University of Texas at Galveston (Clinical Investigator on FIAU). On this day, the Director, OHSR reports the complications occurring on NIH protocol 93-DK-31 (PPPC) to the Office for Protection from Research Risks.

July

PPPC At this time, NIH investigators learn of the death of patient 408 (R90) on May 16, 1992. This patient had been treated with FIAU for 12 days in November of 1991 and retreated for 14 days in January of 1992.

PPPC 2- A second meeting was held on FIAU toxicity at NIH.

PPPC 5- Patient #3D (Lilly #001-2002) dies of Lactic acidosis and cardiovascular collapse one day after an unsuccessful liver transplantation.

PPPC 6- Patient #2B (Lilly #001-3004) dies of lactic acidosis and cardiovascular collapse two days after an unsuccessful liver transplantation.

PPPC 9- Patient #6C (Lilly #001-6003) receives a liver transplant.

PPPC 12- A meeting of the Senior Clinical Staff, NIDDK was held and protocol 93-DK-3l's severe complications were reviewed.

PPPC 27- At a regularly scheduled meeting of the NIDDK IRB, patient updates were given, and the committee commended the group for their immediate reaction to the new FIAU side effects and diligent follow-up. It was noted that all patients had been informed in advance of the earlier death of a FIAU patient, and this had been documented in the patient charts.

PPPC 30- Patient #3A (Lilly #001-3001) dies of sever pancreatitis and relentless lactic acidosis.

1993

August

PPPC 4- Patient #1C (Lilly #001-1003) undergoes a successful liver transplantation.

PPPC 13- Patient #6C (Lilly #001-6003) undergoes a second liver transplantation.

PPPC 31- Patient #6C dies of multiorgan failure.

September

PPPC 22- The Director, OHSR wrote to OPRR providing all available documentation regarding the protocol and informing that office that review of the materials indicated that the protocol had been conducted in accord with the terms and conditions of the NIH Multiple Project Assurance.

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C

Institute of Medicine Committee to Review the Fialuridine (FIAU/FIAC) Clinical Trials

First Committee Meeting
Monday and Tuesday, July 25-26, 1994
The Foundry Building (Room 2004)

AGENDA

MONDAY, July 25, 1994

8:30 a.m. **EXECUTIVE SESSION**

Welcoming remarks, introductions and charge to committee

Joseph S. Cassells, M.D.
(IOM Interim Executive Officer)

Morton Swartz, M.D.
(Professor of Medicine, Harvard Medical School; Chief, James Jackson Firm; and Emeritus Chief, Infectious Disease Unit, Medical Services, Massachusetts General Hospital)

Frederick J. Manning, Ph.D.
(Study Director)

Discussion of bias/conflict of interest issues

Joseph Cassells

10:15 a.m. *Break*

10:30 a.m. **Findings of the FDA Office of Compliance**

Mary L. Richardson
(Acting Director, Division of Scientific Investigations, Office of Compliance, CDER, U.S. Food and Drug Administration)

	Ross Pierce, M.D. *(Medical Officer, Clinical Investigations Branch, Division of Scientific Investigations, Office of Compliance, (CDER), U.S. Food and Drug Administration)*
12:00 Noon	*Luncheon Buffet, Meeting Room 2004*
1:00 p.m.	**Report of the FDA Task Force on Fialuridine: Hepatic and Pancreatic Toxicity**
	Roger L. Williams, M.D. *(Associate Director for Science and Medical Affairs, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration)*
2:00 p.m.	**Role of the Division of Anti-Vital Drug Products**
	David Feigal, M.D. *(Director, Division of Anti-Viral Drug Products, Office of Drug Evaluation, CDER, U.S. Food and Drug Administration)*
3:15 p.m.	*Break*
3:30 p.m.	**Review of Studies R91-010 and PPPC**
	Jay H. Hoofnagle, M.D. *(Director, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health)*
5:00 p.m.	Meeting Adjourns for the Day
TUESDAY, July 26, 1994	
8:00 a.m.	**Review of Studies R89-001 and R90-001**
	Lawrence Corey, M.D. *(Professor, Laboratory Medicine, Microbiology and Medicine, Virology Office, University of Washington, Seattle)*

	Douglas D. Richman, M.D. *(Professor of Pathology and Medicine, University of California, San Diego)*
	Stephen E. Straus, M.D. *(Chief Laboratory of Clinical Investigation, Medical Virology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health)*
10:00 a.m.	**Review of Preclinical Studies**
	John Emmerson, Ph.D. *(Distinguished Lilly Research Scholar, Toxicology Division, Eli Lilly)*
11:00 a.m.	**Eli Lilly Overview**
	Donald G. Therasse, M.D. *(Director, Anti-Infective Division, Eli Lilly Research Laboratories)*
	Allan J. Weinstein, M.D. *(Vice President, Eli Lilly Research Laboratories)*
12:15 p.m.	*Lunch, Meeting Room 2004*
1:00 p.m.	**Report to the Director, NIH, of the Director's Advisory Committee's (DAC) Subcommittee to Review FIAU Studies**
	David R. Challoner, M.D. *(Vice-President for Health Affairs, University of Florida)*
	David M. Kipnis, M.D. *(Distinguished University Professor of Medicine, Washington University School of Medicine)*
2:15 p.m.	**EXECUTIVE SESSION**
	Barbara Rice, NAS Office of News and Public Information
	Discussion of Work Plan
3:00 p.m.	*Break*
3:15 p.m.	**Continuation of Work Plan Discussion**

5:00 p.m.	Adjourn

INSTITUTE OF MEDICINE COMMITTEE TO REVIEW THE FIALURIDINE (FIAU/FIAC) CLINICAL TRIALS

Second Committee Meeting
Thursday and Friday, September 8-9, 1994
Cecil and Ida Green Building
Room 116

AGENDA

THURSDAY, Sept. 8, 1994

8:00 a.m.	**EXECUTIVE SESSION** *(study outline; tape; report on patient interviews)*
9:30 a.m.	**Presentations to the Committee**
	Judith Fallon, M.D. *(Former Chair, Institutional Review Board NIAID)*
	Howard Austin, M.D. *(Chair, Institutional Review Board NIDDK)*
10:30 a.m.	David Feigel, M.D. *(Director, Antiviral Drug Division CDER, FDA)*
12:00 Noon	Lunch
1:00 p.m.	**Continuation of presentations**
	Barbara Savarese, R.N. *(Study Coordinator R-90, R-91, 6-mo. trials)*
2:00 p.m.	Robin McKenzie, M.D. *(Medical Officer, NIAID, Associate Investigator, 6 mos. trial)*

3:00 p.m.	Yoon Park, R.N. (*Clinical Nurse, Warren Grant Magnuson Clinical Center, R-90, R-91, 6-mo. studies*)
4:00 p.m.	**EXECUTIVE SESSION**
5:00 p.m.	Meeting Adjourns for the Day
FRIDAY, Sept. 9, 1994	
8:00 a.m.	**Presentations to the Committee**
	Peter Barton Hutt, LL.D. (*Former General Counsel FDA*)
10:00 a.m.	Mary Richardson (*Deputy Director, Division of Scientific Investigations, Office of Compliance, CDER, FDA*)
	Ross Pierce, M.D. (*Division of Scientific Investigations, Office of Compliance CDER*)
12:00 p.m.	*Lunch*
1:00 p.m.	**EXECUTIVE SESSION** (*study plan, writing assignments, info needs*)

INSTITUTE OF MEDICINE COMMITTEE TO REVIEW THE FIALURIDINE (FIAU/FIAC) CLINICAL TRIALS

Third Committee Meeting
Wednesday and Thursday, November 16-17, 1994
The Foundry Building
Room 2004

AGENDA

WEDNESDAY, Nov. 16, 1994	
8:30 a.m.	**Review of Draft Report Sections** Each author in turn; see attached outline

10:15 a.m.	*Break*
10:30 a.m.	**Resume Review of Draft Sections**
12:00 Noon	*Luncheon Buffet, Meeting Room 2004*
1:00 p.m.	**Assemble Recommendations and Conclusions**
2:30 p.m.	*Break*
3:00 p.m.	**Revision of Report Sections** On laptops in 2004 or at HSPD Offices
5:00 p.m.	Meeting Adjourns for the Day
THURSDAY, Nov. 17, 1994	
8:00 a.m.	**Review of Revised and New Sections**
10:15 a.m.	*Break*
10:30 a.m.	**Resume Review**
12:00 p.m.	*Lunch, Meeting Room 2004*
1:00 p.m.	**Resume Review**
3:15 p.m.	**Rewrites as necessary**
5:00 p.m.	*Adjourn*

D

Informed Consent Documents

NOTE: All documents reproduced in this appendix are reprinted with the permission of the institution involved.

R-89 (UNIVERSITY OF CALIFORNIA, SAN DIEGO)

UNIVERSITY OF CALIFORNIA, SAN DIEGO MEDICAL CENTER CONSENT TO ACTAS A RESEARCH SUBJECT

89-619
ACTG 122

Drs. Douglas Richman, Stephen Spector, J. Allen McCutchan, Samuel A. Bozzette, Lisa DeJarnette, Samuel Yonren, Brett Cassens, Wayne Dankner, William Freeman and their associates are conducting a study to determine the safety, tolerance, pharmacokinetic profile and effect on viral cultures of an oral form of FIAC. FIAC is a medication that is active against herpes virus infections (herpes simplex, varicella zoster, and cytomegalovirus). FIAC has been used successfully in earlier studies to treat herpes infections in patients who have a compromised immune system. I have been asked to participate because I have a cytomegalovirus infection, but I do not have evidence of CMV retinitis.

Ganciclovir is a drug which is presently used to treat CMV retinitis and other forms of CMV infection. However, ganciclovir must be administered intravenously and for prolonged periods, usually necessitating a central venous catheter. The purpose of my receiving oral FIAC is to test its safety, tolerance, and antiviral effects, so that it may be used to treat patients with serious CMV infections such as CMV retinitis.

If I agree to be in this study the following will be done:

1. I will have a complete history, physical exam, viral cultures, and blood drawn for laboratory tests at the time of enrollment, and at least every other week thereafter for up to 12 weeks.
2. I will receive one of five possible dose regimens or oral FIAC. If my blood and/or urine continues to grow cytomegalovirus, and the dose I am taking is being tolerated by me and other people taking the same dose of FIAC, then I will be increased to the next higher dose level. Once my blood or urine becomes culture negative for CMV for at least four weeks I will remain at that dose level for the remainder of the study.
3. I will not need to be hospitalized; however, I will need to spend at least two hours at the UCSD Treatment Center during the second week and the eighth week in order to have bloods drawn for FIAC levels. If I take part in the pharmacokinetic study, then I will need to spend one day in the Outpatient Clinical Research Unit in order to have blood drawn and urine collected for eight hours after my first daily dose of FIAC.

4. I will have ophthalmologic exams done at my enrollment onto the study and during weeks 2, 4, 8, and 12.
5. If I develop CMV retinitis during the study, I will be allowed to continue FIAC if I desire, or withdraw from the study.
6. I will have electrocardiograms performed at entry and day 7, day 14, and weeks 4, 8, and 12.
7. If I am sexually active I will use effective contraceptive during FIAC treatment and for 30 days following treatment.
8. If I have been taking AZT without difficulty over the past month, then I can continue to take AZT while on the study; however, I must take 600mg. or less per day.
9. I have not taken and I will continue not to use acyclovir, ganciclovir, foscarnet, or interferon during the study. If I have not been taking AZT previously, I understand that I cannot start AZT until after the 12 week study period.
10. After the 12 week study period has ended, I will not continue to receive FIAC.

Participation in this study may involve some added risks or discomforts:

It is possible that FIAC may cause my white blood cells, red blood cells, or platelets to decrease. This may predispose me to bleeding, anemia, and infection. Some other side effects that I may experience include nausea and perhaps vomiting. It is also possible that confusion, jerking, and even seizures may occur while I am taking this medication, although this is unlikely on the doses I will receive.

In animal studies there was evidence of heart damage in those animals receiving very high doses of FIAC. It is not known whether FIAC may cause sterility or infertility in humans, however, this is a possibility. Since interactions between FIAC and other medications are incompletely understood at this time, I must not take other medications without first consulting with my study physician or nurse practitioner.

I realize that I may receive no benefit from participating in this study. The knowledge gained may help others in the future.

Dr. _____ has explained this study to my child and me and answered my questions. If my child or I have other ?? or if we wish to report a research-related problem, I may call Dr. _____ at 298-7021.

If I am injured as a result of participation in this research, the University of California will provide any medical care that I may need to treat those injuries—except when they are a consequence or research designed to benefit me directly. The University will not provide any other form of compensation to me if I am injured. I may call (619) 534-4520 for more information about this.

Participation in research is entirely voluntary. I may refuse to take part or withdraw at any time without jeopardy to my medical care at this institution.

Research records will be kept confidential to the extent provided by law. Study forms will contain only a code number, and perhaps my initials (but not my name) for identification. Study records may be reviewed by the AIDS Clinical Trials Coordinating Center, the NIAID, Oclassen Pharmaceuticals, or the U.S. Food and Drug Administration to ensure that they are accurate and fulfill federal regulations.

I have received a copy of this consent document to keep and a copy of "The Experimental Subject's Bill of Rights."

I agree to take part in this study.

Subject's Signature

Date

Witness

Parent or Legal Guardian

Date

UNIVERSITY OF CALIFORNIA, SAN DIEGO

BERKELEY · DAVIS · IRVINE · LOS ANGELES · RIVERSIDE · SAN DIEGO · SAN FRANCISCO SANTA BARBARA · SANTA CRUZ

VICE CHANCELLOR FOR HEALTH SCIENCES
DEAN, SCHOOL OF MEDICINE

LA JOLLA, CALIFORNIA 92093
M-002

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The faculty and staff of the University of California, San Diego wish you to know:

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be used.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time, and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of a signed and dated written consent form when one is required.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

If you have questions regarding a research study, the researcher or his/her assistant will be glad to answer them. You may seek information from the Human Subjects Committee - established for the protection of volunteers in research projects - by calling (619) 534-4520 from 8 am to 5 pm, Monday through Friday, or by writing to the above address.

R-90 (UNIVERSITY OF WASHINGTON)

UNIVERSITY OF WASHINGTON HARBORVIEW MEDICAL CENTER CONSENT FORM

UW
ORIGINAL CONSENT FORM
The Tolerance of HIV-Infected Patients to Oral Doses of FIAU

Teresa Tartaglione, Pharm.D.	Asst. Professor, Pharmacy	223-3193
Thomas M. Hooton, M.D.	Asst. Professor, Medicine	223-3240
Ann Collier, M.D.	Asst. Professor, Medicine	223-3295
Julie McElrath, M. D., Ph.D	Asst. Professor, Medicine	222-3056
Frudy Jones, A.R.N.P.	Clinician, Medicine	223-3134
Phyllis Holzworth, A.R.N.P	Clinician, Medicine	223-3184
Becky Royer, P.A.C.	Clinician, Medicine	223-3325
Lawrence Corey, M.D.	Professor, Medicine and Laboratory Medicine	526-2117
Emergency 24 hr. number	Page infectious Disease Fellow	223-3000

INVESTIGATOR'S STATEMENT

Purpose and Benefits

Cytomegalovirus (CMV), Varicella Zoster virus (VZV), and Herpes Simplex Virus (HSV) infection are significant opportunistic diseases seen in patients who are immunocompromised. Many HIV-infected patients are also coinfected with hepatitis B virus. CMV is known to cause many serious infections including inflammation of the retina in one or both eves ("retinitis"). This is one of the infections associated with AIDS and may lead to blindness. Although herpes and hepatitis B infections do not cause AIDS, severe herpes and hepatitis B disease may occur following advanced immunocompromised states. FIAU is an investigational new drug which has not been tested previously in humans The United States Food and Drug Administration (FDA) allows the use of FIAU only in research with a limited number of subjects. FIAU is similar to another investigational new drug, FIAC, which has been tested previously in approximately 100 patients, including AIDS patients with CMV infection. The purpose of this research study is to determine the safety and tolerance over a two week period of four different doses of FIAU in HIV-infected patients including some with CMV, VZV, HSV, or hepatitis B infection. You may benefit if your CMV, HSV, VZV or hepatitis B infection improves or stabilizes while receiving FIAU therapy, although no benefits can be guaranteed. The information gained will provide some initial information on the dosing and side effects of FIAU which may be of future benefit to HIV-infected patients.

Procedures

This study will last for 14 days exclusive of the screening and any followup visits. If you agree to participate in this study, you will have a complete history and physical examination performed. At the screening and baseline visits you will have blood drawn for

AIDS virus and immune function tests as well as for routine blood tests (four tablespoons). You will also have other routine baseline studies, including chest X-rays, EKG, urinalysis, stool guaiac (for detection of blood), and an eye examination (only if you are infected with CMV). You will receive FIAU as an outpatient as soon as it has been determined that you meet the criteria for entry. The dose of FIAU will be assigned sequentially (in order of patient enrollment) per kilogram of body weight. Your FIAU dose will range from 1.0 to 5.0 mg/kg/day. FIAU will be given orally every 8 hours with about 2 tablespoons of water and will be Taken either one hour prior to or three hours after meals. You may receive FIAU for up to 14 days or until your CMV, HSV or VZV infection worsens or until you experience significant toxicity.

You will have regular check-ups to monitor your infection and your tolerance of FIAU. These will be performed on days 2, 3, 5, 7 10 and 14. Treatment may be discontinued or modified depending on your response. Standard blood tests, urinalysis, stool guaiac, CMV, HSV, VZV and/or HBV (hepatitis B virus) tests, eye exams, EKG, and tests measuring the concentration of FIAU in your blood will be done at some of these visits. Approximately 17 tablespoons of blood will be drawn during the two week study. You are requested to avoid heavy exercise for 1 day prior to each day that blood is to be drawn (e.g., days 2, 3, 5, 7, 10, and 14). if you have chronic HBV infection, you will be required to have a one week and four week followup visit. At this visit you will have a brief history and physical exam; blood (2 teaspoonfuls) will also be drawn at each of these visits.

While you are taking FIAU you may not take acyclovir (Zovirax^{R}), ganciclovir (DHPG), foscarnet or interferon. You may be allowed to take zidovudine (also known as azidothymidine AZT, Retrovir^{R}) for the duration of the this study if you've been taking the drug for at least 6 weeks, if you are receiving less than or equal to 600 mg per day, and if your red cell, white cell and platelet counts have not dropped significantly. If you start taking AZT after you've begun this FIAU study, you will be dropped from the study. You are allowed to take aerosolized pentamidine for prevention of Pneumocystis carinii pneumonia.

Risk and Discomforts

Although FIAU has not been administered to humans, there are a number of known side effects of FIAC that patients have experienced in other studies. You may experience nausea and vomiting. FIAU may also cause toxicity to your blood-forming cells; specifically your white cells, red cells and platelets may be reduced in number. Reduction of your white cells may cause you to experience more frequent infections. A decrease in red blood cells can cause fatigue and too few platelets may cause bleeding. With FIAC, these effects reversed with lowering of the dose or drug discontinuation. Some of your blood chemistry values may change while on FIAU therapy. Reversible neurologic toxicity following FIAC administration has been infrequently reported but FIAU may also cause confusion, muscle jerking and seizures. Polymyositis

(inflammation of many muscles) has been reported in one patient receiving FIAC and was reversible with drug discontinuation. Non-reversible cardiac toxicity (damage or death to heart muscle and tissue) at very high FIAC doses has been observed in animal studies. These neurologic and cardiac effects may occur with FIAU. FIAU may also affect the production of healthy sperm and/or fetal development. Since FIAU is an investigational drug, there may be other previously unknown side effects. The risks of drawing blood include mild pain, bruising, or rarely infection at the needle site.

If you take this drug during pregnancy you may expose your unborn child to significant hazards of deformity. if you are a woman, you must avoid pregnancy while taking this drug, and, if you are sexually active, you must agree to use some form of barrier contraception while you participate and for at least 3 months following study completion. If you are a woman of child-bearing potential, you will be required to have a serum (blood) pregnancy test prior to entry in the study. If you do become pregnant while on this study, you must notify the investigator immediately. If you are a man with a female partner of child-bearing age, should your partner become pregnant, there is the possible risk of deformity in the child. Therefore, it is important that you or your partner use barrier contraception.

The amount of radiation exposure from the chest x-rays will be about 110 mrem; this is about the same as normal exposure from background radiation in Seattle during one year.

Alternatives

If you choose not to participate in the study, it will have no effect on your continued care. Other alternatives at this point include careful observation by your doctor and either treatment by Foscarnet, interferon or Ganciclovir depending on your individual infection. Other treatment includes treatment against human immunodeficiency virus (HIV) which causes AIDS (such as Zidovudine), in order to contain the underlying HIV infection which made you vulnerable to infections.

Other Information

All information and test results will be strictly confidential. You and your laboratory samples will be identified by code. All records with identifying information will be kept in locked files, and will be available only to the investigators with the following exception. Representatives of the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), Oclassen Pharmaceuticals (makers of the drug) will have the right to review study data and will have access to identifying information. The FDA,. the NIH, and Oclassen Pharmaceuticals reserves the right to review subjects' personal medical records as relevant to this study. You should also understand that the investigators of this study are requesting your permission to review your medical records for purposes of this research study. The medical records utilized

in this study will be entered into a centralized computer data base but only code numbers will be used. No publication or public discussion of the results of this research will contain information that could identify you. The research records will be kept indefinitely. Part of the blood samples will be saved, and may be used in the future for other HIV-related tests. These samples will be identified only by code number and will be accessible only to studies involving current University of Washington investigators.

The study drug, FIAU, laboratory tests, and clinic visits will be provided free of charge. However, costs of hospitalization and/or medications required for treatment of side effects will be the financial responsibility of you and your insurance company. Some insurance companies may not reimburse you for expenses arising from investigational studies. If significant findings are noted during the study that might affect your willingness to continue hue to participate, these findings will be provided to you.

Investigator's Signature

Date

SUBJECT'S STATEMENT

I am 18 years of age or older. The study described above has been explained to me. I understand that I may refuse to participate and may withdraw from the study at any time without penalty and without loss of benefits to which I am otherwise entitled. I understand that if I withdraw, the investigators will retain access to my study data and any stored specimens. I was given an opportunity to ask questions and understand that future questions I may have about the research or my rights as a research subject will be answered by the investigators listed on page 1.

Subject's Signature

Date

Copies to: Subject

Investigators' file

tart/cf-fiau.doc 9/14/90

UNIVERSITY OF WASHINGTON HARBORVIEW MEDICAL CENTER CONSENT FORM

19
REVISED CONSENT FORM
The Tolerance of HIV-Infected Patients to Oral Doses of FIAU

Teresa Tartaglione, Pharm.D.	Asst. Professor, Pharmacy	223-3198
Thomas M. Hooton, M.D.	Asst. Professor, Medicine	720-4200
Ann Collier, M.D.	Asst. Professor, Medicine	223-3293
Julie McElrath, M.D., Ph.D	Asst. Professor, Medicine	326-4179
Trudy Jones, A.R.N.P.	Clinician, Medicine	223-3184
Lawrence Corey, M.D.	Professor, Medicine and Laboratory Medicine	526-2117
Emergency 24 hr. number	Page Infectious Disease Fellow	223-3000

INVESTIGATOR'S STATEMENT

Purpose and Benefits

Many HIV-infected patients are coinfected with hepatitis B virus. Although hepatitis B infections do not cause AIDS, severe hepatitis B disease may occur following advanced immunocompromised states. FIAU is an investigational new drug which has recently been tested in a small number of humans. The United States Food and Drug Administration (FDA) allows the use of FIAU only in research with a limited number of subjects. FIAU is similar to another investigational new drug, FIAC, which has been tested previously in approximately 100 patients, including AIDS patients with CMV infection. The purpose of this research study is to determine the safety and tolerance over a two to six-week period of two different doses of FIAU in HIV-infected patients with hepatitis B infection. You may benefit if your hepatitis B infection improves or stabilizes while receiving FIAU therapy, although no benefits can be guaranteed. The information gained will provide some initial information on the dosing and side effects of FIAU which may be of future benefit to HIV-infected patients.

Procedures

If you agree to participate in this study, you will have a complete history and physical examination performed. At the screening and baseline visits you will have blood drawn for AIDS virus and immune function tests as well as for routine blood tests (four tablespoons). You will also have other routine baseline studies, including chest X-rays, EKG, urinalysis, and stool guaiac (for detection of blood). You will receive FIAU as an outpatient as soon as it has been determined that you meet the criteria for entry. Your FIAU dose will range from 0.1 to 1.0 mg/kg/day. FIAU will be given orally every 8 hours with about 2 tablespoons of water and will be taken either one hour prior to or three hours after meals. You may receive FIAU for up to 14 days.

You will have regular check-ups to monitor your infection and your tolerance of FIAU. These will be performed on days 2, 3, 5, 7, 10 and 14. Treatment may be discontinued or modified depending on your response. Standard blood tests, urinalysis, stool guaiac, hepatitis B virus (HBV) tests, EKG, and tests measuring the concentration of FIAU in your blood will be done at some of these visits. Approximately 17 tablespoons of blood will be drawn during the two week study. You are requested to avoid heavy exercise for 1 day prior to each day that blood is to be drawn (e.g., days 2, 3', 5, 7, 10, and 14). You will be required to have a one week and four week post-treatment followup visit. At this visit you will have a brief history and physical exam; blood (2 teaspoonfuls) will also be drawn at each of these visits.

At the end of the 14 days of treatment, you will be evaluated (with blood tests) to determine if your hepatitis B infection improved. If your hepatitis B infection did not improve, your participation in the study will be completed. If your hepatitis B infection improved (according to blood test results) during treatment with 1.0 mg/kg/day dose but showed signs of worsening off treatment, you will have the option of being treated for another 2 weeks with FIAU with the same followup schedule as for the initial treatment. If you were treated with either the 0.1 mg/kg/day or the 0.5 mg/kg/day dose and showed improvement, which then worsened off treatment, you will have the option of being treated for another 4 weeks with FIAU. Followup will be the same as with the initial dose except that at weeks 3 and 4 of treatment you will undergo the same evaluation as at week 1. If your hepatitis infection shows improvement with either dose of FIAU, you will be asked to return monthly for one year at which time you will have 1 tablespoon of blood drawn for hepatitis and liver funtion evaluation.

If you are chosen to receive either the 0.1 or 0.5 mg/kg/day FIAU dose, you may be asked to participate in two daytime studies to determine the blood concentrations of FIAU. Following your first dose of FIAU on day 1 multiple blood samples (each 15 cc or one tablespoonful) will be collected over an 8 hour interval from an indwelling catheter. Following your last dose of FIAU on day 14, multiple blood samples (each one tablespoonful) will be obtained over a 12 hour interval. Additionally, you will be asked to save your urine for the initial 8 hours of this second study. These studies will be conducted at the AIDS Clinical Trials Unit. A maximum of 20 tablespoons of blood will be collected in both of the blood concentration studies.

While you are taking FIAU you may not take acyclovir (Zovirax^{R}), ganciclovir (DHPG), foscarnet or interferon. You may be allowed to take' zidovudine (also known as azidothymidine, AZT, Retrovir^{R}) for the duration of this study if you've been taking the drug for at least 6 weeks, if you are receiving less than or equal to 600 mg per day, and if your red cell, white cell and platelet counts have not dropped significantly. If you start taking AZT after you've begun this FIAU study, you will be dropped from the study. You are allowed to take aerosolized pentamidine for prevention of Pneumocystis carinii pneumonia.

Risk and Discomforts

You may experience fatigue, headache, nausea, and/or vomiting. FIAU may also cause toxicity to your blood-forming cells; specifically your white cells, red cells and platelets may be reduced in number. Reduction of your white cells may cause you to experience more frequent infections. A decrease in red blood cells can cause fatigue and too few platelets may cause bleeding. With FIAC, these effects reversed with lowering of the dose or drug discontinuation. Some of your blood chemistry values may change while on FIAU therapy. Reversible neurologic toxicity following FIAC administration has been infrequently reported but FIAU may also cause confusion, muscle jerking and seizures. Polymyositis (inflammation of many muscles) has been reported in one patient receiving FIAC and was reversible with drug discontinuation. Non-reversible cardiac toxicity (damage or death to heart muscle and tissue) at very high FIAC doses has been observed in animal studies. These neurologic and cardiac effects may occur with FIAU. FIAU may also affect the production of healthy sperm and/or fetal development. Since FIAU is an investigational drug, there may be other previously unknown side effects. The risks of drawing blood include mild pain, bruising, or rarely infection at the needle site.

If you take this drug during pregnancy you may expose your unborn child to significant hazards of deformity. If you are a woman, you must avoid pregnancy while taking this drug, and, if you are sexually active, you must agree to use some form of barrier contraception while you participate and for at least 3 months following study completion. If you are a woman of child-bearing potential, you will be required to have a serum (blood) pregnancy test prior to entry in the study. If you do become pregnant while on this study, you must notify the investigator immediately. If you are a man with a female partner of child-bearing age, should your partner become pregnant, there is the possible risk of deformity in the child. Therefore, it is important that you or your partner use barrier contraception.

The amount of radiation exposure from the chest x-rays will be about 110 mrem; this is about the same as normal exposure from background radiation in Seattle during one year.

Alternatives

If you choose not to participate in the study, it will have no effect on your continued care. Other alternatives at this point include careful observation by your doctor and treatment with interferon depending on your individual infection. Other treatment includes treatment against human immunodeficiency virus (HIV) which causes AIDS (such as Zidovudine), in order to contain the underlying HIV infection which made you vulnerable to infections.

Other Information

All information and test results will be strictly confidential. You and your laboratory samples will be identified by code. All records with identifying information will be kept in locked files, and will be available only to the investigators with the following exception. Representatives of the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), Oclassen Pharmaceuticals (makers of the drug) will have the right to review study data and will have access to identifying information. The FDA, the NIH, and Oclassen Pharmaceuticals reserves the right to review subjects' personal medical records as relevant to this study. You should also understand that the investigators of this study are requesting your permission to review your medical records for purposes of this research study. The medical records utilized in this study will be entered into a centralized computer data base but only code numbers will be used. No publication or public discussion of the results of this research will contain information that could identify you. The research records will be kept indefinitely. Part of the blood samples will be saved, and may be used in the future for other HIV-related tests. These samples will be identified only by code number and will be accessible only to studies involving current University of Washington investigators.

The study drug, FIAU, laboratory tests, and clinic visits will be provided free of charge. However, costs of hospitalization and/or medications required for treatment of side effects will be the financial responsibility of you and your insurance company. Some insurance companies may not reimburse you for expenses arising from investigational studies. If significant findings are noted during the study that might affect your willingness to continue to participate, these findings will be provided to you.

Investigator's Signature

Date

SUBJECT'S STATEMENT

I am 18 years of age or older. The study described above has been explained to me. I understand that I may refuse to participate and may withdraw from the study at any time without penalty and without loss of benefits to which I am otherwise entitled. I understand that if I withdraw, the investigators will retain access to my study data and any stored specimens. I was given an opportunity to ask questions and understand that future questions I may have about the research or my rights as a research subject will be answered by the investigators listed on page 1.

Subject's Signature

Date

Copies to: Subject

Investigators' file

hs (cf-fiau.doc) 11/1/91

R-90 (UNIVERSITY OF CALIFORNIA, SAN DIEGO)

UNIVERSITY OF CALIFORNIA, SAN DIEGO MEDICAL CENTER CONSENT TOACT AS A RESEARCH SUBJECT

7/24/90
ACTG
90-530

Drs. Douglas Richman, Stephen Spector, J. Allen McCutchan, Samuel A. Bozzette, Leland Rickman, Diane Havlir, Wayne Dankner, William Freeman and their associates are conducting a study to determine the safety, tolerance, and effect on vital cultures of an oral form of FIAU. FIAU is a medication that is active against herpes virus infections (herpes simplex, varicella zoster, and cytomegalovirus) and hepatitis B. FIAU has not been used in human subjects but a related antibiotic FIAC has been successfully used to treat herpes virus infections in patients who have a compromised immune system. I have been asked to participate because I have a cytomegalovirus ,other herpevirus infection or hepatitis B infection.

The purpose of my receiving oral FIAU is to test its safety, tolerance, and antiviral effects, so that it may be used to treat patients with serious CMV, herpes virus and hepatitis B infections.

If I agree to be in this study the following will be done:

1. I will have a complete history, physical exam, viral cultures, and blood drawn for laboratory tests at the time of enrollment, and on at least 3 days over a period of 2 weeks.
2. I will receive one of four possible dose regimens of oral FIAU for a total of 14 days.
3. I will not need to be hospitalized; however, I will need to spend at least two hours at the UCSD Treatment Center during the first day in order to have bloods drawn for FIAU levels. -.
4. I may have ophthalmologic exams done at my enrollment onto the study and at the end of the study if I have CMV.
5. If I develop CMV; retinitis during the study, I will be allowed to continue FIAU if I desire, or withdraw from the study.
6. I will have electrocardiograms performed at entry and days 7 and 14.
7. If I am sexually active I will use effective contraceptive during FIAU treatment and for 30 days following treatment.

8. If I have been taking AZT without difficulty over the past 6 weeks, then I can continue to take AZT while on the study; however, I must take 600 mg or less per day.
9. I have not taken and I will continue not to use acyclovir, ganciclovir, foscarnet, or interferon during the study. If I have not been taking AZT previously, I understand that I cannot start AZT until after the 2 week study period.
10. After the 2 week study period has ended, I will not continue to receive FIAU.

Participation in this study may involve some added risks or discomforts:

It is possible that FIAU may cause my white blood cells, red blood cells, or platelets to decrease. This may predispose me to bleeding, anemia, and infection. Some other side effects that I may experience include nausea, vomiting, or muscle inflammation. It is also possible that confusion, jerking, and even seizures may occur while I am taking this medication, although this is unlikely on the doses I will receive.

In animal studies there was evidence of heart damage in those animals receiving very high doses of FIAC. It is not known whether FIAU may cause sterility or infertility in humans, however, this is a possibility. Since interactions between FIAU and other medications are incompletely understood at this time, I must not take other medications without first consulting with my study physician or nurse practitioner.

I realize that I may receive no benefit from participating in this study. The knowledge gained may help others in the future.

Dr. _____ has explained this study to me and answered my questions. If my child or I have other questions, or if we wish to report a research-related problem, I may call Dr. Havlir at 543-8080.

If I am injured as a result of participation in this research, the University of California will provide any medical care that I may need to treat those injuries—except when they are a consequence or research designed to benefit me directly. The University will not provide any other form of compensation to me if I am injured. I may call (619) 534-4520 for more information about this.

Participation in research is entirely voluntary. I may refuse to take part or withdraw at any time without jeopardy to my medical care at this institution.

Research records will be kept confidential to the extent pro?? by law. Study forms will contain only a code number, and perhaps

my initials (but not my name) for identification. Study and other medical records may be reviewed by the AIDS Clinical Trials Coordinating Center, the NIAID, Oclassen Pharmaceuticals, or the U.S. Food and Drug Administration to ensure that they are accurate and fulfill federal regulations.

I have received a copy of this consent document to keep and a copy of "The Experimental Subject's Bill of Rights."

I agree to take part in this study.

Subject' Signature

Date

Witness

Parent or Legal Guardian

Date

UNIVERSITY OF CALIFORNIA, SAN DIEGO

BERKELEY · DAVIS · IRVINE · LOS ANGELES · RIVERSIDE · SAN DIEGO · SAN FRANCISCO SANTA BARBARA · SANTA CRUZ

VICE CHANCELLOR FOR HEALTH SCIENCES
DEAN, SCHOOL OF MEDICINE

LA JOLLA, CALIFORNIA 92093
M-002

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The faculty and staff of the University of California, San Diego wish you to know:

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be used.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time, and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of a signed and dated written consent form when one is required.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

If you have questions regarding a research study, the researcher or his/her assistant will be glad to answer them. You may seek information from the Human Subjects Committee - established for the protection of volunteers in research projects - by calling (619) 534-4520 from 8 am to 5 pm, Monday through Friday, or by writing to the above address.

R-90 (NATIONAL INSTITUTES OF HEALTH)

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient

INSTITUTE: _____

STUDY NUMBER _____ PRINCIPAL INVESTIGATOR: Dr. Stephen E. Straus

STUDY TITLE: The Tolerance of HIV-infected Patients with Herpes Group or Hepatitis B Virus Infections to Oral Doses of FIAU.

INTRODUCTION

We invite you (or your child) to take part in a research study at the National Institutes of Health. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the staff members who explain it to you

People infected with the Human Immunodeficiency Virus (HIV) are at risk for complicating infections. Among these are infections with herpesviruses including herpes simplex virus, the varicella-zoster virus,, the cytomegalovirus (CMV) as well as hepatitis B virus (HBV). Herpes simplex and varicella-zoster viruses are frequent causes of blistering and ulcerating skin sores in patients with HIV infection. CMV is capable of causing destruction of retina of the eye as well as serious infections of the brain, lungs, and other organs in patients with HIV infection. HBV can cause slowly progressive destruction and failure of the liver. As a person whose immune defenses have been weakened by HIV and who may have evidence of active infection with one or more of these viruses, you are invited to participate in a study of a new drug designated to control one or more of these infections and their potential serious consequences in people with impaired immune systems.

The present study is designed to determine how well patients like yourself can tolerate various doses of the antiviral drug FIAU. In the laboratory, FIAU is capable of blocking the growth of herpes simplex virus, varicella-zoster virus, CMV, and hepatitis B virus. Past experience with drugs closely related to FIAU suggests that we might be able to give patients oral doses of FIAU that are adequate to block the growth of these viruses while causing minimal side effects. To arrive at an answer as quickly as possible, this study is being conducted in conjunction with AIDS experts at three major universities. We will be starting patients at low doses of FIAU and gradually raising the dose with subsequent patients, until we find a level that may be capable of blocking growth of the viruses or until toxic side effects occur (see page 3), whichever comes first. Even if FIAU appears safe and capable of suppressing herpes group or hepatitis B virus infections, we cannot give more of it to you until the Food and Drug Administrations approves our doing so.

PATIENT IDENTIFICATION	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: _____ CONTINUATION: page 2 of 6 pages.

ELIGIBILITY

To be eligible for the study, you must be 13-65 years of age and have proven infection with HIV. You must be strong enough to carry on normal activities of daily living, have no significant kidney problem and be able to come to the clinic on your own for all the visits that the study requires. The immune status of all patients must be such that the total number of CD4-positive lymphocytes be greater than or equal to 200/mm³. If you are taking AZT, you are eligible for this study only if you have been receiving doses of 600/mg/day or less for 6 weeks or more before stating FIAU. If you are not currently taking AZT, it cannot be started during the 2 week FIAU treatment. Both men and women participants must agree to use birth control for the entire 2-week study period, and 3 months thereafter, because FIAU, like its related antiviral drugs, could damage the ability of men and women to conceive or deliver normal babies. Women who participate in the study will undergo a pregnancy test within 2 weeks prior to starting FIAU.

Patients who have evidence of any other serious complications of HIV infection, or who are taking any other antiviral or immune-stimulating drug, cannot participate. You cannot be on acyclovir within 1 week of starting treatment and thought the 2-week period of FIAU treatment. Aerosolized pentamidine treatment and other non-experimental medications may be continued.

You may be eligible for the study if you have active infections with herpes simplex virus, varicella-zoster virus, CMV, and/or hepatitis B virus. If you have active herpes simplex or varicella-zoster virus infections, you may receive FIAU only if your infections have proven unresponsive to acyclovir treatment. If you have CMV infection, you cannot receive FIAU if you have evidence that the virus is actively injuring the retina of your eye or other organs. Before starting treatment, an ophthalmologist will examine your eyes to be sure there are no signs of CMV infection. Patients who have chronic active hepatitis B virus infection can participate in this study only after a given FIAU dose level has proven to be well tolerated in individuals who are otherwise the same, but do not have chronic hepatitis.

STUDY PROCEDURES

If you have been screened and found eligible for this study, FIAU will be dispensed to you from our NIH pharmacy as a liquid which you will mix in a glass of water to drink 3 times a day for 14 days. You will receive the same dose of FIAU for all 14 days. It must be taken at least 1 hour before or 3 hours after meals, so that food will not interfere with its absorption into the blood stream. You will need to come to the NIH pharmacy once a week to pick up your prescribed FIAU.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH 2514-1 (10-84) NIH 2514-2 (10-84) P.A. 09-25-0099

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: _____ CONTINUATION: page 3 of 6 pages.

On study day 1, you will be required to be in the clinic to take your first dose of FIAU, and to return 8 hours later, just before your second dose, so that we can draw blood to evaluate the levels of the drug in your blood stream at that time. You will then be asked to return to the clinic on days 2, 3, 5, 7, 10 and 14 following your first dose of FIAU, for examinations and repeated tests of blood, urine and stool. Your participation in this study ends after the 14th day unless you have chronic hepatitis B virus infection. If you have chronic hepatitis B virus infection, we will examine you briefly in clinic and obtain additional blood samples at days 21 (1 week post treatment) and 42 (4 weeks post treatment). Your participation in this study may also be ended should treatment side effects be too bothersome (see below), or if you fail to take the FIAU properly or keep many of the clinic appointments.

This study requires us to draw blood tests on every visit. The total amount of blood to be drawn will be less than 150cc (about 10 tablespoons). All blood samples will be drawn from a vein in your arm. Blood drawing hurts briefly, can occasionally lead to a local bruise, and rarely triggers fainting.

Also, we will have to test you stool for trace amounts of blood to determine if FIAU is causing bowel or stomach irritation. The stool samples can be provided by you or, if more convenient, may be taken by a brief rectal insertion with a gloved finger. There will be four such tests in the course of the study.

TOXIC SIDE EFFECTS

FIAU is a new drug that has not previously been given to patients. However, it is very closely related to another drug that has been given by mouth and intravenously to well over 100 patients. That drug, known as FIAC, is rapidly broken down in people's bodies to FIAU, therefore, we think that the potential side effects should be virtually the same as those found with FIAC. Since FIAU is a new drug, all of its short or long term side effects are not yet known.

FIAC is known to cause some side effects when given intravenously or orally at doses that would produce FIAU concentrations in your blood equivalent to or many time higher than that achieved in the present study. For example, high doses of FIAC can cause a fall in the number of red blood cells (anemia). It is unlikely that the degree of anemia would be great at the dosage of FIAU you will be taking, but if you are also taking AZT, these side effects may be more severe and more blood transfusions may be required than would be necessary to treat anemia due to AZT alone. High doses of FIAC can also cause a fall in the number of white blood cells (leukopenia). Again, if you are on AZT this problem could become worse, such as to increase your risk of other complicating infections. Some infections that occur in people with very low white blood cell counts can be very serious, even fatal, but these are uncommon in people with HIV infections. Similarly, FIAC can lead to a decrease in platelets, the blood elements required for clotting.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH 2514-1 (10-81) NIH 2514-2 (10-81) P.A. 07-25-0093

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: _____ CONTINUATION: page 4 of 6 pages

Throughout treatment with FIAU, the number of your red and white blood cells and platelets will be measured repeatedly. If we detect any clinically significant decreases in the cells or platelets, we may stop your FIAU treatment. Very high doses of FIAC also were associated with reversible lung congestion and neurologic problems like seizures. Certainly, if necessary, standard medical therapy of these complications will be provided and treatment can be stopped whenever needed or desired.

In some HIV infected patients treated with FIAC in another study, we noted that there was a rise in blood levels of a muscle enzyme called CPK. This is a chemical released into the blood stream any time there is a degree of inflammation and/or damage to muscles. One of the few individuals in whom this was observed had muscle aches, but the rest of the individuals were entirely unaware of the proces. That individual also had some temporary kidney function abnormality and a hallucination. It was realized that only individuals with CD4 counts of less than 200/mm³ had these side effects of FIAC. It is our hope that by selecting patients in this study such as yourself with CD4 counts of 200 or greater, we can avoid these side effects. Nonetheless, we will go to considerable lengths in this study to avoid any side effects of FIAU related to muscle. We urge all patients not to engage in strenuous physical activity during the time of treatment. Strenuous activity itself could raise blood CPK levels. We will be checking blood CPK levels during the study as well as doing a simple test of muscle strength in which we determine how long takes an individual to rise ten times from a sitting position in an ordinary chair.

Based upon our experience with FIAC, it is possible that FIAU could cause stomach upset, nausea, or even vomiting. If needed, we will give you medications to try to control these side effects. If these medications fail to help you, we will stop the FIAU completely.

ALTERNATIVE TREATMENTS

There are alternative treatments to FIAU for some of the types of viral infection we are studying:

For HSV infection — The antiviral drug acyclovir is the standard treatment for active HSV infections. You have been chosen for FIAU treatment only because your HSV infection has failed to show an obvious clinical response to acyclovir pills. Alternative treatment to acyclovir pills would include admitting you to the hospital for intravenous acyclovir treatment or attempting to get another experiment drug for refractory HSV infections, a drug known as foscarnet. That drug is also given intravenously and has known side effects. Should you have active HSV infection, your oral acyclovir treatment would need to be stopped for 1 week prior to starting FIAU.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH 2514-1 (10-84) NIH 2514-2 (10-84) P A 09 25-0099

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: _____ CONTINUATION: page 5 of 6 pages.

Varicella-zoster virus - Should you have an active zoster infection, you will be eligible for FIAU treatment only if your infection has proven refractory to treatment with acyclovir pills. Alternative treatments include admitting you to the hospital for intravenous acyclovir or attempting to get another experimental intravenous medication known as foscarnet.

CMV infections - Should you be chosen to be treated with FIAU for CMV infection, it would be done so with the understanding that you do not at the present time have evidence of an active CMV infection involving the eyes or other vital tissues. Should you have CMV infection of the retina or other tissues, you will not be eligible for this study. It is generally not considered necessary to treat the asymptomatic CMV infections in patients with HIV. We would choose to do so in you as an experimental test of the drug FIAU.

HBV infection - There are no proven alternative therapies for chronic HBV infections in patients who are also infected with HIV. Patients who are not also infected with HIV have shown temporary or even permanent improvement of the HBV infection by long-term injections with the drug interferon. Prior to your considering this study, you will be counseled regarding your suitability for interferon treatment as an alternative to FIAU.

POTENTIAL BENEFITS

Besides helping us learn about treatments for vial infections in individuals with HIV, you may benefit from participating in this study in several regards. First, if you have otherwise refractory herpes simplex or zoster infection, that infection may improve during FIAU treatment. Second, it is conceivable that what we learn about FIAU may provide us simpler and more effective ways of treating CMV infections. Third, should you be treated for chronic HBV infection, we may identify a drug that could benefit your infection. Because FIAU has not been used previously, there is no way of determining whether any of these potential benefits are likely.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84) NIH-2514-2 (10-84) P.A. 09-25-0099

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient	continuation page 6 of 6 pages

[illegible] NUMBER

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records of Clinical Center patients are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.

2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any physical injury resulting from your participation in research here. Neither the Clinical Center nor the Federal government will provide long-term medical care or financial compensation for such injuries, except as may be provided through whatever remedies are normally available under law.

3. **Payments.** If you are a patient, you are not paid for taking part in NIH studies. Exceptions for volunteers will be made by Clinical Center policies.

4. **Problems or Questions.** Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research, or with regard to any research related injury, you should contact the principal investigator, Stephen E. Straus, M.D., or these other staff members also involved in this study: Barbara Savarese, R.N.

   Building 10 Room 11N113 Telephone (301) 496-5221
   National Institutes of Health
   Bethesda, Maryland 20205

5. **Consent Document.** It is suggested that you retain a copy of this document for your later reference and personal records.

COMPLETE APPROPRIATE ITEM BELOW, A or B:

A. Adult Patient's Consent.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient & Date Signed

B. Parent's Permission for Minor Patient.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent & Date Signed

[illegible] (parent, specify relationship)

Signature of Investigator & Date Signed

Signature of Witness & Date Signed

PHOTOIDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY
• Adult Patient or • Parent, for Minor Patient

P A : 09 25 0099

R-91 (NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISORDERS)

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient

INSTITUTE: NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

STUDY NUMBER 91-DK-AI-213 PRINCIPAL INVESTIGATOR: Jay H. Hoofnagle, M.D.

STUDY TITLE: A Four-Week Course of FIAU for Chronic Hepatitis B

INTRODUCTION

We invite you (or your child) to take part in a research study at the National Institutes of Health. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the staff members who explain it to you.

As a patient with chronic hepatitis B, you are invited to take part in this research study designed to test the medication FIAU for its effect on your liver disease. The full name of FIAU is 1-2' deoxy-2' fluoro-1-beta-D-arabinofuranosyl-5-iodo-uracil. This medication was developed originally to treat herpesvirus infections and is similar to other antiviral drugs such as AZT and acyclovir. FIAU has recently demonstrated activity against hepatitis B. We used FIAU to treat six patients who had AIDS and hepatitis B. We found that FIAU led to a rapid decrease in levels of hepatitis B virus in the blood, and in some patients this decrease lasted for weeks to months. An effect on hepatitis B virus lasting this long may be permanent. In further studies, a much lower dose of FIAU was found to inhibit hepatitis B just as well as the higher dose. In these studies, patients were treated for only 14 days, which may not be long enough to cure hepatitis B virus infection. On the other hand, longer treatment may lead to more side effects. For these reasons, this study will test four different doses of FIAU given for 28 days.

Therefore, we are asking you to enter this study in which you will receive FIAU for 28 days. At the beginning you will be assigned to receive one of four doses of FIAU, which are equivalent to the doses of FIAU used in the original studies. Both during and after treatment you will be monitored closely for any side effects or changes in your chronic hepatitis. You will be told about any significant findings from this study (whether positive or negative) regarding the effects of FIAU on chronic hepatitis, and you will be informed if any alternative treatments become available during the course of this study.

PATIENT IDENTIFICATION	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate in A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate in A Clinical Research Study

STUDY NUMBER: 91-DK-AI-213 CONTINUATION: page 2 of 6 pages.

This is an experimental study. It has not yet been proven that FIAU is effective in treating hepatitis B, and its side effects have not been studied in many patients. At the present time, however, treatment for hepatitis B is not very satisfactory. Alpha interferon has been effective in some patients with hepatitis B. For instance, we find that 40% of patients respond to interferon treatment with long-term improvement in their liver condition. The remaining 60% of patients, however, do not obtain lasting benefit. Because interferon has to be given by injection, has frequent side effects, and only benefits fewer than half of patients, we continue to search for better treatments for hepatitis B.

Interferon, however, does work in some people. If you have never been treated with interferon, it may be best for you to try interferon before you enter this study. In general, we find that persons with severe hepatitis B have a high likelihood (greater than 50%) of responding to interferon, whereas persons with relatively mild disease are unlikely (less than 10%) to respond. Therefore, if you have a severe case of hepatitis B, you should try treatment with interferon first. If you have a mild or moderate case, trying FIAU before interferon is a reasonable. However, if you do not have long-lasting improvement after treatment with FIAU, you should at some time in the future receive a course of interferon. Of course, if you have received interferon in the past and have not responded or couldn't tolerate its side effects, a reasonable decision on your part would be to enter this study of FIAU.

NATURE OF STUDY

This study will last approximately six months. At the start you will be admitted to the National Institutes of Health (NIH) Clinical Center for a complete medical examination and liver biopsy. You will then begin taking FIAU. You will be watched closely to monitor the effect of FIAU on your hepatitis and for any side effects. A complete explanation of this study is given below:

(1) You will be admitted to the Clinical Center where we will do a complete medical history and physical examination.

(2) You will have a series of laboratory studies to define your overall medical condition, the degree of liver disease, and level of hepatitis virus infection. These studies will include multiple blood tests, a urine analysis, and a 24-hour urine collection, a chest X-ray and electrocardiogram (heart tracing), and a abdominal ultrasound (sound-wave test to evaluate the liver). If you are a woman, you will have a pregnancy test. One blood test that you will have is for antibody to the human immunodeficiency virus (anti-HIV), the cause of acquired immune deficiency syndrome (AIDS). You will be notified promptly of the results of the anti-HIV test.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84)

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 91-DK-AI-213 CONTINUATION: page 3 of 6 pages.

If you are found to have this antibody (anti-HIV), you will be expected to inform your sexual partner(s) that they may have been exposed to this virus. We will help you and your sexual partner(s) obtain information regarding the meaning of this test and ways of preventing spread of this infection. This test will be repeated at the end of the study.

(3) At the beginning of this study, you will undergo a liver biopsy to assess the degree of injury done to the liver by your chronic hepatitis. You will not have to have a liver biopsy if you have had one within the last year. This procedure will be fully described to you and you will be asked to sign a separate consent form for this liver biopsy.

(4) You will then be assigned to a dose of FIAU and will begin taking it. Four doses of FIAU are being evaluated; the dose that you receive will be based upon the order in which you enter the study. FIAU is given in the form of a liquid suspension that you will drink three times a day for 28 days. You will be taught in the clinic how to measure out the correct amount of FIAU so you can take it at home.

(5) While taking FIAU you will be seen on day 3 and then weekly in the clinic and have blood drawn to carefully monitor side effects and the effects of FIAU on the hepatitis. On one day during the first week and on one day during the last week of treatment you will be asked to stay in the outpatient clinic for a few hours to have your blood drawn immediately before you take the FIAU and exactly 2 hours afterwards. This is to measure how well you absorb FIAU and whether its levels slowly build up during treatment.

(6) After treatment you will be seen in the clinic for brief visits and to have blood drawn every one to two months until six months after starting FIAU when you will have a thorough evaluation in the outpatient clinic which will include a medical history, a physical examination, multiple blood tests and a urine test. At that point, this study will be over, but you will be eligible to enter other studies of therapy for chronic hepatitis B or to be followed without treatment in the outpatient clinic.

(7) If you are capable of bearing or fathering children, you will have to practice an effective method of birth control (both men and women) for the 28 days of treatment and for two months thereafter. The risks of FIAU to an unborn fetus or to developing sperm are not known. If you are pregnant you cannot participate in this study.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84)

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 91-DK-AI-213 CONTINUATION: page 4 of 6 pages.

RISKS AND DISCOMFORTS

(1) The local pain or discomfort of having blood drawn. You may have as many as 20 blood drawings during the six months of this study. No more than 14 ounces (approximately 28 tablespoonfuls) of blood will be taken for research purposes during any six-week period. Drawing blood occasionally causes a bruise in the skin where the needlestick occurs. Rarely, fainting occurs after blood drawing.

(2) The pain and risks of liver biopsy. Liver biopsy is performed using a needle that is passed through the skin into the liver to obtain a piece of liver about two inches long and 1/16 of an inch in diameter. About 20% of persons having a liver biopsy have some degree of pain over the liver that may last from a few minutes to several hours. This rarely requires pain medication and always disappears within a day or two. Some patients faint after liver biopsy. This can usually be avoided and can be treated if it occurs.

Some rare complications of liver biopsy are infection, puncture of another internal organ, and bleeding. Infections in the blood can occur after a liver biopsy but they can be treated with antibiotics. Puncture of another internal organ such as the lung, gall bladder, intestine, or kidney can occur when a liver biopsy is attempted. To prevent this, we always perform an ultrasound before the biopsy to identify where all the internal organs are and where it is best to carry out the liver biopsy. A rare complication of liver biopsy is severe bleeding such that a blood transfusion or even an operation to sew up the hole in the liver is needed. This complication which occurs less than one in 1,000 times. In less than one in 10,000 cases, death has occurred from bleeding after a liver biopsy. At the time of the liver biopsy you will be given a more complete and detailed consent form that outlines how the liver biopsy is done and its complications.

(3) The risks and discomforts of taking FIAU for 28 days. FIAU is a new medication, and its side effects have not been completely described. In studies of persons taking FIAU for 14 days, it was very well tolerated. Some side effects that have been reported or could occur are:

(a) Fatigue, irritability, trouble sleeping (insomnia). These are mild and disappear when treatment is stopped.

(b) Nausea and upset stomach. These intestinal complaints are common with the highest dose of FIAU that we will be using. These side effects are usually mild and disappear quickly when treatment is stopped.

(c) Skin rashes. Rarely patients who take drugs similar to FIAU develop mild, red, itchy rashes that last a few days only.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84)

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 91-DK-AI-213 CONTINUATION: page 5 of 6 pages.

(d) Bone marrow suppression, or a decrease in the red and white blood cells and platelets in the blood. Drugs similar to FIAU may lower the number of red blood cells, making some patients mildly anemic, or lower the number of white blood cells, which make up your immune system, thereby making you more susceptible to infections. However, you are unlikely to develop a serious infection because we will stop treatment if the white blood cell count falls too low. Drugs like FIAU can also decrease the number of platelets, which are responsible for blood clotting. A low platelet count may make you more prone to bleeding, but this should not cause serious bleeding. The effects of FIAU on the bone marrow will be monitored closely, and the dose will be lowered if the white blood cell or platelet count decrease too much. All of the bone marrow side effects have been mild in the few patients who have been treated with FIAU and they resolved quickly when treatment was stopped.

(e) Seizures. Some patients receiving very high doses of drugs similar to FIAU have developed seizures. These patients had AIDS and many serious problems, and the doses used were much higher than you will receive. Also it is still not clear whether the seizures were due to the treatment or to the underlying AIDS in these very ill patients.

(f) Pains in the arms and legs can occur with high doses of FIAU. This side effect is also seen with other antiviral medications and may be due to irritation of the nerves or the muscles of the arms and legs. These pains can be severe and last for weeks to months. In some cases, a permanent decrease in nerve function is found. Because of this side effect, we are testing low doses of FIAU and are monitoring patients carefully. If you develop leg or arm pains, we will stop the FIAU and treat you with pain medications.

If you develop a severe side effect such as nerve and muscle pains, seizures, large decreases in the blood cell counts, or extreme fatigue, we will stop the FIAU. In addition, if you are a woman and become pregnant, FIAU will be stopped.

BENEFITS

The benefits of participating in this study are the following:
(a) You will have a thorough medical evaluation of your condition.
(b) Your chronic hepatitis B may improve as a result of treatment.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84)

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient	continuation: page 6 of 5 pa

STUDY NUMBER: 91-DK-AI-213

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records of Clinical Center patients are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.

2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any physical injury resulting from your participation in research here. Neither the Clinical Center nor the Federal government will provide long-term medical care or financial compensation for such injuries, except as may be provided through whatever remedies are normally available under law.

3. **Payments.** If you are a patient, you are not paid for taking part in NIH studies. Exceptions for volunteers will be guided by Clinical Center policies.

4. **Problems or Questions.** Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research, or with regard to any research-related injury, you should contact the principal investigator, Dr. Jay H. Hoofnagle, or these other staff members also involved in this study: Dr. Stephen Straus, Dr. Adrian Di Bisceglie ; _____ :
Building 10, Room 4-D-52. Telephone: (301) 496-1721
National Institutes of Health
Bethesda, Maryland 20205

5. **Consent Document.** It is suggested that you retain a copy of this document for your later reference and personal records.

COMPLETE APPROPRIATE ITEM BELOW, A or B:

A. Adult Patient's Consent.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

_____
Signature of Adult Patient & Date Signed

B. Parent's Permission for Minor Patient.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

_____
Signature of Parent(s) & Date Signed

_____
(if other than parent, specify relationship)

_____
Signature of Investigator & Date Signed

_____
Signature of Witness & Date Signed

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY
• Adult Patient or • Parent, for Minor Patient

MEDICAL RECORD	INFORMED CONSENT STATEMENT FOR HIV BLOOD TESTING

We request your permission to test your blood for the presence of antibodies to the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS). In order to perform the test, a small amount of blood (approximately 2 teaspoons) will be withdrawn from one of your arms with a needle. You may experience some slight discomfort at the needle entry site and there may be some bruising. In addition, there is a very small risk of your fainting or of infection at the needle entry site. If your test results are found to be positive, or if you are otherwise diagnosed as having AIDS, you should be aware of the following Clinical Center HIV Testing Policy:

1. Your physician will notify you promptly of the HIV test results.
2. Your physician and/or the Clinical Center HIV counselor will offer you, and any current and/or ongoing sexual partner(s) (spouses are generally considered to be current or ongoing sexual partners) or needle-sharing partner(s) you identify, information on the meaning of the test results and how to prevent the spread of the infection.
3. Because the virus may be transmitted in several ways, it is important that you inform sexual and/or needle-sharing partner(s) that any, or all, of them may have been exposed to the HIV virus and encourage them to be tested. If you request it, staff at the Clinical Center will assist you in notifying your partner(s) and arrange counseling for them through an HIV counselor.
4. The results of your HIV test and/or documentation of the diagnosis of AIDS will become a part of your Clinical Center medical record and, as such, will be protected from unauthorized disclosure by the Federal Privacy Act of 1974. In general, access to your medical record will be restricted to those health care professionals directly involved in your care or in the conduct of ongoing biomedical research, and information is not usually released to other third parties without your permission or that of your designated representative. However, there are some particular routine uses of such information of which you should be aware.
   a. If you are unwilling or unable to notify your partner(s), the Clinical Center is responsible for attempting to contact and inform them of their possible exposure to the virus. Reasonable attempts will be made to protect your identity including withholding your name when notifying any partner(s) of their possible exposure. Some notification or counseling of current and/or ongoing partners may be carried out through arrangements with, or referral to, local public health agencies.
   b. A summary of your care at the Clinical Center will be sent to the physician who referred you here for treatment.
   c. The Clinical Center may report certain communicable diseases, including AIDS, to appropriate State and Federal government agencies.

If you have any questions regarding the HIV testing or the information provided above, you are encouraged to discuss them with your physician and/or a Clinical Center HIV counselor (496-8955).

Complete Appropriate Item Below, A or B:	
A. Adult Patient's Consent: I have read the explanation about the blood testing and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this blood testing.	**B. Parent's Permission for Minor Patient:** I have read the explanation about the blood testing and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this blood testing.
Signature of Adult Patient _____ Date _____	Signature of Parent(s) _____ Date _____
	(If Other than Parent, Specify Relationship) _____
Signature of Witness _____ Date _____	Signature of Witness _____ Date _____
Patient Identification	INFORMED CONSENT STATEMENT FOR HIV BLOOD TESTING NIH-2663 (2-89)

PPPC

CONFIDENTIAL

MEDICAL RECORD | CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY
• Adult Patient or • Parent, for Minor Patient

INSTITUTE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

STUDY NUMBER 93-DK-31 PRINCIPAL INVESTIGATOR Jay H. Hoofnagle, M.D.

STUDY TITLE. A Six-Month Course of FIAU for Chronic Hepatitis B

INTRODUCTION

We invite you (or your child) to take part in a research study at the National Institutes of Health. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the staff members who explain it to you.

As a patient with chronic hepatitis B, you are invited to take part in this research study designed to test FIAU for its effect on your liver disease. FIAU is an antiviral medication whose full name is 1-2' deoxy-2' fluoro-1-beta-D-arabinofuranosyl-5-iodo-uracil. In a previous study, we found that FIAU inhibits the levels of hepatitis B virus in the blood of patients with chronic hepatitis B. In a small number of patients, this inhibition was strong enough to cause the hepatitis B virus to disappear completely; these patients had an improvement in their liver condition. In other patients, however, the treatment did not have a lasting effect, either because the medication was not strong enough or was not given for a long enough time. For these reasons, we are planning to treat patients for a longer period - for six months - to see if a prolonged course of FIAU will cause a permanent improvement in the hepatitis.

We are asking you to enter this study in which you will receive FIAU for a total of 24 weeks. At the beginning of the study you will undergo a medical evaluation and a liver biopsy if you have not had one in the previous year. You will then will be assigned to receive one of two doses of FIAU; these doses were found to be most effective and yet best tolerated in the original study. Both during and after treatment you will be monitored closely for any side effects or changes in your chronic hepatitis. You will be told about any significant findings from this study (whether positive or negative) regarding the effects of FIAU on chronic hepatitis, and you will be informed if any alternative treatment becomes available during the course of this study.

PATIENT IDENTIFICATION | CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY
• Adult Patient or • Parent, for Minor Patient
NIH-2514-1 (9-91)

CONFIDENTIAL

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate in A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate in A Clinical Research Study

STUDY NUMBER: 93-DK-31 CONTINUATION: page 2 of 6 pages

NATURE OF STUDY

The study will last for one year. It is explained below:

(1) You will be seen in the outpatient clinic of the NIH Clinical Center where we will do a complete medical history and physical examination.

(2) You will have a series of laboratory studies to define your overall medical condition, the degree of liver disease, and level of hepatitis virus infection. These studies will include multiple blood tests and a urine analysis. One blood test that you will have is for antibody to the human immunodeficiency virus (anti-HIV), the cause of acquired immune deficiency syndrome (AIDS). You will be notified promptly of the results of the anti-HIV test. If you are found to have this antibody (anti-HIV), you will be expected to inform your sexual partner(s) that they may have been exposed to HIV. We will help you and your sexual partner(s) obtain information regarding the meaning of the test and ways to prevent spread of the infection. You will be retested for anti-HIV at the end of the study.

(3) If you are a woman, you will have a pregnancy test.

(4) You will have a nerve conduction studies to test your peripheral nerves in your arms and legs. In this test, the physician will hold a electrode probe against your skin that delivers a small electrical pulse of current. You will also have small metal electrodes taped onto the skin on your arms or legs which are attached to a computer which measures the response to the pulse. The pulse will cause a tingling sensation or a muscle twitch, which enables us to measure how well the nerve is working.

(5) If you have not had one within the previous year, you will undergo a liver biopsy. For the biopsy you will be admitted to the NIH Clinical Center for 1 to 2 days. The liver biopsy is to confirm that you have chronic hepatitis and to assess the degree of liver injury caused by the hepatitis. The liver biopsy will be described and you will be asked to sign a separate consent form at the time.

(6) You will also have an abdominal ultrasound (an examination of the liver using sound waves), an electro-cardiogram (heart-tracing) and a chest X-ray. These tests also will only be done if you have not had them during the previous year.

(7) You will then be assigned to receive one of the two doses of FIAU that we are studying. The assignment will be made randomly by computer generated numbers.

(8) You will then begin taking FIAU. FIAU will be provided as a liquid which we will teach you to measure correctly. You will take FIAU three times a day for 6 months (24 weeks).

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84) NIH-2514-2 (10-84) P.A. 09-25-07

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MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate in A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate in A Clinical Research Study

STUDY NUMBER 93-DK-31 CONTINUATION: page 3 of 6 pages

(9) While taking FIAU, you will need to be seen weekly for two weeks and then monthly in the clinic. Blood will be drawn to monitor drug side effects, if any, and the effects of FIAU on the hepatitis.

(10) After you have been on FIAU for approximately three months, you will have the nerve conduction tests done again. This will be done in the clinic and takes about one hour. Also if you have any symptoms of nerve damage during this study, you will have these tests done once more.

(11) After the treatment is stopped, you will be seen in the clinic for brief visits with blood drawing every one to two months until 12 months after starting FIAU. At the 12 month point, you will have a thorough evaluation including a medical history, a physical examination, multiple blood tests and a urine test in the outpatient clinic. At that point, this study will be over, but you will be eligible to enter other studies of therapy for chronic hepatitis B or to be followed without treatment in the clinic.

(12) If you are capable of bearing or fathering children, you will have to practice an effective method of birth control (both men and women) for the 24 weeks of treatment and for two months thereafter. Chromosomal changes have been detected in mice given high doses of FIAU; the effect of this in humans is unknown. Similarly, the risks of FIAU to an unborn fetus or to developing sperm are not known. If you are pregnant, you cannot participate.

RISKS AND DISCOMFORTS

(1) The local pain or discomfort of having blood drawn. You may have as many as 20 blood drawings during the 12 months of this study. No more than 14 ounces (approximately 28 tablespoonfuls) of blood will be taken for research purposes during any six-week period. Drawing blood occasionally causes a bruise in the skin where the needlestick occurs. Rarely, fainting occurs after blood drawing.

(2) The pain and risks of liver biopsy. This procedure uses a needle that is passed through the skin into the liver to obtain a piece of liver about two inches long and 1/16 of an inch in diameter. About 20% of persons who undergo a liver biopsy experience pain in the side of body over the liver that usually last from a few minutes to several hours. This rarely requires pain medication and disappears within a day or two. A rare complication of liver biopsy is bleeding severe enough to require a blood transfusion or even surgery to sew up the tiny hole in the liver made by the biopsy, a complication which occurs less than one in 1,000 times. Very rarely, in less than one in 10,000 cases reported worldwide, death has occurred from bleeding after a liver biopsy.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84) NIH-2514-2 (10-84) P.A. 09-25-0099

CONFIDENTIAL

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate in A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate in A Clinical Research Study

STUDY NUMBER: 93-DK-31 CONTINUATION: page 4 of 6 pages.

(3) The risks and discomforts of having nerve conduction tests done before treatment and again after three months of treatment. In this test, small amounts of electrical current are given to you as a pulse through an electrode that is held against your skin. The pulse of electricity causes a tingling sensation or a muscle twitch, which may feel uncomfortable. However, this test is entirely safe and without serious side-effects. There is no electrical hazard such as electrocution and the nerves are not damaged by the test. Nerve conduction tests have been done on many patients who are receiving antiviral medications and are usually very easy to tolerate. We will stop the test if you request it, and you can refuse this part of this study and still receive FIAU.

(4) The risks and discomforts of taking FIAU for 24 weeks. FIAU is a new medication, and its side effects have not been completely described. In studies of persons taking FIAU for 4 weeks, it was very well tolerated. Some side effects that have been reported or could occur are:

(a) Fatigue, irritability, trouble sleeping (insomnia). These are mild and disappear when treatment is stopped.

(b) Nausea and upset stomach. These intestinal complaints are not common with the doses of FIAU that we will be using. They are usually mild and disappear quickly when treatment is stopped.

(c) Skin rashes. Rarely patients who take drugs similar to FIAU develop mild, red, itchy rashes that last a few days only.

(d) Bone marrow suppression, or a decrease in the red and white blood cells and platelets in the blood. Drugs similar to FIAU may lower the number of red blood cells, making some patients mildly anemic, or lower the number of white blood cells, which make up your immune system, thereby making you more susceptible to infections. However, you are unlikely to develop a serious infection because we will stop treatment if the white blood cell count falls too low. Drugs like FIAU can also decrease the number of platelets, which are responsible for blood clotting. A low platelet count may make you more prone to bleeding, but this should not cause serious bleeding. The effects of FIAU on the bone marrow will be monitored closely, and the dose will be lowered if the white blood cell or platelet count decrease too much. All of the bone marrow side effects have been mild in the few patients who have been treated with FIAU and they resolved quickly when treatment was stopped.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84) NIH-2514-2 (10-84) P.A. 09-25-0099

CONFIDENTIAL

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 93-DK-31 CONTINUATION: page 5 of 6 pages

(e) Seizures. Some patients receiving very high doses of drugs similar to FIAU have developed seizures. These patients had AIDS and many serious problems, and the doses used were much higher than you will receive. It is still not clear whether the seizures were due to the treatment or to the underlying AIDS in these very ill patients.

(f) Pains and numbnessin the arms and legs can occur with high doses of FIAU. This side effect is also seen with other antiviral medications and may be due to irritation of the nerves or the muscles of the arms and legs. These pains can be severe and last for weeks to months. In some cases, a permanent decrease in nerve function is found. In our studies of FIAU given for 4 weeks, two patients complained of numbness or pains in the legs. However, these symptoms appeared several months after treatment and both patients had other reasons for having a neuropathy, so that we are not sure that these symptoms were due to the FIAU treatment. Because of the potential of this side effect, we are testing low dose of FIAU and are monitoring patients with nerve conduction tests. If you develop leg or arm pains, we will stop the FIAU and treat you with pain medications.

If you develop a severe side effect such as nerve and muscle pains, seizures, large decreases in the blood cell counts, or extreme fatigue, we will stop the FIAU. In addition, if you are a woman and become pregnant, FIAU will be stopped

BENEFITS

The benefits of participating in this study are the following:

(a) You will have a thorough medical evaluation of your condition.

(b) Your chronic hepatitis B may improve as a result of treatment.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84) NIH-2514-2 (10-84) P.A. 09-25-0099

CONFIDENTIAL

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient	continuation: 6 page ___ of ___ pages

STUDY NUMBER 93-DK-13

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records of National Institutes of Health or Clinical Center patients are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.

2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any physical injury resulting from your participation in research here. Neither the National Institutes of Health, Clinical Center nor the Federal government will provide long-term medical care or financial compensation for such injuries, except as may be provided through whatever remedies are normally available under law.

3. **Payments.** If you are a patient, you are not paid for taking part in National Institute of Health studies. Exceptions for volunteers will be guided by the National Institutes of Health or Clinical Center policies.

4. **Problems or Questions.** Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research, or with regard to any research-related injury, you should contact the principal investigator Dr. Jay H. Hoofnagle or these other staff members also involved in this study: Dr. Michael Fried, Dr. Adrian Di Bisceglie, Dr. Stephen Straus

Building 10, Room 9-C-1036, Telephone: (301) 402-3236
National Institutes of Health
Bethesda, Maryland 20205

5. **Consent Document.** It is suggested that you retain a copy of this document for your later reference and personal records.

COMPLETE APPROPRIATE ITEM BELOW, A or B:

A. Adult Patient's Consent.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient & Date Signed

B. Parent's Permission for Minor Patient.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s) & Date Signed

(If Other Than Parent, Specify Relationship)

Signature of Investigator & Date Signed

Signature of Witness & Date Signed

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY (Continuation Sheet)
• Adult Patient or • Parent, for Minor Patient
NIH-2514-1 (9-91)
P.A. 09-25-0099
Fwg in Section 4, Physician Consent

PPPA (UNIVERSITY OF TEXAS, GALVESTON)

IRB: 2/26/93

SUBJECT CONSENT

I have been asked to participate in a research study entitled "FIALURIDINE (FIAU): Pharmacokinetic/ Pharmacodynamic Dosing Regimen Study in Patients With Compensated Chronic Hepatitis B" under the supervision of Dr. David Paar and associates at The University of Texas Medical Branch at Galveston. I understand that The University of Texas Medical Branch is one of two centers in the United States where this study is being conducted.

PURPOSE OF STUDY

My doctor has explained to me that I have chronic hepatitis B. The purpose of this study is to determine whether two different doses of FIAU given at different intervals for 90 days are effective in reducing or eliminating the hepatitis B virus.

Fialuridine (LY303256, FIAU) is a new investigational anti-hepatitis B drug. My part in this study will last 17 to 29 months and will include 14 to 16 visits to my doctor. Approximately 35 other people will also be in this study. I will be followed for two years after I stop taking the medication if I benefit from the study drug or for one year after I stop taking the medication if tests do not show sufficient improvement.

QUALIFICATIONS:

I must have a pregnancy test prior to enrollment if I am a female of childbearing potential. My doctor has told me that I cannot be in this study or I may be discontinued after enrollment if I am or have any of the following:

- Pregnant;
- Breastfeeding an infant;
- Concurrent viral infection(s) (AIDS/HIV, hepatitis C, hepatitis D);
- Low blood count teats;
- Had antiviral, immunologic, or other investigational drug therapy within the last six months;
- Advanced cirrhosis on liver biopsy or significant liver disease other than hepatitis B;
- Any liver function tests that do not meet entry requirements;
- Abnormal kidney function;
- Abused alcohol or drugs within the preceding 6 months;
- Any significant underlying disease which, in the opinion of my doctor, could interfere with his determining the response of therapy;

STUDY PROCEDURE

I understand that while I am in this study I will not be allowed to take any immunologic therapy (e.g., corticosteroids or Imuran® (azathioprine), or other investigational drug therapy or antiviral (e.g., Intron® A (interferon-alpha-2b), acyclovir) riot used in the study. Only FIAU, a drug being investigated for treating patients with the hepatitis B virus will be given to me in this study. I will be assigned to one of six drug treatment groups. The medication is a syrup that I will take by mouth as instructed by my physician (at least one hour before eating or at least two hours after

eating) for the 90 days of treatment. My doctor will tell me how much syrup I should take. I will measure each dose amount of syrup with a syringe given to me with the study medication bottle(s).

I understand that my doctor has examined me to determine that my chronic hepatitis is the type that meets the entry requirements to enroll in this study. Approximately one week before I begin treatment, I will have a liver biopsy if I have not had a liver biopsy within the past six months and adequate tissue is available for analysis. I may have to remain at the hospital for approximately one day for this procedure at no cost to myself. Also my blood will be drawn for analysis. One of the blood tests will verify that I am not infected with the human immunodeficiency virus (HIV), which can cause AIDS. My doctor has explained the risks and benefits of the test for AIDS. Other blood tests will verify that I am not infected with the hepatitis C or D virus. Based on the results of my liver biopsy, I will have my study admission visit approximately seven days later. I will not eat after midnight until my admission visit the next morning. At or before the admission visit, chest x-rays, an ECG, my medical history, and current assessment of my symptoms will be obtained. In addition, if I am a female that can have children, I must have a negative pregnancy test (urine teat) before I may be enrolled in the study. Prior to receiving my first dose of study drug, my blood will again be drawn for analysis and I will provide a urine specimen. I will receive the first dose of study drug at the doctor's office, and blood will be drawn immediately before the dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 hours after the dose. In addition, I may have additional blood drawn at 12 and 24 hours after the dose depending on the treatment group to which I am assigned. Follow-up evaluations (laboratory and/or clinical) will be performed on Days 7, 14, 21, 28, Month 2, and Month 3. On Days 7, 14, and 21 my blood will be drawn right before my morning dose. I will take this dose at the doctor's office. The night before these visits, I will not eat after midnight until my visit the next morning. In addition, on Day 21, my blood will be drawn at the same times as on Day 1.

The Day 28, Month 2 and Month 3 visits will involve a physical examination, current assessment of my symptoms, blood test and a urine test, until I finish taking my study medication. I will then have a visit to the doctor's office every 3 months. One year after I have completed study drug therapy, I will have a liver biopsy; if my lab tests show that I have not benefited from the study drug, my physician will instruct me on when my next visit will be. Blood draws for each visit will require approximately 2-4 tablespoonfuls (30-60 ml) of blood. All evaluations and laboratory tests for this study will be free of charge.

I understand that during my dosing period, I will bring my study medication bottle(s) with any remaining syrup still in them to the doctor's office and give it to the person designated by the doctor for recording and collecting or reissuing.

If I am a female of childbearing potential, I understand that I should use adequate birth control (such as oral contraceptives, diaphragms with contraceptive jelly, cervical caps with contraceptive jelly, condoms with contraceptive foam, intrauterine devices (IUDs), Norplant®, or abstinence). If I am a male, my partner and I should use similar methods of birth control.

I also understand that my physician, or Eli Lilly and Company may stop my participation in the study at any time without my agreement. The FDA may also stop the study for safety reasons at any time without my agreement If I stop being in the study, I understand that further treatment of my infection, if needed, will be discussed with me by my physician.

BENEFITS

I understand that because I have chronic hepatitis B, an infection for which the new drug is being considered as therapy, I may benefit medically from being a part of this study; however, I may receive no benefit at all. If I do not receive personal benefit, society as a whole will have benefited from my participation as the questions of whether this is a useful drug will have been answered.

REIMBURSEMENT

I understand that I will receive $15.00 per clinic visit at the time of the visit while participating in the study up to a maximum of $300.00 for completion of the study. I understand that medical evaluations, laboratory tests, and study medications required by the study protocol will be provided free of charge.

POTENTIAL RISKS OF STUDY

I understand that there may be risks for me if I agree to be in this study. FIAU is a new investigational drug for chronic hepatitis B. Fifty-four patients with chronic hepatitis B have been treated with this medication for 14 to 28 days. In addition, 100 patients have been treated for up to eight weeks with FIAC, a similar drug that is converted into FIAU in humans. Both drugs appear to have similar side effects. These side effects include anemia (abnormally low number of red blood cells in the bloodstream), changes in laboratory tests that measure liver, kidney, and muscle function, stomach pain, nausea, vomiting, headache, fatigue, and muscle aches. These laboratory changes are expected to improve once the study drug is stopped. Changes in heart, muscle, sperm, and fetuses have been found in laboratory test animals given extremely high doses of FIAU and FIAC. Additionally, chromosomal changes have been detected in mice given high doses of FIAU. The effect of this in humans is unknown.

The major effects of liver biopsy are pain, fainting, bacteria in the blood, puncture of an internal organ (other than the liver), and bleeding. Local pain and discomfort at the liver biopsy site occurs in 1 out of 5 patients, is usually mild, and lasts 1 to 12 hours. Fainting and bacteria in the blood occur in 2% or less of the patients biopsied. Puncture of an internal organ other than the liver and internal bleeding are very rare.

In addition, I understand that blood samples will be obtained for laboratory measurement during the study. I will experience some minor discomfort when blood is being drawn from my vein. Bleeding, bruising, or infection may also occur at the needle site where blood samples are obtained. The amount of total blood withdrawn will be approximately 600 ml, or 20 ounces over the 2-year and 3-month period.

Drugs and procedures in this study may involve risks to me or an unborn child that are not yet known. I understand that I am to tell Dr. Paar at (409) 772-2222 immediately if I have any unusual health experience, injury, or bad effect.

The study medication must be taken only by me, and it should be kept out of the reach of children and other adults.

COMPENSATION FOR INJURY

I understand that if I am physically injured because of any substance given to me or procedure properly performed on me under the plan for this study, Eli Lilly and Company will reimburse me for the reasonable medical expense, a for the treatment of that injury which are not covered by my own insurance or health care program. No other compensation is available from Eli Lilly and Company if any injury occurs. I understand, however, that I am riot waiving any of my legal rights by participating in this study.

ALTERNATIVE THERAPIES

As an alternative to participation in this study, I understand that interferon is approved by the FDA for the treatment of chronic HBV infection. I understand that I could choose this drug rather than participate in this research study.

STATEMENTS

1. I understand that informed consent is required of all persons in this project.
2. The principal and alternative procedures, including the experimental procedures in this project, have been identified and explained to me in language that I can understand.
3. The risks and discomforts from the procedures have been explained to me.
4. The expected benefits from the procedures have been explained to me.
5. An offer has been made to answer any questions that I may have about these procedures. If I have any questions before, during or after this study, I may contact Dr. David Paar at (409) 772-2222.
6. I have been told that I may stop my participation in this project at any time without prejudice or jeopardizing my medical care at UTMB. All new findings developed during the course of this research which may influence my desire to continue to participate in this study will be provided to me as such information becomes available.
7. I have been told that The University of Texas Medical Branch at Galveston, like virtually all other universities in the United States, does not have a mechanism for compensation of the injured research subject. Therefore, I understand that I cannot look to any such mechanism to receive financial remuneration for any such injuries resulting from my participation in this project. If physical injury occurs as a direct result of this research, emergency treatment, which is available to the general public, will be available to me. Neither UTMB nor Dr. David Paar can assume financial responsibility or liability for the expense of such treatment.
8. If I have any questions regarding my rights as a patient participating in this study or research-related injury, I may contact Dr. E. Ray Stinson, Director of the Office of Sponsored Programs-Academic at (409) 772-3482.

9. I have a right to privacy, and all information that is obtained in connection with this study and that can be identified with me will remain confidential as far as possible within state and federal law. Information gained from this study that can be identified with me will be released to no one other than the investigators, my physician, Eli Lilly and Company (the sponsor), and the United States Food and Drug Administration, which through its regulatory powers, may inspect records involving research participants. The results of this study may be published in scientific journals without identifying me by name.

I voluntarily agree to participate as a subject in the above named project. I understand that by signing this document I am not waiving any of my legal rights. I have read or had read to me all pages of this consent form. The study and this consent form have been explained to me. My doctor has answered all of my questions to my satisfaction. I believe that I understand what will happen if I agree to be part of this study. I understand that the original copy of the document will be retained by Dr. Paar with the study records and that I will receive a signed copy of this form. A copy of the signed consent form will be sent to the sponsor.

March 15, 1993
Date

Signature of Subject

Subject Name (Printed)

I have witnessed the signing of this consent by the subject or patients or his or her parent or guardian whose signature appears hereon. I have been assured by that person that the signing of this consent has been done freely and voluntarily.

3-15-93
Date

Dave RN BSN
Signature of Witness

Using language that is understandable and appropriate, I have discussed this project and the items listed above with the subject and/or his/her authorized representatives. I have offered to answer any questions and have fully answered such questions. I believe that the patient, subject, or legal representative fully understands my explanation and has freely given informed consent.

3/15/93
Date

FIAU2.wpm
2-2-93

David Paar, M.D.
Signature of Project Director or
his/her Representative

Protocol: H3X-MC-PPPA
Investigator: David Paar, M.D.
Patient Number: 9082/21

PPPA (NEW ENGLAND MEDICAL CENTER, BOSTON)

NEW ENGLAND MEDICAL CENTER HOSPITAL DEPARTMENT OF MEDICINE, DIVISIONOF GASTROENTEROLOGY

FIALURIDINE(FIAU): PHARMACOKINETIC/PHARMACODYNAMIC DOSING REGIMEN STUDY IN PATIENTS WITH COMPENSATED CHRONIC HEPATITIS B PROTOCOL H3X-MC-PPPA

Principal Investigator:	Marshall M. Kaplan, MD
Co-Investigators:	David Greenblatt, KD
	Young Mee Lee, KD
	Minh Nguyen, MD
	Thomas Sepe, MD
	George Dickstein, MD
	Andrea Fribush, MD
	Daniel Pratt, MD
Study Coordinators:	Augusta McKusick, RNC, BS
	Marian Harvey, RN, BS

Purpose of Study:

You are invited to participate in a research study of a new investigational anti-hepatitis B drug, fialuridine (LY303256, FIAU). This drug has been used to treat chronic hepatitis B in 54 patients, for up to 28 days and has been well tolerated. However, it has had limited use in humans, and limited use for prolonged periods of time. Your part in this study will last 17 to 29 months and will include 14 to 16 visits to the doctor. Approximately 35 other people will also be in this study at this site and one other.

Your doctor has explained to you that you have chronic hepatitis B. The purpose of this study is to determine whether two different doses of FIAU given at different intervals for 90 days are effective in reducing or eliminating the hepatitis B virus. You will be followed for two years after you stop taking the medication if you benefit from the study drug or for 1 year after you stop taking the medication if tests do not show sufficient improvement.

FIAU is an oral (syrup) medication which is an antiviral medication acting to interrupt the virus's ability to reproduce itself. During this study you will not be allowed to take any immunologic therapy (e.g. corticosteroids or Imuran^{R} (azathioprine)), other investigational drug therapy or antiviral (e.g. Intron^{R} A (interferon alfa-25), acyclovir) not used in the study. Only FIAU, a drug being investigated For treating patients with hepatitis B virus will be given to you in this study.

Two different total daily doses of FIAU will be studied. (1) 0.1mg/Kg body weight daily and 2) 0.25 mg/Kg bony weight daily. In each of these two dose groups, there will be 3 subgroups - A) Patients who take all the daily dose ONCE A DAY; B) Patients who divide the total daily dose, taking it TWICE A DAY, and C) Patients who divide the total daily dose, taking it THREE TIMES. A DAY. Thus there are S possible dose/time schedules. You will be assigned randomly (that is by chance) to one of these 6 treatment groups. You will be instructed in how and when to take your specific dose. It should be taken on an empty stomach, at least one hour before eating, or at least 2 hours after eating.

Approved 2/26/93

Valid through 1/19/94

FIAU/HEPATITIS B
Marshall H. Kaplan, MD

Procedures to be Followed

You have previously been evaluated, and the results of your examination and laboratory values indicate that you have chronic hepatitis B, and you do meet all the entry requirements required to enroll in this study.

Approximately one week before beginning treatment, you will have a liven biopsy if you have not had a liver biopsy, that we can use, within the past year. A liver biopsy means that the skin on your right side will be numbed and a needle will be inserted to remove a small piece of liven tissue. You will be instructed in breathing techniques to make the procedure easier and safer. After the biopsy you will lie on your right side for several hours You will have to remain at the hospital for approximately one day for this procedure. Also your blood will be drawn for analysis. One of the blood tests will verify that you are not infected with the human immunodeficiency virus (HIV), which can cause AIDS. A separate consent form will be signed permitting us to test you for HIV. Your doctor has explained the risks and benefits of the test for AIDS. other blood tests will verify that you are not infected with hepatitis C or D virus. Based on the results of your liver biopsy, you will be enrolled in the study at a visit approximately seven days later. You will not eat after dinner on the day before your admission visit and will not have breakfast until after you are seen the next morning. At the admission visit, chest x-rays, a EKG, your medical history, and current assessment of your symptoms will be obtained. In addition, if you are a female capable of having children, you must have a negative pregnancy test (urine test) before you may be enrolled in the study. Prior to receiving your first dose of study drug, your blood will be drawn for analysis and you will provide a urine specimen. You will receive the first dose of study drug at the hospital and blood will be drawn immediately before the dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 hours after the dose. In addition, you may have additional blood drawn at 12 and 24 hours after the dose depending on the treatment group to which you are assigned. Follow-up evaluations (laboratory and/or clinical) will occur on Day 7, 14 and 21 of your treatment period. On Day 7 and Day 14, your blood will be drawn right before your morning dose. The night before these visits, you will not eat after dinner until your visit the next morning.

At your Day 21 visit, you will take your morning dose of study drug at the hospital and your blood will be drawn immediately before the dose and after the dose at the same intervals as your first visit. After you have taken one month of study drug therapy, you will begin monthly visits to the hospital. You will continue the monthly visits, which will involve a physical examination, current assessment of your symptoms, blood tests and a urine test, until you finish taking your study medication. You will then have a visit to the hospital every a months.

One year after you have completed study drug therapy, you will have a liver biopsy, if your lab tests show that you have benefitted from the drug and you will continue to see the physician every six months for one more year. If your lab tests show that you have not benefitted from the study drug, your physician will instruct you on when your next visit, will be. Blood draws for each visit will require approximately 2-4 tablespoonsful (30-60 ml) of blood. All evaluations and laboratory tests for this study will be free of charge.

Approved 2/26/93

FIAU/HEPATITIS B
Marshall M. Kaplan, MD

During your dosing period, the first 3 months in the study, you will bring your study medication bottle)s) with any remaining syrup still in them to the hospital and give it to the person designated by the doctor for recording and collecting or reissuing drug. You rill be given a flow sheet of your specific appointments, dates and instructions.

Risks and Possible Side Effects

There may be risks for you if you agree to be in this study. FIAT is a new investigational drug taken for 14 to 28 days by 54 patients with chronic hepatitis B. An additional 100 patients have been treated for up to 8 weeks with a similar drug, FIAC that is turned into FIAU in humans. Both drugs appear to have similar side effects, These side effects are primarily nausea and fatigue but may include stomach pain, vomiting, headache, and muscle aches. Changes in laboratory tests that measure liver, kidney, and muscle function, and anemia have also occurred. These laboratory changes are expected to improve, once the study drug is stopped. In laboratory test animals given extremely high doses (much higher than in this-study), changes in heart muscle with nonreversible toxicity, skeletal muscle, the formation and production of sperm, fetal development and kidney toxicity have been found. Additionally, chromosomal changes have been detected in mice given high, doses of FIAU. The effect of this in humans is unknown. Because this drug may penetrate the skin and become incorporated into your genetics material, you should use caution in handling the medication and wash thoroughly with soap and water should it come in contact with your skin.

The major effects of liver biopsy are pain, fainting, bacteria in the blood, puncture of an internal organ (other than the liver), and bleeding. Local pain and discomfort at the liver biopsy site occurs in 1 out of 5 patients, is usually mild, and lasts 1 to 12 hours. Fainting and bacteria in the blood occur in 2% or less of the patients biopsied, Puncture and bleeding are very rare.

In the event that your blood tests suggest damage to muscle, you may be asked to have a thigh muscle biopsy. This will be done under local anesthesia at no expense to you. This procedure may cause temporary discomfort at the biopsy site.

Some minor discomfort is caused when blood is drawn from my vein. Bleeding, bruising or infection may also occur at the site where blood samples are obtained.

In addition to these effects, other unpredictable bad effects due to the study drug or test procedures may occur.

If you should have an adverse effect any time during the study, you should tell your doctor immediately. Any new significant information developed during the course of this research which may change your wish to continue in this study will be provided to you and to the doctor.

Approved 2/26/93
Valid through 1/19/94

FIAU/HEPATITIS B
Marshall M. Kaplan, MD

For Men and Women of Childbearing Potential:

The medication used in this research study may involve risks to you or to an embryo or fetus if you are pregnant at any time during the study. If you are pregnant or should you intend to become pregnant, you should not be enrolled in this study. Males should also not father a child while in this study. If you choose to participate, you must use adequate birth control to prevent pregnancy during this study, while you are on study medication and for 3 months after the study medication has stopped (up to a total of S months). Adequate methods of contraception include birth control pills, diaphragms, or cervical caps, used with contraceptive jelly, condoms with contraceptive foam, IUD's (intrauterine devices), NorplantR, or abstinence. Should you become pregnant at any time during this time frame, you must immediately notify your physician, and your participation in the study will be terminated. A pregnancy test will be performed prior to your enrollment in the study.

Benefits

It is not known whether you will benefit from this study or not.

Because you have chronic hepatitis B, an infection for which the new drug. is being considered as therapy, you may medically benefit by the partial or complete healing of your infection. The study may also be of benefit to other patients with this type of infection in the future.

Other Treatment

As an alternative to participation in this study, you may be treats with interferon. You understand that you could choose this drug rather than participate in this research study. Therapy for chronic hepatitis B is limited. Only interferon-alpha-2b (Intron-A) is approved in the United States for the treatment of hepatitis B. You understand that you could choose this therapy rather than participate in this research study.

Costs

While you are enrolled in the study, during the medication phase (90 days) and the follow up period (up to 2 years after medication) and during the one week pretreatment phase, all laboratory tests, hospital, outpatient clinic and physician charges will be provided to you at no cost. In addition all study medication will be provided to you at no cost to you or your insurance carrier.

Phone Numbers

If you have any questions or problems during this study, you may call Dr. Marshall Kaplan at (617)-956-5877. Either he or an associate will be available to answer your questions. You may contact the GI Office of Clinical Trials at (617)-956-4532, either study nurse may also he of assistance. In the event of an emergency, call (617)—956—5114 and ask for the "GI Physician on Call" and explain to the physician that you are a part of this study.

Approved 2/26/93

Valid through 1/19/94

FIAU/HEPATITIS B
Marshall M. Kaplan, MD

PARTICIPANT'S STATEMENT

I have read this consent form and have discussed with Dr. Marshall Kaplan or his representative the procedures described above. I have beer give the opportunity to ask questions, which have been answered to my satisfaction. I understand that any questions that I might have will be answered verbally or, if I prefer, with a written statement.

I understand that I will be informed of any new findings developed during the course of this research study.

I understand that my participation is voluntary. I understand that I may refuse to participate in this study. I also understand that if, for as reason, I wish to discontinue my participation in this study at any time. I will be free to do so, and this will have no effect on my future care or treatment by my physicians or this hospital.

I understand that in the event I become ill or am injured as a result of my participation in this study, medical care will be provided to me. If follow the directions of the doctors in charge of this study and I become ill or am injured because of the study drug or because of a properly performed study procedure, Eli Lilly and Company, the sponsor, will pay the medical expenses for the treatment of the injury or illness which are not covered by my medical insurance. I understand that no other compensation for such injury or illness ocher than for medical treatment will be provided.

If I have any questions concerning my rights as a research subject in this study, I may contact the Human Investigation Review Committee at (617)-956-7512.

I have been fully informed of the above-described study with its risks and benefits, and I hereby consent to the procedures set forth above. A copy of my signed consent will be reviewed by a representative of Eli Lilly and Company and I will receive a copy.

I understand that as a participant in this study my identity and my medical records and data relating to this research study will be kept confidential, except as required by law, and except for inspections by the U.S. food and Drug Administration which regulates investigational drug studies, and the study sponsor.

Approved 2/26/93
Valid through 1/19/94

PPPG

Fialuridine (LY303256): Bioequivalence of Syrup and Tablet Formulations, and Influence of Timing of Meals on Pharmacokinetic Variables

Informed Consent Document

INTRODUCTION

You are invited to take part in a research study of an investigational drug for the treatment of hepatitis B (viral liver infection) known as fialuridine (FIAU, LY303256). We plan to study up to 22 volunteers. Your participation in this study is expected to last up to 4 weeks.

PURPOSE

The purposes of this study are to determine how your body handles a syrup form and two tablet forms of FIAU, and to determine the influence of food on how your body handles FIAU.

PROCEDURES

Before entering the study you were interviewed by a physician who asked about your medical history and completed a general physical examination. In addition, you have had blood and urine tests done, a heart tracing performed, and may have had a chest x-ray performed if you had not had one within the last six months. Based upon these tests you are being invited to participate in this study.

Your participation in this study will require that you be admitted to the Lilly Clinic. You will receive five single doses of FIAU on five separate dosing days, with each dose being given at approximately 8 AM. Each dose of FIAU will be separated by 3 to 7 days without dosing. Each dose will be 5 mg of FIAU, either as a single 5 mg tablet, as five 1 mg tablets, or as I teaspoonful of syrup. On three of the dosing days you will receive one of these dose forms following an overnight fast and will continue to fast for 4 hours after receiving the dose. The total fasting time is up to fifteen hours. On one dosing day you will receive the 5 mg tablet following an overnight fast and immediately before a

standard breakfast, and on one dosing day you will receive the 5 mg tablet following an overnight fast and at some time between 1 hour before and 2 hours after a standard breakfast.

You will not smoke, or drink caffeine-containing beverages during the study. You will not take any medications (except for an occasional pain medicine) during the study period.

Prior to the start of dosing a blood sample will be obtained. On each dosing day approximately 12 blood specimens will be drawn. A blood specimen for safety analysis will be obtained the day after each dose of FIAU. The total volume of blood collected from you during the study will be about 517 ml, which is about one pint.

RISKS

You understand that there may be risks for your being in this study.

FIAU is a new investigational drug taken for 14 to 28 days by 54 patients with chronic hepatitis B. An additional 100 patients have been treated for up to 8 weeks with a similar drug, FIAC, that is turned into FIAU in humans. Both drugs appear to have similar side effects. These side effects include stomach pain, diarrhea, nausea, vomiting, headache, and muscle aches or fatigue. Changes in laboratory test values that measure liver, kidney, and muscle function, and anemia (low blood count) have also occurred. These laboratory changes are expected to improve, once the study drug is stopped. In addition, laboratory test animals given extremely high doses of FIAU by mouth (3,500 times more than the dose planned for this study, adjusted for different animal weights) have shown decreased sperm production, and animals given extremely high doses directly into their veins (7,000 to 14,000 times more than the dose planned for this study, adjusted for different animal weights) have shown heart muscle damage.

Needle punctures for blood draws are usually well-tolerated by most people. However, they may cause bleeding, bruising, discomfort, infections and/or pain at the needle site and dizziness.

In addition to these effects, fialuridine (FIAU, LY303256), or the procedures in this study, may have other unknown effects. In case you have any bad effects, make sure that you immediately tell the nurses or Dr. Hyslop at the Lilly Clinic at 276-4757.

You should not participate in this study if you have:

- Concurrent viral infection(s) (AIDS/HIV, hepatitis C, hepatitis D).
- Low blood count tests.
- Received medical therapy for viral infections such as AIDS or hepatitis, including therapy with drugs under investigation as treatment for these infections, within the last six months. Such treatment could include drugs such as zidovudine, didanosine, zalcitabine, and interferon.
- Advanced cirrhosis on liver biopsy or significant liver disease.
- Abused alcohol or drugs within the preceding 6 months.

VOLUNTARY PARTICIPATION

Your taking part in this study is entirely voluntary. You may refuse to take part in the study or you may quit the study at any time without a penalty or loss of benefits to which you were entitled before taking part in the study. If you decide to stop being part of this study, Dr. Hyslop will talk to you about the process for stopping and the medical consequences of your making this choice. Dr. Hyslop or Eli Lilly and Company (the sponsor of this study) may stop this study, or your being a part of it at any time without your consent.

TREATMENT AND COMPENSATION FOR INJURY

If you follow the directions of the doctor in charge of this study and you are physically injured due to any substance or procedure given during your participation in this study, Eli Lilly and Company will decide either to provide treatment for the injury, or to pay for

those medical costs that are not covered by your medical insurance. Eli Lilly and Company does not agree to pay any additional money for injury. For further information about compensation or treatment available if injury occurs, contact Dr. Hyslop at 276-4757.

BENEFITS

You will be paid for taking part in this study. Since you do not have any of the conditions for which this drug is being developed, you will not medically benefit from being a part of this study. However, information obtained from the study will be of benefit to Eli Lilly and Company and may benefit patients in the future.

QUESTIONS

If you have any questions about this study or your rights, please contact Dr. Hyslop at 276-4757. If any important new information is found during this study that may affect your wanting to continue to be part of this study, you will be told about it.

CONFIDENTIALITY

If you agree to participate in this study, the information obtained will be shared with Eli Lilly and Company, the United States Food and Drug Administration, and similar agencies in other countries, all of whom may look at your medical records. Medical records that contain your identity will be treated as confidential by Eli Lilly and Company and will be shared only with these agencies or as required by law.

This informed consent has been read to me and all my questions have been answered to my satisfaction. I voluntarily agree to be part of this research study. I am between the ages of 21 and 55 years of age inclusive and as far as I know, am healthy.

I understand that I may freely stop being a part of this study at any time.

I have received a copy of this informed consent form to keep for myself. I understand that a copy of this form will also be retained by Eli Lilly and Company.

Volunteer's Name: _____

Volunteer's Signature: _____

Witness (Investigator): _____

Witness (Other): _____

Date: _____

Time: _____

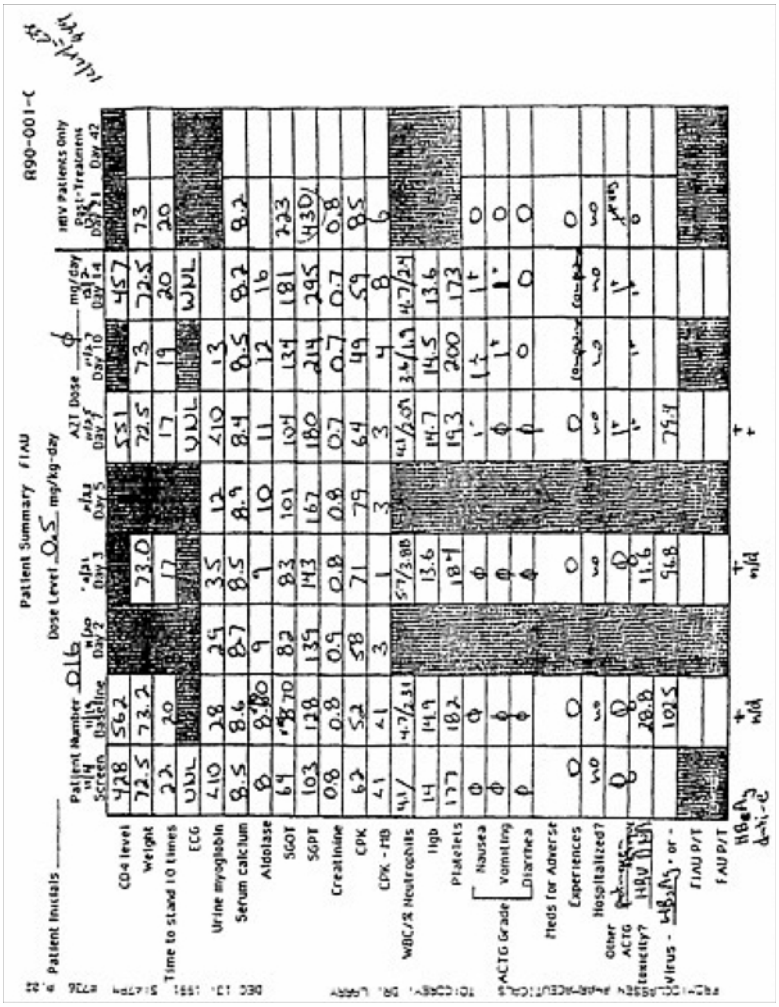
You will be paid $25.00 for each day you participate in this study. In addition, if you satisfactorily complete your part in this study, you will receive an additional payment (Satisfactory Completion Payment) calculated at the rate of $15.00 for each day of your participation.

Estimated Payment Schedule (calculated for 27 days total participation)

Hospital stay - 27 days x $25.00/day =	$ 675.00
Satisfactory Completion Payment =	$ 405.00
TOTAL PAYMENT =	$1080.00

E

Example of Oclassen Fax Data Summaries



F

FIAC and FIAU Preclinical Toxicity Studies

FIAC ACUTE TOXICITY STUDIES

The acute intravenous lethal dose (LD50) of FIAC is reported to range from 500 to 1,000 mg/kg in mice, rats and monkeys. Cardiotoxicity was observed at dosages greater than 500 mg/kg in rats.

Multiple Dose Studies

Mice were treated for 5 days with 500 or 1,000 mg/kg/day, administered intraperitoneally. Half of the animals given 1,000 mg/kg/day died; decreased body weight gain was observed at 500 mg/kg/day. A similar study was performed in rats with analogous results. Cardiotoxicity was observed in rats following 1,000 mg/kg/day.

Dogs were intravenously treated (24, 48 mg/kg/day) with FIAC for 10 days. Decreased food intake, weight loss, intestinal changes and hematopoietic depression were noted at 48 mg/kg/day.

Mutagenicity Studies

FIAC is reported to be devoid of mutagenic activity in an Ames test study.

Comments

FIAC preclinical evaluation studies are not extensive, since interest in this substance waned early. The limited information, however, is of interest since FIAU is reported to be a metabolic product of FIAC. Qualitatively speaking, the studies indicate that the toxic effects of FIAC reported in different laboratory animal species are similar to those obtained with FIAU.

FIAU ACUTE TOXICITY STUDIES

After a period of observation of 14 days, the lethal dose after a single oral administration in male rats was estimated to be greater than 3,000 mg/kg. Blood from rats receiving 3,000 mg/kg was analyzed for alanine aminotransferase activity (ALT), hemoglobin concentration, and urea nitrogen concentration up to 1 week post-treatment; all parameters were found to be in the normal range. In addition various clinical signs were also normal.

A limited single-dose oral study was conducted in cynomolgus monkeys (1 animal per dose level) with dosages of 50, 250, or 500 mg/kg. The animals were observed for 14 days. Slight to mild elevations in alanine aminotransferase activity were observed in animals given micronized or nonmicronized material (50 and 250 mg/kg) but not in the 3 monkeys treated with lyophilized material at 25, 250, or 500 mg/kg.

After a single intravenous administration (10 males, 10 females per group) and a period of observation of 14 days, the lethal dose in mice was estimated to be between 600 and 1,000 mg/kg; in rats (10 males, 10 females per group), between 500 and 800 mg/kg; in monkeys, between 1,000 and 1500 mg/kg. In rats and monkey, only cardiotoxicity (myocardial degeneration) was observed.

Multiple Dose Studies

Rats (4 males per group) were treated with oral dosages of 1,000-1,500 mg/kg per day for 7 days. No clinical signs of toxicity were observed. Furthermore, no changes in clinicopathology (differential blood counts, alanine aminotransferase activity, urea nitrogen concentration) were detected on days 4 and 7. After intravenous injection (500-750 mg/kg), deaths (3/4) occurred between days 1 and 4 at 600 and 750 mg/kg. Some clinicopathology was observed in the surviving animals on days 4 and 7 (decreased erythrocytes, leukocytosis, lymphocytosis). Changes in alanine aminotransferase or urea nitrogen concentration were not seen.

A 1-month subchronic study was performed in cynomolgus monkeys, where 3 or 4 animals per dose level, treated orally twice daily, received 5, 20, or 80 mg/kg/day. Three of four 80-mg/kg/day animals were moribund and sacrificed on days 23, 25, and 27; clinical signs of toxicity included weight loss, diarrhea, hypoactivity, and hypothermia. Stomach erosion and ulceration, as well as hypocellularity of the bone marrow were observed. A decline in white cell counts, decreased uterine weight, and thymus weights were described. At 5 mg/kg/day, no consistent or apparent treatment-related changes were found.

In mice (160 mice total), oral treatment with daily dosages of 10, 50, or 250 mg/kg/day for 90 days yielded no adverse effects at 10 or 50 mg/kg/day. At 250 mg/kg/day, 4/50 mice died; renal toxicity was noted, as well as lesions in the testes. No tissue lesions were observed in the 10 mg/kg/day group.

Rats (15 males, 15 females per group) were intravenously treated with 10, 25, 50, 250, or 500 mg/kg/day, daily for 1 month. Five of 30 rats given the highest dose died between day 5 and 13. Significantly lower body weight gains were observed at 250 and 500 mg/kg/day. No significant drug-related clinical pathological changes were observed, except for a decreased

leukocyte and reticulocyte count in 1 male rat in the high dose group. Tissue signs indicative of cardiotoxicity were found in the high dose group. The spleen was affected at dosages of 50 mg/kg/day or higher; reduction in nucleated cells in the bone marrow, reduced spermatogenesis, and tubular alterations in the seminiferous tubules occurred at the high dose. Lymphoid and hematopoietic tissues recovered after a 6-week recovery period, while the cardiotoxicity was irreversible. No effects were observed at 10 or 25 mg/kg/day.

A pilot multiple dose study was performed in cynomolgus monkeys, where 1 animal per dose level received 300, 400, or 500 mg/kg daily orally for 7 days. Body weight losses were observed. A slight decrease in hemoglobin and erythrocyte count was seen on day 7 in monkeys treated with 300 and 500 mg/kg/day; slight to moderate elevations in alanine aminotransferase were noted on day 4 in the monkey treated with 300 mg/kg/day and on days 3 and 7 in the animal treated with 500 mg/kg/day.

A limited study was performed in dogs, where the animals were treated for 10 days orally or intravenously with dosages ranging from 5-25 mg/kg; the lethal dose was estimated to be 14 mg/kg/day. Hematopoietic depression, damage to the intestinal mucosa, and decreased spermatogenesis were observed.

A 1-month intravenous study (3 males, 3 females per group) was performed in cynomolgus monkeys, using dosages of 25, 75, or 150 mg/kg/day. With the high dose, 5/6 animals died; 1/6 died at the intermediate dosage level. Body weight losses were observed at all dosage levels. On days 8, 29, and 71, hematologic and serum chemical measurements were obtained; urinalysis was performed on days 29 and 71. Suppression of the hematopoietic tissues occurred in a dose-related manner, being prominent at 150 mg/kg/day and absent at 25 mg/kg/day. At the highest dose, elevated urea nitrogen concentrations were obtained; these were reversible after a 6-week recovery period. Gross examination of organs and tissues revealed marked atrophy of the thymus and watery or gelatinous bone marrow in the high dose animals that died. Drug-related histological changes were observed mostly in the high dose and some of the intermediate-dose groups; these included hematopoietic changes, vacuolation and presence of pigment in hepatocytes, renal cortical tubular dilatation, cytostatic enteropathy of the large intestine and acinar cell atrophy in the salivary gland, giant cell formations in the testes, and myocardial degeneration. All, except the heart, were considered reversible. No changes were observed in the low-dose animals.

Chronic Study

Mice (20 males, 20 females per group) were treated daily with oral doses of FIAU for 6 months (10, 50, or 150 mg/kg/day), followed by a 1-month reversibility period. At 150 mg/kg, nephropathy was observed in both males and females; testicular toxicity (decreased weight, hypospermatogenesis) was observed in males; 2/20 male mice died, while 10/20 females died. Decreased lymphocytes were observed in female mice given 150 mg/kg; slightly elevated alanine aminotransferase and aspartate transaminase was seen in male mice, but no histological correlates were noted. Kidney lesions were inconsistently observed in female mice at 50 mg/kg. No effects were seen in either sex at 10 mg/kg/day.

Mutagenicity Studies

FIAU was assessed for possible mutagenic effects in 7 different in vitro tests (4 Ames tests; mouse lymphoma assay; forward mutation Chinese hamster ovary cells; chromosome aberrations in Chinese hamster ovary cells). The compound was devoid of mutagenic activity in these studies, except for a positive induction of chromosomal aberrations in CHO cells. FIAU was considered active in the in vitro neoplastic transformation assay. In vivo, FIAU was tested for its ability to induce micronuclei in bone marrow of mice and rats. With large oral dosages (1,000 or 2,000 mg/kg), the agent was considered positive in mice, but not in rats.

The battery of mutagenicity studies performed indicate that FIAU was negative in many tests, but at high dosages could modify a few specific parameters. This finding is not unusual, considering the biological characteristics of the agent.

Reproduction Studies

Male rats were orally treated daily (25, 100, or 350 mg/kg/day) with FIAU for 2 weeks, followed by a 2-week recovery period. At the two higher dosages, depression of food consumption and body weight gain were observed, but no apparent adverse effects on sperm production, sperm quality, mating performance, or fertility occurred in this study.

The potential to produce developmental toxicity was evaluated in rabbits at dosages of 2, 10, or 50 mg/kg/day on gestation days 6-18. A red discharge of unknown origin was noted with several animals in the high dose group, 2 rabbits in the high dose group aborted. With 10 and 50 mg/kg/day, body weight gain was diminished but food consumption was not affected. Fetal viability was depressed at all dosages. Fetal malformations were observed at all doses, and fetal weight was depressed at 50 mg/kg/day. It was concluded that FIAU was toxic to the developing embryo.

Male mice were treated with the agent for 2 weeks (10, 50, 250 mg/kg/day) before cohabitation with females. Females were treated for 2 weeks before cohabitation and until gestation day 17. With 250 mg/kg/day, 2 mice died as a result of treatment. Mating index was slightly diminished at 250 mg/kg. Hypospermatogenesis occurred in all male mice treated with 250 mg/kg, whereas slight effects were seen at 50 mg/kg. Nephropathy was noted in 4 male mice at 250 mg/kg and in 1 male at 50 mg/kg; 5/25 females given 250 mg/kg and 2/25 given 50 mg/kg developed nephropathy. Fetal growth retardation occurred in the groups treated with 50 or 250 mg/kg/day.

Comments

The preclinical toxicity studies conducted in different species prior to the start of the last PPPC clinical trial indicate that, indeed, the nucleoside FIAU can cause severe toxic effects when administered in large dosages. The major effects include: myocardial degeneration, suppression of the hematopoietic tissues, reduction in spermatogenesis, and nephropathy. Most of the effects, except the cardiotoxicity, were reversible when the animals were observed for

an extended post-treatment period. It is noteworthy, however, that while mild excursions in serum alanine or aspartate aminotransferase activity were observed in some studies, no corresponding morphologic hepatic changes were reported. Furthermore, no mention of pancreatic changes are noted in the reports.

The preclinical toxicity data available prior to the PPPC clinical trial was judged to be adequate by the Food and Drug Administration, and, therefore, the clinical trial could proceed as planned. A retrospective evaluation of the material available in 1993 still supports this position. The acute and multiple dose studies performed in different laboratory animals (mice, rats, dogs, and monkeys), a chronic study in one species (mice), a battery of mutagenicity studies, and studies on reproduction yielded patterns of observations that were more or less consistent with the biologic characteristics of FIAU. Furthermore, dose-dependent relationships were generally clear, and the toxic effects usually occurred at dosages near the maximum tolerated range in each species. There was nothing in the preclinical toxicity studies that was suggestive of the tragic episode that transpired in the PPPC clinical trial. Furthermore, unfortunately, there is nothing to indicate that other laboratory animal studies would have been more appropriate or capable of better prediction of the fatal outcome.

G

Patient Summaries, Lilly Trial H3X-MC-PPPA

UNIVERSITY OF TEXAS GALVESTON SITY

Three patients were treated at the Galveston study center (patients 21-23). Patient 21 is a 42-year-old man with known chronic HBV infection since 1990. His only symptoms were persistent fatigue. He had previously undergone a 6-month course of interferon therapy which failed to clear his infection. During the final week of interferon therapy he had a grand mal seizure, for which he has since taken phenytoin. At entry into the PPPA trial physical examination and chest radiograph were normal; screening labs met study requirements. He had a liver biopsy on April 16, 1993, which showed a lymphocytic portal infiltrate but no piecemeal necrosis, fatty metamorphosis or cirrhosis. Treatment with FIAU was started on May 14, 1993, at a dose of 0.05 mg/kg bid. At study entry AST (27 U/L) and ALT (41 U/L) were in the normal range, but serum HBV DNA was 2,752 pg/mL. On his 21st day of FIAU he had 2 tonic seizures, and FIAU was discontinued for 5 days because of concern that they may have been FIAU related. When phenytoin levels were found to be subtherapeutic, his dose was increased to provide adequate levels, and no further seizures occurred. At the time of his 5th weekly study visit on June 18 he complained of fatigue that interfered with his daily activities (attributed by the patient to the increased dosage of phenytoin). On June 26 FIAU was discontinued because of suspected toxicity at another study site.

During the 43 days of FIAU therapy there was some evidence of a therapeutic response with a drop of serum HBV from 2752 to 916 pg/ml. During the trial the AST levels remained normal (25-28 U/L) as did the ALT levels (38-42 U/L). Because of the toxicity in patients at another study site the patient had repeated transaminase measurements at intervals of 1-2 weeks (for the next 2 months) and then at monthly intervals for 4 more months (last measurement on January 12, 1994). Five days after discontinuing FIAU his serum HBV DNA level rose to 1,722 pg/ml, and thereafter remained between 1,399 and 4,486 pg/ml. AST levels repeatedly ranged from 25-30 U/L and ALT likewise remained in the normal range. Lactate levels, performed at weekly intervals during the 2 months following cessation of therapy with FIAU, were always in the 1.0-1.9 mmole/L range, (normal 0.3-2.6 mmole/L). He had no complaints (other than maxillary sinusitis in Nov. 1993) and his physical examinations remained unremarkable. A biceps muscle biopsy to assess subclinical FIAU myopathy was normal by light microscopy and histochemical staining of mitochondria.

Patient 22 is a 37-year-old man with HBV infection, known since 1988. His only complaints were mild fatigue and arthralgias. He had known about interferon but had been unwilling to undergo that type of therapy. Physical examination was unremarkable except for spider angiomata on his upper back and over both deltoid areas. Chest radiograph was normal,

and screening laboratories met the study criteria. A pre-study liver biopsy as showed a lymphoplasmacytic infiltrate, piecemeal necrosis and prominent focal portal fibrosis. At the time of starting FIAU (0.125 mg/kg p.o. bid) on June 8, 1993, the level of serum HBV DNA was 3715 pg/ml, and liver function tests showed an AST level of 76 and an ALT of 115. On June 15, his second study visit, his only complaints were of a metallic taste in his mouth which he attributed to FIAU, and persistent pain at the site of liver biopsy done 2 weeks earlier (the latter improved over the next week). Serum HBV DNA was 1,981 pg/ml, and AST and ALT were essentially unchanged. On June 22, after 2 weeks of FIAU, his HBV DNA level had dropped to 904 pg/mL, and AST and ALT were 81 and 114 U/L, respectively. FIAU was discontinued on June 27 because of the events at NIH.

Following cessation of FIAU he was followed with weekly visits for the next 2 months, monthly visits for the next 4 months, and at trimonthly intervals thereafter (last recorded visit October 31, 1994). During the first 2 months of follow-up the HBV DNA levels progressively fell to < 0.7 pg/ml. He felt well and his level of fatigue returned to what it had been before taking FIAU. There were no symptoms of peripheral neuropathy. During this period his only findings on examination were mild hepatic tenderness which cleared in 3 weeks. AST and ALT levels, which had reached 95 and 135 U/L, respectively, at the time of drug cessation, subsequently declined to 31 and 35 U by 2 months later. Follow-up included lactate determinations, which were always within the normal range. During long term (2-14 mos. after discontinuance of FIAU) follow-up, HBV DNA remained ≤ 2.2 pg/ml for 5 months, but at 8 months and at 10 months had reached levels of 4,057 and 229 pg/ml, respectively. AST (22-49 U/L) and ALT (21-66 U/L) remained in the normal range. At the most recent (October 31, 1994) follow-up visit he complained of a few episodes of nausea, and he was referred for consideration of interferon therapy.

Patient 23 is a 62-year-old man whose chronic HBV infection followed a blood transfusion in 1985. His only symptoms possibly referable to HBV infection were pruritus and early morning nausea. He had a history of coronary artery bypass surgery, performed in 1981 and 1985. His medications consisted of oral propranolol and diltiazem. Physical examination was unremarkable. Chest radiograph showed a slightly enlarged heart. Screening laboratory testing met study criteria. Liver biopsy had been performed earlier (February 15, 1993) and revealed a chronic portal inflammatory infiltrate, focal piecemeal necrosis, fatty metamorphosis and portal fibrosis (without overt cirrhosis).

At the time (June 10, 1993) of starting FIAU (0.125 mg/kg p.o. bid) the serum HBV level was at 4,736 pg/ml, and the AST and ALT levels were mildly elevated at 95 and 169 U/L, respectively. A week later, at his second study visit, he complained of early morning nausea (which he considered probably his baseline) for which compazine was prescribed. At that visit the serum HBV DNA level had dropped to 228 pg/ml and the AST and ALT levels had risen to 146 and 230 U/L, respectively. On the 3rd study visit (June 24) he had no complaints and had taken compazine on only 3 separate occasions. HBV DNA was 106 pg/ml; AST had almost doubled (179 U/L) and ALT was similarly elevated (288 U/L). Two days later, FIAU was discontinued, after a total of 16 days, again because of the serious toxicity noted at another study site.

Nine days after stopping FIAU (July 6) he complained of several days of nausea (more than his baseline) and of lower extremity weakness. He was admitted to the hospital for

evaluation (July 6-9). General physical and neurological examinations were unremarkable. AST was 124 U/L (normal range by impatient testing, 13-40 U/L) and ALT 252 (impatient normal range, 9-51 U/L). Lactate level was 1.1 mmol/L (normal 0.3-2.6). Electromyography and nerve conduction studies were normal. Symptoms improved and he was discharged.

Over the next 2 months he was seen at follow-up at weekly intervals initially and then at 2 week intervals. A muscle biopsy was normal. HBV DNA started to rise (173 pg/mL) on July 1, reaching a peak of 750 pg/ml on August 24. AST was in the 62-83 U/mL range (outpatient testing normal, 10-78 U/mL), and ALT was in the 100-144 U/L range (outpatient testing normal, 5-95 U/mL). Lactate levels remained in the normal range. The next month (September 29), 3 months after discontinuing treatment, he had some intermittent epigastric pains for which he took antacids. No other complaints were noted and his examination was unremarkable. AST had risen to 250 U/L and ALT had risen to 333.

On January 2, 1994, 6 months after cessation of FIAU, he was admitted to another hospital because of abdominal pain. A laparoscopic cholecystectomy was performed the following day after ultrasound demonstration of gallbladder sludge and thickening of the gallbladder wall and some ascites. Cholangiogram showed no stones and histologic examination of the gallbladder showed chronic cholecystitis.

On January 27, 7 months after FIAU was stopped, he was again seen in follow-up. He was jaundiced, weak, and orthopneic, and ascites was present on physical examination. HBV DNA level was 50 pg/ml; AST 353 U/L; and ALT was 222. During hospital admission (January 31-February 12) therapeutic paracentesis showed fluid that was unremarkable. PT was 14.8 seconds; total bilirubin was 3.3 mg/dl, coming down to 2.0 mg/dl; AST and ALT were 408 and 262 U/L, coming down to 270 and 206, respectively, by the time of discharge. Abdominal CT showed ascites and a normal pancreas, but the serum amylase rose from 129 U/L (normal, 35-110) to 272 U/L at the time of discharge. Liver biopsy showed cirrhosis (mixed micro-macronodular pattern), slight microdroplet steatosis (amount of microdroplet steatosis considered nonspecific), and moderately active chronic active HBV hepatitis.

During March-April the patient was followed as an outpatient continuing on diuretic therapy (spironolactone and furosemide) with control of his ascites and requiring only one further paracentesis. On his most recent follow-up (September 8, 1994) he was feeling well, and laboratory test results had not yet returned.

TUFTS NEW ENGLAND MEDICAL CENTER SITE

The first patient treated with FIAU at Tufts New England Medical Center is a 38 year old man with a past history of alcohol and parenteral drug abuse; his chronic compensated HBV hepatitis was diagnosed in 1990. Liver biopsy one week before starting FIAU showed chronic active hepatitis (focal inflammatory infiltrate as well as piecemeal necrosis and bridging). Secondary conditions included migraine, anxiety and depression. Treatment with FIAU (0.10 mg/kg/day in 2 divided doses) was begun on June 1, 1993 and continued through

June 28, (trial termination), for a total of 191 mg. Serum HBV DNA[1] at study entry was 232 Eq/mL x 10^6 and over the next 4 weeks the level steadily dropped to 12 Eq/ml x 10^6 remaining at about this level over the next two months. Symptoms reported by the patient during the 4 weeks of treatment included: mild chills and myalgias for 24 hours on the second day of treatment; moderate diarrhea on the 10th to 12th days of treatment; and moderate vomiting for 2 days. During the month of FIAU treatment, the serum ALT level rose from the pretreatment value of 65 to 103 U/L on the 6th day, and then fell to 61 and 65 U/L during the 2nd and 3rd week. However, at 1 month the ALT was 122 and peaked at 206 U/L at 5 weeks after starting FIAU. The ALT then gradually dropped over the succeeding 7 weeks to 49 U/L. At 4-5 months after starting treatment ALT reached its nadir of 23 U/L, only to rise again to 211 U/L, at the end of 7 months.

During the 6 months follow-up period, the patient reported several symptoms: mild abdominal pain (July 8-15); asthenia (July 8 to August 4); tremor of the hands (July 15 to August 10); anorexia and weight loss (July 21-August 8); and mild leg pain/numbness (starting October 22). Upon report of the last of these symptoms he was seen by a neurologic consultant who found evidence of a primary sensory neuropathy. Neurologic follow-ups on March 11, 1994 and on June 21, 1994 indicated that the patient continued to have numbness to the level of the knee and electric shock-like pains in the lower legs, preventing him from jogging or standing on his feet for any length of time, Subjectively the patient sensed that these symptoms had worsened over the 8 month period. Neurologic examinations showed loss of pain and cold perception up to the knees, absent ankle jerks, absence of vibration sense in the great toes, and some wasting of intrinsic foot muscles. Electrophysiologic studies indicated the presence of an axonal neuropathy with principally sensory involvement but some motor involvement as well. Over a 6 month period of neurologic evaluation it was felt that there had been neither significant changes on neurologic examination nor on nerve conduction studies, but subjectively the patient felt that the symptoms had worsened.

The second patient in this trial is a 24-year-old male. Liver biopsy performed 5 days before starting the trial showed chronic active hepatitis with moderate portal area inflammation, abundant piecemeal necrosis and marked fibrosis. Treatment with FIAU (0.25 mg/kg/day in 2 divided doses) was begun on May 3, 1993 and continued through June 27 (trial terminated because of serious adverse events in FIAU study H3X-MC-PPPC). He received 55 days of therapy, representing a total dose of 963 mg of FIAU. Serum HBV DNA was 3034 Eq/mL x 10^6 at study entry, 271 at 7 days, and subsequently dropped to 110 by the end of the first month of treatment. At the end of the 55 days of treatment the HBV DNA level was 29 (1% of the baseline value). Over the next 7 weeks levels increased, ranging between 147 and 545 Eq/mL x 10^6 at the end of 8 months it was 978. The only adverse effect reported by the patient was one day's mild nausea 10 days prior to FIAU discontinuation. Serum ALT level on study

[1] Measured by a new Chiron measurement system reported in Equivalents/ml x 106. For conversion from Equivalents to picograms:

$$\frac{\text{No. Equivalents/ml}}{\text{280,000 equivalents/pg}} = \text{no. pg/ml}$$

entry was 88 U/L and remained between 73 and 84 at weekly measurements over the first month of therapy. On the day of cessation of FIAU therapy the ALT was 161 (increased to 1.8-fold of baseline). Over the next 2 1/2 weeks it rose to a peak of 241 U/L (increase of 2.7-fold) and then gradually fell reaching a level of 64 at 8 months after the start of the study.

When the study was stopped on June 27, 1993, because of his 55 day course of FIAU totalling 963 mg, he was offered the option of hospitalization for observation and I.V. thymidine rescue therapy from possible subsequent manifestations of FIAU toxicity.

On return from vacation on July 6 he agreed to hospital admission. Serum lactate levels were normal and muscle biopsy showed normal results. He was asymptomatic on admission and received 8 gm/m^2 (14 gm) of thymidine for 7 days via continuous I.V. infusion as FIAU washout treatment. Also, he received carnitine and thiamine as part of the rescue therapy. During the subsequent 6 month follow-up period, fatigue (noted on study visits at 17 days and 5 weeks after the last dose of FIAU) and headaches (noted on study visits 17 days, 6 wks and again 5 months after stopping FIAU) were reported. The fatigue was short-lived, lasting 1 day on the first occasion and 11 days on the second. The headache lasted 1 or 2 days except on the last occasion when it persisted in a mild form for 11 days. Headaches had been present for some years in the past, and he had taken tylenol (325 mg) for them intermittently since 1989.

SUMMARY OF TRIAL H3X-MC-PPPA

Five patients were enrolled in the study and received either 0.10 or 0.25 mg/kg/day FIAU in bid aliquots in liquid form. The 90-day planned treatment was halted prematurely by the Sponsor because of major adverse events that occurred in FIAU Study H3X-MC-PPPC that was taking place concurrently. The 5 patients received FIAU for 17-56 days. Serum HBV DNA levels decreased significantly in all patients during the first week of therapy and remained markedly lower throughout the treatment period. This reduction in the level of this marker of HBV disease is considered a favorable response to therapy. Three of the 5 patients had transient ALT elevations shortly after the reduction in HBV DNA which were considered by the investigators, quite reasonably, as a reflection of immune activation (causing a hepatocellular reaction) and a favorable response to therapy.

There have been no deaths of study subjects, nor were there any serious adverse events during the course of FIAU therapy. All patients had asthenia at some time and 4 of 5 experienced some nausea (3 reported emesis). Two patients in the 0.25 mg/kg/day group experienced dizziness. Abdominal pain, anorexia, diarrhea, or myalgia occurred once in both treatment groups. During the 6-month post-therapy follow-up, one patient was hospitalized 3 times (once each for nausea, cholecystectomy, and liver biopsy). One patient developed symptoms of peripheral neuropathy 5 or 6 months after his last dose of FIAU. The neuropathy was confirmed on neurologic consultation and by nerve conduction studies.

None of the patients in this study developed the severe FIAU toxicity (hepatic failure, lactic acidosis, pancreatitis) observed in trial H3X-MC-PPPC. Three patients did develop mild transient amylase elevations but there was no clinical evidence of pancreatitis.

H

Statistical Analysis of Mortality in the FIAU/FIAC Clinical Trials

Table H-1 provides a synopsis of the design features of the 4 trials. The first trial (R89) involved AIDS patients with CMV. The second trial involved HIV+ patients some of whom also had HBV. The 3rd trial involved previously untreated (in the sense of exposure to FIAU or FIAC) patients with chronic HVB. The fourth trial involved HVB patients, the majority of whom had been previously treated with FIAU (11 of the 15 enrolled). None of the trials involved a randomized control group, hence, statistical assessments of the results observed must be based on the assumed background mortality rates applying to the populations under study. Three hypothetical death rates (proportion of the patients expected to die each year) were used for each of the analyses that follow:

	Low	Int	High
R89	0.10	0.15	0.20
R90	0.04	0.08	0.12
R91	0.02	0.03	0.04
PPPC	0.02	0.03	0.04

These rates correspond to the median life expectancies in years listed below. The median life expectancy, assuming a constant mortality rate, is 0.7 divided by the rate (Kalbfleisch and Prentice, 1980). The corresponding standard error for the rate is the rate divided by the square root of the number of events observed.

	Low	Int	High
R89	7.0	4.7	3.5
R90	17.5	8.75	5.83
R91	35.0	23.3	17.5
PPPC	35.0	23.3	17.5

The labels *low, intermediate*, and *high* are labels of convenience for the presentation that follows. They are not to be construed as qualitative labels for the presumed actual underlying mortality rates for the populations of interest. The true underlying rates may, in reality, be higher than the levels indicated for the set carrying that label. For example, the median life expectancy for the population enrolled into R89 (AIDS patients with CMV) is, in all probability, less than the 3.5 years listed for the "high" rate. The same is likely to be true for the population studied in R90. The estimated median life expectancy is around 10 years from conversion. The population studied is likely to have been positive for some time and, hence, has a life expectancy considerably less than that.

The data used for the reanalyses are as given in Table H-2, as derived from the FDA report. The closing date for recruitment into the individual trials is assumed to correspond to the date of the last dose for the trials, as recorded in the report. The period of recruitment is assumed to be that interval from enrollment of the first patient into a trial and the date of the last dose. The rate of enrollment was assumed to be constant over that interval. The actual period is less than that used herein by a matter of days or a few weeks, depending on the trial.

For the analyses presented below to be informative on a real time basis, one would have to have close surveillance of each study person so as to learn of deaths as they occur or within a matter of days after they occur. Lags in detection or reporting of deaths to the analysis site would degrade the value of the analyses as a real time decisionmaking tool.

Similarly, to be useful, one has to have 100% surveillance of all persons enrolled for mortality, regardless of their status in the trial (i.e., such surveillance including dropouts). We have no way of knowing the extent to which deaths noted in the FDA are the result of such surveillance. The report does not indicate the methods used to identify deaths occurring after the defined period of treatment and followup for the trials discussed. Hence, we have no way of knowing the extent to which the surveillance can be viewed as complete. There is, in fact, intrinsic evidence to suggest it is incomplete simply from the counts of deaths provided. For example, one would expect most of the patients in R89 to have died by mid 1993. The median life expectancy for the population enrolled into that trial was not likely to be much more than a year, if that.

The caveats regarding followup need to be kept in mind when reviewing the results below. An under-reporting of deaths would mean that the actual p-values noted in the tables below would be smaller than given and that the powers would be larger than indicated. Since the ability to trace people diminishes as a function of the time of the last contact, we surmise that the quality of followup was better for the 26 week period of followup than for followup through 27 June 1993. Hence, the emphasis is on analyses relating to 26 weeks of followup.

The results for each trial analyzed separately is given in Tables H-3, -4, and -5 for the low, intermediate, and high rates. The first panel of each table is at the close of each trial assuming 26 weeks of followup for each person enrolled. Note that for this method of analysis only 4 of the 9 deaths observed in the first three trials are counted. The other 5 deaths occurred beyond the closing date for followup and are censored. The second panel is for followup through 27 June 1993.

The sample size, assuming a uniform rate of enrollment over the interval defined by enrollment of the first patient to the last administration of treatment in a given trial is given in the column labeled **N**.

Expected deaths are calculated assuming the specified event rate for a table or a panel within a table. The total number of expected person years contributed by a total of N persons followed to death or to the indicated end of followup, is given in the fifth column of the tables 3, 4, 5 and 6. For example, it is 5.40 person years for R89 assuming 26 weeks of followup (i.e., 0.90 times 6.0). The expected number dead is 0.60 (i.e., 6.0 times 0.10). The expected deaths in table 6 correspond to the sum of expected deaths at the time of a death. For example, the value of 1.700 at the start of PPPC for first panel of table 6 is the sum of 0.60 + 0.86 + 0.24 (for R89, R90, and R91, respectively).

The p-values are for differences between the observed and expected numbers of deaths, and are derived using a technique described by Breslow and Day (1987) involving standardized mortality rates and the Poisson distribution. The p-values are for a two-tailed alternative. The calculations are made assuming the comparison of two groups, each having the sample size of that for the indicated trial.

The direction of the observed treatment effect is determined by the sign of the difference resulting from subtracting expected deaths from observed deaths (column 9 in Table H-s 3, 4, and 5, column 6 in Table H-6). A positive difference corresponds to an excess (measured against the number expected given the underlying mortality rate) of deaths associated with the test treatment. A negative difference corresponds to fewer than the number of deaths expected. The latter difference is indicative of a positive treatment effect and the former is indicative of a negative treatment effect. For the 3 trials done prior to PPPC and for the 26 weeks of followup, two were indicative of varying degrees of a negative treatment effect (R89 and R91) and one of varying degrees of a positive effect (R90). A positive treatment effect is one where the expected number of deaths is larger than the number actually observed and a negative treatment effect is one where the reverse is true.

Powers are presented in the last two columns of Tables H-3, -4, and -5 for a specified negative and positive alternative. Power is the probability of rejecting the null hypothesis, that the test treatment has no effect on mortality, when, in fact, it has the indicated negative or positive effect. Powers of 0.80 or higher are desired when designing randomized controlled trials with a calculated sample size. The power calculations are made with the type I error (a) fixed at 0.05 and correspond to powers calculated prior to the start of the trials.

The negative alternative considered is that the test treatment produces a 100% increase in mortality and the positive alternative is that it produces a 50% reduction in mortality. For example, if the assumed background mortality rate is 0.10, than the negative alternative is that the actual rate, in the presence of the test treatment, is 0.20 instead of the of the 0.10 hypothesized and that it is 0.05 instead of the 0.10 hypothesized if the effect of the test treatment is positive. In the case of R89, for 6 months of followup for a presumed low underlying mortality rate of 0.10 (Table H-3), the calculated power prior to the start of the trial against the two alternatives, given a sample size of 12 for both the test and control treated groups, is 0.08 and 0.07, respectively. A power of 0.08 means that, given the sample size of 12 per treatment group, the trial would have only about 1 chance in 12 (8 in 100) of detecting a 50% true positive effect of the drug and about the same chance of detecting a 100% negative effect of the drug, given a hypothesized underlying rate of 0.10 for the control treated group.

Not surprisingly, given the size of the trials, all of the powers are low. Given the relatively nominal nature of the observed difference and the resulting p-values, the calculated

powers suggest the need for a good deal of skepticism in concluding for or against the test treatment based on any single trial. In other words, one runs the risk of drawing the wrong conclusion regarding the treatment, even when the observed difference in a trial is indicative of harm.

The only trial that produces, according to a criterion based on p-values, any convincing evidence of harm is PPPC, and all of that information accumulated after the investigators had already taken action, based on morbidity, to stop the trial.

Even if one were to assume the form of analysis described in Table H-6, combining data from all trials in cumulative fashion, the information against the drug prior to the deaths in PPPC is weak. The smallest p-values are after the third death. The p-values observed at the start of PPPC are unimpressive, ranging in size from 0.19 to 0.77 for differences (observed minus expected deaths) ranging from 2.300 to -0.260.

The approach for Table H-6 is that of an analyst performing a new analysis each time another death is observed over the course of the 3 trials. The three panels in the Table are for 26 weeks of followup, with censoring occurring at the start at the 27th week after enrollment of a patient. The person-years recorded in Table H-6 are the sums of those available from the three trials at the indicated point of analysis. For example, the maximum amount available for 26 weeks of followup at the death of patient 4D, 6 Jan 1993, was 6.000 person years for R89, 21.500 for R90, and 11.099 for R91, for a total of 38.6 person years. (The study still generating information at 26 weeks of followup at that point in time was R91. R89 and R90 would have completed 26 weeks of followup on patients enrolled in those trials prior to 6 Jan 1993. There were 3 deaths observed within the defined period of followup prior to the one in question, for a total of 4 at the point of analysis.) The expected number of deaths is the sum of the products of person years of experience from a specific trial multiplied by the presumed underlying mortality rate for that study population; for example, 0.10(6.0) + 0.04(21.5) + 0.02(11.1) for a total of 1.68.

The analyses summarized in Table H-6 are for deaths occurring within 26 weeks of enrollment. Deaths beyond that point are not counted. The analyses do not take account of the redosing of 4 patients in R90 (401, 406, 408, and 409) or of the 3 deaths occurring among them them (401,406, and 408) because the redosing and deaths occurred after their respective 26th weeks of followup. A different approach is needed to deal with all deaths regardless of time from enrollment. That approach is represented in Table H-7.

The meta-analytic approach underlying Table H-7 is akin to that which could be used if investigators, just prior to starting their next trials, were to perform an analysis using all data accumulated up to that point to help them decide whether they should proceed to the next trial. The smallest p-value indicated of possible harm is the one for low underlying mortality rates for data accumulated just prior to the start of R90. The smallest p-value indicative of possible benefit is the one for high underlying mortality rates for data accumulated just prior to the start of PPPC.

The analyses are instructive only to the degree that one has faith in the underlying morality rates used and in the validity of the assumptions made, and among those, principally the one having to do with completeness of followup. The likelihood is that we have been conservative in the range of morality rates investigated. Hence, "low" may be too low and "high" may not be high enough. Obviously, any increase in assumed underlying rates weakens

the case for harm known in advance of PPPC. Conversely, the analysis is, in effect, a "best case" analysis in regard to completeness of followup for deaths. The analyses performed assume 100 percent ascertainment for deaths. Under that assumption, persons not located when the FDA task force report was complied are assumed to have been alive. The report does not contain details on completeness of followup. Hence, we could not perform analyses under other assumptions regarding patients not located at the time the report was complied.

Neither of the analyses in Tables H-6 or -7 take account of actual amount of drug administered and, hence, are not helpful in addressing the broader question as to whether the studies taken together are indicative of increasing probability of death with increased exposure to the drug. The relative risk (per unit increase of dose on the log scale) are 2.6 and 4.6, respectively, for censoring of followup at 26 weeks after enrollment (4 deaths) and March 24, 1993, (9 deaths; the point just prior to the start of PPPC), as obtained via Cox proportional hazards analyses (Cox, 1972). The p-values corresponding to the relative risks resulting from the two forms of censoring were 0.18 and 0.013, respectively. To be sure, all analyses involving dosage administration are problematic to the extent that dosage is a function of other intervening variables. Hence, the interpretation given to these results, even differences yielding a p-value as small as the one for the latter form of censoring, has to be treated with caution.

Tables H-1 through H-7 follow.

Table H-1. Design Features of Individual Trials

	R89-001	R90-001	R91-010	H3X-PPPC
Phase	I/II Dose escalation	I/II Dose escalation	I/II Dose escalation	I/II Treatment
Randomized control	None	None	None	None
IND	Oclassen 33,638	Oclassen 34,973	Oclassen 34,973	Lilly
No. of centers	2	3	1	1
Investigators	Richman Corey	Richman Corey Straus	Hoofnagle	Hoofnagle
Performance sites	U. of Cal. S.D. U. of Wash., Seattle	U. of Cal., S.D. U. of Wash., Seattle NIH, Bethesda	NIH, Bethesda	NIH, Bethesda
Drug	FIAC	FIAU	FIAU	FIAU
Treatment period	28 days	14 days	28 days	168 days
1st dose	17 Nov 89	9 Oct 90	13 Apr 92	24 Mar 93
Last dose	25 May 90	29 Jun 92	10 Sep 92	28 Jun 93
No. enrolled	12	43	24	15
Enrollment period	188 days	628 days	150 days	95 days
Enrollment rate	15.67 days	6.05 days	6.25 days	6.33 days
No. of Deaths	4	4	1	5
Prior FIAC/FIAU	No	No	No	Yes (11)
Study pop.	AIDS (2) AIDS+CMV (10)	HIV (13) HIV+HVB (30)	Compensated HVB	Compensated HVB
Treatment and follow-up	35 days	42 days	168 days	168 days
Dose				
Low	0.6 mg/kg/day	0.1 mg/kg/day	0.05 mg/kg/day	0.10 mg/kg/day
High	1.0 mg/kg/day	1.7 mg/kg/day	0.5 mg/kg/day	0.25 mg/kg/day

Project titles:
R89-001: Efficacy and safety of oral FIAC in AIDS patients with cytomegalovirus infection: A dose-ranging study.
R90-001: The tolerance of HIV-infected patients with herpes-group infections to oral doses of FIAU.
R91-010: FIAU oral dose-ranging study in patients with compensated chronic hepatitis B.
H3X-MC-PPPC: FIAU redosing for the treatment of patients with compensated chronic hepatitis B: a six-month course.

Table H-2. Death Experience by Calendar Time

	Event	PI	Cum. N	Deaths	Cum. % Dead	Study Time
17 Nov 89	**1st dose R89-001**	Richman,	1			
10 Jan 90	103 enrolled					
6 Feb 90	105 enrolled					
22 Feb 90	107 enrolled					
15 Mar 90	110 enrolled					
15 Apr 90	105 died			1		10 wks
18 May 90	110 died			2		9 wks
25 May 90	**Last dose R89-001 (n=12)**		12		16.7	
2 June 90	107 died				3	17 wks
9 Oct 90	**1st dose R90-001**	Richman,	13			
11 Mar 91	103 died	Corey,		4		60 wks
16 Apr 91	401 enrolled	Straus				
29 May 91	101 enrolled					
4 Jun 91	406 enrolled					
3 Nov 91	408 enrolled					
13 Apr 92	**1st dose R91-010**	Hoofnagle	56			
16 May 92	408 died			5		27 wks
29 Jun 92	Last dose R90-001 (n=43)		55		9.1	
5 Aug 92	4D enrolled					
11 Aug 92	406 died			6		62 wks
2 Sep 92	101 died			7		65 wks
10 Sep 92	**Last dose R91-010 (n=24)**		79		10.1	
18 Oct 92	401 died			8		78 wks
6 Jan 93	4D died			9		22 wks
24 Mar 93	**1st dose H3X-MC-PPPC**	Hoofnagle	80			
24 Mar 93	001-2002 enrolled					
24 Mar 93	001-3001 enrolled					
7 Apr 93	001-6003 enrolled					
14 Apr 93	001-3004 enrolled					
15 Apr 93	001-5003 enrolled					
28 Jun 93	**H3X-MC-PPPC stopped (n=15)**	94			10.4	
5 Jul 93	001-2002 died			10		14 wks
6 Jul 93	001-3004 died			11		13 wks
16 Jul 93	001-5003 died			12		14 wks
30 Jul 93	001-3001 died			13		19 wks
31 Aug 93	001-6003 died			14		17 wks
					14.9	

Table H-3. Results per Individual Trial for Low Underlying Mortality Rates

				Person-yrs		Deaths				Power	
	Rate	N	Avg FU	Exp	Obs	Exp	Obs	Diff	p-value	Neg	Pos
26 week followup											
R 89	0.10	12	0.50	5.40	5.19	0.60	3	2.40	0.05	0.08	0.07
R 90	0.04	43	0.50	20.64	21.50	0.86	0	-0.86	—	0.13	0.09
R 91	0.02	24	0.50	11.76	11.92	0.24	1	0.76	0.43	0.06	0.06
Total		**79**	**0.50**	**37.80**	**38.61**	**1.70**	**4**	**2.30**	**0.19**		
27 June 93 followup											
R 89	0.10	12	3.58	38.66	30.49	4.30	4	-0.30	0.75	0.19	0.13
R 90	0.04	43	1.50	61.92	62.97	2.58	4	1.42	0.52	0.20	0.12
R 91	0.02	24	1.33	31.28	31.01	0.64	1	0.36	0.94	0.08	0.06
PPPC	0.02	15	0.13	1.91	1.95	0.04	0	-0.04	—	0.08	0.06
Total		**94**	**1.50**	**133.77**	**126.42**	**7.56**	**9**	**1.44**	**0.69**		

Assumptions and notes: Enrollment period from 1st dose to last dose; uniform rate of enrollment over that period; instantaneous treatment effect (ie, no treatment lag); instantaneous reports of deaths; 100% followup for mortality over defined followup period; assumed underlying annual mortality rates: R89, 0.10; R90, 0.04; and R91, 0.02.

Table H-4. Results per Individual Trial for Intermediate Underlying Mortality Rates

				Person		Deaths				Power	
	Rate	N	Avg FU	Exp	Obs	Exp	Obs	Diff	p-value	Neg	Pos
26 week followup											
R 89	0.15	12	0.50	5.10	5.19	0.90	3	2.10	0.12	0.10	0.07
R 90	0.08	43	0.50	19.78	21.50	1.72	0	-1.72	—	0.22	0.13
R 91	0.03	24	0.50	11.64	11.92	0.36	1	0.64	0.60	0.07	0.06
Total	**79**	**0.50**	**36.52**	**38.61**	**2.98**	**4**	**1.02**	**0.70**			
27 June 93 followup											
R 89	0.15	12	3.58	36.52	30.49	6.44	4	-2.44	0.23	0.24	0.16
R 90	0.08	43	1.50	59.34	62.97	5.16	4	-1.16	0.49	0.32	0.20
R 91	0.03	24	1.33	30.96	31.01	0.96	1	0.04	1.00	0.09	0.07
PPPC	0.03	15	0.13	1.89	1.95	0.06	0	-0.06	0.24	0.05	0.05
Total	**94**	**1.50**	**128.71**	**126.42**	**12.62**	**9**	**-3.62**	**0.24**			

Assumptions and notes: Enrollment period from 1st dose to last dose; uniform rate of enrollment over that period; instantaneous treatment effect (i.e., no treatment lag); instantaneous reports of deaths; 100% followup for mortality over defined followup period; assumed underlying annual mortality rates: R89, 0.15; R90, 0.08; and R91, 0.03.

Table H-5. Results per Individual Trial for High Underlying Mortality Rates

	Rate	N	Avg FU	Person-yrs Exp	Person-yrs Obs	Deaths Exp	Deaths Obs	Deaths Diff	Deaths p-value	Power Neg	Power Pos
26 week followup											
R 89	0.20	12	0.50	4.80	5.19	1.20	3	1.80	0.24	0.11	0.08
R 90	0.12	43	0.50	18.92	21.50	2.58	0	-2.58	—	0.29	0.18
R 91	0.04	24	0.50	11.52	11.92	0.48	1	0.52	0.76	0.07	0.06
Total		**79**	**0.50**	**35.24**	**38.61**	**4.26**	**4**	**-0.26**	**0.77**		
27 June 93 followup											
R 89	0.20	12	3.58	34.37	30.49	8.59	4	-4.59	0.06	0.27	0.19
R 90	0.12	43	1.50	56.76	62.97	7.74	4	-3.74	0.10	0.43	0.26
R 91	0.04	24	1.33	30.64	31.01	1.28	1	-0.28	0.56	0.10	0.08
PPPC	0.04	15	0.13	1.87	1.95	0.08	0	-0.08	—	0.10	0.08
Total		**94**	**1.50**	**123.64**	**126.42**	**17.69**	**9**	**-8.69**	**0.02**		

Assumptions and notes: Enrollment period from 1st dose to last dose; uniform rate of enrollment over that period; instantaneous treatment effect (ie, no treatment lag); instantaneous reports of deaths; 100% followup for mortality over defined followup period; assumed underlying annual mortality rates: R89, 0.20; R90, 0.12; and R91, 0.04.

Table H-6. Analysis on the Occurence of Each Death Based on 26 Weeks of Followup from Enrollment

	Enrolled N	Enrolled N-yrs	Deaths Obs	Deaths Exp	Diff	p-value
26 week followup						
Low Mortality (R89 0.10; R90 0.04; R91 0.02)						
105	10.6	1.931	1	0.193	0.807	0.35
110	11.5	2.881	2	0.288	1.712	0.07
107	12.0	3.230	3	0.323	2.677	0.01
4D	79.0	36.920	4	1.648	2.352	0.17
PPPC start	79.0	39.500	4	1.700	2.300	0.19
Intermediate Mortality (R89 0.15; R90 0.08; R91 0.03)						
105	10.6	1.931	1	0.290	0.710	0.54
110	11.5	2.881	2	0.432	1.568	0.14
107	12.0	3.230	3	0.485	2.515	0.03
4D	79.0	36.920	4	2.903	1.097	0.66
PPPC start	79.0	39.500	4	2.980	1.020	0.70
High Mortality (R89 0.20; R90 0.12; R91 0.04)						
105	10.6	1.931	1	0.386	0.614	0.64
110	11.5	2.881	2	0.576	1.424	0.23
107	12.0	3.230	3	0.646	2.354	0.06
4D	79.0	36.920	4	4.167	-0.167	0.81
PPPC start	79.0	39.500	4	4.260	-0.260	0.77

Assumptions and notes: Enrollment period from 1st dose to last dose; uniform rate of enrollment over that period; instantaneous treatment effect (ie, no treatment lag); instantaneous reports of deaths; 100% followup for mortality over defined followup period; new analysis at the time of each death.

Table H-7. Analysis at the Start R90, R91, and PPPC Bases on all Deaths Regardless of Time Since Enrollment

	Enrolled		Deaths			
Start	No.	No. PYs	Obs	Exp	Diff	p-value
Follow up to start of indicated trial						
Low (R89 0.10; R90 0.04; R91 0.02)						
R90	12	6.6	3	0.6	2.400	0.05
R91	51	49.0	4	3.1	0.900	0.75
PPPC	79	113.1	9	5.7	3.300	0.25
Intermediate (R89 0.15; R90 0.08; R91 0.03)						
R90	12	6.6	3	1.0	2.000	0.16
R91	51	49.0	4	5.3	-1.300	0.45
PPPC	79	113.1	9	10.0	-1.000	0.66
High (R89 0.20; R90 0.12; R91 0.04)						
R90	12	6.6	3	1.3	1.700	0.28
R91	51	49.0	4	7.4	-3.400	0.13
PPPC	79	113.1	9	14.2	-5.200	0.11

Assumptions and notes: Enrollment period from 1st dose to last dose; uniform rate of enrollment over that period; instantaneous treatment effect (ie, no treatment lag); instantaneous reports of deaths; 100% followup for mortality over defined followup period; new analysis just prior to start of a new trial. PY = person-years.

Glossary

ALT: alanine aminotransferase, an enzyme present in liver cells and a marker of liver injury when present in quantity in the blood

amylase: an enzyme that catalyzes the hydrolysis of starch into smaller molecules

ascites: retention of fluid in the abdomen

AST: aspartate aminotransferase, an enzyme present in liver cells and a marker of liver injury when present in quantity in the blood

AZT: zidovudine, formerly known as azidothymidine, a synthetic thymidine analog that inhibits the human immunodeficiency virus that causes AIDS

CAH: chronic active hepatitis

CFR: Code of Federal Regulations

cholangiolitis: inflammation of cholangioles, one of the fine terminal elements of the bile duct system

cholestasis: stoppage or suppression of the flow of bile, having intrahepatic or extrahepatic causes

chorioretinitis: inflammation of the choroid and retina

choroid: the thin, pigmented, vascular coat of the eye; it furnishes the blood supply to the retina and conducts arteries and nerves to the anterior structures

cirrhosis: liver disease characterized pathologically by loss of the normal microscopic lobular architecture, with fibrosis and nodular regeneration

CMV: cytomegalovirus, a pathogen that causes chronic disease in immunocompromised but not immunocompetent patients

coagulation: the process of clot formation

CRF: clinical report form, used to record patient data, in summary form, in clinical trials

ddC: dideoxycytidine, a nucleoside analog used in the treatment of human immunodeficiency virus infection

ddI: dideoxyinosine, a nucleoside analog used in the treatment of human immunodeficiency virus infection

didanosine: ddI

encephalopathy: any degenerative disease of the brain

FIAC: fiacitabine, a pyrimidine nucleoside analog originally synthesized by Fox and his colleagues at Memorial Sloan-Kettering cancer center to be used in the treatment of herpes group virus infections (See figure 1, chapter 4)

FIAU: fialuridine, the principal metabolite of FIAC, also a pyrimidine nucleoside analog

flare: a rise in serum aminotransferases (AST and/or ALT) prior to normalization of liver enzymes, frequently associated with clearance of hepatitis B virus from the liver

Gilbert's syndrome: an inborn error of bilirubin metabolism, probably autosomal dominant, a benign elevation of unconjugated bilirubin with no liver damage or hematologic abnormalities

glomerulonephritis: a variety of nephritis (inflammation of the kidney) characterized by inflammation of the capillary loops in the glomeruli of the kidney

half-life: the time that it takes for the concentration of drug in plasma or the amount of drug in the body to be reduced by 50 percent

HBV: hepatitis B virus

HCC: hepatocellular carcinoma

HCV: hepatitis C virus

hepatic steatosis: fatty deposits in the liver

hepatocellular steatosis: fatty deposits within or around hepatocytes

hepatocyte: a parenchymal liver cell, an essential element of the organ

hepatotoxicity: the quality or property of exerting a destructive or poisonous effect liver cells

HIV: human immunodeficiency virus

hyperbilirubinemia: excessive concentrations of bilirubin in the blood, which may lead to jaundice

hypoalbuminemia: an abnormally low albumin content of the blood

H3X-MC-PPPA: FIAU study conducted on five hepatitis B virus-positive subjects at the New England and Galveston sites, sponsored by Eli Lilly. Referred to in this report as Trial PPPA.

H3X-MC-PPPC: FIAU study conducted on 15 hepatitis B virus-positive subjects at the National Institutes of Health Clinical Center, sponsored by Eli Lilly. Referred to in this report as Trial PPPC.

H3X-MC-PPPG: FIAU study conducted on 17 healthy males at the Lilly Laboratory for Clinical Research, sponsored by Eli Lilly. Referred to in this report as Trial PPPG.

ICD: informed consent document

IND: investigational new drug application

interferon: a naturally occurring protein produced by lymphocytes and fibroblasts in response to chronic viral infection which has been used in the treatment of chronic hepatitis B virus infection since the 1970s

IRB: institutional review board

jaundice: yellowish skin

lactic acidosis:	severe and rapidly progressing accumulation of lactic acid in the blood
laparoscopic cholecystectomy:	surgical removal of the gall bladder
leukopenia:	reduction in the number of leukocytes in the blood, the count being 5,000 or less
lipase:	glycerol-ester hydrolase; any of a group of widely occurring enzymes that catalyze the hydrolysis of ester linkages between the fatty acids and glycerol of the triglycerides and phospholipids
macrovesicular steatosis:	accumulation of fat droplets around the cells of an organ
membranoproliferative glomerulonephritis:	a chronic glomerulonephritis characterized by the mesangial cell proliferation and irregular thickening of the glomerular capillary wall
microvesicular steatosis:	accumulation of fat droplets within the cells of an organ
morbidity:	the extent and frequency of disease symptoms and their impacts on daily activities
mortality:	the frequency with which infection results in death
murine:	pertaining to or affecting rats or mice
myelosuppression:	suppression of bone marrow activity, resulting in a reduction in the number of platelets, red cells, and white cells
myopathy:	damage to the muscles in the arms and legs
NAI (No Action Indicated) letter:	from the Office of Compliance of the Food and Drug Administration to the investigators and/or sponsors to inform them that violations have been identified but that no action is required
NDA:	new drug application
neuralgia:	paroxysmal pain that extends along the course of one or more nerves
neutropenia:	a decrease in the number of neutrophilic leukocytes in the blood
nucleoside analog:	molecules similar to the building blocks of deoxyribonucleic acid [DNA] that become incorporated into the viral DNA as the virus divides, inhibiting and interrupting this replicative machinery
NIAID:	National Institute of Allergy and Infectious Diseases
NIDDK:	National Institute of Diabetes and Digestive and Kidney Diseases
OAI (Official Action Indicated) letter:	from the Office of Compliance of the Food and Drug Administration to investigators and/or sponsors intending to warn them of an impending action and that requires a response within 15 working days
OPPR:	Office for Protection from Research Risks
pancreatitis:	inflammation of the pancreas
pancytopenia:	deficiency of all cell elements of the blood; aplastic anemia
pathogen:	a specific cause (bacterium or virus) of a disease
peripheral neuropathy:	damage to the nerves in the arms and legs
Phase I study:	Usually the first stage in testing an investigational new drug application to the Food and Drug Administration, done to generate preliminary information on the chemical action and safety of the new drug, and it is usually not controlled

Phase II study: Usually the second stage of testing it is carried out on persons having the disease or condition of interest, determining the efficacy of the drug along with providing information on safety

Phase III study: Usually the third and final stage of testing; it is concerned with assessment of dosage effects, efficacy, and safety, the design usually includes a control treatment, and the drug manufacturer or sponsor may request permission to market the drug for the indication or condition covered in the testing

proteinuria: An excess of serum proteins in the urine; also called albuminuria

protocol: the plan or schedule of events to be followed in a study or investigation or in an intervention program

R89-001: FIAC study conducted on 12 human immunodeficiency virus-positive/cytomegalovirus positive subjects at the University of Washington and University of California at San Diego, sponsored by Oclassen Pharmaceuticals. Abbreviated throughout this report as R89.

R90-001: FIAU study conducted on 42 immunodeficiency virus - positive/cytomegalovirus positive subjects at the University of Washington, University of California at San Diego, and the National Institutes of Health Clinical Center, sponsored by Oclassen Pharmaceuticals. Abbreviated throughout this report as R90.

R91-010: FIAU study conducted on 24 immunodeficiency virus - positive/cytomegalovirus positive subjects at the National Institutes of Health Clinical Center, sponsored by Oclassen Pharmaceuticals. Abbreviated throughout this report as trial R91.

SGOT: serum glutamic oxaloacetic transaminase; older term for AST

SGPT: serum glutamic pyruvic transaminase; older term for ALT

steatosis: fatty deposits

subcutaneous: under the skin

thrombocytopenia: decrease in the number of blood platelets

transaminase: aminotransferase; class of enzymes present in serum and in various body tissues, especially in the heart and liver and released into the serum as a result of tissue injury

VAI (Voluntary Action Indicated) letter: from the Office of Compliance of the Food and Drug Administration that requests a response from the investigators and/or sponsors within 30 working days of receipt with a proposal for correcting or preventing future problems or deviations

varices: an enlarged and tortuous vein, artery, or lymphatic vessel

VZV: varicella-zoster virus

WHV: woodchuck hepatitis virus

zidovudine: azidothymidine (AZT), a nucleoside analog used in the treatment of human immunodeficiency virus infections