Figure 2.3b. STUDY ERROR: ***Miracle cure that kills claims fifth victim***

EM9330: The Globe and Mail, September 1, 1993, pages A1, A10

Miracle cure that kills claims fifth victim

Experimental hepatitis B drug trial goes fatally wrong after doctors miss early clue

BY LAURAN NEERGAARD
Associated Press

A fifth volunteer died in the United States yesterday from an experimental drug touted as a miracle cure for hepatitis B. The patient was beyond medical rescue even as scientists unravelled the mystery of what went gravely wrong in a clinical trial.

The first clue was in plain sight a year ago, but researchers at the National Institutes of Health did not know enough about the drug to recognize what it meant, the study's lead scientist said.

"Something terrible happened and we missed it," Dr. Jay Hoofnagle said in an emotional interview describing the horror of realizing the drug was killing people months after they stopped taking it.

"The dreadful thing [is] waiting to see what will happen," he said, his voice trembling, before learning of the latest death. "I just hope we're over the worst."

The drug Fialuridine (FIAU) had shown great promise for fighting the hepatitis B virus, which can cause deadly cirrhosis and liver cancer. When dogs passed toxicity tests unharmed, the Food and Drug Administration approved FIAU for human trials.

Too late, scientists would discover that in humans, FIAU stealthily attacks the very building blocks of cells in livers, kidneys and nerves.

Five people treated with FIAU have died of liver and kidney failure, despite liver transplants for three of the patients. Yesterday, a 37-year-old woman died after two months in critical condition and two liver transplants at the University of Virginia Medical Center. One volunteer remains in serious condition there.

Another is recovering from an Aug. transplant at Emory University Hospital in Atlanta.

Dr. Hoofnagle now fears that other anti-viral drugs such as the AIDS drugs AZT and ddI – known to be toxic – may attack patients as FIAU does.

The first clue that FIAU was dangerous appeared in August of last year when a man who had taken FIAU developed painful nerve damage. Paul Melstrom of Pheonix and 23 other volunteers participated in a 28-day NIH study of FIAU, from mid-April to mid-May. Almost four months later, Mr. Melstrom, 53, contracted severe neuropathy in his feet and legs. Another patient had minor neuropathy.

"It was so obvious to me it was the FIAU," Mr. Melstorm said from Arizona. "There's nothing about my life that changed in 1992, but there was one hallmark event. That was the taking of the FIAU."

But the NIH could not prove that FIAU was to blame. Many factors cause neuropathy, including alcohol. Mr. Melstrom is a recovering alcoholic and once had a bout with mild neuropathy.

So the agency continued the trial this spring, giving the drug to 15 otherwise healthy hepatitis patients for up to 11 weeks. Dr. Hoofnagle did warn volunteers beforehand that neuropathy was a possible side-effect and tested them for symptoms.

In early June, two volunteers developed neuropathy symptoms and immediately stopped taking FIAU. By mid-month, they were hospitalized with liver poisoning, unrelated to their hepatitis but similar to the late toxicity Mr. Melstrom had experienced.

Dr. Hoofnagle halted the trial, but the horror was just beginning.

One by one, from June 16 through August, seven people fell ill with damaged livers, kidneys and nerves, as frustrated doctors and frightened fellow volunteers looked on.

Now, with five of the seven dead, the remaining eight patients in the trial are being watched to determine whether they escaped serious harm.

What happened? This is Dr. Hoofnagle's theory:

A virus cannot reproduce on its own, so it instead takes over a cell's DNA, the cellular blueprint that maps how each person's unique genes are continuously reproduced. The virus uses the DNA to replicate itself furiously.

In the trials, FIAU foiled the hepatitis B virus by forming a bogus link in a hepatitis-infected DNA chain that stopped it from reproducing.

FIAU did not stop there, however. It also tricked sub-units of the body's cells called mitochondria, which have their own DNA that FIAU also crippled. This crippled DNA produced a second generation of flawed mitochondria that killed the cells dependent on them for energy.

Stopping the drug at that point did not halt the problem because the genetic damage had already been done.

Mr. Melstrom exhibited that damage sooner than the other patients because the mitochondria of nerve cells reproduce faster than those of liver cells, Dr. Hoofnagle said. Doctors did not realize, however, that his neuropathy signalled worse disease to come.

"In retrospect, [the connection] seems obvious," Dr. Hoofnagle said. "But we followed on course because we hoped FIAU would make their hepatitis get better. We weren't looking for toxicity any more."

The NIH now knows that FIAU did not poison the test dogs because dogs have a natural enzyme that renders the drug inactive, Dr. Hoofnagle said.

Government scientists will meet on Sept. 21 in Washington to review Dr. Hoofnagle's data, including his concern that similar anti-viral drugs could also be dangerous.

"This toxicity is not in FIAU alone," Dr. Hoofnagle said. "This toxicity ..... probably has been seen for many years and not recognized."

At least one expert on antiviral drugs is skeptical.

Dr. Raymond Schinazi of Emory University found in 1986 that FIAU under certain conditions would metabolize into a very toxic compound. He thinks the NIH volunteers fell victim to that still-unexplored metabolite of FIAU, rather than to damaged mitochondria.

And, he says, AIDS drugs don't attack mitochondria.

"They're very different," Dr. Schinazi said. "AZT doesn't kill people the way FIAU does."

But Dr. Hoofnagle thinks scientists will be amazed by what they don't know about mitochondria.

"It was considered a minor issue," he said. "This is going to change all that."

(*continued overleaf*)

☐ The article EM9330 reprinted overleaf on page 2.35 illustrates the difficulty of assessing the effects of a drug on *humans* on the basis of its effects on laboratory *animals*; this is a major dilemma for medical research. [Another case, in the 1950s with wide implications, involved birth defects induced world-by *thalidomide*, a drug taken by some pregnant women to combat morning sickness.]

It is useful practice to apply the terminology we have introduced for data-based investigating and the FDEAC cycle to describe the central issue raised by the article reprinted overleaf on page 2.35; we can do so by identifying:

- the *target* population for the investigation;
- the *study* population for the investigation;
- the *sample* for the investigation.

Based on your three identifications, describe briefly the *reason* for the difficulty that arose – *we* describe this difficulty as a *limitation* imposed by study error on an Answer.

Such a limitation on an Answer arises in essentially *all* work on the development of new drugs for treating serious illness.

The following *Science* Editorial [**270**: 215, 13 October, 1995] EM9532 broadens the scope of the issues raised by the article EM9330 reprinted overleaf on page 2.35; in doing so, it makes clear the *importance* of our distinction in the FDEAC cycle between the *target* population and the *study* population.

- **Target population**: the group of elements to which the investigator(s) want Answer(s) to the Question(s) to apply.
- **Study population**: a group of elements *available* to an investigation.

EM9537:

Flaws in Risk Assessments

Chemical risk assessment studies conducted with rodents have helped to justify expenditures of more than a trillion dollars over the past 20 years. Large additional outlays are planned, although it has not been shown that such studies have substantially benefited human health. In fact, it has become increasingly clear that the main causes of untimely human death are smoking and diet. For example, a recent article in the *New England Journal of Medicine** indicates that excess weight has a wide range of deleterious effects on health.

The risk assessment procedures used by the Environmental Protection Agency (EPA) have been criticized for many years and for many reasons. Their quality has recently come under intensified criticism, as is evident in the proceedings of a July 1995 meeting sponsored by Toxicology Forum of Washington, D.C., and in a recently published book, *Dietary Restriction*.† The critics point out that rodent risk assessment studies lack reproducibility because of genetic drift in the test animals and because of a failure to control their consumption of food.

Most standard risk assessment experiments expose rodents to large doses of a test chemical for about 2 years, which is approximately their natural life-span. For most tests, one or more of three strains of rodents are used: Sprague-Dawley (SD) rats, Fischer (F-344) rats, and B6C3F1 mice. These animals have a higher natural incidence of tumours than do humans, and some of the tumours are not common to humans. These rodent strains were adopted in the belief that they would exhibit less variability than wild-type animals do. On the basis of this assumption, enormous effort has been expended in studies of about 500 different chemicals. Each experiment has involved comparison between dosed and nondosed animals (controls). Thus a large database is available concerning the weight, longevity, and pathology of control animals. Data cited in the Toxicology Forum proceedings and in *Dietary Restriction* indicate that, during the past 25 to 30 years, the adult body weight of rodents from most of the strains used in toxicity testing has increased 20 to 30%. Degenerative diseases and tumour incidence also have increased. Rodent survival has decreased. At the Merck Research Laboratory in the 1970s, the survival rate at age 2 of SD rate used as controls was 58%. In the 1980s it was 44%, and in the 1990s it had dropped to 24%. A different laboratory compiled data on F-344 rats. In 1970, 80% of males survived for 2 years. In 1981, 60% survived. Their current survival rate is 36%. The incidence of tumours in control rodents has also changed with time. For example, the number of liver tumours in control B6C3F1 mice increased from an average of 32% in 1980 to about 50% in 1984. In tests at various laboratories, liver tumour incidence in male B6C3F1 mice has varied between 10 and 76%.

A partial explanation for this variability in longevity and health lies in practices at the breeder companies. Apparently, they have unwittingly caused genetic drift by their methods of selecting breeding stock. The standardized procedure at risk assessment laboratories has also been a factor. In general animals are fed *ad libitum* (*ad lib*); that is, they are given as much food as they want to eat. As a result of overeating, the health of *ad lib* animals is impaired. This is clearly shown by the fact that if the food intake of littermates of *ad lib* animals is reduced to 70% or less of *ad lib* amounts, rodent health and longevity are much improved. A recent experiment using SD rats compared the longevity of control rats fed *ad lib* with that of rats fed 65% of the *ad lib* amounts. At maturity, the *ad lib* males weighed 60% more than did the diet-restricted males. Only 7% of the *ad lib* males lived as long as 2 years. In contrast, 72% of the diet-restricted rats survived for more than 2 years. They were sleek and healthy. Although this phenomenon has been widely observed and well known for many years, the standard protocol still calls for *ad lib* feeding, so that in effect, when animals are exposed to chemicals in risk assessments, they simultaneously receive one potential carcinogen and one known carcinogen – their food.

When scientists plan experiments, they seek to control the important variables and to achieve time-invariant reproducible results. Those at EPA with the responsibility for establishing protocols for risk assessment experiments have acted as if they did not share these goals.

Philip H. Abelson

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*J.E. Manson *et al*., *New Engl. J. Med.* **333**: 677 (1995). [DC Library call number: PER R11.B7]

†R.W. Hart, D.A. Neumann, R.T. Robertson, Eds., *Dietary Restriction: Implications for the Design and Interpretation of Toxicity and Carcinogenicity Studies* (ILSI Press, Washington, DC, 1995).

The articles EM9330 and EM9537 reprinted overleaf on page 2.35 and above are also used in Figure 3.1 of the STAT 231 Course Materials and in Statistical Highlight #22.