Plutonium Experiment Recalled

A generation-old experiment involving the injection of plutonium, an extremely potent carcinogen, into human subjects has finally gotten a public airing after years of obscurity. The project, initiated in the waning days of the Manhattan Project, seems appalling in light of the ethics of the 1970's, particularly since informed consent apparently was not obtained from the subjects. Yet, according to a scientist who tracked down 17 of the 18 subjects, the one-of-a-kind experiment proved to be of "inestimable use" in setting standards for plutonium workers. There is no evidence that any of the people suffered ill effects—in fact, although all were supposed to be terminally ill, three of them are still alive.

The experiment was conducted between 1945 and 1947, shortly after the construction of the first plutonium bomb, by investigators for the Manhattan Engineering District (MED). According to Patricia W. Durbin of Lawrence Berkeley Laboratory, there was an urgent need for data on the rate at which the human body excretes plutonium so that safe exposure levels could be set for bomb workers. Because ingested plutonium emits very weak radiation, the only way to measure its retention is through measurement of alpha particles in the urine. Experiments had been conducted in which plutonium was injected into rats and dogs but, says Durbin, because the two species excrete it at different rates, they offered no guidelines for humans.

So 18 patients, all of whom were thought to have fewer than 10 years to live, were selected at four hospitals—those at the universities of California, Chicago, and Rochester, and the MED hospital in Oak Ridge, Tennessee. They ranged in age from 4 to 69 and were afflicted with many things including cancer, heart disease, Cushing's syndrome, Addison's disease, and cirrhosis. Each was given a single intravenous plutonium injection that amounted, in most cases, to about 5½ times what was considered an acceptable amount to be ingested by a plutonium worker over a 50-year span. Informed consent is known to have been obtained in only one case, from a man who was injected in 1947, after the Atomic Energy Commission (AEC) had taken over from the MED.

Durbin and her colleague, R. E. Rowland of Argonne National Laboratory, have located information on all but 1 of the 18 subjects. Eight of them survived at least 8 years following the injections, and at least 3 of the 18 were autopsied. None of the available evidence shows that the plutonium injections influenced the course of the patients' diseases. As of 1974, four of the subjects were still alive. One was still ill and has since died, one had ulcers misdiagnosed as stomach cancer, another was freed of cancer after his leg was amputated, and the disease of the fourth was not revealed by Durbin. That year the AEC contacted the doctors of the four and asked them to tell them about the injections; this was done except in the case of the woman who was ill.

Durbin says the absence of contemporary written records indicates that everything was very secret and most communications were probably oral. She says that if there was any follow-up on the patients it did not last long—both the new AEC and the investigators involved felt embarrassed and ashamed about the study and wanted to put it behind them as quickly as possible.

Another reason for the lack of follow-up is that the sole purpose of the study was to find out how fast the body gets rid of plutonium. It was discovered that human kidneys are at least 50 times less efficient than animal kidneys at removing plutonium. "If animal data had been used," says Durbin, "permissible levels would have been set much higher."

Mention has been made of the experiment in various scientific journals throughout the years and in 1972 Durbin wrote it up for a book called *Radiobiology of Plutonium* (J. W. Press, University of Washington, 1972). The newsletter *Science Trends* gave the first news account of it after Durbin and Rowland presented a paper last October at a workshop on plutonium and radium. They concluded from their investigation of the study that "bone-tumor risk from plutonium is no greater than that from radium, and might be less." As for cancer of the liver, the other most likely site, the authors say the doses weren't high enough to make its occurrence likely. The experimental group was too small and the survival times too short, given the long latency period for cancer, for the project to have yielded any more definite information.—C.H.

PAM and women randomly assigned to the "experimental" group receive L-PAM plus 5-fluorouracil (5-Fu).

Before long, according to Fisher, patients receiving L-PAM plus 5-Fu will become the control group while women in the experimental group will be given one of three combinations of three drugs.† New protocols are before NCI now and will be reviewed within a week or so. "We are going about this in a very orderly manner," says Fisher. "First, we tested a drug versus nothing, then one drug versus two. Now, we'll look at other combinations. The point is to find the minimal treatment that will do the job with minimal toxicity. We're putting everything we know on the line in breast chemotherapy now. The next 10 years will be the ones that count in telling us whether we're succeeding."

While the NSABP study was going on, NCI investigators were experimenting with the three-drug CMF therapy, which they developed, and the Institute was anxious to initiate a controlled clinical trial using it. Fisher's group, which includes collaborators all over the country, was already tied up in the L-PAM study. NCI looked around the country for a large institution that would be willing to conduct the CMF study but found none. Surgeons at one leading institution, for example, refused to cooperate because they still do not believe there is a role for drugs in breast cancer therapy. So, the NCI turned to Bonadonna and his group in Milan. There is a lot of breast cancer in Italy and the Milan cancer institute sees a large number of patients, which is important if one wants to get useful data in a reasonable amount of time. And the group there was enthusiastic about doing the study. It was begun late in 1973 and has, by now, included 386 women, each of whom had radical surgery for breast cancer with lymph node involvement.

Bonadonna and his colleagues declare in their article that "These results should be considered with caution, since, at present, the effect of this therapy on survival and possible long-term side effects remain unknown." They call their results "promising" but say, "This optimism should be tempered by a few important considerations." It is too early to tell whether CMF therapy is merely delaying recurrence or actually lengthening survival. There is evidence, the Italian team notes, that breast cancer behaves as a "chronic disease" and may reappear as many as 20 years after initial surgery. Furthermore, it is not yet possible to tell whether the CMF

†The three-drug combinations are L-PAM + 5-Fu + Methotrexate, L-PAM + 5-Fu + C-parvum, an agent that stimulates the immune system, and L-PAM + 5-Fu + Tamoxifen, an anti-estrogenic compound.