compare the effects of coronary bypass surgery to the effects of drugs on the longevity of patients with certain forms of angina pectoris, or chest pains arising from atherosclerosis. A large number of poorly controlled studies had already been published, most of which indicated that surgery prolongs the lives of these patients. As a result, many cardiologists and surgeons are already convinced that it would be unethical to deny their patients what they believe are the life-prolonging benefits of surgery. These physicians not only are not participating in the NHLBI study, but some say they will not accept the trials' results unless surgery is vindicated.

The Veterans Administration (VA) decided a decade ago to study the effects of bypass surgery on the mortality of patients with angina pectoris. In 1968, when the VA began its randomized controlled trial, the Vineberg procedure was the operation of choice. In this procedure, clogged coronary arteries are bypassed with internal mammary arteries. Soon after the VA trial began, the Vineberg procedure was replaced by the operation still popular today—a bypass that makes use of a vein from the patient's leg. The VA then had to redesign its trial to study the vein bypass instead. It can be argued that the VA started its trial too soon and that the NHLBI may have started its trial too late.

Once a randomized controlled trial is under way, investigators often see trends in the accumulating data that make them ask whether the trial should be halted. These trends may indicate that a particular treatment may be harmful or that a treatment may be beneficial or that one treatment may be more harmful than another. At this point they are faced with a difficult ethical question. If they end the trial before they obtain statistically significant results, they run the risk of denying patients the best treatment because they will never know whether the suspected hazardous or helpful treatment is actually as good or bad as it appears to be. If they wait too long, patients may suffer needlessly.

According to Paul Meier of the University of Chicago, the current trend is to terminate a trial when there is some evidence that a treatment is harmful, even when the evidence is not statistically significant. In the past, the tendency was to continue until significant results were obtained.

At the conference on clinical trial methodology, Meier discussed several examples of studies that were ended prematurely for ethical reasons to the detriment of the studies' conclusions. One example involves clinical trials comparing the effects of simple and radical mastectomies on the survival of breast cancer patients. Meier contrasts two studies, both of which were terminated prematurely, that came to contradictory conclusions. The first of these studies was conducted in Cambridge, England, and was terminated when an early trend in the results seemed to favor simple mastectomies. The decision to end the study was made because the trial's designers felt that it was unlikely that radical mastectomies would turn out to improve the patients' survivals. Meier stated that, "Nothing was yet significant, and a decision was reached, not on the grounds of evidence about a true difference, but on grounds of evidence about a future significance level."

A similar study of mastectomies was conducted in London, but this trial was terminated prematurely in favor of radical mastectomies. As Meier said, "Once again, results at the bare margin of statistical significance were deemed to require cutting off the study on ethical grounds."

Another trial that was ended prematurely has actually led to a lawsuit. This trial, conducted by the University Group Diabetes Project (UGDP) was conducted to determine whether oral hyperglycemic drugs can delay retinal damage, liability to infection, and other complications of adult onset diabetes. The study was ended when it appeared that some of the drugs might cause excessive mortality from heart disease. The UGDP investigators concluded that the benefits of these drugs, if any, could not outweigh this risk. Still, said Meier, it was far from certain that the drugs were harmful and "a great deal in convincingness was lost by not continuing until the evidence became clearer." Now a group of physicians and drug companies has brought suit against the UDGP, claiming that patients are being denied possibly beneficial drugs.

Meier discussed a final example of a premature trial termination to illustrate how investigators often unconsciously make value judgments when they end trials. More than 20 years ago, a randomized controlled study was conducted to determine the effects of the administration of oxygen to premature infants. Some evidence from uncontrolled studies indicated that oxygen might cause a form of blindness, known as retrolental fibroplasia. Yet the babies were often gasping for air, and it was believed that oxygen might save their lives.

When the randomized controlled trial was conducted, investigators found that the infants given oxygen were indeed more likely to become blind. The study was terminated before they could determine whether the oxygen saved lives as well. Meier pointed out, however, that the decision to terminate the trial was based on a possibly inadvertent judgment about the value of a dead as opposed to a blind baby. "The data [in favor of termination] are conclusive only if you think a dead baby is 2½ times worse than a blind one," he said.

Each stage of the progress of a randomized controlled clinical trial, from the decision to begin to the decision to end, meets with resistance caused by a combination of social, political, and ethical forces. Finally the results must face the test of justification, were they worth the time and money? Clinical investigators are hoping that their experiences in this age of clinical trials will increase their awareness of the pitfalls associated with such trials and lead to new ways to avoid the pitfalls. If so, the theoretical advantages of randomized, controlled clinical trials will more likely be reflected in practice.—GINA BARI KOLATA

RECENT DEATHS

Brian B. Blades, 71; former chairman of surgery, George Washington University; 28 September.

Martin W. Davis, 53; professor of sociology, University of the District of Columbia; 21 September.

Henry Erdman, 92; professor emeritus of agricultural economics, University of California, Berkeley; 19 September.

Alfred M. Freudenthal, 71; professor emeritus of civil and materials engineering, George Washington University; 27 September.

Melville Sahyun, 82; biochemist and founder, Sahyun Laboratories; 12 August.

June Sklar, 34; research demographer, University of California, Berkeley; 19 August.

Gitel P. Steed, 63; professor of anthropology, Hofstra University; 6 September.

Lyell J. Thomas, 84; professor emeritus of zoology. University of Illinois, Urbana-Champaign; 22 August.

Frank M. Weida, 86; professor emeritus of statistics, George Washington University; 13 September.