Clinical Trials: Methods and Ethics Are Debated

This is the age of clinical trials. They are not only coming into increasing use but they are becoming increasingly sophisticated, increasingly costly, and many now involve enormous numbers of participants. Not surprisingly, clinical trials are also becoming increasingly controversial, as was evident at a recent National Conference on Clinical Trials Methodology.

A decision to start a large-scale clinical trial is a decision to commit a great deal of money and effort over a long period of time—often as long as a decade—in the hopes of deciding whether a treatment or preventive measure is worthwhile. Not all clinical trials are successful, however, and possible failures of large trials are becoming a bone of contention among medical scientists.

What irks some critics of clinical trials is that certain trials seem to have been initiated for political reasons. For example, the National Heart, Lung, and Blood Institute (NHLBI) has been pressured to come out in favor of cholesterol-lowering diets to prevent heart disease. However, according to Basil Rifkind of the NHLBI, there is no direct evidence in humans that these diets are worthwhile. The NHLBI therefore began two clinical trials that bear on the diet-heart disease question. For financial and logistical reasons, both trials necessarily involved methodological compromises and both have been criticized for this reason.

One of these trials, which is directed by the Lipid Research Clinic (LRC) of the NHLBI, is specifically designed to determine whether lowering blood cholesterol concentrations can prevent heart disease. Rifkind, who is head of the LRC, says that if the LRC trial demonstrates that cholesterol lowering prevents heart disease, he and Robert Levy, head of the NHLBI, would be prepared to advocate a national program to change peoples' diets. However, there is a disagreement about whether the current trial can possibly produce the data that would be needed to back such a position.

Looking back on their experiences with the NHLBI and other trials, medical researchers are asking whether certain trials should be conducted at all and, if so, when. Further problems arise once trials are under way, not the least of which is to decide when to end a trial. Often one group of trial participants seems to be harmed by a treatment being tested. If this occurs, some researchers argue, the trial should be ended for ethical reasons, even before statistically significant results are obtained. Others say that certain trials have been ended too soon and thus their results will always be under question. No hard and fast answers to the problems arising from clinical trials are forthcoming, but some changing trends in researchers' attitudes toward trials are apparent. As a by-product, this questioning is bringing to the fore avid discussions of medical ethics.

According to Robert Levine of Yale University School of Medicine and Karen Labacqz of the Pacific School of Religion in Berkeley, California, the Conference on Clinical Trial Methodology held at the National Institutes of Health on 3 and 4 October 1977 was actually "all about ethics." They point out that most people assume that the major ethical issue relating to clinical trials involves how to obtain informed consent. However, a question such as, When should a clinical trial be stopped? "is an ethical question that cannot be resolved by looking only to scientific considerations," they said. Researchers must consider the possibility of harming trial participants as well as that of harming patients waiting for the development of new treatments. Similar ethical issues underlie all aspects of the design and execution of these trials.

Despite the controversy surrounding many trials, the scientific merits of randomized, controlled clinical trials are generally acknowledged. In these trials, participants are assigned at random to treatment and control groups. One group is given a new or experimental treatment; the control group gets conventional treatment or a placebo. The randomization is designed to average out possible pertinent differences among the trial participants, such as age, sex, and general state of health. The treatment and control groups, then, should be medically equivalent.

Among the most difficult trials to design, and the most controversial, are those testing various ways to prevent chronic diseases, such as heart disease. For example, designers of trials testing treatments of heart disease must contend with the fact that an average of only 1 out of every 100 middle-aged men suffers a heart attack each year. To see whether a particular preventive measure decreases rates of heart attack in the general population of middle-aged men would require more resources than the government or any private organization has available. Trials for new treatments are less expensive than prevention trials and require fewer participants. For example, in a trial designed to test ways of treating heart attack patients, the participants would have already developed heart disease and so would be more likely to die of heart attacks in the near future than members of the general population.

Many researchers believe that trials for preventive measures must still be conducted, even if the trial designs must be compromised in order to make them feasible. For example, the ideal way to run a trial on cholesterol and heart disease would be to randomly assign trial participants to two groups. Members of one group would follow their normal diets and members of the other group would follow a cholesterol-lowering diet. This sort of trial cannot be conducted, however, for even if compliance with the diets could be ensured, the trial would involve far too many people for far too long a time before any effects could be seen. In fact, in 1969 a National Institutes of Health Study Group concluded that such a trial would require 50,000 to 100,000 people, 30 years of follow-up, and as much as $1 billion.

As an expedient, the LRC designed a trial whose participants are men with cholesterol concentrations within the top 5 percent of the normal distribution in this country. Because the designers of this trial found that it would take too many participants and too much time if diet alone were used to lower cholesterol, they decided to use the drug cholestyramine to lower the participants' cholesterol concentrations more significantly. Diet, Rifkind points out, can only reduce cholesterol concentrations by 5 to 10 percent. The trial involves 3600 men, will continue for 7 years, and is expected to cost more than $100 million.

Proponents of the LRC trial argue that the trial is worthwhile because prevention, not treatment, is the key to lowering the toll taken by heart disease. Thomas Chalmers of Mt. Sinai Medical Center says that the cost of a prevention

trial must be compared to the cost of medical care rather than to the cost of doing other kinds of research. Each day a patient spends in a coronary care unit, he says, costs about $1000. And there are about 1 million heart attacks each year in the United States. Many of these heart attack victims die before they ever reach the hospital, but Chalmers points out that those who die represent a significant economic loss to the country.

Critics of the prevention trials contend that the trials would undoubtedly be worthwhile if they indeed showed that particular preventive measures were use-

Briefing

UFO's Just Will Not Go Away

Federal science officials are now being visited by what many of them regard as a nightmare—an upwelling public interest in Unidentified Flying Objects (UFO's) and requests that the government "do" something about the possibility that they exist. One course of action now being considered is another scientific review similar to the report completed in 1969 for the Air Force by a panel led by the late Edward U. Condon.

The issue arose in July, when the mounting number of inquiries began coming into the White House about UFO's. The White House press office asked Presidential Science Adviser Frank Press whether he could do something about answering this mail. Press's investigation of the matter showed that inquiries from UFO buffs get quite a run around: the White House answers one way, the other federal agencies have their own stock answers, and the Air Force, which has chief responsibility for the issue, says something else. So Press wrote the Administrator of the National Aeronautics and Space Administration (NASA) asking if that agency would take the lead in answering incoming mail.

It was Press's by-the-by paragraph that kicked off the fuss, when he suggested that it might be time for another study of the issue. He even suggested that a new study panel include well-known scientists such as astronomer Carl Sagan of Cornell, who is something of a media star, but is said not to believe Earth has been visited by UFO's.

It should be no surprise to anyone familiar with science-government matters that NASA officials are not relishing the thought of launching such an inquiry and have sidestepped the request by assigning an official to the job of looking at the need for a study. NASA seems to fear that the reopening of the question of the genuineness of visitors from outer space will legitimize a subject most establishment scientists consider phony and a waste of time.

What makes NASA's damned-if-they-do and damned-if-they-don't dilemma interesting, and even important, is that there is indeed a resurgence of public feeling about UFO's, perhaps due to the hit movie *Star Wars*. According to its promotors, *Star Wars* has sold more than 400 million tickets (a fact all the more significant because there are only 200 million people in the entire United States). A new film, *Close Encounters of the Third Kind*, has just been released, about a Citizen Joe whose belief in extraterrestrial visitors is eventually proved right—despite NASA, the Air Force, and everyone else. It is likely to also be a box office hit. Surely it will increase the White House UFO mail.

Indeed, there may be evidence that President Carter once was, or now may be, among the 54 percent of the American public that a recent Gallup Poll found believes in UFO's. While Governor of Georgia, Carter filed a report that he had seen a UFO while standing with a group of men at 7:15 p.m. on an October evening outside the Leary, Georgia, Lions Club. The Naval Academy graduate—apparently not aware that the object was probably the planet Venus—described it as being a big as the moon. He wrote "it came close, moved away—came close then moved away . . . then disappeared."

Moreover, during his presidential campaign, Carter is said to have promised he would release all government information concerning UFO's—a promise which UFO buffs have not let him forget, because of their fervent belief that for many years the government has been covering up its encounters of the third kind.

Truth is as strange as fiction. The Air Force, officials say, indeed classifies some results of its inquiries made after UFO "sightings"—many of which are made near military bases, and by men trained to observe the skies, and a few of which are investigated by Air Force men going up in planes. Press's office says that these facts, together with the conflicting responses the government hands out to UFO buffs who write in, keep alive this belief in a cover-up. Policies like these, officials say, need review and perhaps changing.

In the present climate, then (and who knows when *Close Encounters* will be shown to the First Family), it may become more difficult to avoid another UFO study. Further, it can be argued that scientists in government incur some obligation to respond to the concerns of the public, which, after all, is paying them. On the other hand, it seems clear that federal science officials hope that if push ever comes to shove on the issue of reopening the government's UFO book, the push does not come from them.

SIPI Sells (Out?) Environment Magazine

Environment magazine, which broke the first stories on mercury pollution, polychlorinated biphenyls (PCB's), and the hazard of steam explosions in nuclear reactors, will close down in its present form at the end of December—a victim of the problems small-circulation journals have in finding a suitable, profitable niche.

The Scientists' Institute for Public Information (SIPI), which owns and publishes *Environment*, has agreed to sell it for $20,000 to Heldref Publications, a Washington firm that publishes technical journals such as the *Journal of Environmental Health* and *Current*. SIPI will aid Heldref in soliciting outside manuscripts; but there will be no more staff-written articles, which tended to be the news-making ones.

The decision to cut the SIPI-*Environment* umbilical cord has exposed some of the strains within SIPI, an old, New York-based organization that recently has been growing and expanding into new projects such as sponsoring seminars on energy or genetic engineering for members of Congress in Washington (*Science*, 9 April 1976, p. 122). The sale has sparked a number of resignations, on the editorial board and board of directors, by those who say that *Environment*, which is published in St. Louis, Missouri, is more important to SIPI than SIPI's current leaders think.

By selling *Environment* outright, SIPI

ful and if people then employed those measures. But a trial such as the LRC trial, they say, can have a marginal effect at best in preventing heart disease. After years of public education campaigns by the American Heart Association and others, many people in the United States are already convinced that cholesterol-lowering diets will prevent heart disease. Those who are still skeptical of the diet heart disease hypothesis may be unlikely to change their minds on the basis of the LRC study. Thus even a positive result from the LRC trial could be a mere whistling in the wind.

Briefing

eliminated the magazine's $20,000 debt and the specter of having to raise from private sources the estimated $40,000 deficit the magazine would run next year. The magazine was founded in the late 1950's as an information sheet. In the 1960's it was called *Scientist and Citizen*. In 1969 it acquired its current name and a large Mellon Foundation grant to boost circulation, which eventually peaked at 25,000. Lately, the Mellon money has run out, operating costs have risen, and the magazine's circulation has declined to some 18,000.

The chairman of the magazine's editorial board, Donald Dahlsten, of the University of California at Berkeley, resigned from the board after the sale was agreed upon. Dahlsten charges that SIPI's leading light, Barry Commoner of Washington University in St. Louis, and the SIPI people in New York deliberately let the magazine go because it was not reflecting enough of their current thinking. Also David W. Swetland and Daniel H. Kohl have resigned as members of the editorial board and from SIPI's board of directors. "I think we should have done everything possible to keep the magazine alive," Dahlsten says.

Queried by *Science*, Commoner vigorously denied the charge. "I have as strong a sentimental tie to the magazine as anyone," he replied. "I mimeographed the first issue back in 1958." As for his view of the magazine's direction, he said, "There was a time when the magazine encompassed most of what SIPI was doing" in environmental pollution and related issues, he said. "SIPI's activities have naturally gotten broader, while the magazine continued to represent—very well—that segment that SIPI did some time before."

Environment's ten-member staff, in St. Louis, are unhappy, obviously, and are rumored to be even bitter about the decision, since they will lose their jobs and none has settled on other employment. Publisher Julian McCaull sounded resigned. "I guess it was unavoidable," he said.

Among the small magazine's achievements have been the PCB and mercury stories, both of which were published in 1969, and a 1976 story by co-editor Kevin Shea about the possibility of major explosions in nuclear reactors, based on a report leaked from Sandia Laboratories. In recent years also, *Environment* has been a sort of "roots" for modern technology and its problems, delving back into the origins of medical practice, urban industrialization, and the electric power industry, to name a few.

Role of Science in China's Development

While inquiries into the achievements of Chinese science have tended to the arcane, the Congressional Research Service (CRS) has just published a study of China's central accomplishment, her apparent ability to control population growth and keep her 850 million people adequately fed.

The Role of Science and Technology in China's Population/Food Balance, by China expert Leo Orleans, delves into such Oriental mysteries as whatever happened to the famous "Eat tadpoles" method of contraception which the Chinese once advocated in international forums; how China developed an oral contraceptive when no papers on the subject appear in her technical literature; and whether she will be able to feed her people in the future. On the last point, the study is optimistic, and concludes that the rest of the developing world can learn from China's methods.

Traditional Chinese medicine has opposed abortion and other drastic population control measures, and instead has harkened to ancient potions, such as "the paper on which silkworm eggs have been hatched" or "fried oil and quicksilver," or "Shui yin" which contains poison. Political leaders advocated even less efficacious methods in the 1950's, when Western bourgeois medicine was in particular disrepute, such as acupuncture or swallowing 14 live tadpoles on the third day after menstruation.

But in other, more candid times, the Chinese scientific establishment has disputed these methods and admitted their inefficacy. Since the 1960's, the Chinese government has encouraged its technical community to develop a variety of approaches to contraception, including even making abortion easily available to women who already have some children, and other methods. Even the "barefoot doctors" who serve in the countryside have been trained in a simple sterilization procedure using acupuncture as an anesthetic. The CRS report notes that one paramedic thereby becomes "a family doctor, an anesthesiologist, a surgeon and a sex therapist." But, it adds, "it seems to work."

The Chinese conducted major research into developing oral contraceptives during the 1960's, the report says, despite some earlier reports that it did not have a pill. The work was done at just a few institutions, the report says, which explains why there was no need to communicate widely about it through established scientific journals. Field testing may have been done on women in other countries, possibly Malaya. The Chinese have developed the world's first low-dose oral contraceptive, as well as "paper forumulations" that, like a sheet of stamps, can be torn off at the perforations, one at a time, and eaten.

The report attributes China's increased agricultural productivity again to its diversity of approaches: good pest control, extensive use of unskilled manual labor to literally build new fields in difficult areas, importation of chemical fertilizer, and for the future, the 13 new fertilizer plants it ordered from abroad in 1972. China's diversified national diet also helps. While most Western experts measure a nation's agricultural productivity and self-sufficiency in terms of grain, the Chinese rely on a large share of vegetables and other things in their diet—roots, grasses, berries, seaweed, sea urchins, snails, snakes, insects, birds' nests, and even camels' humps!

A major ingredient in China's success has been her stress on national "self reliance" in bringing population and food production into balance, according to the study. And while China apparently does little preaching to developing countries on what policies they should follow, the study seems to say that self reliance is the key lesson she has to teach.

Deborah Shapley

Water Act Revision Complete

Congress was expected in early December to endorse and send on to the President the 1977 amendments to the Clean Water Act of 1972. The measure, commonly referred to as the act's "midcourse correction" on the road to "zero discharge," has been subjected to 2 years of deliberation. Environmentalists and industry both appear to be reasonably satisfied with the results, which include a 1-year extension of interim deadlines for industrial waste cleanup.

The two most controversial aspects of the new bill relate to industrial point source polluters and to the dredging and filling of wetlands.

The bill breaks pollutants into three categories: "conventional" (dirt, sewage, organic waste); "toxic" (the Environmental Protection Agency has a tentative list of 129 toxic chemicals); and "nonconventional"—a new category of chemicals, including some pesticides and heavy metals, whose toxicity is yet to be determined. The deadline for installation of "best available control technology" (BAT) for conventional pollutants has been moved from 1983 to 1984, although waivers may be applied for in cases where BAT is not deemed to be cost-effective. For toxic pollutants, the deadline is 1984, with no exceptions.

Some environmentalists are concerned that dangerous chemicals may stay interminably on the unconventional list, thereby escaping the stringent controls applied to those on the toxic list. However, an EPA official says the bill has been designed, through elimination of formal hearing requirements and additional discretion given the EPA administrator, so that it will not be as difficult as it has been in the past to have a chemical regulated as "toxic."

Compromise on Wetlands

As for wetland dredging, the House-Senate conference committee made a major concession to the House when it voted that permits would not be required for discharge of dredge or fill in projects "specifically authorized by Congress." This covers many of the big government stream channelization and dam projects. Instead of getting a permit, the agencies involved will be required to submit environmental impact statements (EIS's) to the relevant congressional committees. Environmentalists consider this exemption outrageous, and the EIS provision silly since the committees are scarcely equipped to evaluate such statements. An EPA official explains that members of Congress "don't want EPA and the Corps of Engineers [the permit-granting authorities] second-guessing Congress and the President" on big projects, or jumping in to halt half-completed ones.

Otherwise, the bill embodies a continuing evolution of the original wetlands policy. States will be given control over permit programs on other than major bodies of water if they have a plan approved by the EPA. Also, the bill resolves a controversy that began a couple of years ago when the Corps put out a press release saying that farm plowing might require a permit (the plow being a "point source," and the dirt "fill"). The law now specifically exempts discharge activities in what are defined as "normal" farming, mining, and timbering practices.

Finally, there is a new, futuristic clause that would permit states to forget about permits altogether if they submit to EPA an acceptable statewide regulatory scheme covering all point source dredging and filling operations.

Among other items covered in the bill is continuation of the federal grant program for sewage treatment plants, with $24.5 billion authorized over the next 5 years. The federal share of the cost of treatment facilities is 75 percent, but that can go up to 87.5 percent in cases where "alternative or innovative" treatment technologies are being tried.

The need to renew the sewage grants was the main reason Congress wanted to get the bill out this year. Jim Banks of the Natural Resources Defense Council adds that environmentalists are pleased that the extension was for 5 rather than 2 years—not only because it helps cities to plan, but because the water act is less likely to be brought up for tinkering and possible weakening before the expiration of the sewage authorization.—C.H.

George Mann of Vanderbilt University, a forceful critic of the diet-heart disease hypothesis, believes that the LRC results could not be extrapolated to the general population because they involve a select group of high-risk men who are not representative of the rest of the population. Moreover, cholesterol is lowered with a drug, not by a diet alone, which further confounds the results.

According to Mann, at least one planner of an NHLBI prevention trial admits privately that the trial he is involved with cannot produce meaningful results. But, Mann says, the planners of these prevention trials "get so involved in obtaining financial support that they'll do and say just about anything to keep their trials going."

Closely related to the problem of deciding whether to start a randomized, controlled clinical trial is the problem of deciding when such a trial should begin. Usually, a randomized controlled trial is suggested on the basis of presumptive evidence that a particular treatment or preventive measure is useful. However, Chalmers estimates that fewer than 20 percent of trials testing new therapies are well-controlled. And this percentage can be far smaller than 20. A few years ago, Chalmers surveyed the clinical-trial abstracts submitted to the annual meeting of the American Gastroenterological Association. He noted that only 4.5 percent of those trials appeared to be well-controlled.

Many physicians prescribe treatments on the basis of results from uncontrolled or poorly controlled studies. They often come to believe in the efficacy of those treatments and feel ethically constrained from allowing their patients to participate in randomized controlled trials. They cannot in good conscience risk denying a patient what they believe to be the best treatment, even if their belief is not scientifically justified.

Clinical investigators are often in a quandary when they must decide when to start a randomized controlled trial. To start when a great deal of presumptive evidence favoring a treatment has been published is to risk fighting physicians who already believe in the treatment. To start too soon is to risk wasting years and a great deal of money testing a treatment that, by the time the trial results are out, has been modified, replaced, or discarded. Both of these difficulties arose when investigators planned randomized controlled trials of the effects of coronary bypass surgery.

Recently, investigators at the NHLBI initiated a randomized controlled trial to

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.