Research Frontiers—Whither the Quest?

Reorganized as a health-science university, Loma Linda still produces more research than any other Seventh-day Adventist college or university. What are the prominent areas?

by Clark Davis

LOMA LINDA UNIVERSITY'S INNOVATIVE THERAPIES in cardiac infant transplantation and proton therapy for cancer have received international media exposure while its research has received little attention outside the scientific community, for example, its work in perinatal biology and mineral metabolism. The opening of the present university medical center in 1967 helped to spawn an invigorated and more ambitious stance toward medical research and innovative clinical procedures.

The number of research papers published by LLU faculty more than tripled between 1981 and 1991. In the 1990-1991 school year, Loma Linda University faculty members participated in 1,597 research projects and other scholarly activities (916 as principal investigators), published 1,342 articles in professional journals and 138 in lay publications, and made 1,738 public presentations. Loma Linda's total research budget for the 1990 fiscal year totaled more than $6 million.

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Infant Heart Transplantation

When Loma Linda University cardiac surgeon Leonard Bailey transplanted the heart of a baboon into Baby Fae in October of 1984, Loma Linda was placed in the international media spotlight as never before. Yet this pivotal moment was actually part of a steady process of infant cardiac clinical research in transplantation begun at Loma Linda in 1977 and continued after the Baby Fae incident.

Now, in 1992, Loma Linda has emerged as the world leader in infant heart transplantation. Approximately 50 percent of the world's heart transplantations in infants less than six months of age have taken place at Loma Linda, with more than 80 percent of the 120-plus infants surviving surgery. The longest survivor recently celebrated his sixth birthday. Numer-

ous adults and children have also undergone heart transplants at Loma Linda.

In the years since the Baby Fae incident, Bailey has enlarged the transplant team to now include three cardiac surgeons, three general pediatricians, four pediatric cardiologists, three neonatalogists, two immunologists, one infectious disease specialist, four nurse coordinators, two clinic nurses, and a host of other support and consultative personnel.

Alongside the transplant program's clinical success, it has emerged as a major research and education center for infant heart transplantation, fostering an international network of transplant professionals. Loma Linda University Medical Center regularly hosts numerous transplant physicians and nurses who study the program as a model for their own institutions. In March 1990, the transplant team sponsored the first Loma Linda International Conference on Pediatric Heart Transplantation, drawing 500 transplant professionals together to share their experience.

Dr. Bailey and his team at Loma Linda have taken their role as leaders in infant heart transplantation seriously. Growth of transplantation is limited by the paucity of human donors. Addressing this problem has led researchers to look at the use of hearts from different species (xenografts) to serve as a bridge to transplantation (to span the time until a human heart would become available). The first international conference on xenotransplantation will take place at the University of Minnesota, where Loma Linda University will present its research data on cross-species heart transplantation.

The question of graft growth was an important one in relation to heart transplantation. Would transplanted hearts continue to grow with the recipient infant? Dr. Bailey's research in animal models demonstrated that the heart would grow along with the recipient. That model has held true, as has been reported in the scientific literature by Loma Linda University's pediatric cardiologists.

Other investigators has attempted to reanimate hearts that have already stopped beating. Being able to revitalize hearts that have sustained a cardiac death would greatly enhance donor status. Research led by Steven R. Gundry in Loma Linda's animal laboratory shows that it is possible to restore cardiac function 30 minutes after the heart has stopped beating.

Another strategy evaluated has been that of utilizing anencephalic infants as potential donors. In 1988, neonatologists at Loma Linda piloted a program to modify the care of 12 live-born anencephalic infants for one week to determine whether organ viability could be maintained and whether the criteria for total brain death could be met. This study suggested that it is usually not feasible, with the restrictions of current law, to procure solid organs for transplantation from anencephalic infants.

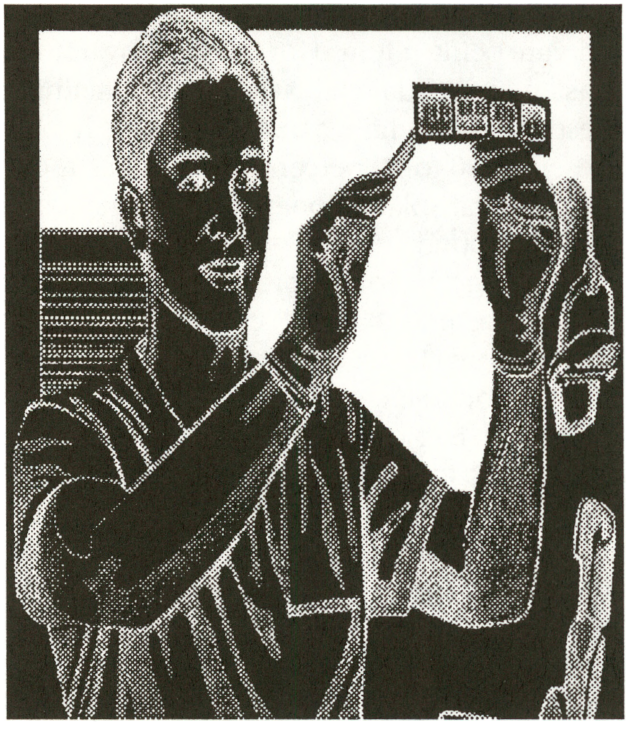
Because transplantation has now become a reasonable option for the treatment of otherwise uncorrectable heart disease, more infants are being referred for this therapy. Efforts must now be directed towards maintaining these infants while awaiting donor hearts. Presently, 20 to 30 percent of all babies registered for transplantation die before a suitable donor is found.

Buying time for the procurement of donor organs presents a great challenge to heart centers. Loma Linda University Medical Center has developed techniques to extend the waiting period. Babies has successfully been managed for up to three months before an appropriate donor has been identified. Clinicians have engineered a low-oxygen environment that helps to decrease selective blood flow to the lungs—blood flow that would literally steal away blood that is needed to go to the body.

Another strategy for extending a safe waiting time has been to facilitate in-utero diagnosis of lethal heart disease. An unborn fetus could then be placed on the national waiting list at 36 weeks gestation while waiting safely in the mother's womb until a donor search is successful.

Loma Linda University's infant heart transplant team is also active in immunological research. Scientists in the immunology center are looking at infant recipients, trying to define the norms of the infant immune response. Medical center immunologists are testing the hypothesis that there is an immunological window of opportunity in these infants. These infants have lived through an in-utero experience with mothers who are distinctly immunologically different from them. Perhaps the tolerance achieved in the womb carries over into early infancy, allowing a less-aggressive response to a foreign graft. The idea of introducing graft tolerance in the immediate post-operative period tantalizes investigators.

Loma Linda University clinicians are looking at ways to non-invasively monitor rejection of the heart graft. In adults, endomyocardial biopsies are the standard for determination of rejection. A scissor-like device is inserted into the right side of the heart and little snippets are taken out to be evaluated under a microscope. Because infants have tiny hearts, LLU physicians deemed it impractical and potentially hazardous to rely on biopsy to reveal rejection. So a variety of non-invasive procedures are constantly being assessed.



Perinatal Biology

When the Surgeon General wanted someone to write the section dealing with the effects of smoking on the unborn fetus for his "Report on Smoking and Health," he turned to Lawrence D. Longo, distinguished professor of physiology and obstetrics and gynecology. The selection of Longo surprised no one in the scientific community. As dean of researchers at Loma Linda, he has developed the uni-versity's division of perinatal biology into one of the very best perinatal groups in the country.

Perinatal biology is the study of the physiology and cell biology of the developing fetus, the changes associated with birth, and the ways in which the newborn infant handles the stresses of living outside the womb.

Gordon G. Power, professor of physiology and medicine, is a founding member of the division of perinatal biology. His research interests center about the changes ring occur at birth that enable the previously sheltered fetus to survive in the less-friendly surroundings of the outside world. His experiments begin with pregnant sheep and progress to computer modeling where possible. Working in collaboration with Raymond D. Gilbert, professor of physiology, Power has found that important changes occur even in the first few minutes of the life of a newborn. The rate of

the baby's metabolism increases manyfold. This large increase can be critical for baby animals born during the cold winter months.

Dr. Power's research suggests that the placenta has a vital role in the change in metabolic activity. Before birth, the placenta transfers nutrients and other chemicals between the mother's bloodstream and the bloodstream of the fetus. It appears that before birth the placenta also secretes a chemical inhibitor that inhibits the metabolic activity of the fetus. After birth the inhibitor is, of course, lost, and the rate of the infant's metabolism speeds up dramatically. Dr. Power and his collaborators have evidence that the inhibitor is adenosine and have proposed that one cause of abnormally small babies might be excessive adenosine released by a diseased placenta.

Steven M. Yellon, associate professor of physiology, is an expert in the neuroendocrinology of puberty and in biological clocks, the daily rhythms of the body that are influenced by secretion of the hormone meltonin from the pineal gland. These daily rhythms are involved in such diverse reproductive processes as the onset of puberty and the initiation of labor. Yellon is working with graduate students Kevin Buchanan and Eda Marie Apostolakis in study of how light and dark cycles appear to affect the onset of birth and puberty.

Charles Duscay, assistant professor of physiology, has focused on the causes of premature labor and delivery. He and fellow researchers have demonstrated that placing rhesus monkeys in an altered light cycle with light at night but darkness during the day reverses the pattern of cortisol secretion and uterine contractions. This switch also reverses the normal time of day of delivery. More important, using dexamethasone to suppress estrogen production by mother and fetus stopped the daily contraction of the uterus. It is hoped that this research will lead to better treatments to prevent premature births.

Longo, Gilbert, and other collaborators are researching the effect of high altitude on pregnant sheep and their fetuses. The pregnant sheep are kept at the Bancroft Laboratory at White Mountain, California (elevation 12,820 ft.) where the reduced partial pressure of oxygen in the air lowers the oxygen concentration in the ewe and hence the fetus. After four months the sheep are returned to Loma Linda where their adaptation to the low oxygen levels is studied. This research has shown that changes in calcium levels in heart muscle cells are one factor that helps the fetus adapt to low oxygen concentrations. Such studies have important implications because many human fetuses also experience prolonged shortages of oxygen in women who reside at high altitude, those who engage in strenuous physical activity at work, those who are anemic, or those who smoke.

Today, the research about which Longo is most excited is in the area of cell and molecular biology. Working in collaboration with Christopher Cain, assistant professor of bio-

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chemistry, Longo is studying the enzyme ornithine decarboxylase in the brain. The levels of enzyme activity peak in response to low oxygen concentrations, and this is followed by a peak in synthesis of polyamines in the brain. Longo and Cain hypothesize that this is a mechanism to protect against harmful effects of low oxygen.

William J. Pearce, assistant professor of physiology, researches brain blood vessels in sheep, even arteries smaller than one-hundredth of an inch in diameter. Because arteries of the brain are more permeable at birth and less permeable as the infant matures, Pearce is looking for the mechanism that controls the permeability of the blood vessels. His work is particularly relevant for understanding the high incidence of intracranial (brain) hemorrhages in premature babies, especially after they have suffered from a lowered oxygen level.

Proton Therapy Research

From their inception, the proton accelerator and facility at Loma Linda University Medical Center were meant to stimulate research. At the Proton Treatment Center, a research program is in place, attracting physicians, physicists, and other scientists from around the world. The Proton Treatment Center at Loma Linda encompasses the first accelerator and beam-delivery systems designed for patient treatments. The facility which houses them is the first in the world conceived and built to exploit protons for therapy. The unique nature of the facility and its contents attracts researchers interested in clinical and basic research in protons. The research program has two major divisions: basic and clinical science.

Basic scientific research includes several aspects, such as radiobiological studies, engineering investigations including computer science and electrical engineering, and physics. Some physics investigations concern the effects of protons in living tissue, with potential applications for treatment; others concern the protons themselves.

Clinical research studies occur on several levels. One focus of current study is the brain. A primary goal on this avenue of investigation is to identify the sequence of cell population changes that produce the tissue and organ changes, commonly known as late reactions, found months to years after a therapeutic course of irradiation has been completed. A second goal is to identify new time-dose strategies; that is, to develop proton radiation treatment schedules capable of improving cancer control while sparing normal brain tissue.

With the assistance of Joseph Thompson, of the section of neuroradiology, and Andrew Kennedy, of the LLUMC house staff, radiation medicine investigators are performing analyses of tissue to determine the degree to which changes in tissue can be inferred from image changes, and thus, the degree to which magnetic resonance imaging can be employed as a measure of the brain's response to radiation. Thus far, the effort has enabled the investigators to identify graded changes in the brain following different total doses and different fractions of proton irradiation.

The immediate goal of this three-dimensional work is to test the hypothesis that the microvasculature is the tissue most sensitive to irradiation; that damage to the microvessels results in changes in other tissues, which in turn can produce the well-known long-term sequelae. Two-dimensional measurements of the microvasculature, made on microscopic sections, do not sufficiently describe post-radiation effects, nor do they show the relationships within or between the components of tissue volumes. Using a special staining technique they developed, however, and employing computer-assisted three-dimen-

sional reconstructions, McMillan and Marie-Helene Archambeau are evaluating the changes in brain microvessels and are comparing those changes observed with the same vessels in unirradiated brain tissue.

Loma Linda is working closely with the Lawrence Laboratory at the University of California at Berkeley and the Cyclotron Laboratory at Harvard University, two other institutions where patients are treated by charged particles. This work has led to a proposed Proton Radiation Oncology Group, which is intended to conduct national trials under the auspices of the Nation Cancer Institute. These trials will identify and document the role of proton therapy in the management of malignant and benign tumors.

It is anticipated that the Proton Radiation Oncology Group will be the foundation of an international proton therapy consortium that will include clinical and basic scientists from Europe, Asia, and other parts of the world.

Epidemiologic Studies

A non-smoking, relatively thin Adventist who emphasizes fruit and vegetables and exercises moderately may reasonably expect an extra 10 to 12 years of life as compared to a relatively obese, non-exercising, high-fat/meat-consuming Adventist. Such are the preliminary results of the Adventist Health Study, a series of major Loma Linda University research initiatives begun in 1974.

In the nearly two decades since the study began, it has garnered increasing attention by scientists around the nation and world for being one of the most interesting and probing analyses of the effects of life-style on health. The National Institutes of Health and other funding agencies have contributed more than $11 million to these studies.

The Adventist Health Study (which followed the Adventist Mortality Study begun in the early 1950s), began as a cancer investigation with Roland Phillips, as the principal investigator. In 1981, a cardiovascular component was added to the study, directed by Gary Fraser.

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Initiated in 1974, the study enrolled 34,198 California Adventist men and women. Each of these subjects completed two extensive questionnaires containing about 350 different items of information. Between 1976 and 1982, each subject also completed an annual questionnaire reporting any hospitalizations. Loma Linda researchers would then visit the hospital records rooms and collect extensive diagnostic data if there was any indication of coronary heart disease or new cancer. Thus, it was possible to relate different health habits to the risk of developing a new cancer or fatal or non-fatal heart attacks.

Loma Linda researchers use the data to compare the relative health of Adventists who exhibit different life-styles.

In brief, the study has suggested that particularly for cancers of the gastrointestinal, lung, and urogenital systems, higher consumption of fruit and beans and lower con-

sumption of animal flesh foods are associated with a lower risk. The study did not show any definite association between diet and risk of breast cancer, one of the most common cancers in women. For fatal coronary heart disease, men who consumed beef at least three times a week had a 60 to 70 percent increased risk, and similar women had about 30 percent increased risk. The study also suggested that consumption of whole wheat bread was associated with about 40 percent decrease of both fatal and non-fatal heart disease.

Perhaps one of the most exciting and completely new findings was that frequent consumption of nuts (at least four times a week) was associated with roughly a halving of risk of both fatal and non-fatal coronary events when compared to people who ate nuts hardly at all. It should be pointed out that these results both for cancer and heart disease have all be adjusted for a large number of traditional risk factors where relevant.

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Loma Linda researchers have also reported a number of relationships between non-dietary variables and risk of cancer and heart disease, many of which have been found in non-Adventist populations. For instance, the usual associations between cigarette smoking and lung cancer, bladder cancer, and pancreatic cancer were documented. Only 1 to 2 percent of the Adventist survey population admitted current smoking, but about 23 percent had smoked at some time in the past. These people continued to be at higher risk.

Similarly, Loma Linda researchers reported that a history of cigarette smoking or particularly current smoking had a clearly defined association with risk of coronary heart disease. Hypertension, physical inactivity, obesity, and diabetes mellitus were also related to risk of heart attack in the same way as has been reported from the Framingham and many other epidemiologic studies. The Adventist Health Study also evidences that a history of cigarette smoking or current smoking was associated with a substantially elevated risk of leukemia and myeloma.

Risk of breast cancer was related to age at menarche and age at menopause, age at birth of first child, and history of breast cancer in the mother. These findings are of some importance, as they tend to negate the argument that because the Adventists are a special population, findings based on surveys of Adventists may not apply to the general population. However, for those diseases in which the epidemiology is well understood—such as coronary heart disease or breast cancer—Loma Linda researchers demonstrate the identical findings that others have found in many diverse populations.

Thus, researchers at Loma Linda believe their dietary findings and other new findings from this population almost certainly have application to non-Adventist populations as well.

David Abbey, professor of biostatistics, has taken the opportunity to identify a subset of the Adventist Health Study population: Adventists who live in the smog basins of California. He has expended a great deal of effort to carefully document exposure of these subjects to various pollutants in smog and has then related this to risk of various diseases.

This substudy has followed a cohort of approximately 6,000 members of the Adventist Health Study who have lived 10 years or longer within five miles of their present residence. Respiratory symptoms have been ascertained on the subcohort in 1977 and again in 1987. Statistically significant associations have been found between total suspended particulates and all-cause cancer in females as well as development of respiratory symptoms. A strong trend association has been noted between ozone and respiratory cancer.

This substudy has been funded by the California Air Resources Board and the Environmental Protection Agency and is being used as epidemiological evidence in support of air-pollution standards. The effects of past and passive smoking are also being investigated on this data set under funding from tobacco tax money in California.

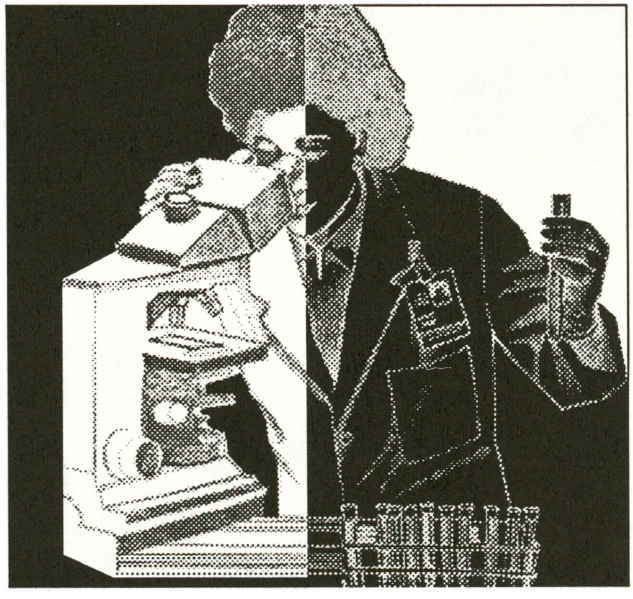
Mineral Metabolism Unit

Loma Linda University's Mineral Metabolism Unit, directed by David J. Baylink, has become a leading international center for the study of osteoporosis, a crippling bone disease that affects more than 15 million people in the United States alone. The research unit is a multidisciplinary and multinational team of approximately 60 persons, receiving well over $1 million each year in federal research funding. The 10 principal investigators have published nearly 200 academic papers during the past 10 years.

The principal investigators each conduct a major research initiative. Subbaraman Mohan, associate professor of medicine, and Thomas Linkhart, associate research professor of pediatrics, for instance, are currently studying the factors behind the regulation of bone growth. Mohan's work isolates the growth factors involved in bone development in order to understand their components and mechanisms. He has found what is now called insulin-like growth factor II (IGF-II). This growth factor is produced in bone cells, and when added to cells of all types, stimulates their division and subsequent growth. IGF-II interacts with another protein termed insulin-like growth factor binding protein, or BP4, which slows its effects.

Graduate fellow Donn LaTour, together with Linkhart, Mohan, and Donna Strong, assistant research professor of medicine, has been involved in studying the dynamics of BP4. They have found that the body uses the two proteins to regulate the rate of bone growth and deterioration in a process called "remodeling." By isolating and understanding the proteins employed by the body to regulate bone growth, the research by Mohan and his collaborators will assist medical scientists in therapeutically manipulating these factors in patients experiencing bone deterioration.

K. H. William Lau, associate professor of medicine, is leading another research initiative toward understanding bone deterioration. Lau is studying the ways in which fluoride can be an effective agent in the treatment of osteoporosis. Fluoride is considered the single



most important agent in increasing bone density. Lau has discovered that fluoride works by inhibiting an enzyme in bone osteoblasts called acid phosphatase, which regulates cell growth. Scientists have long detected the presence of enzymes in bone tissue. Lau is making sense of these enzymes, their functions on bone growth, and subsequently how they can be manipulated.

In essence, Lau has shown that fluoride and the insulin-like growth factors studied by Mohan can have the same result, though by different mechanisms. Fluoride enhances growth factors by inhibiting proteins that inhibit bone growth. The introduction of fluoride can have tremendous impact in the fight against osteoporosis.

Another major research initiative with Baylink as the principal investigator, is an effort to develop serum assays to measure bone development and deterioration. These tests will allow physicians to monitor the rate of bone formation and breakdown. The assays will provide the means for assessing the effects of new bone therapies and for more rapid and accurate diagnoses of bone diseases.

Other major research advances at the mineral metabolism unit include bone-forming effects of calcitonin (John R. Farley); establishment of role for grow-stimulating substances in diseases such as osteoporosis (Richard Finkelman, associate professor of periodontics); understanding the bone diseases at the molecular biology level (Donna D. Strong); and discovery of a new protein factor that helps in the maturation of bone-forming cells (Jon E. Wergedal, associate research professor of medicine).