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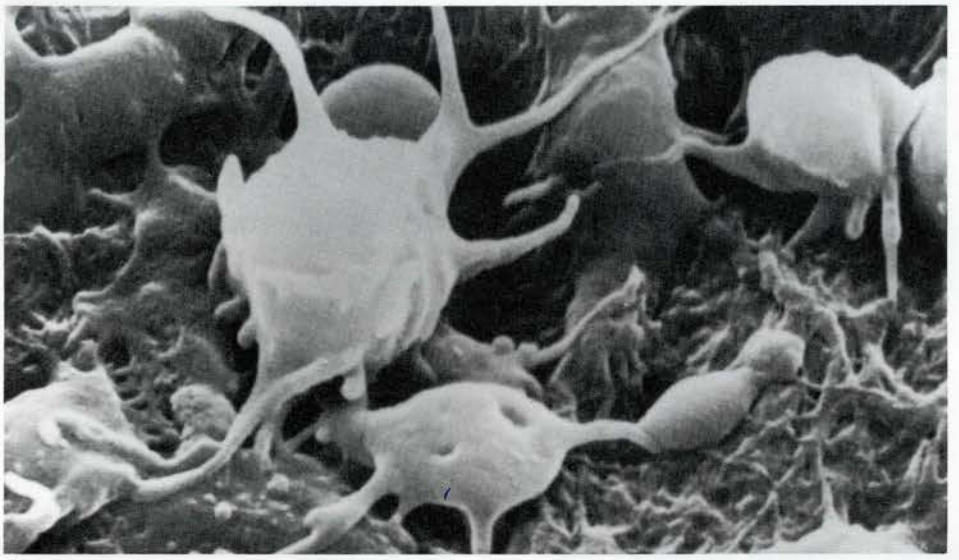
**What personality traits found in a 2-year-old can be recognized in that same person at age 25? A unique BUSM study, which follows the psychological development of about 30 individuals, promises to provide interesting answers to this question. See story on page 3.**



*This scanning electron micrograph shows an experimental vein graft that has been injured at the time of implantation. Twenty-four hours later, numerous platelets can be seen attached to the damaged wall of the graft. (Photo by William Quist)*

## Scientists at BUSM seek to prevent 'delayed failures' in bypass surgery

Of the many forms of surgery performed today, few have the image of risk and boldness associated with blood-vessel bypass operations.

Yet while there is clearly some risk involved for patients undergoing bypass surgery, blood-vessel grafts have become a relatively routine procedure for experienced surgeons, said Frank W. LoGerfo, M.D. Even the much-publicized triple bypass heart surgery—where grafts are used to replace three of the arteries that supply blood to the heart—has become a relatively safe procedure.

"The mortality of bypass operations is very low—usually around 1 or 2 percent," said LoGerfo, an associate professor of surgery and director of vascular surgery training at BUSM, and associate visiting surgeon and coordinator of the Renal Transplant Service at University Hospital, a principal teaching hospital of BUSM.

"On the other hand," he added, "there is a very serious problem associated with these operations in that a great many of the grafts fail within the first year."

Such delayed failures occur in 20

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## Researcher aims to determine if backyard pesticides really are 'safe'

Toxic waste dumps and chemical spills are among the unfortunate byproducts of our technological world. Television and newspaper reports of toxic sites confront us daily. The frequent media coverage of these potential or existing chemical hazards has made toxic waste one of the most controversial issues of our time.

But all chemical hazards do not come in the frightening form of barrels rotting in a backlot. Far less obvious is the possible danger from toxic substances that we encounter through ordinary activities, hidden substances with effects that may take years to surface. Judith Marquis, Ph.D., is investigating the possibility that certain "safe" pesticides that rid backyard vegetable or flower gardens—and vast acres of agricultural produce—of insects ultimately may produce harmful effects in humans and animals.

Marquis, an associate professor in the Department of Pharmacology and Experimental Therapeutics at Boston University School of Medicine, is the principal investigator of a three-year $250,000 investigation of pesticide toxicity. She started the federally funded project last year.

Marquis is examining the group of

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**Pesticides...**
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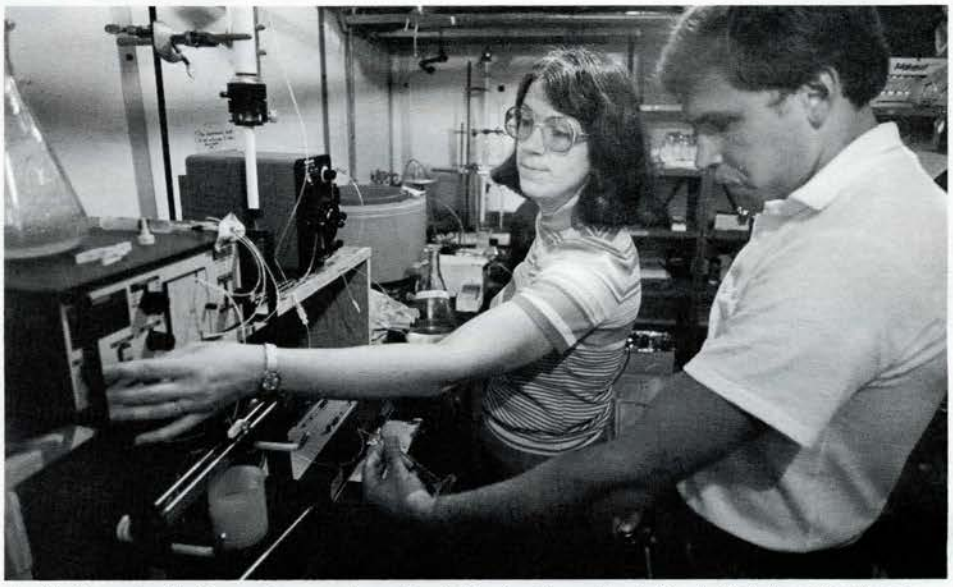
pesticides known as organophosphates: Parathion, Malathion, Azinphos-Methyl ("Guthion") and Diazinon. "These pesticides are used by greenhouses and home gardeners as well as by large-scale agriculturalists," said Marquis.

While it is known that the pesticides are highly toxic to organisms exposed to them in high concentrations, little is known about the effects of lesser amounts, particularly on humans. "These pesticides are considered to be selective—that is, they are more lethal to insects than they are to people or animals," Marquis explained.

According to Marquis, who currently is conducting tests on low-level pesticide toxicity using animal tissues, the organophosphate pesticides exert lethal action by affecting the cholinergic system, the network of nerves and chemicals that controls muscle response. The neurotransmitter called acetylcholine, one of the chemicals that occurs naturally in the body and carries information from nerves to muscles, is an integral part of this system. Acetylcholine carries signals to skeletal muscles, controlling movement, and to the central nervous system, signaling memory function in the brain. It also functions in transmitting sensory information by carrying input from outside the body to the brain through the central nervous system.

Neurotransmitters usually are released by nerves in little "packages" of molecules. These molecules travel across a very small area of the nerve (a few microns long) called a synapse. At the other side of the synapse, the molecules interact with what are called receptor proteins, triggering a response in a nerve or muscle.

The combination of acetylcholine and the receptor protein produces a contraction in the muscles. For example, when skeletal muscles contract, they produce movement. Contraction of the diaphragm allows breathing to occur, and the contraction of the smooth muscle of the gut makes the digestive system function.



*Judith Marquis, Ph.D., and research assistant Charles Cyr collect data in their investigation of organophosphate pesticides. (Photo by Bradford F. Herzog)*

However, muscles cannot function in a continuously contracted state, but must relax and contract to be effective. An enzyme called acetylcholinesterase regulates this process. Acetylcholinesterase is found in the postsynaptic membrane along with the receptor proteins, and it destroys the acetylcholine molecule after it has combined with the receptor proteins. This allows the muscle to relax.

According to Marquis, the organophospate pesticides block the enzyme acetylcholinesterase by mimicking the actions of acetylcholine. By interacting with acetylcholinesterase in the same way that acetylcholine does, the organophosphates prevent the enzyme from performing its function. "Once the organophosphates bind to the enzyme, the enzyme is tied up," said Marquis. "The chemical interaction between the insecticide and the enzyme is very tight."

According to Marquis, this process ultimately results in the destruction of the cholinergic function. She and her research team are exploring the cholinergic system, examining in detail the enzymes involved and the effect of toxic substances on cholinergic function.

"We are conducting basic molecular pharmacology research on the enzymes acetylcholinesterase and serum cholinesterase. We're asking a number of questions about these enzymes: What are the different forms of the enzymes? How do they work? What will alter their function? How does the cholinergic system function in general?," Marquis explained.

So far Marquis' study has concentrated on isolated model systems using calf brain. She also uses a form of cholinesterase purified from human blood serum in her research. Later Marquis will work with organ systems in live animals. Such techniques as ultraviolet and fluorescence spectrophotometry are used to study the properties of the isolated proteins and enzymes, and to monitor their interaction with drugs and toxic substances. Marquis also tests

the effects of experimental compounds, many of them not yet marketed, on the proteins.

In addition to determining whether there are any serious health effects from repeated exposure to very low doses of insecticide, the researchers aim "to define the mechanisms of pesticide toxicity so as to permit the development of antidotes for these substances and also the development of newer, safer pesticides with greater selectivity," Marquis said.

Marquis' research to date has revealed several previously unidentified characteristics of organophosphates.

"We have determined that very low doses of organophosphate insecticides do alter proteins other than the target enzyme acetylcholinesterase in the mammalian brain," Marquis said.

Her work also has revealed that a purified form of acetylcholinesterase can be chemically modified in the laboratory to form an enzyme that is highly resistant to inhibition by organophosphates, but is still completely functional. "We don't know at this point whether such protective modification is possible in the natural enzyme in mammals," she said.

Marquis hopes her research will shed light on the problem of pesticide disposal. Marquis said that organophosphates are not highly water-soluble, but still could present problems to communities with shallow water tables through run-off or careless waste disposal. "These pesticides may be getting into our water supplies now, and it's a frightening situation because we just don't understand their low-level, long-term health effects," she said.

*—Marilyn J. Davis*

**Suggested Further Readings:**

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2. Katz, B.: Nerve, Muscle and Synapse. McGraw-Hill Co., 1966.

# BUSM researchers near completion of 30-year human development study

Scientific studies that span three decades are relatively uncommon. Studies that examine 30 years of life of one group of human subjects, beginning at infancy, are even less common in the scientific world. At Boston University School of Medicine such a follow-up study is in its final stages.

The research began three decades ago in the months before the subjects were born. Today these subjects are adults working at a full range of careers, and the researchers at BUSM are looking at them once again—attempting to gain an overall, long-term perspective of human psychological development.

Among other things, the scientists are seeking clues to how early experiences shape the way people act and perform in later life: The researchers are asking how an individual's personality organization at age 2 can provide the clues for recognizing that same person at age 25.

"In a time when so much scientific interest has been focused on infancy and early childhood developmental research, there is an urgent necessity that a broader long-term perspective be gained of the early developmental process," said Louis W. Sander, M.D., a former professor of psychiatry at BUSM, who has been involved in the study since it began. Sander, now a professor of psychiatry in the Division of Child Psychiatry and Senior Scholar at the University of Colorado, hopes that this BUSM study will do much to fill that need.

In 1954, a group of BUSM faculty members, headed by Eleanor Pavenstedt, M.D., then chief of the Department of Child Psychiatry, began an investigation in which they closely monitored the lives of 30 children, born at University Hospital (then called Massachusetts Memorial Hospitals), until their first year of school. One pregnant woman was chosen each month until the researchers had 30 subjects.

"Dr. Pavenstedt's aim was to carry out in great detail a longitudinal study of early personality development," said Sander. "This was based on several aspects: first, observation of mother-infant interaction; second, the repeated examination of infant behavior; and finally, the repeated gleaning of information from parents about the gradual changes in their children's behavior and the changes in the family."

So intense was the data collection process that the investigators actually watched the babies being born to record details of the first moments of life. They watched the infants eat, sleep and cry in their first days of life (including a continuous eight-hour observation of each child's fourth day).

As the children got older, the researchers tested their psychological development, watched them play and visited them at home. They learned about the children's interaction in the life of the family through extensive interviews with the mothers.

The researchers monitored the children's development in this extremely rigorous manner until the children were 3 years old.

During the children's first year of school, the investigators again studied the youngsters' lives—in classroom observations, interviews with parents and teachers, school records, home visits, play sessions and psychological testing.

"In the 1950s, such extensive, detailed, systematically collected and multileveled data covering the first three years of life and over the first grade at school was unique. It still is," Sander said of the study, which was presented at the First World Congress of Infant Psychiatry and

described in "Frontiers of Infant Psychiatry" (Basic Books, Inc., New York, 1983).

The analysis of the data from the original study led Sander to propose a model of early childhood development that has become widely adopted by other investigators over the past 20 years.

The model is based on the idea that each stage of the infant's development presents an adaptive challenge to the family system. For example, as the baby, primarily through its own growth, becomes an initiator of plans, activities and social contacts, there is a new and different demand placed upon the family system.

The new demand is worked out, or negotiated, through the many parent-infant interactions that occur daily. The overall pattern of these interactions shape the particular adaptation which the baby and the family system evoke for that issue.

Though Pavenstedt's original study design did not call for a follow-up when the children became older, Sander, along with Gerald Stechler, Ph.D., a BUSM professor of psychiatry, and Padraic Burns, M.D., a BUSM associate professor of psychiatry, believed a follow-up study would be extremely useful because of the thoroughness of the original data.

"It is a rarity in the scientific world that a sample of infants can be followed over 25 years of development by the same investigators," said Sander. "Development as a process does not end at infancy...but there has been little opportunity to examine later aspects in the developmental process when there also is a richly-detailed account of the very earliest years (of the subjects' lives). Here we have such a unique chance."

So in 1979, the researchers began the follow-up study. However, there were problems to overcome. In the 25 years since the first project began, the "children" had become adults; all were in their mid-20s. Some had children of their own.

"We didn't know how to go about looking for them. We had old addresses, but nothing current. But then there was a very simple solution. Dr. Sander simply went down to the Registry of Motor Vehicles and immediately found 27 of the 30 families. And they were all within a 40-mile radius of Boston," said Burns.

Sander, who had developed close relationships with some of the families over the years, began calling the individuals and found them willing to be interviewed for a follow-up study.

The Spencer Foundation and the MacArthur Foundation, two private philanthropic organizations, donated funds for the study and so, 25 years after the first subjects were born, the project once again was alive.

The researchers divided into five teams working independently of one another and their work continues today. One group is reviewing the data from the observations of the subjects' first two years of life—putting together detailed personality profiles of each subject as a toddler. A second group, the follow-up team, is extensively interviewing the subjects to learn their life story—how the subjects think they developed and what their lives are like now.

The third team is giving the subjects a wide-range of psychological tests aimed at describing their current personality characteristics. A fourth team is retesting the mothers of the subjects with the same tests that were administered during their pregnancies, and the parents of the subjects are the focus of interviews being conducted by the fifth team.

Sander hopes that all the data collection will be concluded by December; then, for the next two years, the investigators will analyze the tremendous amount of information.

"There is a vast number of interesting possibilities of what we can learn with this data once it is put together," said Burns.

One of the first aspects of the study the researchers will complete

*Padraic Burns, M.D., interviews subject 20 years after she was first interviewed at age 5 (shown in inset). (Photo by Bradford F. Herzog; inset by Duette Photographers)*

when the data is collected is a recognition test. "We'll end up with a profile from the first two years of life and try to match that to a similar profile of the current young adult life, to see if we can recognize something of the adult from child and vice versa," said Burns. "Our question is whether there is something in the organization of behavior in early development that is specifically unique and will be recognizable in the way the individual organizes his life later on."

When this test is complete, the team will examine dozens of aspects of the lives of the subjects. "One obvious but interesting question," said Burns, "is this: Is there any connection between their first-grade school activity and their young adult achievements?"

In addition, the effects of accidental happenings on some of the children—such as serious illness or death of a close relative—will be examined. "We will try to find what impact these happenings seem to have on a child's development," said Burns.

"What has been a problem in developmental research is that there is a vast amount of data on the first couple of years of life. And there also is data on later life. But there has been very little to connect the very early life picture with the adult picture in the same individuals," said Sander. "We're trying to gain a perspective on development that really shows what aspects of development take place after the first years of life and how we can define that longer-term developmental process."

*—Paul D. Vaskas*

**Suggested Further Readings**


1. Sander, L.W.: A 25-year Follow-up of the Pavenstedt Longitudinal Research Project, Its Relation to Early Intervention. In: Frontiers of Infant Psychiatry. J.D. Call, E. Galenson, and R.L. Tyson, eds. Basic Books, Inc., New York, 1983, p. 225.
2. Pavenstedt, E.: The Drifters: Children of Disorganized Lower-Class Families. Little Brown and Co., Boston, Mass., 1967.


***Bypass grafts...***
*continued from page 1*

to 30 percent of all grafts in which veins are used. For grafts involving prosthetic vessels—made either of synthetic materials like Dacron, or of other kinds of human or animal vessels—the failure rate can exceed 50 percent.

Whether the grafts make use of veins or prosthetic materials, the reason for such failures is similar. The blood vessels with grafts are afflicted by a narrowing effect similar to that associated with atherosclerosis.

For vein grafts, this phenomenon is known as intimal hyperplasia. For prosthetic grafts, it's called anastomotic hyperplasia.

LoGerfo and his associates, in related research projects, are seeking ways to prevent hyperplasia in both vein and prosthetic grafts.

"The saphenous vein, which is the vein in the leg that is most often used in blood-vessel grafts, seldom develops clots when it's in its normal location," said LoGerfo. "Our view has been that if we could preserve most or all of the anti-clotting mechanisms in that vein when it's transplanted, there would be a good chance of achieving better results in vein grafts."

The investigators particularly want to protect the endothelium—the inner lining of the vessel. The endothelium, though but a single cell thick, is thought to play a critical role in preventing the events in the blood vessel that are a prelude to hyperplasia.

One of those events, said LoGerfo, is a buildup of blood elements called platelets along the vessel wall. "We think that the aggregation of platelets along the vessel wall is the first step in intimal hyperplasia. One of the main reasons we think so is the fact that platelets produce a substance, called platelet-derived growth factor, that causes the smooth muscle cells in the vessel wall to proliferate."

This proliferation, in turn, leads to the vessel shrinkage that is the hallmark of hyperplasia, he added.

*Frank W. LoGerfo, M.D., right, discusses studies in the Vascular Dynamics Laboratory with research technician Paul Andrew, left. (Photo by Educational Media, BUSM)*

Knowing that any blood vessel's reaction to trauma is a sharp constriction, the investigators decided that one way to protect the endothelium might be to head off that reaction before the vein was removed.

The technique chosen, said LoGerfo, was to inject a muscle-relaxant called papaverine into the area around the vein before the vessel was removed. This method was devised in collaboration with Christian C. Haudenschild, M.D., BUSM associate professor of pathology, a specialist in blood vessel injury and repair at Boston City Hospital.

This approach, tested first in laboratory animals, had the desired effect. Examination of the endothelium from the pretreated veins showed none of the rips and malformations found in the cells lining untreated veins.

The investigators, again using laboratory animals, then showed that the technique could help prevent delayed failures of vein grafts.

The approach, said LoGerfo, seemed promising enough to be tried with patients. The investigator, who is also a vascular surgeon, said that

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in the 28 patients on whom it has been used, the results have been excellent—only two delayed failures have occurred.

LoGerfo emphasized that his use of papaverine-treated veins did not constitute a controlled clinical trial, since there was no comparable group of patients with whom traditional procedures were used. He added, though, that the better than 90 percent success rate achieved has sparked considerable interest in the technique.

In their work with prosthetic grafts, LoGerfo's group has been trying to solve one of the most nettlesome problems associated with such grafts—the high failure rate in smaller arteries.

"In large blood vessels, like the aorta, grafts using materials such as Dacron work very well," explained LoGerfo. "But once you get down below a certain size—it appears to be around 8 millimeters or so—the problem of hyperplasia becomes severe enough to cause a very high rate of late failures."

Investigating the reasons for such failures, the surgeon and his associates found the narrowing always occurs at the downstream end of the graft.

"One obvious possibility," said the surgeon, "is that the platelets are stimulated by contact with the inner lining of the graft, but can't do anything about it until they get to the smooth-muscle cells in the artery that the graft is hooked up to."

To test this hypothesis, the investigators have embarked on a joint research venture with C. Robert Valeri, M.D., a professor of medicine and director of the BUSM-based U.S. Naval Blood Research Laboratory; and Bernard E. Statland, M.D., Ph.D., a professor of medicine and pathology at BUSM and director of laboratory medicine at University Hospital.

The project, said LoGerfo, involves studies of blood from patients with kidney failure, whose blood must be purified by artificial means.

Samples of the blood before it enters the tubes leading to the dialysis, or purifying, device are compared with samples of blood that has been through the tubes. The aim, said the surgeon, is to identify changes in the blood that result from its contact with the artifical surface.

Although the work is in its early stages, LoGerfo said the preliminary results suggest that the investigators are likely to succeed in identifying the blood changes linked to passage through the tubes. If they do, the project may shed light on what accounts for late failures in prosthetic grafts. At the same time, by providing benchmarks to use in assessing potentially harmful changes in blood that passes through synthetic materials, it may offer an effective new technique for evaluating different materials for their usefulness in prosthetic grafts.

"If we can identify a good way to evaluate one synthetic material as opposed to another (for use as a graft), it would be a big step forward," said LoGerfo. "We might be able to develop new kinds of prosthetic grafts that avoid this high failure rate. In fact, we've already initiated an effort to improve the surface of Dacron grafts in collaboration with Dr. Carl Franzblau." (Carl Franzblau, Ph.D., is professor and chairman of the Department of Biochemistry at BUSM.)

"This would mean a greatly improved outlook for patients who get prosthetic grafts in small-artery bypass operations," said LoGerfo. "It also would mean that we could substitute prosthetic grafts for vein grafts much more often, and avoid all the trouble and time that's involved in transplanting a vein."

*—Richard P. Anthony*

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2. Sharefkin J.B. et. al.: Early normalization of platelet survival time by endothelial seeding of Dacron arterial prostheses in dogs. Surgery *92*: 385, 1982.

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