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'Quality of life' may play a key role in determining outcomes of major surgery, according to research conducted by School of Medicine scientists C. David Jenkins, Ph.D., and Babette-Ann Stanton, Ph.D. See story on page 3.



A University Hospital patient is prepared for cardiac catheterization, a procedure that resembles that of transluminal angioplasty. (Photo by Bradford F. Herzog)

Angioplasty works — but how and why? BUSM study looks for answers

One of the newest and most promising innovations in the treatment of coronary artery disease in humans is transluminal angioplasty, a technique in which a balloon-tipped catheter is used to dilate a partially blocked segment of a coronary artery, creating a wider opening for the passage of blood to the heart.

Animal studies being conducted at Boston University School of Medicine under the leadership of Assistant Professor David P. Faxon, M.D., aim

to elucidate how and why the procedure works, and to make it even more effective and broaden its use for humans.

Transluminal angioplasty has been successfully used as an alternative to coronary bypass surgery for some 1,800 carefully selected patients worldwide. It also has been successfully applied to atherosclerotic narrowings in the peripheral blood vessels of the legs, and in the renal and
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Alcohol's effect on the brain is focus of BUSM research team

Doctor: Do you remember about two minutes ago I told you how long you've been in this hospital and what hospital you were in?

Patient: No, I don't remember.

Doctor: Do you remember the house you first lived in as a child?

Patient: Fourth house up from the corner. It was a gray one — four or five tenements. It was one of the biggest houses on the street.

The above is a dialogue between a Boston University School of Medicine researcher and an alcoholic patient who has Korsakoff's syndrome, a complex psychological and neurological disorder generally characterized by a particular type of amnesia — a loss of memory for very recent events, but a fairly good memory for events of early childhood and before the onset of the disease.

Named after the Russian neurologist who first described the disorder in the late 1800s, the syndrome often is associated with long-term chronic alcoholism accompanied by malnutrition. It can, however, accompany serious disorders involving the intestinal tract and often is attributed to damage of structures deep inside the brain, such as the thalamus and the hypothalamus, according to Marlene Oscar Berman, Ph.D. An associate professor of
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Alcohol's effect . . .*continued from page 1*

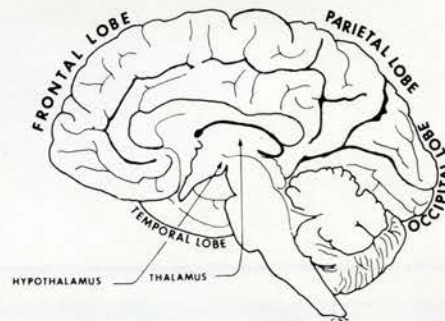
neurology (neuropsychology) at the School, Berman has done a great deal of research on Korsakoff patients in her 11-year study on the effects of long-term chronic alcoholism on the brain.

"Though Korsakoff's syndrome affects only a small percentage of alcoholics, its effects are profound and offer important clues to how the brain works. I am interested in how the brain controls behavior, and I want to get a good handle on what deficiencies occur in the brain as a result of chronic alcohol abuse," said Berman, who does most of her research at the Boston Veterans Administration Medical Center, a principal teaching facility of BUSM. "I hope that this research will aid in the understanding of such disorders as amnesia and be useful in the diagnosis and treatment of persons who have abused alcohol," she added.

Berman, who also directs the Laboratory of Neuropsychology in BUSM's Department of Biobehavioral Sciences of the Division of Psychiatry, this year received grants totaling nearly \$500,000 to support her continuing research. The grants were from the National Institute for Alcohol Abuse and Alcoholism of the U.S. Department of Health and Human Services and from the Veterans Administration.

She is affiliated with BUMC's Aphasia Research Center headed by Harold Goodglass, Ph.D., a professor of neurology (neuropsychology). Others conducting alcohol research in the Aphasia Center include Nelson Butters, Ph.D., a professor of neurology, and Laird S. Cermak, Ph.D., an associate professor of neurology. Berman is assisted in her research by psychology technician Robert Bonner.

It is generally accepted that chronic alcohol abuse can lead to cirrhosis of the liver and damage the



Marlene Oscar Berman, Ph.D., at left, discusses her research. Cross-sectional diagram of human brain, above, shows the thalamus and hypothalamus. Damage to these structures is believed to be related to alcoholic Korsakoff's syndrome. (Photo by Bradford F. Herzog; diagram by BVAMC Medical Media)

circulatory, muscular, endocrine and nervous systems, but relatively little is known about how brain damage caused by alcohol affects behavior.

Berman has found that patients with Korsakoff's syndrome, though they might have normal or above-normal IQs, have subtle deficiencies in attention, perception and motivation processes that are thought to contribute to the patients' memory loss.

To determine whether or not Korsakoff patients had perception or attention difficulties, the researchers used a machine called a tachistoscope (t-scope) to measure the amount of time it took alcoholic Korsakoff patients to analyze incoming visual information. The researchers measured the amount of time a word or figure was shown on the screen of the t-scope before the patients could identify what they had seen. They found that Korsakoff patients needed nearly three times the amount of viewing time as normal subjects and alcoholic patients with no clinical signs of Korsakoff's syndrome.

In other tests, Berman found that:

- It took Korsakoff patients twice as long to categorize and convert infor-

mation about a visual stimulus no longer present on the t-scope into the short-term memory than it did normal control subjects. "It became clear that Korsakoff patients do not process incoming visual information as efficiently as control subjects. This was our first evidence that the memory impairment of Korsakoff patients might be confounded with other deficits, in this case a limited information processing capacity," Berman said.

- Korsakoff patients responded prematurely to incoming information, particularly when required to withhold a response for a period of time. They also tended to repeatedly use incorrect strategies in problem-solving, even after they had been told they were wrong. "Similar tests run on nonalcoholic brain-damaged individuals in the control group showed that these patients were able to formulate and use hypotheses normally, suggesting that brain damage alone is not responsible for the pattern of results obtained in those with alcoholic Korsakoff's syndrome," Berman explained.

- In tests of motivational skills, the alcoholic Korsakoff patient cooperated fully and wanted to participate, but exhibited an abnormally low sen-

sitivity to existing reward contingencies. "Abnormalities in sensitivity to available rewards can have direct bearing on the ability to learn new material. If someone is only dimly aware of the relevance of a particular item, or some piece of information is seemingly unimportant, that item or information may never be learned," Berman said. "Like deficits in perceptual processing or attention, defects in learning may appear as problems of memory.

"The functions that are disrupted in alcoholic Korsakoff's disease are themselves very much intertwined," she added. "Memory depends upon what has been learned, and vice versa. Learning and memory depend upon attention, motivation and the amount of information that can be processed. A minimal level of arousal is needed to process information. Arousal and attention are heightened by increases in perceptual processing and motivation.

"In the years since Korsakoff first described the disease, much has been added to our facts about organically-based memory disorders, but the amnesias are still far from being fully understood. Perhaps after another decade of research the problem will be solved — but not forgotten," she said.

— *Marjorie H. Dwyer*

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Unique study aims to document factors affecting recovery from heart surgery

Candidates for heart surgery who are likely to have successful outcomes and those who might need extra services to improve their chances for full recovery are expected to become more easily identifiable as a result of research being conducted at Boston University School of Medicine.

For six years, C. David Jenkins, Ph.D., a professor of psychiatry, and Babette-Ann Stanton, Ph.D., an assistant research professor of medicine (health-care research) at BUSM, have been conducting studies of persons who have undergone coronary artery bypass graft and cardiac valve replacement to determine what such factors as attitude, emotions, or social relations have on the course of recovery and rehabilitation following surgery.

"This new knowledge may lead to better patient selection and more complete postoperative services," Jenkins said of the study, which is funded by the National Heart, Lung and Blood Institute.

The research effort is believed to be one of the first of its type to evaluate the medical significance of what some call the "quality of life," or the sum total of a person's health and well-being.

"With few exceptions, previous researchers have limited their evaluations to morbidity and mortality rates and other medical outcomes following heart surgery, or to future risks of severe complications," Stanton said. "Other studies have investigated reduction of anginal pain after surgery or have followed patients to see if they returned to work," she continued.

"Although these are all important components of the quality of life," Jenkins added, "they do not provide an adequate evaluation for many persons who undergo heart surgery

after their retirement or for those patients who did not have serious angina pain before surgery.

"The goal of medical care should be to preserve, restore and extend the quality of life," he continued. "The evaluation of the degree to which a health-care technique or program achieves that goal calls for the application to patients of valid, reliable and convenient measures of the quality of life concept," he said.

"It is urgent that medical and surgical intervention be evaluated from a broad perspective of total human well-being, and to this end we have assembled and are using a comprehensive array of scales in an attempt to move toward a reliable measurement of a complete spectrum of essential components of the concept of the quality of life," Jenkins explained.

The investigators developed an extensive questionnaire containing 1,000 queries relating to such areas as health (rehospitalization, degree of disability, new medical diagnoses implying risk), emotional states (anxiety, depression, fatigue, hostility, vigor, hope), self-esteem, satisfaction with one's career, family life, standard of living, and educational level.

The study also includes questions pertaining to such daily activities and role functions as physical activity levels, family and marital roles, recreational activities, occupational roles, retirement activities and social participation.

Social participation is an important aspect of one's quality of life, Jenkins noted. For example, he said, physical disability can prevent the mobility necessary to go out and visit friends. Depression and hostility may separate a person from others, while the individual who returns to work can maintain social contacts. "For these reasons," he said, "we judged it im-



Investigators C. David Jenkins, Ph.D., and Babette-Ann Stanton, Ph.D., who are studying heart surgery outcomes, discuss data in their Medical Center office. (Photo by Bradford F. Herzog)

portant to obtain direct measures of the quantity and quality of interpersonal interactions." Questions about income levels also were included in the study.

"The design of the study is unique," Stanton explained. "It involves the collection of baseline data in the days immediately preceding heart surgery, a brief interview in the hospital nine days after surgery, and extensive follow-up — both through interviews and a questionnaire — at 6, 12, 18 and 24 months following surgery. This is the greatest number of follow-up variables ever studied in a project of this type," she said.

Currently 520 persons are enrolled in the study and postoperative information has been compiled on approximately 334 participants. The four study sites include Boston University Medical Center, Beth Israel Hospital in Boston, the University of Massachusetts Medical Center in Worcester, Mass., and Albert Ein-

stein Medical Center in New York City.

The baseline interview, conducted one or two days prior to surgery, contains several standard scales measuring emotional states. The investigators found that the anxiety levels in their sample were lower than expected, perhaps in part because 27 percent were prescribed preoperative tranquilizers. Patients anticipating a valve replacement experienced slightly less depression than bypass patients, but the other mood scales did not show any consistent patterns of differences.

Valve patients, in general, were more hopeful about their life situations following surgery than were bypass patients, but there was little difference between the groups in a measure of current life satisfaction. When all patients were asked about their expectations of the impact of surgery on their future quality of life, more than half were extremely op-

timistic. Fewer than 5 percent of the patients were unsure or pessimistic about their quality of life after surgery. "This attests to the excellent preparation surgeons, their staffs and nurses gave these patients prior to surgery," Stanton said.

"We believe that profiles of the multiple dimensions of quality of life can provide insights into which components of a comprehensive care system need strengthening," Stanton said. "Such data also could provide the basis for special forms of supplementation to the process of patient education, such as more emphasis on return-to-work counseling for heart-surgery patients.

"If there are common factors behind the great individual differences in profile of recovery," she concluded, "such data could be used to improve patient selection as well as for early identification of persons with a high probability of difficulty with a specific aspect of recovery, such as proneness to depression or marital conflict."

Working with Jenkins and Stanton on the study are Michael Klein, M.D., an associate professor of medicine at the School of Medicine, and Judith A. Savageau, M.P.H., a research associate in psychiatry.

Robert L. Berger, M.D., a professor of surgery at the School of Medicine and chief of cardiothoracic surgery at University Hospital, and John R. McCormick, M.D., an assistant professor of surgery, are collaborators for the project.

— Susan B. Saperstein

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Angioplasty . . .

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even the cerebral arteries of patients.

The procedure's brief history began in the early 1960s, when a radiologist named Charles Dotter, using a catheter to explore arterial narrowings, got the idea of using a slightly larger catheter not only to probe but to widen the narrowed vessels. He applied the technique successfully in the iliac arteries in the legs of patients with atherosclerosis, or hardening of the arteries.

Some 10 years later, a German physician named Zeitler adapted the procedure, again for use in leg arteries. But it was a student of Zeitler, a young German named Andreas Gruntzig, who added the ingenious refinement that gives the procedure its importance today as a therapeutic tool. Gruntzig added to the catheter a small plastic balloon that could be guided to an area of arterial narrowing and there inflated with fluid to a predetermined size to widen the arterial opening. Having used the technique with great success on arteries of the legs, Gruntzig went on to devise a very tiny balloon for use in the coronary arteries, and used it successfully on his first heart patient in September 1977.

News of Gruntzig's experiment caused great excitement in the world of cardiology. Preliminary experiments in this country prompted the National Institutes of Health to set up a data registry to follow up on all patients treated by the procedure.

Faxon was among the cardiologists attending the 1977 Miami meeting where Gruntzig first described the procedure. Two years later, Faxon, who also is the director of the Cardiac Catheterization Laboratory at University Hospital, went to Zurich to learn the technique from Gruntzig himself. Since then, he and his UH associates have treated 26 patients with the technique, with results Faxon describes as "very

good."

Approximately 70 percent of the 1,800 angioplasties that have been done worldwide have successfully decreased the arterial narrowing by 20 percent or more. About 15 to 20 percent of these patients, however, experienced a return of the stenosis, or narrowing, within six months to a year. (Interestingly, these outcomes are similar to those of coronary bypass surgery, in which a comparable percentage of patients experience clogging of the new bypass graft within six months to a year, Faxon noted.) Why this happens, and what factors determine who will experience restenosis (return of the narrowing), are among the many questions challenging the researchers.

"After we had done the angioplasty procedure on patients here and read the literature, it became immediately obvious that no one understands how it works or why it enlarges the internal size of the arteries," Faxon explained.

He formed a research team that set out with three primary goals: to develop an animal model suitable for angioplasty; to find out how the procedure works; and to try to learn what factors might prevent re-narrowing. The project is supported by a three-year grant from the Na-

tional Heart, Lung and Blood Institute.

The research was done in rabbits, whose iliac arteries are similar in size to human coronary arteries. Rabbits also can be induced to develop significant arterial narrowing in as little as six to 10 weeks.

The rabbits were divided into two main groups in which different kinds of atherosclerotic lesions were to be induced since atherosclerosis begins with an injury to the artery wall. Rabbits in Group I were subjected to de-endothelialization — the gentle scraping away of the inner lining of cells at a particular point in the iliac artery. The animals then were placed on an extremely high cholesterol diet.

The Group II animals had their lesions induced by surgically placing a small polyethylene catheter in the artery and leaving it there for eight weeks. These animals were then subdivided into two groups: the first was fed a high-cholesterol diet and the second, a normal diet of rabbit food.

After eight weeks, the rabbits' arteries were examined by angiography; most were found to have significant narrowing. Angioplasty then was performed on all the animals, and the next day they were sacrificed so that their tissues could be examined under the microscope.



Photo on left shows rabbit artery that has undergone the transluminal angioplasty procedure. Note that the vessel opening has been enlarged by the procedure. Photo on right shows the re-narrowing of a rabbit artery that has undergone angioplasty four weeks following the procedure. (Mallory Institute of Pathology photos)

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"We found that the type of lesion determined what you found (after angioplasty)," Faxon reported. Group I animals had developed concentric, fatty, so-called foam-cell-type lesions. After angioplasty, four of the six rabbits in this group were found to have suffered a partial rupture of the vessel wall, extending through the intima (the inner layer of cells, or endothelium) and in some cases part-way into the media, the vessel's second, muscular layer of cells.

Group II rabbits tended to form eccentric lesions — that is, plaques that built up on only one side of the artery; these lesions tended to be harder and more fibrous than those in Group I. In these animals, angioplasty tended to stretch the normal portion of the vessel wall, rather than the more resistant lesion, causing an aneurism.

In another study of the long-term results of transluminal angioplasty, the researchers found that the rabbits on high-cholesterol diets tended to redevelop atherosclerosis at the site of the angioplasty more rapidly than in other parts of the vessel. Six out of nine animals had restenosis of more than 20 percent. Furthermore, the animals that showed the greatest improvement from angioplasty were the most likely to develop restenosis.

"We don't know why this should be so," Faxon said. "Maybe it has to do with the amount of damage you do (to the artery) with the initial angioplasty."

Faxon's six-member research team includes Christian Haudenschild, M.D., an associate professor of pathology at BUSM and a pathologist

at the Mallory Institute of Pathology, who is an expert in animal atherosclerosis.

In the next phase of its research, the team will attempt to alter the restenosis rate by giving the rabbits blood-thinning drugs and a calcium-blocking agent. Later, the researchers will examine the effects of variations in the angioplasty technique. Currently, a patient receives angioplasty once, in a procedure that usually involves inflating the balloon three times, to a pressure five times normal atmospheric pressure, Faxon explained.

Although only about 10 percent of those who are candidates for coronary bypass surgery currently qualify for angioplasty because of guidelines set up by NIH, Faxon predicts that improvements in equipment coupled with increased familiarity with the procedure among physicians causing it to be viewed as no longer experimental will mean a significant increase in the percentage of patients qualifying for angioplasty in the not-too-distant future.

Despite Faxon's findings, which suggest that transluminal angioplasty not only fails to prevent renarrowing of the arteries, but may actually encourage it, he is convinced of the technique's long-range value. "Our

results only tell us that it's not perfect . . . They also tell us that some of the animals, like most of the people, do very well.

"In the animal, we see in a four-week period what might take 10 years to develop in a human being. But if we can determine what makes the procedure more successful and apply that to humans, then maybe the 10 years (before restenosis occurs) can be extended to 20. If you have a procedure that can let you go 20 years without heart surgery, that's enormously important."

— Lorraine W. Loviglio

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