lyst of the type that is widely used in the petroleum industry. Kaesz would like to use this approach to synthesize multimetallic clusters—that is, clusters consisting of more than one kind of metal—with compositions and structures that do not occur in bulk metal alloys (*Science*, 30 August 1974, p. 772). Such catalysts are now produced in other ways and are often superior to monometallic clusters, but it is difficult to control the uniformity of the dispersed metal particles.

Taking a clue from certain naturally occurring metalloenzymes, Collman and his colleagues at Stanford are investigating the possibility of immobilizing binary porphyrin complexes on graphite in order to build a reversible oxygen electrode for fuel cells. Another application could be the electrolytic reduction of atmospheric nitrogen for the production of nitrogen-bearing chemicals.

So far, the Stanford group has synthesized several binary porphyrin complexes containing cobalt or copper. The complexes are in the form of so-called face-to-face porphyrins in which two porphyrin rings are held in a parallel configuration (Fig. 2). Two metal atoms, one from each ring, could then act together to bind and reduce oxygen or nitrogen molecules in the gap between the rings. Yet to come are syntheses of iron- or ruthenium-containing complexes for oxygen reduction and molybdenum- or vanadium-containing complexes for nitrogen reduction, as well as attaching such complexes to graphite. Studies of the cobalt- and copper-containing rings have focused on determining which of several possible complexes actually exhibit the face-to-face structure.

As with polynuclear metal clusters, the future importance of immobilized homogeneous catalysts is shrouded by the proprietary nature of much industrial research. In addition, uncertainties surrounding the nature and availability of raw materials and future markets have made it difficult for companies to make decisions about funding of research. Nonetheless, observers detect a growing enthusiasm for ways to tailor the properties of homogeneous catalysts, such as immobilizing them on solid supports. Despite the fact that the first wave of easy experiments has been done and some difficulties have emerged, such approaches to tailoring are just in their infancy.—ARTHUR L. ROBINSON

Coronary Bypass Surgery: Debate Over Its Benefits

Cardiologists are becoming more and more adept at diagnosing coronary artery disease (*Science*, 3 December 1976). But once they find that a person's coronary arteries are obstructed, they may be faced with a dilemma about what sort of treatment to prescribe. Many recommend coronary bypass surgery—a procedure in which a vein from a patient's leg is grafted onto the clogged coronary artery to shunt blood past the obstruction into the heart. Others are very cautious about endorsing this procedure and believe drugs may provide benefits that are comparable to those conferred by surgery.

Despite its controversial status, coronary bypass surgery has become a big business in the United States. According to Richard Ross of Johns Hopkins University, about 25,000 operations were performed in 1971 and, by 1973, this number had doubled. He estimates that at least 65,000 operations were performed last year and that each cost at least $10,000. (This price includes the surgeon's fee and charges for hospitalization, laboratory tests, equipment, and medical care.) Thus, about $650 million was spent on coronary bypass operations last year. In contrast, the budget of the National Heart, Lung, and Blood Institute (NHLBI) was $400 million.

In recent years, bypass surgery has become commonplace at many community hospitals, but most of the operations are performed at teaching hospitals and medical centers such as the Cleveland Clinic, the Texas Heart Institute in Houston, and the Mayo Clinic in Rochester, Minnesota. For example, 2,700 operations were performed at the Cleveland Clinic last year and 12,000 were performed there in the past decade, according to Donald Effler, who was formerly at the Cleveland Clinic and is now at Saint Joseph's Hospital in Syracuse, New York.

Most patients who have had this operation are extremely enthusiastic about it, as are many surgeons who perform it and cardiologists who recommend it. Effler, Mason Sones of the Cleveland Clinic, Denton Cooley of the Texas Heart Institute, and other proponents of the operation state unequivocally that it relieves symptoms of coronary artery disease and prolongs lives. Some cardiologists recommend this operation even for asymptomatic patients with coronary artery disease. A number of investigators, however, are asking whether the operation actually improves blood flow to the heart and whether people treated with surgery live longer than those treated with drugs.

Results from numerous studies have established that as many as 90 percent of patients with chest pains (angina pectoris) obtain partial or complete relief after coronary bypass surgery. Angina pectoris occurs when narrowed coronary arteries can no longer sustain an adequate blood flow to the heart. The heart muscle is consequently deprived of oxygen and pain results.

To assess the results of coronary bypass surgery, investigators have looked at changes in blood flow to the heart after the operation. A common way to determine blood flow in coronary arteries is to use contrast angiography. In this procedure, a catheter is inserted into the patient's heart, a radiopaque medium is injected, and x-ray pictures of the coronary arteries are made.

Lawrence Griffith, Stephen Achuff, and their associates at the Johns Hopkins University Medical School used contrast angiography to determine that a significant number of occlusions occur in coronary arteries after bypass surgery, thus impeding blood flow. This result was confirmed by six other groups of researchers. Specifically, the Hopkins group compared patients' coronary arteries before surgery to their arteries 6 months after surgery and found that 40 percent of the arteries had new occlusions. These investigators also looked at the arteries of a group of patients who were not operated on. Only 6 percent of the arteries of this control group had new occlusions after 6 months.

Most of the new occlusions that followed surgery were in the bypassed artery and were upstream from the graft. (Between the point of narrowing in the coronary artery and the point of attachment of the graft.) This is less significant than if they were downstream but it still means that the blood supply to the heart becomes dependent on the grafted vessel remaining open. This may affect only a small proportion of patients since most grafts do remain open. Floyd Loop and his associates at the Cleveland Clinic found that 83 percent of 185 grafts were open 4 years or more after surgery. For those few patients whose grafts close,

new occlusions in the bypassed arteries may cause irreversible damage to heart muscle.

Although most people with angina pectoris obtain symptomatic relief immediately after surgery, this relief may not continue indefinitely. E. L. Alderman and his associates at Stanford University School of Medicine found that 40 percent of 350 patients who had angina pectoris and who had this operation had a recurrence or worsening of their chest pain within 2 to 5 years after surgery. These investigators also reported that the chest pains of a small number of patients lessened with time but that a significant fraction of these people developed infarctions, or dead areas of heart muscle, before their pain disappeared.

Relief of pain just after bypass surgery may not necessarily be due to improved coronary circulation. Other explanations are also possible. For example, new infarctions may occur during or just after the surgery and may deaden the heart muscle that had been causing the pain.

Many cardiologists believe that only a small percentage of patients have new infarctions immediately after bypass surgery, but this belief was recently questioned by Melvin Platt, James Willerson, Frederick Bonte, and their associates at the University of Texas Health Center at Dallas. In order to detect new infarctions, these researchers injected patients with a radionuclide tracer that lodges in recently damaged heart muscle. The damaged tissue can then be seen because the radionuclide emits γ-rays that can be detected with a scintillation camera. Platt and his associates studied 48 patients between 3 and 5 days after surgery. They found evidence of newly damaged heart muscle in 15 patients (31 percent). In contrast, when they looked for damage with electrocardiograms or with analyses of two enzymes that appear in the blood when heart muscle dies, they found new damage in only 6 of these patients (12 percent). Electrocardiograms and the presence of these enzymes are the techniques most often used to determine whether new infarctions occur after bypass surgery. Incidences of new infarctions may vary from hospital to hospital, however. Loop reports that only 4 percent of patients at the Cleveland Clinic have post-operative infarctions as measured by enzymes, electrocardiograms and also by angiography, which is more accurate than these latter two methods.

Another explanation for the immediate relief of angina is that surgery acts as a placebo. Ross has described an example of how powerful such a placebo effect can be. About 20 years ago, it was commonplace to ligate patients' internal mammary arteries in order to relieve their angina pectoris. The operation achieved this purpose, but, in 1959, an experiment was performed to determine whether there was a physiological reason for the pain relief. (For ethical reasons, this experiment could not be performed today.) Patients with angina pectoris were randomly divided into two groups. Those in one group had their internal mammary arteries ligated. Those in the other group underwent sham operations. About 70 percent of the patients from each group had no angina following their surgery. Members of both groups had improved performance as measured by exercise electrocardiograms. (Some investigators object to this example of placebo effects. Loop, for example, claims that placebo effects of sham operations tend to wane by 6 months after surgery and are almost always gone by 1 year.) Relief of pain following bypass surgery, however, generally lasts for years.

Despite these questions about why coronary bypass surgery relieves pain, most cardiologists recommend it for patients with severe angina pectoris that is not relieved when the people are given drugs such as nitrates and propranolol. Sones, however, does not think that this is a valid criterion. He points out that a physician's recognition of the kind of pain a person suffers is limited by the person's ability to describe it. And the patient's perceptions of pain can be greatly affected by emotional stress. According to Sones, as many as 25 percent of the people who are referred to the Cleveland Clinic because they have chest pains and who are being treated by their referring physicians for coronary artery disease turn out not to have occluded coronary arteries. Sones advocates coronary bypass surgery for people with significantly occluded coronary arteries independently of whether they have angina pectoris. The operation, he contends, will prolong these peoples' lives.

Sones, Effler, and others are so convinced that coronary bypass surgery prolongs lives in comparison to medical treatment that they believe randomized controlled clinical trials of the effects of this operation on mortality rates are unethical. Sones believes that people could not possibly give informed consent to enter a randomized trial. Anyone who does give consent cannot be adequately informed, he says. Nonetheless, a number of randomized trials are being conducted. Those conducting the trials are as convinced that the question of whether coronary bypass surgery prolongs lives when compared to medical treatment is still open as Sones and others are that it is not.

Evidence that coronary bypass surgery prolongs lives comes from studies of patients who were not assigned treatments at random. For example, in one often-cited study, William Sheldon and his associates at the Cleveland Clinic compared the mortality rates of 1000 people who had this operation at the clinic to the mortality rates of 469 people who were diagnosed at the clinic as having coronary artery disease but not operated on. These controls were all diagnosed between 1960 and 1965, which is before the bypass operation was developed. Those patients who were diagnosed between 1960 and 1965 and who subsequently underwent the operation were excluded from the control group. The average mortality per year in the surgical group was 3.3 percent. In the nonsurgical group it was 8.8 percent.

Many investigators are unconvinced by results of studies, such as the Cleveland Clinic study, in which "historical controls" are used. They point out that the patients studied in the past are not necessarily comparable to those studied more recently. Means of diagnosis change, supportive care changes, and random changes can occur with time in the type of patients admitted to an institution such as the Cleveland Clinic. In addition, several investigators, such as Robert Rosati of Duke University and Richard Kronmal of the University of Washington believe that there is a bias in the Cleveland Clinic data that derives from the way the historical controls were selected. Since patients who were diagnosed between 1960 and 1965 and who subsequently had bypass surgery when it was introduced were eliminated from the control group, the control group may have an artificially high proportion of people who died before bypass surgery was introduced or who were too sick to undergo the operation.

Loop contends that this bias did not occur in the selection of the control

Recombinant DNA

A special issue of *Science* to be dated 8 April 1977 will include a number of reports on recombinant DNA research. Deadline for manuscripts is 4 February. Reports providing new data relevant to the containment problem are especially welcome.

group. Only a few patients were eliminated from the control group because they subsequently had the vein bypass operation, he says. Similar studies with historical controls at other institutions, such as the Texas Heart Institute, also indicate that the surgical patients may live longer than those who did not have the operation.

Thomas Killip of Northwestern University Medical School points out that the use of historical controls is justified only if there is no change in the treatment of the control group. But about 5 years ago drugs such as propranolol were introduced to treat people with angina pectoris. These drugs reduce the response of the heart to stress and thereby may prevent the occurrence of irreversible damage to hearts of people with angina pectoris. Killip believes that these new drugs make it equally likely that lives would be prolonged with medical as with surgical treatments.

Rosati and his associates are conducting a nonrandomized trial that compares surgery to medical treatment and that avoids some of these problems with historical controls. The trial participants are people with coronary artery disease who were diagnosed at Duke University Medical Center between 1969 and 1974 and whose treatments were prescribed by their individual physicians. Thus the medical and surgical groups were diagnosed and treated during the same time period. The assumption is that, as a group, physicians decide between medical and surgical treatment at random. Rosati and his colleagues followed 490 people who underwent the operation and 611 who did not. They conclude that surgery did not affect the mortality rates of these groups.

Several large-scale randomized trials are under way, but among them only the Veterans Administration (VA) trial has continued long enough for results to be published. The VA Cooperative Study began in 1970 and includes patients at 13 VA hospitals. So far, 1015 people with angina pectoris have been randomly assigned medical or surgical treatment. For the VA patients as a whole, there are as yet no statistically significant differences in mortality rates of the medical and surgical groups. The VA is, however, looking at subgroups of patients to see if any differences in mortality rates can be discerned.

Of particular interest, because many investigators believe the preliminary data are promising, are patients whose left main coronary arteries are at least 50 percent occluded. The left main coronary artery branches before it reaches the heart, and the two branches supply blood to a large area of heart muscle. Thus extensive coronary damage can result from blockage of this artery. Of the 1015 VA patients, 113 had this artery occluded. According to Timothy Takaro of the VA Hospital in Asheville, North Carolina, the mortality rate of the surgical patients in this subgroup is lower than that of the medical patients at 18, 25, and 30 months after entry into the study. This difference is statistically significant, Takaro claims. At 36 months, however, the number of survivors in the medical and surgical groups was so small that the differences between the two groups became statistically insignificant. Nonetheless, many cardiologists say they are sufficiently convinced by these preliminary results to recommend surgery for people with diseased left main coronary arteries.

Other Clinical Trials

Two randomized, controlled clinical trials of surgical and medical treatments are being conducted by the NHLBI. One of these, the Coronary Artery Surgery Trial (CAST) includes people who have demonstrable coronary artery disease and who satisfy specific clinical criteria. For example, people who have chest pain when they walk a block or climb a flight of stairs but have no pain at rest are eligible. People with more severe angina pectoris are not. The hope is that these clinical criteria will ensure a relatively homogeneous group of subjects for the study and facilitate interpretation of the results. Recruitment for CAST should be completed by January 1978; between 800 and 1000 patients are anticipated. Mortality rates will be determined during a period of 5 years. In addition, the NHLBI investigators plan to study how the participants feel after medical or surgical treatment by asking them questions about the quality of their lives.

The second NHLBI clinical trial involves people with unstable angina pectoris. The designers of this trial define unstable angina in two ways. First, it can mean angina pectoris that is of recent onset either at rest or on exertion. Alternatively, it can mean angina pectoris that had previously occurred in predictable circumstances—after climbing two flights of stairs, say. If this angina suddenly begins to occur under different circumstances—climbing one flight of stars, for example—the NHLBI group defines it as unstable angina pectoris. Unstable angina pectoris has been thought to signal an imminent threat to patients' lives, and many cardiologists have advised emergency coronary bypass surgery. Preliminary results of the NHLBI trial indicate that the prognosis for people with unstable angina pectoris is not necessarily so grave.

Recruitment for the NHLBI study of unstable angina pectoris began in August 1972 and is still continuing. According to Peter Frommer of the NHLBI, about 280 people have been recruited so far, and recruitment will end when 300 are recruited or as of 31 December 1976, whichever comes first. The follow-up time for this trial is something of a problem. When the trial was designed, unstable angina pectoris was thought to be such a serious condition that 1 year would be sufficient to see whether medical or surgical treatments affected mortality rates. This turned out to be inadequate, and the question of the length of the follow-up period is now under study.

One of the aims of the randomized trial of treatments of unstable angina pectoris is to identify subsets of patients with high risk compared to others with this condition. Some investigators, however, think that the ongoing clinical trials are likely to yield convincing data on long-term survival rates only when the trial participants are considered as a whole and not when they are broken down into subsets on the basis of specific diagnostic criteria. This makes it difficult to determine who will benefit from the surgery. Cardiologists can always argue that their patients are individuals and they must prescribe for their patients as individuals and not on the basis of the average behavior of a large group of trial participants. And patients with coronary artery disease are likely to be receptive to the suggestion that, for them, this surgery will be of benefit. As Effler points out, patients even now go to the Cleveland Clinic, where cardiologists are enthusiastic about bypass surgery, rather than to institutions where cardiologists are more hesitant to endorse this procedure.

Some cardiologists who advocate this surgery argue that the ongoing clinical trials cannot determine whether surgery can prolong lives when compared to medical treatment. The problem, they say, is that the current success and popularity of the surgery make it hard to design a good clinical trial. These advocates of surgery claim that institutions where surgery is good and whose patients have low mortality rates are unwilling to participate in randomized clinical trials. The ongoing trials may thereby yield misleadingly poor results of surgery. Thus results from current research on the question of whether coronary bypass surgery prolongs lives in comparison to medical treatment may not settle the debate over this question.—GINA BARI KOLATA