cal mass density to arrive at a symmetry-breaking energy of 10^6 GeV or less. The conclusion follows from the argument that gravitinos (the supersymmetric partner to the quantum of the gravitational field, the graviton) cannot be too heavy or else the expansion of the universe would be slowing down faster than it is. Weinberg took the opposite tack and considered very massive gravitinos. If these particles were heavy enough, they would decay early in the history of the universe and not contribute to the present deceleration of the universe's expansion. He arrived at the conclusion that a breaking of supersymmetry at energies of at least 10^{11} to 10^{16} GeV is allowable, although this would not help with the solution of the hierarchy problem.

One other consequence of supersymmetry in grand unified theories occurs in proton decay. The principal decay mode in a grand unified theory with supersymmetry becomes a positively charged K meson and an antineutrino, according to calculations by Demetrios Nanopoulos and John Ellis of CERN and others.

In addition to grand unified theories and supersymmetric theories, elementary particle theorists have conjured up a host of other models. Many of these require some or all of quarks, leptons, bosons, and the Higgs to be composites of even more elementary entities. Another approach considered independently by Weinberg and by Wilczek and Anthony Zee of the University of Pennsylvania is not to postulate any particular theory at all. The idea is to look at what symmetries or conservation laws are exactly but accidentally obeyed in the standard model, but might not be followed in a more complete theory valid at higher energies. Examples would be nonconservation of the number of baryons or leptons in an elementary particle reaction. Experimental observation of violations of these conservation laws would then point the way to the construction of the larger theory. Weinberg calls this "debris physics" because the standard model is seen as the low-energy residue of the complete high-energy theory that is still hidden.

With no real clue as to which direction to go, theorists have no choice but to heed the advice of Fermilab director Leon Lederman (not a theorist). "As long as there are no answers, the reasonable thing is to pursue experiments at higher energies."

—ARTHUR L. ROBINSON

A Sanguine Future for Biomaterials

The increased flexibility and inherent selectivity for albumin of new polymers may finally make possible small blood vessel repair

The body is an extremely harsh and discriminating environment for implanting foreign material as prostheses. When such materials are implanted, says Allen S. Hoffman of the University of Washington, "the body generally has two responses: wall it off or destroy it." Those responses lead to many problems, such as the formation of clots or thrombi. What is needed, says Donald J. Lyman of the University of Utah, is a "polymer that is compatible with its environment, and we are now beginning to approach that situation."

One area where that approach is being made is in the repair of small blood vessels—those with a diameter of less than 6 millimeters. Thrombogenesis causes most potential small blood vessel replacements to be blocked or occluded, often in less than an hour. When small vessel repair is required now, the material of choice is a saphenous vein from the leg. But this procedure requires the trauma of two operations—removal of the vein from the leg and reimplantation elsewhere—and as many as 25 percent of prospective patients do not have a satisfactory saphenous vein. Lyman estimates that as many as 300,000 individuals could be helped each year if a synthetic small blood vessel replacement were available.

Such help may be on the way. Lyman announced at the recent Macromolecular Symposium of the International Union of Pure and Applied Chemistry that he has a synthetic vessel that will enter clinical trials in humans before the end of the year. Hoffman, at the same meeting, disclosed that he hopes soon to begin long-term trials of a small artificial blood vessel in baboons. Although neither will reveal the precise compositions of their potential prostheses until patent applications have been filed, the two materials are obviously quite different. The two products are characteristic of a dichotomy that pervades the entire field, and they illustrate many of the problems that are involved in the use of biomaterials.

A major problem is that the nature of the interaction between blood and polymer is still largely a mystery. The large synthetic vessels that were first implanted in the 1950's, says James M. Anderson of Case Western Reserve University, "were so successful that nobody looked to see why they worked." Only recently have scientists begun to investigate the interaction in detail, and their success has been limited. "If you really look at it," says Lyman, "none of us knows what we are talking about. We have our own hypotheses, we think thrombogenesis occurs in certain ways, and this helps us design our experiments. Another group may have their own hypotheses that are quite different, but that help them design their experiments. . . . These controversies add to the excitement because we are pioneering into a whole new level of understanding."

While the details of mechanism may remain a mystery, a more general overview is emerging. One key event, nearly everyone agrees, is the adhesion of platelets to the polymer surface. That event initiates a complex chain of reactions that results in formation of a thrombus. Platelet adhesion, however, is controlled by an earlier event, the deposition of a layer of protein on the surface of the polymer.

It has been recognized since the 1950's that a surface coating of albumin seems to reduce thrombogenicity, but the reason for this remains a mystery. Nonetheless, the goal of most investigators has been to find some way to coat the surface of the polymer with albumin.

There are two principal ways to produce a surface coating of albumin. Lyman has sought to synthesize new or altered polymers that have an intrinsic attraction for albumin. Hoffman and others, in contrast, have sought to modify the surface of existing polymers to increase compatibility while maintaining the mechanical and permeation characteristics of known materials.

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Lyman has worked primarily with block copolymers of ethers or esters with urethanes or urethane and ureas; that is, long segments of polyether, for instance, interspersed among somewhat longer segments of polyurethane. These combinations have a relatively high selectivity for albumin. Even so, there is a wide range of selectivities depending on the relative proportions of the two components, the length of the ether chains, which component lies on the surface, and so forth—a complex of properties that Lyman characterizes as a balance between hydrophobic and dispersive forces. "Subtle variations in structure," he says, can have "dramatic biological impacts."

After what Lyman characterizes as "10 years of quite hard work," the group found the composition that seemed to be best and began implanting artificial vessels of small diameters into dogs. To their great disappointment, the implants failed within 200 hours. Examination showed that it was not the synthetic vessels that were being occluded but the natural vessels next to the implant. This phenomenon, which was previously known, is called an anastomotic effect because it is caused by the juncture, or anastomosis, between the natural and synthetic vessels.

A variety of causes are thought to be responsible for this effect, including the trauma of surgery, the nature of the stitches used to join the vessels, differences in the surfaces of the materials, the loss of endothelial cell linings at the juncture, and differences in the elasticity or compliance of the vessels. Whatever the cause, the eventual result is the proliferation of smooth muscle cells within the vessels, impeded blood flow, and occlusion of the vessel. Lyman concluded that the most important factor was the difference in compliance. "The polymers were as stiff as steel pipes in comparison to the natural vessels," he says. The natural vessels can change their diameters by as much as 30 percent during the pulsation of blood, whereas the diameter of polymeric vessels remains essentially unchanged. This creates an impediment to blood flow at the anastomosis and leads to the eventual failure.

Lyman's group thus began to fashion vessels of greater compliance by a variety of techniques. "When we implanted the first one in a dog," says Lyman, "we were a little sloppy because our results had been so poor in the past. When we took it out 3 months later to look at it, however, it was still functioning beautifully." The group then synthesized and tested a series of vessels of varying compliance. "We were able to demonstrate, I think quite conclusively, that as we matched the elastic index of the natural vessel, our success rate just climbed." A similar approach has been taken by David Annis of the University of Liverpool.

Current implants with matched compliance have a survival rate of more than 90 percent after 3 months, and some have been in animals for as long as 29 months. Lyman has also successfully implanted vessels as small as 0.8 millimeter in diameter. "Nobody has gotten the results we have in small vessel repair," he argues—with justification.

Lyman hopes to begin implanting the artificial vessels in humans by the end of the year but does not look for dramatic results. The initial studies will most likely be conducted on patients facing amputations, "who are perhaps in such poor condition that nothing short of replacement of all blood vessels in the limb can help. If we can extend the survival of the limb even a short time without adverse effects, then we will feel confident in moving on to patients whose conditions are not quite so serious." Lyman has used a similar approach to design artificial ureters that have survived as long as 2 years in dogs.

> "We are pioneering into a whole new level of understanding."

Hoffman and his colleagues, in contrast, have attempted to treat the surface of polyesters and silicone rubbers, which already have many medical uses, to reduce their thrombogenicity. He has done this primarily by grafting vinyl monomers onto the surface. By combining two monomers in various proportions, it is possible to produce surfaces with varying degrees of hydrophilicity.

Hoffman assayed the efficacy of the surfaces by inserting a 10-centimeter segment of tubing, 4 millimeters in diameter, between a vein and an artery in the leg of a baboon and monitoring the disappearance of platelets from the animal's blood. The coating that produced the least destruction of platelets was most desirable. To his surprise, Hoffman found that the most effective coating was relatively hydrophobic, absorbing only about 15 percent water.

Using the same principles, Hoffman's group has subsequently constructed other surface coatings but with different monomers. He told the Macromolecular Symposium that 4-millimeter knitted Dacron polyester tubes coated with these materials remain open in the baboon shunt for at least 3 weeks, the longest time they have so far monitored them; a comparable Dacron graft, in contrast, becomes plugged in less than 2 hours. He anticipates that the vessels will survive much longer, since "the acute phase of the interaction between blood and polymer is most important," and he plans to begin long-term implants in baboons soon.

His optimism must be tempered somewhat, however, in light of recent results obtained by Robert Eberhart and Mark Munro of the University of Texas Health Science Center at Dallas. Munro, a graduate student, noted that there have been reports that albumin selectively adsorbs long-chain fatty acids and suggested to Eberhart that they make use of this phenomenon. The two investigators alkylated the interior of a 4-millimeter polyurethane tube with hydrocarbons containing 16 and 18 carbon atoms. They found that the coated tube had a very high selectivity for albumin in blood; the surface was self-renewing, furthermore, since denatured albumin was sloughed off and replaced with fresh protein.

When 6- and 8-centimeter segments of treated tubing were exposed to the circulatory system of dogs for periods of 30 minutes to 4 hours, they showed little or no trace of fibrin or platelet thrombi; untreated tubes became plugged in as little as 30 minutes. Encouraged, the investigators implanted the tubes for longer periods. Treated tubes examined after 40 to 80 days, however, were found to be completely blocked as a result of the anastomotic effect, a finding which seems to uphold Lyman's conclusions.

Eberhart and Munro are now doing modeling studies to find some way to get around the problem of the anastomoses. Meanwhile, they have alkylated small samples of other polymers used for biomedical applications where blood is contacted. Their preliminary results, Eberhart says, look quite promising. A similar system for coating polymer surfaces has also been developed by Wolfram Krieger of Battelle-Frankfurt in West Germany.

The field of biomaterials is, obviously, still in its infancy. Even Lyman's new material, which is the most advanced, "is not the best polymer or the final one," he says. "I prefer to think of it more as the Model T of the field—it will be superseded by more technologically advanced models, but it will have proved that the concept works."

—THOMAS H. MAUGH II