

Summary

The 25 papers in this publication have been divided into 4 categories: (1) the clinical overview of vascular grafts; (2) the original research and developmental work on material properties, test methods, and aspects of retrieval analysis of implanted grafts; (3) biocompatibility issues; and (4) issues addressing the needs for standards for these devices. A summation session covering discussions of the oral presentations was held at the end of each day. The summation of Plenary Sessions 1 and 2 allowed for a dialogue between the clinicians and the graft manufacturers.

The technical overview by Britain presents the Food and Drug Administration (FDA) view on how vascular grafts are regulated by the FDA. Before 1976, vascular grafts of animal and human origin were regulated as "new drugs," upon enactment of the Medical Device Amendments Act in 1976, these products now fall into the expanded definition of a medical device. Vascular grafts of woven or knitted synthetic materials by law are clarified into one of three regulatory classes based on the level of control required to assure safety and effectiveness. Mr. Britain further explained the Regulatory classes appropriate for these vascular grafts. The first Plenary Session entitled Clinical Overview of Vascular Grafts introduced the clinician's view on currently available vascular prostheses, their use, the development of new and innovative techniques for dealing with specific patients problems, and alternatives to autologous vein grafts. It appears that a performance standard could be developed for grafts with an internal diameter of 6 mm or greater, typically constructed of woven or knitted material, and classified in Class II, the performance standards category. Grafts of less than 6-mm diameter would be classified in Class III and be made subject to pre-market approval.

From the FDA's perspective, the need exists for the development of a standard for these Class II vascular grafts. Formal standards development proceedings were initiated by the FDA in 1983 and Mr. Britain reiterated the need for cooperation and contributions to the development of information essential to the standards development process.

The clinical overview of vascular grafts began with a presentation by Dr. Callow on the historical development of vascular graft prostheses. Dr. Callow points out that despite the most meticulous techniques and extensive experience, the long-term patency rates of large diameter grafts cannot be duplicated in the small caliber graft of the same material by the same skilled surgical team. The human failure to endothelialize synthetic grafts is the major shortcoming of all

small caliber grafts currently available. Current and future directions in these areas must include study of the cellular, humoral, and enzymatic aspects involved in graft/host healing mechanisms and the circulating blood/graft interface responses which may lead to improvements in controlling the problem of neointimal hyperplasia and may ultimately improve the patency rates of small caliber prostheses.

By the early 1960s as a result of the pioneering work of De Bakey in popularizing both woven and knitted grafts, Sauvage's paper directs our attention to the ten Dacron® fabric prostheses currently in active clinical use and outlines several new ones in the process of introduction. This paper suggests explanations for their excellent performance and presents the microanatomy of several Dacron grafts in order to relate structure to function. The highly successful woven crimped Dacron fabric prostheses in the thoracic area, the knitted, crimped nonsupported Dacron in the abdominal aortoiliac area, and the knitted non-crimped supported Dacron for axillofemoral and femoro-popliteal bypass provide insight into the progress of vascular surgery.

The paper by Veith presents the results of his experience with 822 polytetrafluoroethylene (PTFE) grafts in arterial reconstructions for lower limb ischemia. Based on these studies, the autogenous saphenous vein when available and adequate should be the graft of choice for all distal bypasses. PTFE grafts are the acceptable alternative if adequate veins are not available in the involved extremity. Experience with PTFE axillopopliteal bypasses has shown that substantial palliation can be provided by this operation and is probably the procedure of choice for this condition in poor risk patients. A comparison of preliminary results from vein grafts and PTFE grafts infrainguinal arterial reconstructions is given from multicenter randomized controlled and prospective studies. Their late patency results (3 years) for distal bypasses and 5 year results with PTFE femorofemoral bypasses are reported.

The problem of deposition on synthetic graft surfaces leading to thrombus formation is addressed in Stanley's paper. The technique of synthetic graft endothelialization by the seeding of enzymatically derived autologous endothelial cells onto 6-mm diameter Dacron prosthesis was studied in both canine and baboon experimental models. This report includes a survey of select experiments from ten different institutions and defines the current state of endothelial cell seeding of vascular prostheses.

For small vascular grafts the biomaterial surface chemistry may influence the biologic response. Hoffman et al. have reported their results of extensive investigation of the composition of the vascular graft surface by a new gas discharge treatment. Surface composition and topography most strongly influence the composition and organization of the initial absorbed protein layer. It is this layer that mediates the subsequent cellular events at that interface. Hoffman and his group have explored surface treatments using a gas discharge with a monomer tetrafluoroethylene (TFE) gas. The radio frequency glow discharge (RFGD) treatment of small diameter Dacron grafts deposits a thin coating, a bio-

compatible fluoro-polymer surface, without measurable changes in porosity. Electron microscopy for chemical analysis (ESCA) provides a means for analyzing the monomer rearrangements in the deposited polymer. An *ex vivo* femoral shunt in the baboon model provides the quantitative experimental system for measuring platelet interactions. *In vitro* embolization rates and *ex vivo* patency studies are described. Current research is investigating the mechanisms involved in the improved patency and decreased embolization exhibited by the TFE glow discharge treated grafts.

The problems of vascular grafts in cardiac surgery differ from the problems associated with vascular grafts involving larger vessels. The paper by Kantrowitz stresses the fact that cardiac surgeons must deal with small caliber grafts exclusively in coronary bypass procedures where the diameter of the coronary vessels are in the order of 1 to 2 or possibly 3 mm. The current technique for coronary bypass surgery involves harvesting either the saphenous vein from the leg or the internal mammary artery through an open chest. As some 150 000 to 200 000 procedures are done annually, this paper presents an overview of the clinical experience, drug therapies, and statistics with these harvested grafts in coronary bypass procedures.

Dardik reports on his investigations on human umbilical cord vessels as a reliable alternative to the autogenous saphenous vein for lower limb revascularization. His clinical experience with glutaraldehyde-stabilized umbilical vein graft is included with data for graft patency for the major types of reconstructions. The problems associated with perioperative thrombosis, late graft closures, and infection are described. The results of the reconstructions to the popliteal, tibial, and peroneal arteries suggest that in the absence or unsuitability of the saphenous vein that the glutaraldehyde stabilized umbilical vein may serve as an excellent alternative.

The last paper in this session dealt with alternatives for small caliber vascular grafts. Wright et al. review their work on the development of experimental silicone rubber and polyurethane replamineform small caliber vascular grafts. The template for the small prosthetic tubes is fashioned from the calcite spines of the sea urchin. Wright describes the preparation methods for the prosthesis and details the *in vivo* implantation results with regard to surface endothelialization, the advancement of fibrous tissue, capillaries, and tissue ingrowth. Pore size and the type of elastomer implant affect the growth of soft tissue and the healing characteristics. The future design and graft construction are further discussed with regard to the replaminiform technique.

Plenary Session 2 focused on input from the graft manufacturers and dealt with the topics of Material Properties, Measurements, Test Methods, and Retrieval Analysis. The construction of polyethylene terephthalate Dacron polyester synthetic grafts was reviewed by Hoffman of Meadox Medicals, Inc. In addition to their gross characteristics, several features of polyester fibers were emphasized such as molecular orientation, chemical bonding spinning processes, texturi-

zation, and knit or woven construction to represent the effort on part of manufacturers to improve the safety and efficacy of polyester grafts.

McClurken et al. from IMPRA, Inc. reported on the current test method designed to measure the mechanical and bulk properties of PTFE. Grafts made by three suppliers were evaluated by the methods that have evolved over the past ten years for PTFE grafts. A discussion of the role these tests play in assuring safety and efficacy was presented.

The properties and characterization of bioprosthetic grafts were reported by Baier. The potential properties and requirements of synthetic tubes that serve as substitute blood vessels are defined as well as common failure modes. The bovine heterograft and mandril grown ovine grafts are cited as examples of such grafts. The methods recommended for characterizing and demonstrating the suitability of these biosynthetic grafts are explained for human implantation studies.

A key property of vascular prostheses must be longevity, as Synder et al. point out, particularly in large diameter grafts which seldom fail as a result of occlusion but by fatigue. Fatigue failure is described as structural (dilatation), material (rupture), or anastomotic (false aneurysms). Draft standards from the Association for the Advancement of Medical Instrumentation (AAMI) and International Organization for Standardization (ISO) contain strength tests. Fatigue strength is emphasized as a separate parameter from tensile strength and both should be considered in graft design; however, tensile strength is adequate as a quality control tool.

Botzko discusses the problem of comparative porosity measurements. Water porosity testing, as used by the manufacturer, is a quality control measurement and depends on the variability of the textile structures, the amount of tension applied in mounted samples, and the time interval between initiation of flow and the reading taken. Porosity serves as an external quality control check for the manufacturer and indicates to the surgeon the handling and preclotting procedures required. Although used for nearly 20 years, porosity testing techniques and equipment are still not full standardized with regard to the number of variables which can affect the final use.

Anderson's paper on implant retrieval considers the issues of graft preservation techniques and evaluation procedures used in characterizing vascular grafts. While a vast body of literature exists on the patency of grafts used in animals and humans, little is known regarding the pathophysiology controlling their success or failure. Subsequently, little information with regard to prosthesis development and testing is available. Anderson reviews several protocols and procedures applicable to both human and animal specimens.

The biocompatibility issues in vascular grafts were outlined in Plenary Session 3. Research has been directed to examining the blood surface interactions, long-term surface changes, animal models, and methods to analyze the encapsulating graft tissue. New types of graft prostheses were reviewed with respect to the biochemistry of cell seeded vascular grafts, biodegradable vascular

prostheses, the development as cellular matrices, and the sterility and pyrogenicity issues involved with all graft implantations.

The question of species selection for evaluation of vascular grafts was addressed by Didisheim. The hematologic similarities and differences among certain mammalian species are given, and arguments favoring the selection of one species over another are discussed. Since no species is clearly more similar to man than any other, Didisheim suggests that species selection be based on practical considerations such as ease of surgical and anesthetic technique, cost of purchase, and animal maintenance. Based on these criteria, the dog model remains the species of choice.

Anderson discussed the SS polyacrylamide gel electrophoresis analysis of extracted tissues encapsulating Dacron vascular prostheses recovered from humans. Alterations in the collagen type ratios in different layers of encapsulating tissue, and the highest proportion of type V collagen in the pseudointima suggest that some natural mechanism may exist to minimize the thrombogenicity of the human pseudointima.

Sharp et al. discusses the merits of cell seeding techniques from the standpoint of the biochemical production and interaction of the prostaglandins, Prostacyclin (PGI_2) and Thromboxane (TXA_2). The authors have analyzed the production of PGI_2 and TXA_2 on both seeded and nonseeded knitted Dacron grafts sutured to canine carotid arteries. Their report confirms that seeded endothelial cells produce PGI_2 , but that this can be modified by cyclooxygenase inhibitors. The production of TXA_2 by seeded cells has not been completely confirmed. Endothelial cell seeding may be an effective means of improving grafts for the 4-mm arteries.

Griesler has been examining the regeneration of cells with morphologic and functional characteristics of endothelial and smooth muscle cells *in vivo* over absorbable polymeric prostheses. Various woven and knitted absorbable compound polymeric prostheses were implanted in rabbit aortas. His results suggest that certain polymers may activate macrophages to induce migration and eventual differentiation of mesenchymal cells into cells resembling muscle-like myofibroblasts and endothelial-like cells. Dacron, however, inhibits these regenerative activities. The production of 6 keto PGF_1 is monitored for prostheses which demonstrate strength and compliance resembling that of normal aortic tissue.

Brendel et al. have investigated surfaces with the potential to promote endothelialization such as the purified vascular extracellular matrix surface. Again, the importance of the graft blood interface is the key to the patency of small diameter vascular grafts. The extraction of soft tissues from dog carotid arteries by detergents results in acellular matrix tubes that retain the physical properties of the original artery. Their results show that noncross-linked grafts implanted for 18 months were fully endothelialized. The potential for the use of microvascular grafts with lengths in excess of 15 cm are encouraging for bypass procedures, femoral reconstructions where the autogenous vascular conduits are unavailable.

The sterilization techniques, validation methods, physical and biologic effects of sterilization on synthetic vascular grafts were reviewed by Helmus et al. The clinical significance of pyrogen contamination was examined in a series of endotoxin contaminated polyester grafts tested in a canine model. While the majority of graft infections are believed to be the result of direct contamination at the time of implant, strict adherence to technical details could significantly reduce the risk of graft infection.

Plenary Session 4 was devoted to the need for standards for vascular grafts. The issues presented were based on past efforts to develop standards, the actual applicability of standards, and the role of standards as a form of regulation, whether mandatory or regulatory.

Wesolow presented both the historical and surgical perspectives concerning the need for standards. This review was presented in three sections involving investigational research, the scientific community involvement in standardization, and device legislation from the FDA. The author recalls his own involvement as President of the American Society of Artificial Internal Organs, and as representative from the Society of Vascular Surgery to ASTM Committee F-4. The report from the aforementioned committee is included, as it can be adapted as a starting point for the establishment of specifications and standard for cardiovascular implants. The author also reviews his experiences with over 450 different large and small caliber prostheses. His group has elaborated various specifications identified, classified the causes of failure, and suggested further areas of development during the past 30 years of vascular graft study.

Mortensen addresses vascular grafts from the viewpoint of graft applicability. The selection of the appropriate graft in response to the demands imposed by a specific clinical situation remains difficult. Graft applicability with respect to small and large diameter grafts is different. Graft porosity thrombogenicity with respect to intimal hyperplasia, infectivity, hemodynamics compliance, suitability, and implantation in the arterial or venous system remain major considerations in the area of graft standards development from the aspect of graft applicability. The author stresses that development of performance standards must include the existence and significance of a wide variety of graft applicability problems relative to meaningful performance standards for vascular grafts.

The paper presented by the FDA representatives MacNeill and Sung describes the procedures under Section 514 of the Medical Device Amendments Act of 1976. Vascular graft prostheses of 6 mm and greater diameter are subject to regulation by standards. The authors emphasize that the key in the performance standard development procedure is the establishment of a statement outlying the risks associated with the use of the device. The methods of control must also be selected so that the standards development procedure remains manageable and results in an effective performance standard.

Sawyer et al. discusses several properties of blood vessel substitutes that provide some of the conventional characteristics of the normal vasculature. The term porosity is defined from the viewpoints of both electric and ionic porosity which

leads to an explanation of electrochemical properties of graft materials. The phenomenon of "pressure equivalent electro osmosis" is introduced. Collagen as a material for grafts is reviewed and introduction of early data for the NCGT (St. Jude Medical Bio-polymeric) graft are reviewed.

Helen E. Kambic, M.S.

Cleveland Clinic Foundation;
symposium cochairperson and editor

Adrian Kantrowitz, M.D.

Sinai Hospital of Detroit; honorary
symposium chairman and editor

Pei Sung, Ph.D.

Center for Devices and Radiological Health;
symposium cochairperson and editor