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NEW PROGRESS IN BIOMEDICAL POLYMER MATERIALS

Donald J. Lyman

Departments of Materials Science and Engineering, Bioengineering, and

Surgery, University of Utah, Salt Lake City, Utah 84112, USA

Abstract - In this highly complex interdisciplinary area of biomedical polymers, progress is beginning to be made in a variety of implants. Of probable major importance is that of small diameter blood vessel repair. The studies leading to the development of a small diameter vascular graft are discussed to show the interrelationship between polymer surface and bulk morphology, polymer-protein interaction, platelet adhesion, and implant mechanical properties on the performance of the implant in the body.

A variety of polymeric implants have been tried for repair or replacement of damaged or diseased tissues and organs. Initially these implants used polymeric materials developed for other, non-biological applications. As a result, the implants, at best, worked in limited situations, and at worst failed. During this last decade, we have seen a tremendous increase in research on the development of polymer materials for biomedical applications. While some scientific progress has been made, there has not been an accompanying progress in the clinical and surgical utilization of these biomedical materials. Much of this has resulted from a lack of coupling between research in biomedical materials and the development studies related to the end-use applications. If we are to realize the potential in this area in which implant materials are used to restore structure and function of the body, a variety of modified or new materials, designed specifically for use in the body, are needed. However, this requires gaining an understanding of how polymer materials and the biological system interact at the molecular level and the macroscopic (or implant) level.

In this highly complex interdisciplinary area, progress is beginning to be made in a variety of implants. With the variety of excellent papers being presented in this section of the program, I will limit myself to discussing the development of a small diameter vascular graft, and show the interrelationship between polymer surface and bulk morphology, polymer-protein interaction, implant mechanical properties, and polymer degradation on implant performance.

The ultimate goal of these studies is the development of satisfactory replacement materials for damaged or obstructed veins or small diameter (less than 5 mm) arteries. The need for such a prosthesis is not only in the area of peripheral vascular surgery where it is necessary for bypassing arterial obstruction, but also in aorta-coronary surgery where it is estimated 100,000 operations requiring small diameter vessels will be performed in 1977. Currently, the surgeon is forced to use autogenous tissue such as the saphenous vein in these situations. This method has disadvantages in that satisfactory veins are not available in 10 to 25% of patients. Even in patients having satisfactory veins, one is limited in the size and quality available with removal of the veins requiring increased operating time. Therefore, the solving of this problem would be of significance to the surgeon and to the patient.

Currently, available synthetic polymer grafts are made from expanded porous Teflon and Dacron. These materials show patency rates of approximately 50% at the 6 mm ID size

and much less at smaller diameters. Thus, one must search for new polymers that will show an increase in patency rates in small diameter vessels.

There appears to be ample evidence from our studies and those of others to support the contention that protein adsorption is the first event occurring as blood comes in contact with a polymer surface in vivo (1-10). Platelets then adhere to this proteinated polymer surface to varying degrees (11). Studies on the adhesion of platelets to polymer surfaces pre-coated with a variety of proteins have indicated that albuminated surfaces appear to prevent platelet adhesion and confer non-thrombogencity to the base polymer (9,12,13). In contrast, surfaces pre-coated with fibrinogen or γ-globulin show increased platelet adhesion and release reactions leading to thrombosis (1,10,12,14-19). One is lead to the hypothesis that the composition of the protein layer formed in situ as whole blood flows over a polymer surface is not necessarily the same for every polymer, since the degree of platelet adhesion varies from polymer to polymer (11). The data from electrophoretic analyses of proteins desorbed from several polymers exposed to whole blood in situ, compared with platelet adhesion measurements on these same surfaces using our ex vivo flow-through cell (9,11) (see Table 1), parallel that described above for the pre-proteinated surfaces, that is, if the polymer preferentially adsorbs albumin in situ, it shows less platelet adhesion and the polymer should be non-thrombogenic. Conversely, a polymer preferentially adsorbing globulins or fibrinogen adheres platelets readily and should be thrombogenic. Thus, if one compares the three generally different materials, i.e. the thrombogenic fluorinated ethylene/propylene copolymer, the mildly thrombogenic polydimethyl siloxane, and the non-thrombogenic copolyether-urethane, the observed in vivo results of these materials correlate with the protein adsorption and platelet adhesion data. The selectivity of protein adsorption appears to be dictated by the chemical and physical structure of the polymer surface; and it is this selectivity which determines the thrombogenic response of the base polymer (1).

Table 1. The relationship between in vivo protein adsorption on polymer surfaces[1] and platelet adhesion

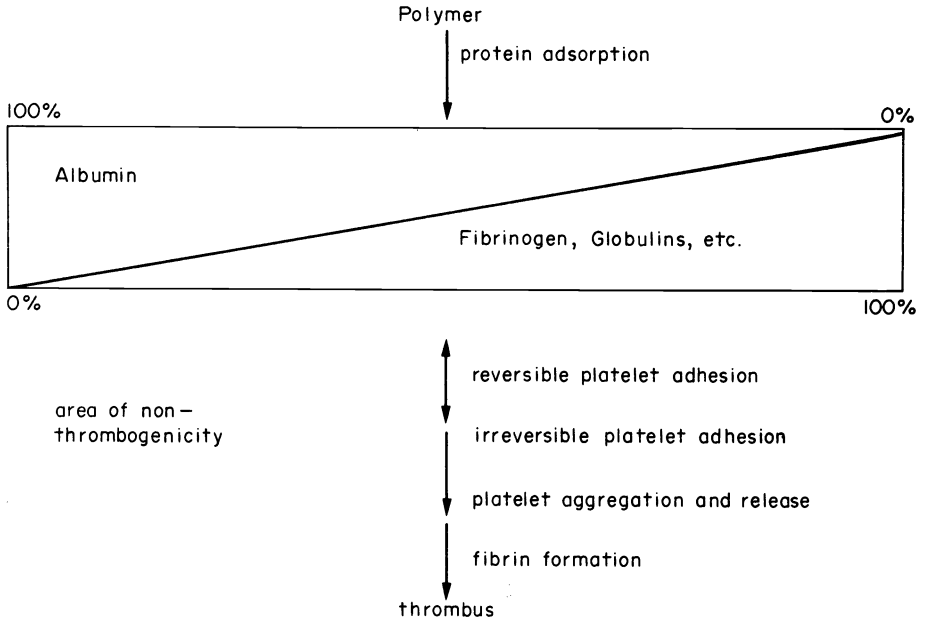
Polymers	% of total protein present			Platelet Adhesion[2]	
	Albumin	γ-Globulin	Other Globulins	1 Minute	5 Minutes
Teflon FEP	30	17	53	5.4	clot
710 PEUU	62	30	8	7.5	25.0
Silastic Rubber	70	20	10	4.6	-
Biomer	98	2	0	2.2	5.7
1025 PEUU	98	0	2	0.2	0.9

[1] Exposure time in recirculation was 45 minutes, except for Teflon FEB which was 30 minutes. This timing approximates time necessary for reaching plateau concentration as per in vitro experiments. The adsorbed proteins were eluted from the polymer surface, then analyzed by acrylamide gel electrophoresis (1).

[2] The mean number of platelets adhering to 20,000 μ^2 surface area exposure to whole blood in the flow through ex vivo cell at various exposure times (1).

It is also interesting to note that not all block copolyether-urethanes are non-thrombogenic. Even a minor change in the size of the ether block (as shown in PEUU 710 versus 1025 in which the molecular weight of the polyether segment changes from 700 to 1000) does affect protein adsorption, platelet adhesion, and the observed thrombogenicity. Chemical or physical changes in the blocks can influence the domain-matrix relationships of this type of copolymer and thus affect their surface interactions. And as we will see later, changes in fabrication variables can also influence the domain-matrix relationships.

On the basis of these results, we proposed the following mechanism for the in vivo initiation of a thrombus on a polymer surface (1,20,21).



Since Silastic Rubber adsorbs 70% albumin on its surface and yet is mildly thrombogenic, one might estimate that the albumin content on the surface must be greater than 70% of the total protein adsorbed if the polymer is to be non-thrombogenic.

Two copolyether-urethanes, one based on polypropylene glycol (PEUU 1025M, synthesized in our laboratory) and one based on polytetramethylene glycol (the commercially available Biomer), have shown improved thrombo-resistance in all tests including the Gott ring test (13,22). Both of these urethane materials fit our proposed clotting mechanism in that they preferentially adsorb albumin in situ and therefore, should be non-thrombogenic. The first smooth urethane artificial hearts implanted in calves were fabricated from PEUU 1025 synthesized in our laboratory (22); and more recently, our Division of Artificial Organs has had several long term survivals (over 123 days) in calves with a total implanted artificial heart made from smooth films of Biomer with no detectable blood damage. This is in contrast to a Silastic Rubber (and fiber-coated Silastic Rubber) heart in which extensive blood damage does occur (23). Thus, if these materials are truly compatible, as these in vitro, ex vivo and in vivo tests indicate, we should be able to use small prostheses made of this material in small diameter vessel replacement.

We fabricated and implanted a series of solid wall vascular grafts which had been solvent-cast over polished aluminum and glass mandrels. One set consisted of a thin, smooth inner wall with an external coating of the foamed urethane, while the other set had a foamed inner wall. The inferior vena cava (below the diaphragm) of dogs was initially chosen as the implantation site since it presents the most severe test. Work by others (24-27) have shown the great tendency of all types of grafts, even autografts, to become occluded when implanted here.

Our initial series of grafts also thrombosed, but the clots were found adhering to the suture-line junction beginning at the distal or outflow end and extending down to the proximal or inflow end of the vein. Again, the thrombus was not adherent to the copoly-urethane. Since our earlier studies on the effect of blood flow rates on platelet adhesion indicated that the major difference between platelet adhesion in arterial and venous systems was the difference in flow rates (28), we investigated the effect of creating an AV fistula in the femoral artery-vein prior to completing the graft anastomoses. Our results with this procedure showed significant improvement. Several 8 mm (ID) grafts were patent for five weeks as determined by vena cavagrams. However, the grafts on removal still had thrombus on the suture-line junction. This appeared to be well organized and was often non-occlusive. Similar results, i.e. well organized thrombus at the natural-artificial artria anastomoses, were also noted in the artificial heart implantation experiments.

These implant studies plus the microscopic examinations of tissue-graft sections of a series of femoral artery vascular implants have suggested that the mode of failure might

be due to a compliance mismatch between the natural vessel and the synthetic vascular graft, and not a surface incompatibility of the copolyether-urethane with blood. [Note: This mismatch of mechanical properties appears to be a contributer in material rejection throughout the body, and not just in the vascular replacements.]

Most vascular prostheses in use today have an elastic moduli about ten times greater than that of the natural vessel (29). Thus, an anastomosis between such a prosthesis and a natural vessel results in a mismatch of compliance. Stresses are set up through the generation of turbulent flow and by mechanical trauma to the natural vessel, which may contribute to suture line disruption and/or thrombosis (29,30). It has been shown (30) that these forces are at a minimum when the ratio of Dacron graft to host artery radius is 1.4; and therefore, compensation for the compliance mismatch may be an important factor in early patency rates for current synthetic grafts. Also, since the compliance of current synthetic arterial grafts have been shown to decrease with time (31), compliance mismatch may be implicated as a possible factor in later failure rates.

Other investigators (32) have laminated films of similar copolyurethane materials to form tubes having lateral to longitudinal compliance ratios similar to the ratios found in the natural vessel as a route to compatible grafts. However, these materials are still too stiff and do not match the actual compliance of the vessel (see Figure 1). We felt that it was necessary to match the actual compliance of the blood vessel in the lateral dimension if we are to achieve a successful implant. To do this required either a new block copolymer or a new fabrication method to modify the bulk structure of our material. Our initial studies emphasized this latter approach, although we were concerned with how any changes in fabrication variables might adversely affect the surface structure of our copolymer. For example, it has been reported that the siloxane-urethane material "Avcothane" can be relatively thrombogenic or non-thrombogenic depending on whether one examines the mold side or the air side of the formed material (33). Similar, but more subtle differences between the glass mold and air side of films have been observed for our copolyurethanes by cell culture (34) and more recently by Electron Spectroscopy for Chemical Analysis (ESCA) and by Fourier Transform Infrared Spectroscopy (FTIR) (35). Other variables such as type of solvent, percent polymer in solution, method of solvent removal, etc., can also influence how these block copolymers form their domain-matrix relationship.

The ESCA carbon peaks of the three polyurethanes which differ only in the molecular weight of the polypropylene glycol block, are shown in Figure 1, illustrating the differences in ESCA spectra due to fabrication (glass versus air surface) and synthetic structure. The differenct chemical structures for the various surfaces are evident in the varying peak areas, although the ratios of peak area to theoretical values give more exciting information about the importance of fabrication variables on surface structure. Although the 2025 polyether-urethane contains twice the number of ether linkages in the bulk, it actually has less sigma bonded carbon-oxygen on the surface than the 1025 or 710 polyether-urethanes. Thus, the surface structure of an implant is not necessarily represented by the bulk structure and is greatly dependent upon the fabrication techniques.

For actually modeling the structure of the surface, FTIR is proving to be a better tool, especially when reflectance spectroscopy (ATR) is coupled to the subtractive capabilities of the instrument (35). For example, a striking difference is noted in the conformation of the ether linkages in the soft segment comprising the matrix. Bellamy (36) describes the trans conformation of the antisymmetric C-O-C having an absorbance peak at 1120 cm^{-1}, while the gauche is at 1068cm^{-1}. The ether absorbance peak is quite broad with the various conformational peaks forming shoulders. Subtraction of polypropylene glycol (the actual intermediate used in synthesis of the polyurethanes) from bulk and surface ATR spectra of the same film indicate a predominance of trans in the bulk as compared to gauche in the near surface of the film as illustrated in Figure 2.

We have now developed a new process for fabricating the copolyurethane material into an essentially nonporous void containing graft (with reduced wall density) whose compliance can be made to approximate that of the natural artery or vein (37), and yet maintain a blood compatible surface. To improve the suturability of the grafts a fabric network was provided in the graft wall. Although the fabric network stiffens the graft somewhat, this composite graft still approximates the compliance of the natural artery (Figure 1).

Two series of these grafts, a total of 11 grafts, ranging in size from 3 mm to 10 mm, were implanted in dogs. Patency was followed by palpitation of femoral pulses in the case of the aortic grafts and by palpitation of distal femoral pulses in the case of the femoral grafts. The dogs were sacrificed when, on the basis of diminished or absent distal pulses, it was felt that the prosthesis had failed. In contrast to the failure of the earlier solid wall grafts, within hours, six of the 11 new compliant copolyether-urethane grafts were patent on sacrifice (37). For example, an 8 mm aortic graft was patent at 30 days and a 4 mm femoral graft was patent at 77 days. The heavy fibrotic reaction noted on the

earlier solid wall non-compliant grafts was not seen on these patent compliant grafts of the current series. Since the grafts were widely patent on recovery, it is believed that they would have remained patent for a much longer time, had the animals not been sacrificed. Of the five failures, two were considered technical failures due to a twisted graft and a graft too small for the natural vessel. The other three failures were of a type similar to those of the earlier solid wall graft, suggesting either a quality control error, a technical error (surgery), possible residual solvent (N,N-dimethylforamide is toxic to cells), or some other unknown tissue reaction. However, since the major variable tested in this study was the increased elasticity (or compliance) of the prosthesis, we feel that this was directly responsible for our greatly improved results.

In a current series of 4 mm vascular implants, 17 of 38 were patent on removal or are presently in the remaining dogs at 13 months implantation time (38). Patency was determined at various time intervals by exposure and direct visualization of the vessel. The one technical failure was due to the wrong suture and needle being used, resulting in tearing of the natural vessel. Pathologies on several of the removed grafts indicated the general hypertrophy leading to occlusion of the graft appeared to be due to how the anastomosis was performed, with a butt type of junction being the worst. There was no foreign body type of cell response noted, and so it would appear that the failures continue to be a result of mismatch of graft-vessel compliance, possibly complicated by surgical techniques, and irregularities in graft quality. However, the long term success in these small diameter vessels does show that we must balance the surface properties needed for blood compatibility with the correct mechanical properties needed for compliance matching.

Similar types of research coupling basic study on polymer/living system interactions with actual implant development, are underway in ureter repair and nerve repair.

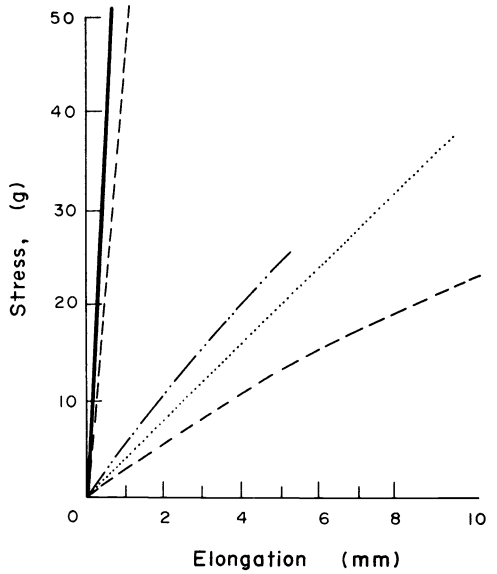


FIGURE 1. Stress-strain curves for the polyether-urethane materials: 3.5 mm thick air dried film (———); 13.5 and 2.7 mm thick precipitated grafts (- - -); composite graft (-··-··); Thoracic Aorta (····).

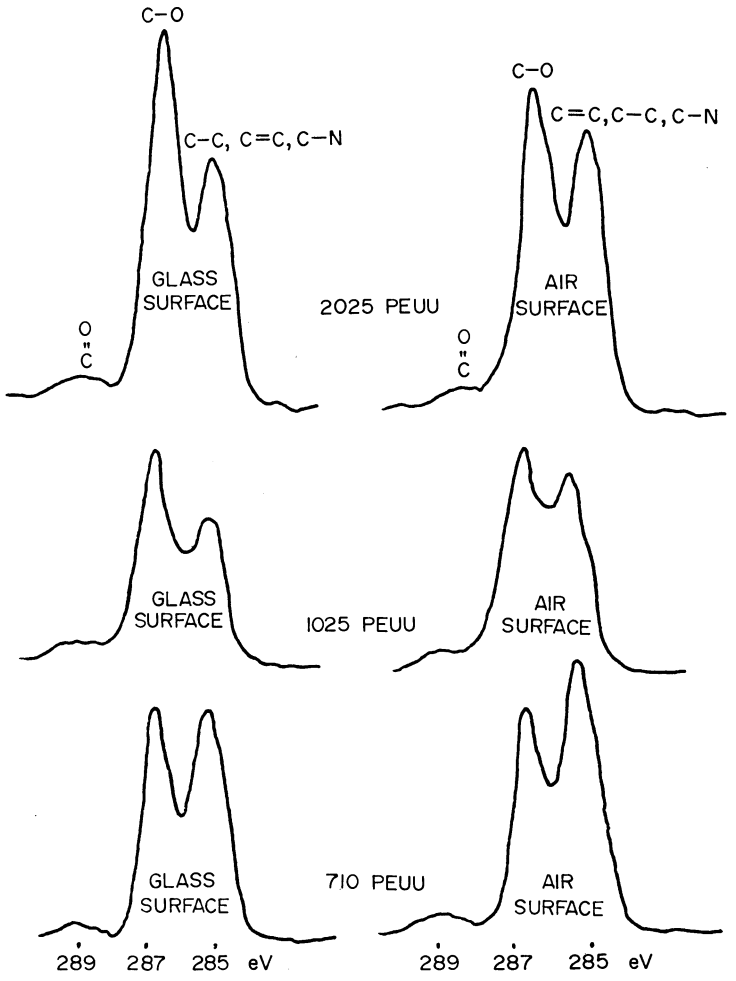


Figure 2
ESCA C_{1s} Spectra of Block Polyether-urethanes

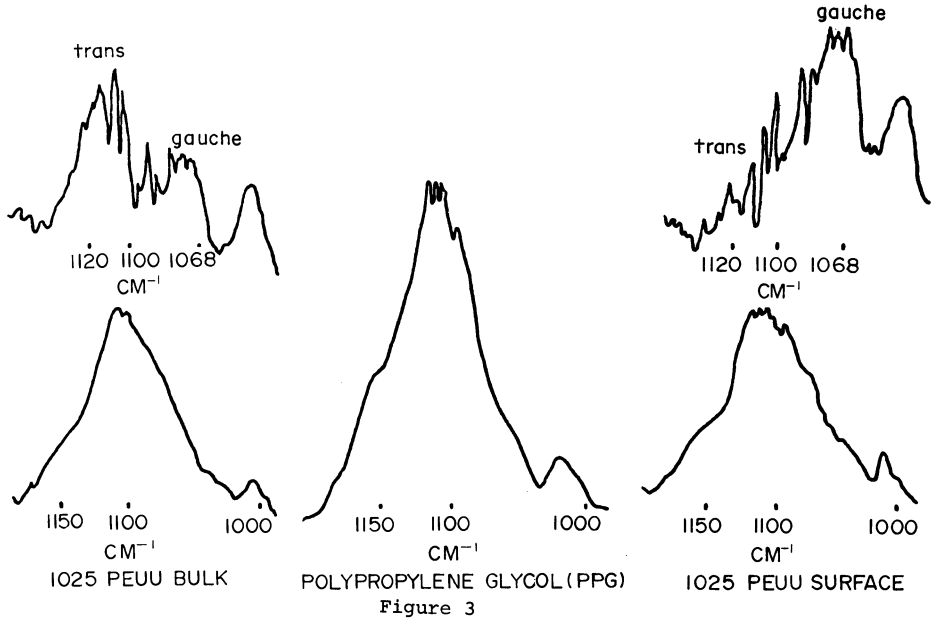


Figure 3
Subtraction of 55% Polypropylene Glycol Spectrum
from 1025 PEUU Bulk and Surface Spectra

REFERENCES

1. D. J. Lyman, L. C. Metcalf, D. Albo, Jr., D. F. Richards and J. Lamb, Trans. Amer. Soc. Artif. Int. Organs 20, 474-479, 1974.
2. E. W. Salzman, Fed. Proc. 30, 1503-1509, 1971.
3. E. Nyilas, Proc. 23rd Ann. Conf. Eng. Med. Biol. 12 147, 1970.
4. R. E. Dutton, R. E. Baier, R. L. Dedrick and R. L. Bowman, Trans. Amer. Soc. Artif. Int. Organs 14, 57-62, 1968.
5. R. E. Baier, R. C. Dutton, J. Biomed. Mat. Res. 3, 191-206, 1969.
6. H. Petschek, D. Adams and A. R. Kantrowitz, Trans. Amer. Soc. Artif. Int. Organs 14, 256-260, 1968.
7. R. E. Baier, G. I. Loeb and G. T. Wallace, Fed. Proc. 30 1523-1538, 1971.
8. A. J. Lande', L. Edwards, J. H. Bloch, R. G. Carlson, V. Subramanian, R. S. Ascheim, S. Scheidt, S. Fillmore, T. Killip and C. W. Lillehei, Trans. Amer. Soc. Artif. Int. Organs 16, 352-357, 1970.
9. D. J. Lyman, K. G. Klein, J. J. Brash, B. K. Fritzinger, J. D. Andrade and F. S. Bonomo, Thromb. Diath. Haemorrhag. Suppl. 42, 109-114, 1971.
10. D. E. Scarborough, R. G. Mason, F. G. Dalldorf and K. M. Brinkhouse, Lab. Invest. 20, 164-169, 1969.
11. D. J. Lyman, K. G. Klein, J. L. Brash and B. K. Fritzinger, Thromb. Diathes, Haem. 23, 120-128, 1970.
12. M. A. Packham, G. Evans, M. F. Glynn and J. F. Mustard, J. Lab. Clin. Med. 73, 686-697, 1969.
13. V. L. Gott, and A. Furuse, Fed. Proc. 30, 1679-1685, 1971.
14. D. S. P. Jenkins, M.A . Packham, M. A. Gucciore, and J. F. Mustard, J. Lab. Clin. Med. 81, 280-290, 1973.
15. J. F. Mustard, M. F. Glynn, E. E. Nishizawa and M. A. Packham, Fed. Proc. 26, 106-114, 1967.
16. S. W. Kim and D. J. Lyman, App. Polymer Symp. 22, 289-297, 1973.
17. S. W. Kim, R. G. Lee, C. Adamson and D.J. Lyman, Preprints of Div. of Plastics and Organic Coatings, ACS, Preprint 165, 36-41, 1973.
18. M. F. Glynn, M. A. Packham, J. Kirsh, and J. F. Mustard, J. Clin. Invest. 45, 1013, 1966.
19. M. B. Zucker, and L. Vroman, Proc. Soc. Exp. Biol. Med. 131, 318-320, 1969.
20. D. J. Lyman and W. J. Seare, Jr., Ann. Revs. Maters. Sci. 4, 415-432, 1974.
21. D. J. Lyman, K. Knutson, B. McNeill and K. Shibatani, Trans. Amer. Soc. Artif. Int. Organs 21, 49-54, 1975.
22. D. J. Lyman, C. Kwan-Gett, H. H. J. Zwart, A. Bland, N. Eastwood, J. Kawai and W. J. Kolff, Trans. Amer. Soc. Artif. Int. Organs 17, 456-463, 1971.
23. J. H. Lawson, D. B. Olsen, E. Hershgold, J. Kolff, K. Hatfield, and W. J. Kolff, Trans. Amer. Soc. Artif. Int. Organs 21, 368-373, 1975.
24. W. Dale, and H. W. Scott, Jr., Surgery 53, 52-73, 1963.
25. H. A. Collins, G. Burrus and M. E. DeBakey, Am. J. Surg. 99, 40-44, 1960.
26. R. Bower, V. Federieci and J. M. Howard, Surgery 47, 132-138, 1960.
27. H. Najafi, M. Hirose, V. Battung, R. A. DeWall, and P. Sarfatis, J. Thor. and Cardiovasc. Surgery 53, 243-247, 1967.
28. D. J. Lyman, and J. E. Lindberg, Manuscript in preparation based on M. S. Thesis submitted by J.E.L.
29. E. R. Gozna, F. W. Mason, A. E. Marble, D. A. Winter and F. G. Dolan, Canadian J. Surgery, 17, 176-181, 1974.
30. C. E. Kinely, P. E. Paasche, A. S. MacDonald, A. E. Marble and E. R. Gozna, Surgery, 75, 28-30, 1974.
31. D. E. Hokanson, and P. E. Strandness, Jr., Surg. Gynecol. Obstet., 127, 57-60, 1968.
32. I. L. Kardos, F. S. Mehta, S. F. Apostolou, C. Thes and R. E. Clark, Biomat. Med. Dev. and Art. Organs, 4, 387-396, 1974.
33. E. Nyilas, W. A. Morton, R. J. Ward and P. N. Madras, Art. Kidney Ann. Report, AK-1-1-2505. PB 226839, 1973.
34. D. J. Lyman, D. W. Hill, R. K. Stirk, C. Adamson, and B. Mooney, Trans. Amer. Soc. Artif. Int. Organs, 18 19-23, 1972.
35. K. Knutson and D. J. Lyman, Manuscript in Preparation.
36. L. J. Bellamy, The Infrared Spectra of Complex Molecules, Vol. 1, 3rd Edition, Halsted Press, 1975.
37. D. J. Lyman, F. J. Fazzio, Jr., H. Voorhees, G. Robinson and D. Albo, Jr., J. Biomed. Mat. Res. 11, in press, 1977.
38. D. J. Lyman, D. Albo, Jr., R. Jackson, and K. Knutson, Trans. Amer. Soc. Artif. Int. Organs 23, in press, 1977.