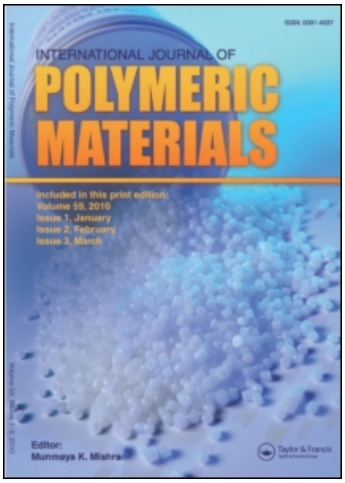

International Journal of Polymeric Materials

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713647664

Polymers in Medicine

Donald J. Lyman[a]
[a] Division of Artificial Organs (College of Medicine) and Division of Materials Science and Engineering (College of Engineering), University of Utah, Salt Lake City, Utah

To cite this Article Lyman, Donald J.(1973) 'Polymers in Medicine', International Journal of Polymeric Materials, 2: 4, 319 — 333
To link to this Article: DOI: 10.1080/00914037308072365
URL: http://dx.doi.org/10.1080/00914037308072365

Intern. J. Polymeric Mater., 1973, Vol. 2, pp. 319–333

Printed in Reading, England

Polymers in Medicine†

DONALD J. LYMAN

Division of Artificial Organs (College of Medicine) and Division of Materials Science and Engineering (College of Engineering), University of Utah, Salt Lake City, Utah

(*Received August 1, 1973*)

The use of polymers in repair of the vascular system and in extracorporeal handling of blood is reviewed. Discussed are the adsorption of protein on surfaces as studied *via* infrared multiple internal reflectance spectroscopy, *in vivo* experiments involving implanted cannulas, pre-coating of polymers with albumin, and the adhesion of baby hamster kidney cells to polymer surfaces.

The use of materials in the body to repair or restore damaged, diseased, or ravaged tissue and organs is not new. First recorded use was that of a gold plate in 1588 to repair a cleft palate. Later in the 1800's, there were numerous reports of metal plates and pins to fix broken bones. However, with the advent of the polymer industry and the ready availability of a variety of materials (polymers) having properties more similar to the body, there was a tremendous increase in the use of materials in surgery. Most of this increase being since the middle 1950's. These uses have been quite broad, ranging from temporary assist materials, such as sutures, staples, surgical adhesives, plasma extenders, bone pins and braces, to relatively simple artificial parts of a more permanent nature, such as vascular grafts, heart valves, hydrocephalic drain tubes, joints, reinforcing meshes, as well as a variety of soft tissue replacement materials for cosmetic surgery, to the more complex devices such as the artificial kidney, the artificial lung, and the artificial heart, which can duplicate some physiological process. Indeed the imagination and skill of the surgeon and the support and technical assistance from companies such as Midland's own Dow Corning Center for Aid to Medical Research have resulted in a great variety of devices being available (See Figure 1). However, even with all these successes there have been many failures. Most of this has been due to improper choice of material for the intended use. These materials are not

†Lecture presented at the Scientific Symposium "Trends in Macromolecular Science", at the Dedication Ceremony of the Midland Macromolecular Institute, September 29, 1972.

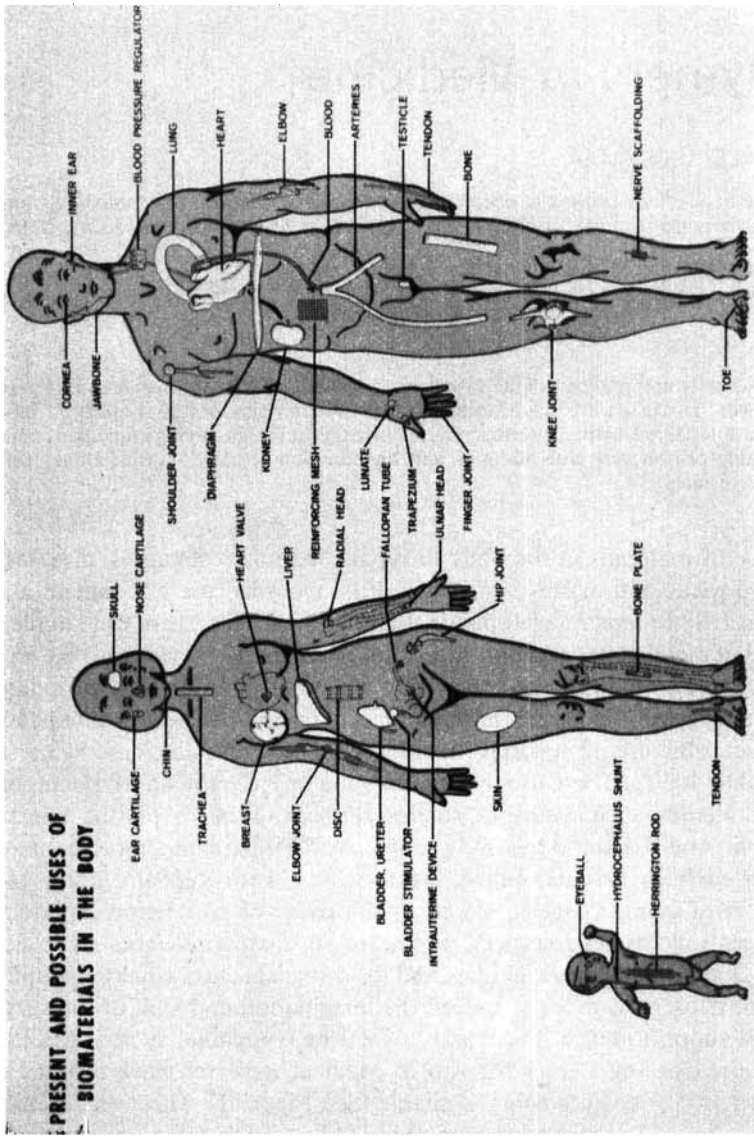

FIGURE 1 Schematic representations of a variety of implanted parts and devices that have been tried in the body.

inert in the body, but do react on and are in turn acted on by the biological environment.[1] Also, the materials often tried were those readily available from many commercial processes. These do not have the purity and reproducibility that we would like in a biomedical material.

As a result, we often find that medical advances have been highly dependent on new polymers becoming available from a variety of industrial or consumer needs, which might also meet these medical needs. During the 1960's, a new research area has developed with the objectives of providing the knowledge of how polymers interact as they interface with the living system so that needed biomedical polymers can be developed in their own right. This research requires the coupling of many traditional disciplines as well as creating new interdisciplinary studies (see Figure 2).

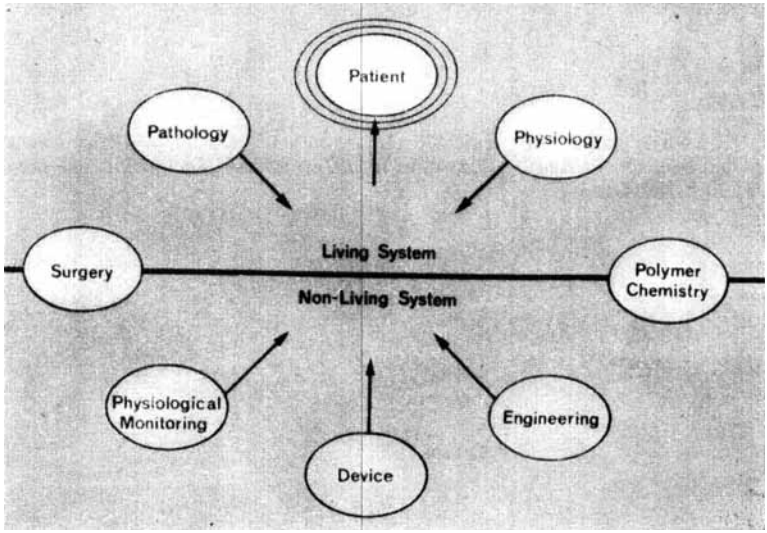

FIGURE 2 The interfacing of the material (and device) with the living system is key to determining the fate of the patient. To study these interface reactions involves the coupling of many disciplines.

The area that I have found most fascinating is the use of polymers in repair of the vascular system and in extracorporeal handling of blood. I would like to describe this work to you, using the artificial heart as the background for my remarks.

For some time, the Division of Artificial Organs, under the direction of Dr. W. J. Kolff, have been developing artificial heart devices. Much of this work has been concerned with a Kwan-Gett hemispherical heart[2] (see Figures 3 and 4) and the development of optimum surgical procedures as well as pre- and post-

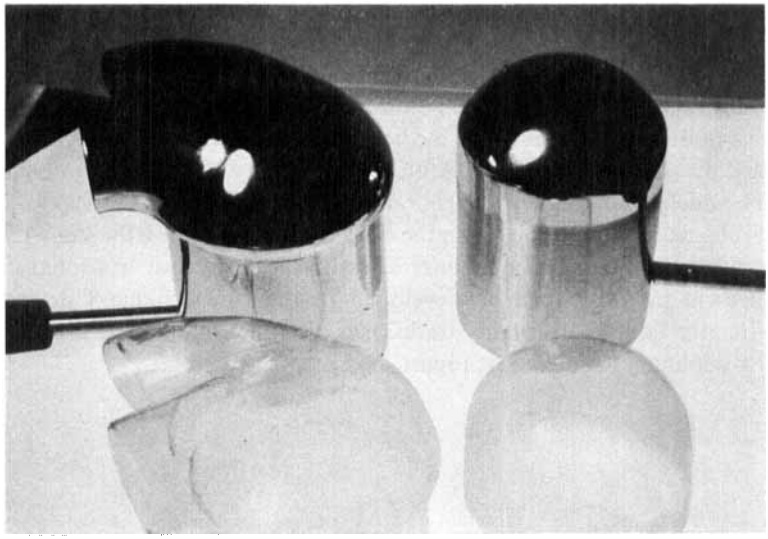

FIGURE 3 The molds and fabricated copolyurethane housing and diaphragm for a Kwan-Gett hemispherical heart. [Reprinted from *Trans. Amer. Soc. Artific. Internal Organs* (Ref. 3), by permission.]

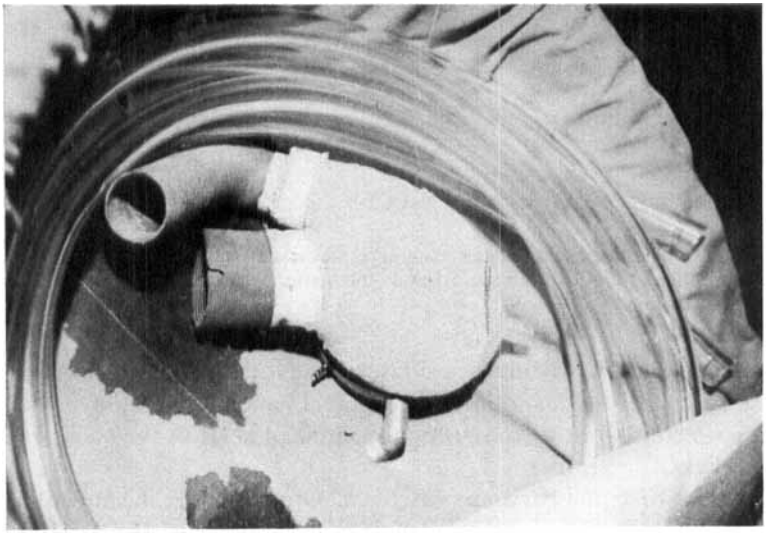

FIGURE 4 An assembled Kwan-Gett hemispherical heart (right ventricle) just prior to implantation. [Reprinted from *Trans. Amer. Soc. Artific. Internal Organs* (Ref. 3), by permission.]

operative care techniques. The Division has made considerable progress as indicated by a world's record survival time of two weeks in a calf. However, there are still problems; such as occasional mechanical failure, poor fit, inadequate pumping, improper blood pumping pressure, need for improved valves, etc. Also, we still do not have an ideal material to interface with the blood. As a result we find clots on the surface of the artificial heart, and evidence of clots which broke loose forming emboli and have damaged distant tissues (see Figure 5). The cellular elements such as red blood cells and platelets are damaged and destroyed (see Figure 6). The protein constituents are also damaged (see Figure 7). While these studies do give an overall picture of the effect of the material on blood, there are two factors that must be kept in mind. First, the animals own defense mechanisms can often clear the damage, thus masking a potential effect. Second, these tests, in themselves, give no clues as to the initiating steps in this damage. We developed[4] a simple *ex-vivo* test which has allowed us to look more closely at this problem. For example, blood flowing over a polyvinyl chloride surface for several minutes in the absence of an air interface, a clot does form (see Figure 8). One can see a platelet on the surface, with fibrin strands extending from the platelet pseudopods, and this fibrous mesh entrapping red blood cells. However, while this has been valuable for guiding research and for screening polymers,[4,5] it still does not explain why the platelets adhere, and to what surface they are actually adhering. Our work has been directed toward answering these questions as well as the related one of how does one synthesize a non-thrombogenic polymer. This requires developing knowledge of the events occurring at the molecular level as the blood comes in contact with the polymer which initiate these adverse reactions. To do this, one must use model experiments (*in-vitro* and *ex-vivo*) to isolate and study the individual events that *might* occur at the molecular level in the *in-vivo* situation.

Blood coagulation has been studied for over 100 years, with many studies being directed toward identification of the activating molecule. These studies reached a high point in 1964 with the proposal of an enzymatic cascade blood clotting mechanism[6] resulting from surface contact of a particular protein molecule.

Our studies began here; on how proteins are adsorbed and activated on polymer surfaces. One tool that we have used extensively in this work has been infrared multiple internal reflectance spectroscopy. This allowed us to examine directly the adsorbed protein–polymer substrate complex, and not rely on indirect methods to estimate the interaction. Since both the adsorbed protein and the polymer infrared adsorption do appear in the spectrum (see Figure 9) one can use ratios of bands to quantitate how much protein is adsorbed[7] and the rates of adsorption.[8] We studied the adsorption of the more common blood proteins on a variety of neutral, hydrophobic polymers.

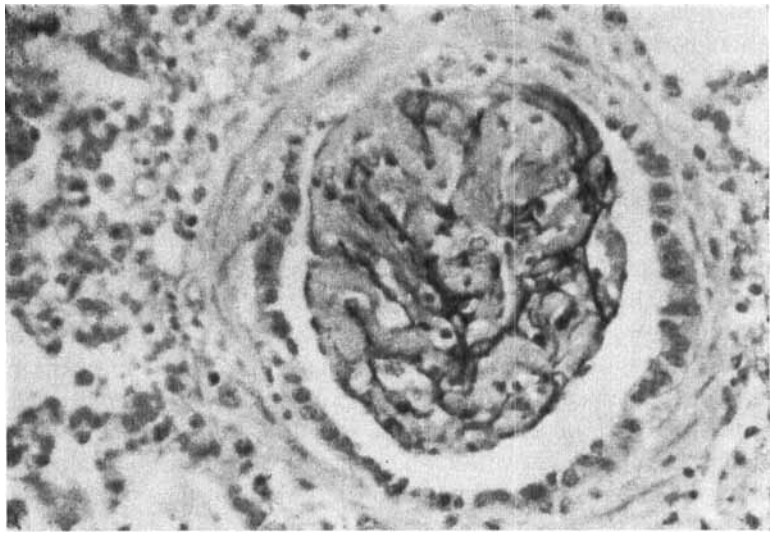

FIGURE 5 An embolus in a small blood vessel in the brain.

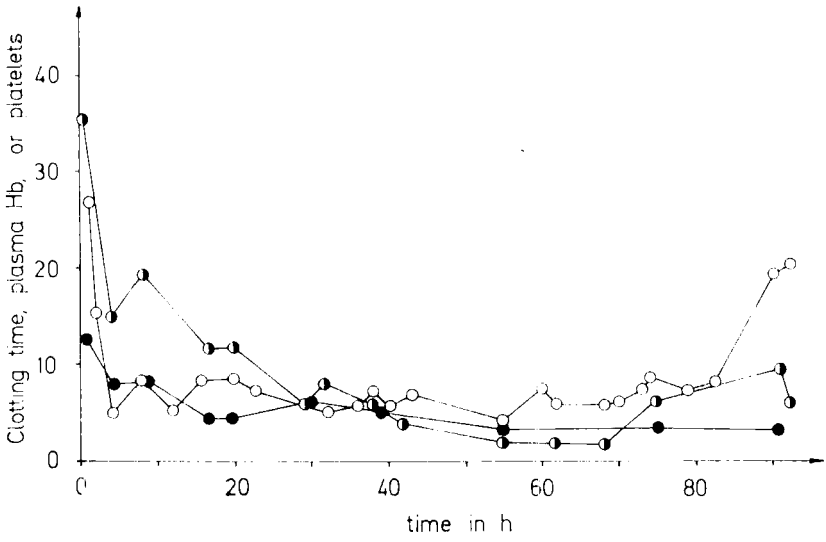

FIGURE 6 Changes in calf blood chemistry after implantation of an artificial heart device. (○) Clotting time in min, (●) Plasma Hb in mg-%, (◑) Platelets in $10^4/cm^3$.

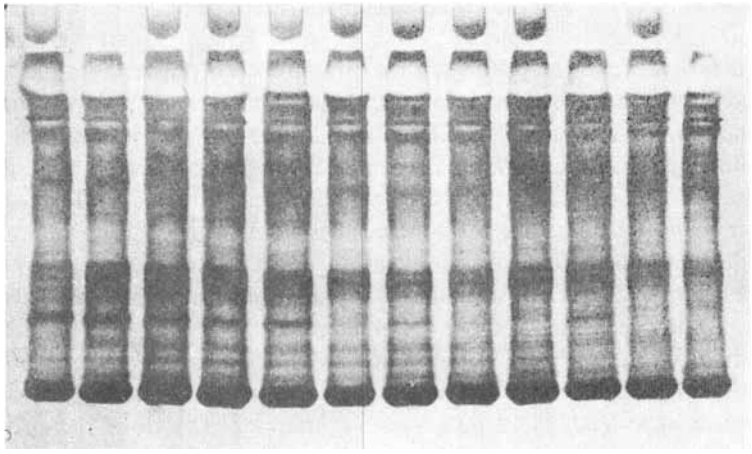

FIGURE 7 Changes in the electrophoretic patterns of plasma with time from a calf with an artificial heart.

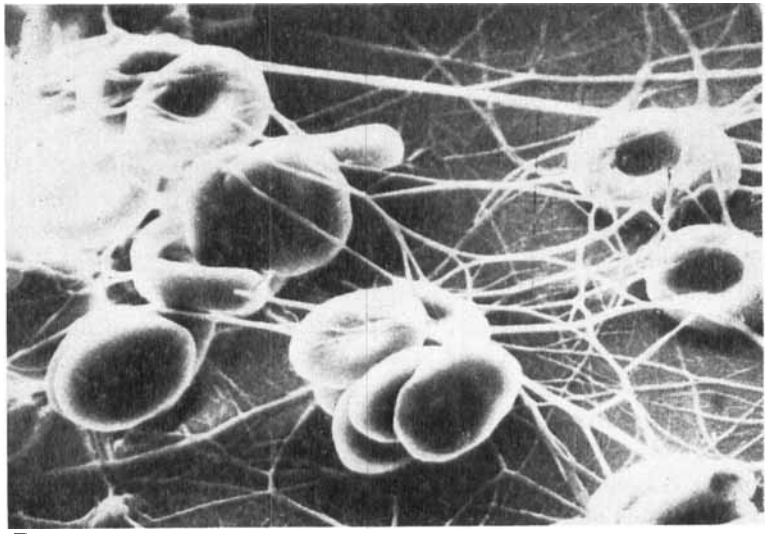

FIGURE 8 Scanning electron microscope picture of a clot formed on a polyvinyl chloride surface in a flow-through *ex-vivo* cell showing platelets on the surface of the material and the fibrin mesh entrapping red blood cells. [Picture by Dr. Rodman, University of Iowa.]

Experiments were done in the absence of an air interface under static and flow adsorption conditions. Figures 10 and 11 show typical adsorption curves. Very quickly it began to appear that the proteins were physically and essentially irreversibly adsorbed to these neutral hydrophobic polymers in a similar manner forming a monolayer. Electron micrographs and infrared spectra data (showing no shifts in Amide I—Amide II bands) indicated that no gross structural alterations occurred, i.e. the adsorbed proteins retained their globular form. As these studies continued we did begin to find differences in rates of adsorption, plateau concentration, effect of flow velocity in amount of adsorbed protein, etc., as we changed the adsorbing protein on the polymer surface. I will discuss this in more detail later.

At this stage, the *in vivo* experiments involving implanted cannulas that we were doing concurrently with the help of Dr. William Edmark (Providence Hospital, Seattle), began to influence our thinking. On all of the surfaces we examined, a platelet plug appeared to be at the site of clot initiation. Indeed, with several surfaces, the total clot appeared to be an aggregated platelet mass. As I pondered these contrasting sets of experiments, I began to feel that there was an overemphasis on "contact surface activation" of Hageman factor (Factor XII) and that the mechanism on the implanted polymer surface might more nearly resemble what happens when the natural vessel wall is cut. We began to study the adhesion of platelets to various polymer surfaces. In the beginning, we simply dipped films into blood, then rinsed and stained the surfaces. All the surfaces had large numbers of platelets on them, and all appeared surprisingly similar. However, since it was known that proteins denature at an air interface and it was possible that we were simply coating our polymer with denatured protein by the dipping—essentially a Langmuir transfer of protein to the surface, we redesigned our system to avoid an air interface. The flow-through cell was quite simple (see Figure 12), a small glass chamber to which we could clamp the polymer films to be examined. The cell system is filled with buffered saline. Human venous blood is introduced directly (via a vena puncture) to the cell, thus displacing the filling solution. Much care had to be taken to avoid air bubbles. The cell was then quickly rinsed and the adsorbed platelets fixed and stained. On some surfaces, you could actually see pseudopod development (see Figure 13), and if the time of exposure was longer, an actual clot which would resemble that shown earlier in Figure 8. As we examined a series of neutral hydrophobic polymers under these conditions and compared the number of platelets adhering at one-minute exposure, there was a definite trend observed: the more platelets, the more thrombogenic the material was.[4] At longer times of exposure, all surfaces began to look rather similar. This is not unexpected, since all were considered thrombogenic, with the only differences being in how long they took to clot.[3,9,10]

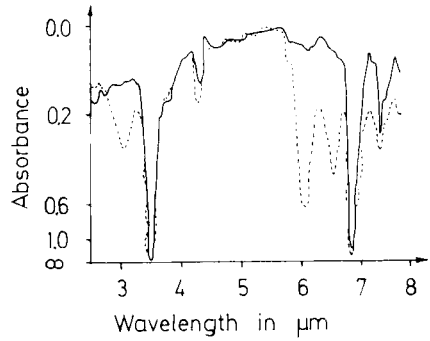

FIGURE 9 Infrared multiple internal reflectance spectra of polyethylene (———) and of γ-globulin adsorbed on polyethylene (- - - - -).

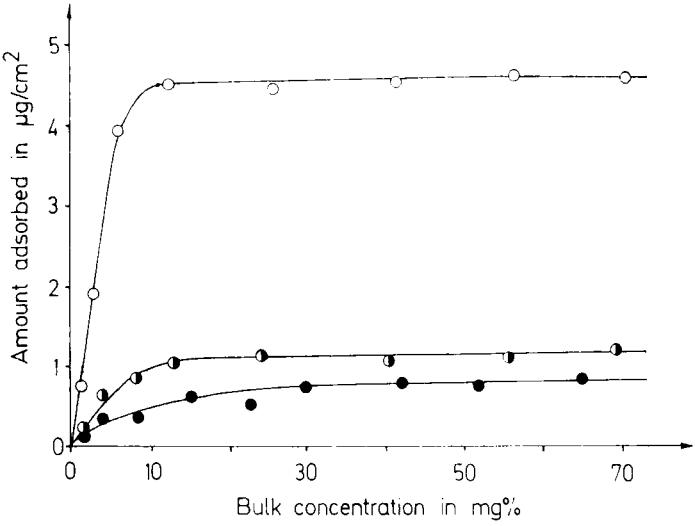

FIGURE 10 Adsorption isotherms of albumin on selected polymer surfaces. (○) Co (polyether/urethane/urea), PEUU-1, (◑) silastic rubber, (●) fluorinated poly(ethylene-co-propylene).

Since our protein adsorption studies indicated that a polymer surface could be coated with a layer of protein without altering the protein structure, we explored the possibility of passifying a polymer by pre-coating it with albumin. Indeed, when we tested such pre-albuminated surfaces in our flow-through platelet test cell, we found essentially no platelet adhesion.[11] If our hypothesis was true, this albuminated surface should be non-thrombogenic. Dr. Lande using albuminated surfaces in his membrane artificial lung[12] also showed markedly reduced platelet damage. Later, Dr. Andrade prepared

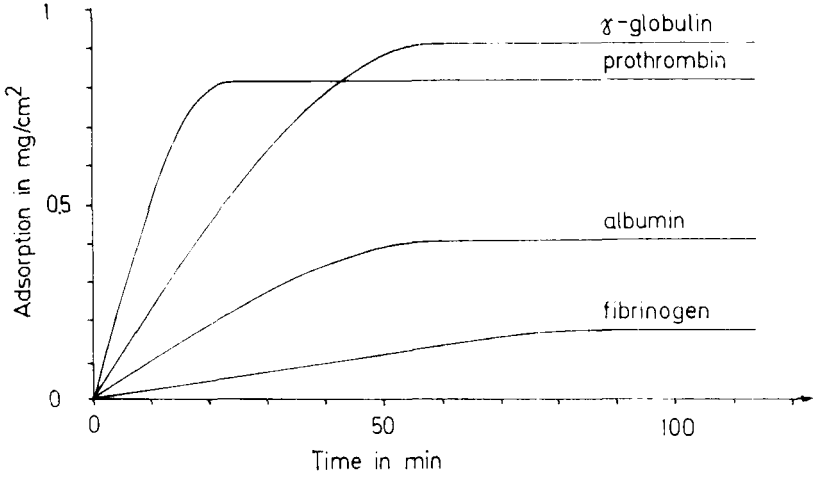

FIGURE 11 Adsorption of various proteins to fluorinated poly(ethylene-co-propylene). [Reprinted from *Advances in Nephrology* (Ref. 22), by permission.]

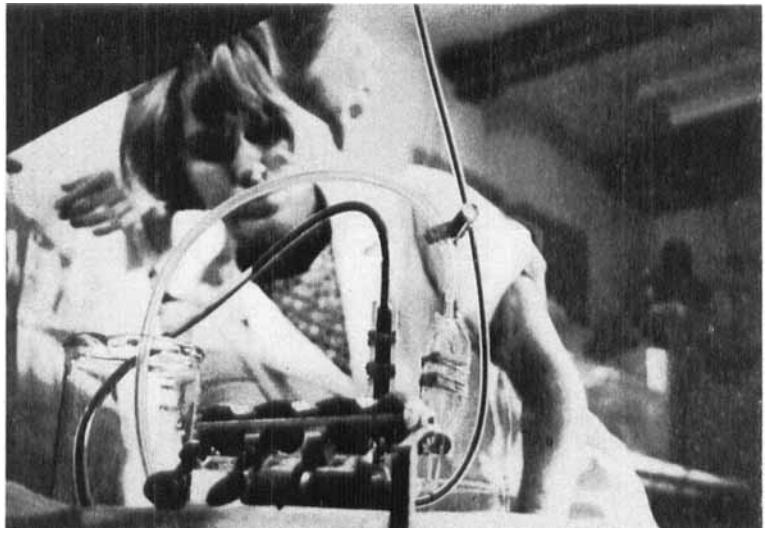

FIGURE 12 Two *ex-vivo* flow-through platelet adhesion cells; the left cell with venous blood flowing through it; the right cell primed with buffered saline.

covalently bonded albumin surfaces on Gott vena cava rings[13] which were then shown to be as non-thrombogenic as heparinized surfaces.[5] Thus, if we could avoid platelets adhering to a surface we should be able to avoid the formation of a clot.

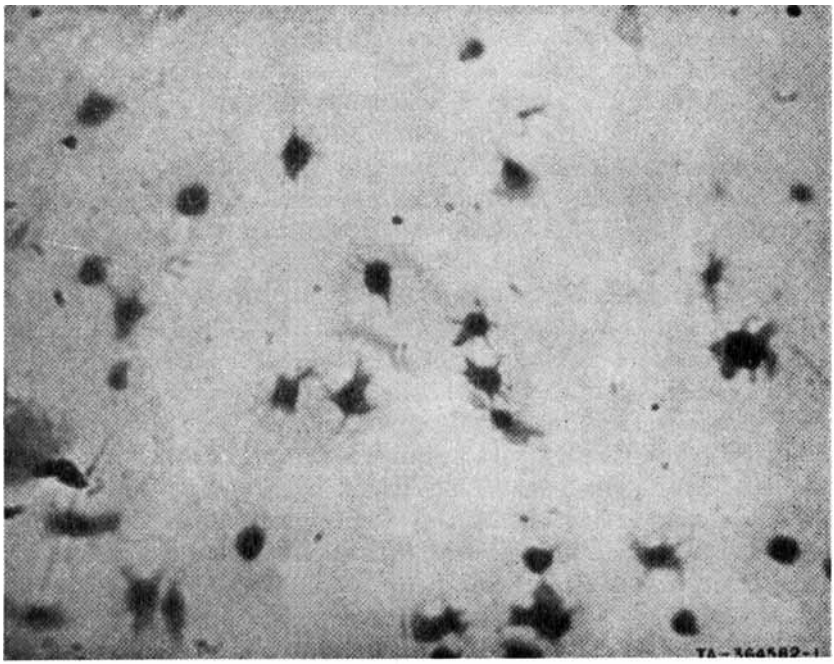

FIGURE 13 Stained platelets adhering to a fluorinated poly(ethylene-co-propylene) surface after exposure in our flow-through *ex-vivo* cell. [Reprinted from *Thrombosis et Diathesis Haemorphagic* (Ref. 4), by permission.]

With the interest in materials for artificial heart devices, we begin to explore a variety of segmented copolyether–urethanes and urethane–ureas for possible candidates. This family of polymers can be tailored to give a great variety of mechanical properties. One of these, a copolymer based on polypropylene glycol, methylene bis(4-phenylisocyanate) and ethylene diamine appeared to have a fair balance of mechanical and fabricating properties. Examination of this copolyether–urethane–urea in our platelet cell gave surprising results: i.e. it showed very low platelet adhesion.[15] Also, when Gott rings were implanted in the inferior vena cava of dogs, they were rated as non-thrombogenic as the heparinized surfaces.[14]

We did some preliminary studies on implanting a polyurethane hemispherical Kwan-Gett heart.[3] Although we did not get long survival in these initial implantations, the heart, on removal, was as clean and shiny as when we put it in. There was no evidence of clots, fibrin deposition or platelet deposits anywhere in the heart. Because of the heavy scheduling of other types

of hearts, and other surfaces such as the fibril coated surfaces,† we shifted our efforts back to gaining an understanding of how these two types of non-thrombogenic surfaces work. What were the similarities, what were the differences between the albumin coated surface and the segmented copoly-ether–urethane–urea surface. Since precoating a polymer surface with albumin pacifies the surface and prevents platelet adhesion, can this same effect be achieved *in situ*, i.e. could the urethane surface preferentially and rapidly adsorb albumin from the blood? As we examined the nature of protein adsorption to polymer surfaces in more detail,[8] data supporting this hypothesis began to emerge. In the series of polymer surfaces examined, those having higher rates of albumin adsorption and also having higher plateau concentrations of albumin on the surface were less thrombogenic. There also appeared to be an inverse relationship for γ-globulin adsorption. That is, the more γ-globulin on the surface, the more thrombogenic the polymer appeared. This is, of course, assuming that adsorptions occurring in a mixture, i.e. whole blood, would be similar to that observed for simple, single solute adsorptions. This is currently being checked. However, supporting this is our platelet adhesion studies which shows that both γ-globulin coated surfaces and fibrinogen coated surfaces are more active toward platelets[8] than are albumin surfaces, and work by other investigators[17,18] showing the adverse effects of γ-globulin on platelet adhesion and release reactions. Thus it would appear that one way to achieve a non-thrombogenic surface is to either pre-coat the polymer with a pacifying layer of albumin or have a polymer of such a chemical structure that it achieves this pacifying albumin coating rapidly *in situ*.

Our work is currently proceeding along several lines of investigation: (1) defining the nature of the protein–polymer interaction; (2) determining the actual chemical and inherent water structure of the proteinated surfaces; and (3) determining the nature of the platelet–protein surface interaction. These studies, I feel, will allow us to develop much of the basic knowledge of blood interactions with polymeric surfaces; knowledge which is necessary if we are to advance the repair of the vascular system and the extracorporeal treatment of blood.

Recently, there has been increased interest in cell culturing on surface as an alternate way to pacify surfaces.[19] The neo-intima which develops provides a natural surface to the blood. However, lack of cellular adhesion to the Silastic Rubber substrate has necessitated the use of Dacron fiber-coated surfaces to prevent the cellular deposits from being stripped off. However, this is not without its own problems. Therefore, Dr. Hill and I investigated the adhesion of baby hamster kidney (BHK-21) cells[20] to polymer

†It should be noted that after much implantation and post-operative study by the Division of Artificial Organs, the world's record long-term survival was achieved with a fiber-coated surface.[16]

surfaces. Normally, if the BHK-21 cell adheres, it will grow to form a monolayer; if it does not adhere, it will ball up and die (see Figure 14). As we examined a series of copolyether-urethane-ureas, which were chemically identical except for the length of the polyether segment, we noticed an interesting phenomena.[21] When the polyether segment had a molecular weight of 400, 700 or 2000, the BHK-21 cells adhered and grew normally; when the polyether segment had a molecular weight of 1000, the cells did not adhere and grow. Parallel experiments on platelet adhesion show similar response; i.e. platelet adhesion on the polymer having the 400, 700, or 2000 molecular weight polyether, but not the 1000 molecular weight polyether. These four types of copolymers showed similar critical surface tensions and protein

(a)

(b)

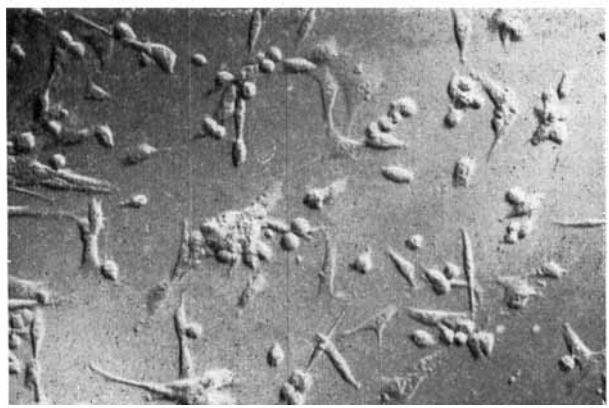

FIGURE 14 Cell culturing of baby hampster kidney cells: (a) onto glass, showing adhesion and growth, (b) onto a polyurethane surface, showing no growth.

adsorption. However, it must be kept in mind that these involve gross measurements, and the cells are apparently recognizing some microarchitectural differences in these copolymers. Indeed, preliminary studies on the tacticity of the polypropylene glycol segments and on the film morphology does indicate that the copolyether-urethane-urea based on the 1000 molecular weight glycol is different from the others. We are now working to define the structure of these surfaces and couple this information with our other blood studies. These studies have double interest to us. Platelets are rather difficult to handle, and so if we do have a cell line that mimics their action, we could do more quantitative studies on the nature of the polymer surface interaction. Also, if each cell line has its own surface recognition pattern, we might be able to make a surface that will preferentially adhere (and grow) one cell line in the presence of others. This would allow us then to develop scaffolding polymers to assist the body in the controlled repair of its own tissue and organs; whether it be a nerve, the trachea, or a blood vessel.

To me, the study of polymers in the body is a most exciting one, and the future is unlimited since the knowledge being developed can also be applied toward preventive medicine. I want to thank the Dedication Committee for allowing me to tell you about some of our work in this area.

Acknowledgments

The work reported here was supported in part under a National Science Foundation Grant No. GK-29382, a National Institute of Arthritic and Metabolic Disease Contract No. NIH-70-2017, and the University of Utah Biomaterials Research and Development Fund.

References

1. D. J. Lyman, *Reviews in Macromol. Chem.* **1**, 355 (1966).
2. C. Kwan-Gett, H. H. H. J. Zwart, A. C. Kralios, T. Kessler, K. Backman and W. J. Kolff, *Trans. Amer. Soc. Artif. Int. Organs* **16**, 409 (1970).
3. D. J. Lyman, C. Kwan-Gett, H. H. H. J. Zwart, A. Bland, N. Eastwood, J. Kawai and W. J. Kolff, *Trans. Amer. Soc. Artif. Int. Organs.* **17**, 456 (1971).
4. D. J. Lyman, K. G. Klein, J. L. Brash and B. K. Fritzinger, *Thromb. Diath. Haem.* **23**, 120 (1970).
5. D. J. Lyman, K. G. Klein, J. L. Brash, B. K. Fritzinger, J. D. Andrade and F. S. Bonamo, *Thromb. Diath. Haem.* (Suppl. **42**), 109 (1970).
6. R. G. MacFarlane, *Nature* (London) **202**, 498 (1964).
7. J. L. Brash and D. J. Lyman, *J. Biomed. Mater. Res.* **3**, 175 (1969).
8. S. W. Kim, R. G. Lee and D. J. Lyman, Manuscript in preparation.
9. L. I. Friedman, H. Lien, E. F. Grabowski, E. F. Leonard and C. W. McCord, *Trans. Amer. Soc. Artif. Int. Organs* **16**, 63 (1970).
10. D. J. Lyman, *Trans. Amer. Soc. Artif. Int. Organs* **16**, 75 (1970).
11. *Chem. & Eng. News*, January 27, 1969—Page 37.
12. A. J. Lande, L. Edwards, J. H. Bloch, R. G. Carlson, V. Subramanian, R. S. Ascheim, S. Scheidt, S. Filmore, T. Killip and C. W. Lillehei, *Trans. Amer. Soc. Artif. Int. Organs* **16**, 352 (1970).
13. V. L. Gott and A. Furuse, *Fed. Proc.* **30**, 1679 (1971).

14. V. L. Gott, M. D. Ramor, F. B. Najjar, J. C. Allen and K. E. Becker, *Proc. Artificial Heart Program Conference*, edit. by R. J. Heggeli, Washington, D.C., U.S. Govt. Printing Office, 1969, Chap. 17, p. 151.
15. D. J. Lyman, J. L. Brash and K. G. Klein, *Proc. Artificial Heart Program Conference*, edit. by R. J. Heggeli, Washington, D.C., U.S. Govt. Printing Office, 1969, Chap. 11, p. 113.
16. E. J. Hershgold, C. J. Kwan-Gett, J. Kawai and K. Rowley, *Trans. Amer. Soc. Artif. Int. Organs* **18,** 181 (1972).
17. M. F. Glynn, M. A. Packham, J. Hirsh and J. F. Mustard, *J. Clin. Invest.* **45,** 1013 (1966).
18. J. F. Mustard, M. F. Glynn, E. E. Nishizawa and M. A. Packham, *Fed. Proc.* **26,** 106 (1967).
19. C. G. LaFarge and W. F. Bernhard, *Proc. Artificial Heart Program Conference*, edit. by R. J. Heggeli, Washington, D.C., U.S. Govt. Printing Office, 1969, Chap. 52, p. 619.
20. J. C. Taylor, D. W. Hill and M. Rogalsky, *Exp. Cell Res.*, in press (1972).
21. D. J. Lyman, D. W. Hill, R. K. Stirk, C. Adamson and B. R. Mooney, *Trans. Amer. Soc. Artif. Int. Organs* **18,** 19 (1972).
22. D. J. Lyman and S. W. Kim, *Advances in Nephrology* (from the Necken Hospital) **2,** 96 (1972) J. Hamburger, J, Crosnier, M. H. Maxwell, eds. Year Book Medical Publishers, Inc. Chicago.