J. BIOMED. MATER. RES. VOL. 1, PP. 33-54 (1967)

Problems of Materials in Mechanical Heart Systems*

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Summary

Currently available materials for mechanical heart systems are surveyed, particularly with respect to long-term implantation, from the viewpoints of availability and workability, mechanical and biological durability, and compatibility with blood and tissue. Some materials have one or more desirable physical properties, but none offers perfect blood and tissue compatibility. Medical grade Silastic, considered best for blood handling parts, has produced promising results in auxiliary ventricle patency experiments. The insufficient tensile strength of Silastic should be increased, and it may be possible to accomplish this while maintaining the present resilience, elongation, and inertness. No long-term data on thrombus formation are available, but clot-retarding quality is essential and may perhaps be obtained by incorporating heparin. Developments in polymer chemistry may also lead to other surfaces with the requisite mechanical properties with blood.

INTRODUCTION

Implantation of artificial heart systems involves many considerations, and among the most fundamental are the technical problems presented by the materials that are used. These materials were originally developed for industrial or commercial purposes, and now they have merely been adopted by the medical profession. Al-

* Supported by U.S. Public Health Service Grant HE-06510 and Contract PH-43-66-7.

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though plastics, metals, and various other materials such as rubber and glass have been used in constructing implantable devices, most materials have not been consistently investigated. Not only do we lack data on a wide range of materials, but no standards have been established for testing materials in biological environments. Absolute criteria may be impossible to set up, for the stringency of such standards will depend on how long a device is to remain implanted. Means unrelated to the material itself may compensate for its mechanical or physical deficiencies more readily in temporary implantations than in permanent devices. In the case of permanent total heart replacement, the demands on material will be highest. However, regardless of where we pause along the scale of perfection, we must consider the following factors when criteria for selecting materials are set up: (*1*) availability and workability, (*2*) mechanical and biological durability, and (*3*) compatibility with blood and tissue.

AVAILABILITY AND WORKABILITY

We do not need to dwell on the fact that rare, expensive materials would present a major obstacle to the development of satisfactory implantable devices for clinical use. Likewise, whether a material is available in solution or as a solid becomes critical only when this factor affects workability. For example, Teflon TFE cannot be supplied in solution, and in the absence of a solvent, it must be glued by a special etching process that is unreliable.

Ideally, an implantable device should be made in one piece of one material, for a pocket that encourages thrombus formation is apt to occur along a junction. Thus, if a material can be worked only with difficulty, this can limit its application or render it totally useless even though it may meet other criteria satisfactorily.

Materials are considered easy to use when they permit fabrication by layering or coating. However, although polyurethane can be cured at room temperature, it is impossible to dry complicated molds completely on the cast, and if removed from the cast before the solvent has evaporated completely, polyurethane will shrink and change its dimensions.

On the other hand, materials are not automatically eliminated if other fabrication techniques such as molding or machining are neces-

sary. Metals or rigid plastics such as Teflon, polystyrene, or polycarbonate can be used for nonmoving parts in an implantable heart device. The high temperatures and pressures required for molding mean that final shaping is easier by machining.

Siliastic is a material with easy workability, for any technique can be used.[1–3] However, when the pumping system of a device requires high pressure, layering is not always dependable because of the high incidence of breakage[4] and tearing, as in the lapel of the ventricles of the sac-type heart.[5]

MECHANICAL DURABILITY

Implantable devices can encounter much physical stress, for example, in the moving parts of an artificial heart system. The mechanical durability of materials used at such points is especially important and we have to be concerned with the "toughness" of a material, which involves a combination of physical properties such as tensile strength, tensile modulus, tear strength, and resilience.

Atsumi et al.[6] have used natural rubber to construct ventricles and bicuspid valves. According to their report, crosslinked rubber cured by organic peroxides is inferior to conventional sulfur-cured rubber in tensile strength but superior in elongation. Accordingly, it has a low tensile modulus, but high tear resistance. However, although the mechanical properties of natural rubber are excellent, it is no longer used because its surface properties cause blood clotting.

The mechanical properties of poly(vinyl chloride) depend on the type and quantity of additives such as plasticizers and fillers. Tensile strength can range from 1500 to 2800 psi, elongation from 125 to 430%. An artificial heart demonstrated by McCabe, and others reported by Akutsu and Kolff[7] and by Barila et al.[8] were all made of poly(vinyl chloride). Yet, the material had to be abandoned because it was cumbersome to handle, the surface encouraged thrombus formation, and leaf-type valves tore easily.

Estane VC[9,10] a polyurethane, is a strong material: tensile strength 5840 psi, elongation 540%, tear strength 430 psi, and resilience 24%. It has been used recently in constructing several types of artificial hearts,[11–18] but it is a bit too stiff, especially for tricusp semi-lunar valves. Leaflets strong enough to resist high pressures do not open sufficiently; if thin enough to insure a wide opening, a tear occurs at the edge close to the commissure.

The material most commonly used at present is Silastic.[19,20] In addition to its prosthetic application, medical grade Silastic 372 has been used as the rolling diaphragm in piston-type heart devices[21,22] and even in complete artificial hearts including the ventricular housing, atria, and vessels.[3,4,6,23] However, poor tensile strength (1000 psi) and poor tear strength (100 ppi) are deficiencies of Silastic.

Experience suggests that ideal mechanical durability would include tensile strength of 4000 to 6000 psi, elongation of 350 to 600%, tear strength of 300 to 600 ppi, and resilience of 40 to 60%. Unfortunately, no available material satisfies all these conditions as well as the other criteria which are yet to be discussed.

On the other hand, a material need not be abandoned merely because its mechanical durability is less than perfect. Design affects the durability of any pumping device, for the flex life of a plastic is directly related to its configuration and the severity of deformation the part must undergo. For example, improper design causing undue stress in a small area can result in easy breakage.[6] In addition to improving the design of a device, the material can be reinforced, as in the case with Silastic reinforced by Dacron mesh. However, Dacron mesh cannot be bonded to Silastic. If the reinforced material must flex and stretch a great deal, shear force will separate the Dacron mesh, cause a loss of strength, and result in eventual tearing.

The greatest hope still lies in finding a material with more nearly ideal qualities or in improving a material in present use. One step in this direction has recently been made with the development of two new rubber products, Silastic 955 and 55, with a tensile strength of 1300 and 1250 psi, respectively, while there was little change in elongation or resilience. Although these materials must still be tested biologically for possible clinical application, it is good to know that Silastic can be improved.

BIOLOGICAL DURABILITY

The plastics used in constructing implantable devices are known to resist strong acid, alkalis, and oil,[9,10,24] but obviously they are not likely to encounter such environments in the cardiovascular system. On the other hand, some plastics have such poor heat resistance, they cannot be autoclaved at 280°F, 25 psi, yet they can certainly withstand body temperatures. Neverthless, long-term

constant contact with blood and tissue can produce definite effects in materials.

Environmental factors affecting durability within the biological system can be both physical (compression and flexion from body movement) and chemical. Biological durability also involves the time factor of material fatigue, especially in moving parts, as well as the environmental factors. For example, Björk and Hultquist[25] predicted on the basis of tests that Teflon aortic valves would function at least 10 years without breakage; in clinical trials, however, fibrin deposit and tissue ingrowth thickened and stiffened the Teflon valves, and material fatigue then caused rupture of the cusp and fragmentation of the edges. Aortic insufficiency resulted between 1 to $2^1/_2$ years after the replacement.

Although plastics have been used for years as implant materials, the literature records little about the host's effect on the plastic; most investigators have been concerned with the effect of the plastic on the host. For example, thousands of pacemakers have been implanted; as they are retrieved, study of the devices will hopefully yield helpful data in just this area.

Of the reports presently available, Harrison published some of the earliest.[26–28] He implanted various prosthetic grafts into the descending aorta of mongrel dogs using Dacron, Ivalon sponge, Orlon, and Teflon. After periods of 1 to 3 years, the tensile strength was compared with the original value. Nylon lost most of its tensile strength or even broke down completely, and Ivalon sponge became hard and brittle so early that tensile strength studies were impossible. Orlon and Teflon showed both gains and losses in tensile strength.

Compared to other reports, Moloney[29] found lower percentage losses (up to 38%) in nylon sutures, gage Nos. 5 and 7, implanted in the human abdominal wall for up to 11 years. This may be due to the fact that monofilament sutures have a comparatively larger diameter than the textile nylons.

Szilagyi et al.[30] inserted long grafts (18 to 26 cm)m ade of Dacron, nylon, and Teflon between the upper thoracic aorta and the lower abdominal aorta in dogs. Observations over extended periods of 3 to 60 months showed that nylon prostheses underwent considerable losses in tensile strength within 9 months, whereas Dacron prostheses maintained an appreciable amount. The tensile strength of Teflon was also reported to be good.

Leininger[31] implanted films of 5 plastics in mongrel dogs (4 mil polyethylene, 5 mil Teflon, 5 mil Type A Mylar, 10 mil nylon, and 5 mil Silastic X 30146). Silastic and Mylar did not show significant changes in tensile strength, but polyethylene and nylon underwent considerable degradation. The increased tensile strength in Teflon, combined with a decrease in elongation, indicated a greater brittleness.

Mirkovitch et al.[32] and Akutsu et al.[33] reported on polyurethane implants in dogs (sponge grafts in the abdominal aorta, smooth solid strips in the abdominal wall, and smooth monocusp valves). Of 6 aortic grafts removed 3 years after implantation, 4 were found to be partly ruptured and distended, creating a false aneurysm. The polyurethane had become stiff and brittle; the strips had lost much tensile strength within 8 months and were completely demolished after 16 months. In 3 dogs with monocusp aortic valves, it was found that the leaflet of the prostheses no longer existed. This type of degradation was also observed in 1 dog in which a polyurethane cylinder valve had been implanted in the mitral area.[34] Chemical analysis of the sponge grafts showed structural changes in the polymer. The brittleness of the strips may depend on the cleavage of the polymer chain, but this could not be proven chemically.

Salvatore et al.[35,36] reported that at least part of their implanted material (polyurethane used in fractured and diseased bones) was excreted in the urine. At autopsy, animals which had been operated on $2^1/_2$ years previously revealed only microscopic traces of polyurethane at the site of the implantation.

In summary, then, many materials (Ivalon, nylon,[37] polyethylene, and polyurethane[38]) appear to be insufficiently resistive to be considered suitable for clinical use, leaving us with Dacron, Mylar, Silastic, and Teflon. However, alterations have been reported even in these materials (after 18 to 24 months) and adequate information on a long-term basis is not available. The chemical changes which take place in the implants and which may explain the alterations must also be investigated along with other effects the host has on various materials in different body environments.

COMPATIBILITY WITH BLOOD AND TISSUE

Materials do affect the host. When criteria are established for selecting materials to be implanted, the following facts should be

recognized: (*1*) Systemic effects or local tissue damage from the implant or its breakdown products appear to differ according to the body site. (*2*) The same material can cause different local reactions according to the form used. (*3*) The same material may evoke significantly different responses in one species of animal as compared to another.

Compatibility tests should therefore employ the material in its intended use or provide for evaluating how any differences in the factors may affect its acceptability. The physical form of the device and the site of application should also provide close analogs to the proposed conditions for clinical use. While favorable experimental results do not necessarily imply the possibility of successful clinical use, it should likewise be recalled that factors which would not be present in clinical use can cause the failure of experiments.

Systemic Effects

Gradual absorption of materials into the vascular system may cause undesirable systemic effects. The potential dangers are antigenic and toxic phenomena such as reticuloendothelial hyperplasia, hepatosplenomegaly, anemia, ascites, hypertension, or nephritis.

Many plasma volume expanders have proven unsuitable because of their antigenicity when injected into the blood stream. This discouraging fact has stimulated research into the biochemical nature of antigenicity. A report by Kantor et al.[39] and Maurer's summary[40] show that certain types of polymers are antigenic. However, no data exist on the antigenicity of the most commonly used materials such as Dacron, Silastic, and Teflon.

Hall and Hall[41] injected poly(vinyl alcohol) subcutaneously in rats and produced anemia, hepatosplenomegaly, hypertension, nephritis, and ascites. They also reported methyl cellulose induced glomerulonephritis and hypertension in rats.[42] Again, it must be emphasized that man and experimental animals may react differently to the same material. For example, there have been no reported toxic effects of Ivalon sponge [compressed poly(vinyl alcohol) foam] used as a patch in heart surgery.

Salvatore et al.[36] used polyurethane foam in experimental orthopedics and studied the acceptance of the material by tissue cultures, hematological studies, implantation, and isotope labeling. The

experimental data indicated no toxicity, which led them to apply the material successfully in 95 patients.

McGregor[43] summarized 27 papers concerning the toxicology of the silicones and presented a review of the data on the subject. When administered subcutaneously, intramuscularly, intraperitoneally, in the vitreous cavity, and as inhalations, silicone fluid or Antifoam A were nonreactive or only slightly toxic. However, they proved to be lethal intravenously, and Antifoam A was lethal in intracarotid injection. No similar data have been reported indicating the toxicities of Dacron, Silastic, stainless steel, and Teflon—all of which are commonly used in the construction of cardiac prostheses.

Local Effects

Tumorigenicity and inflammation are among the undesirable effects of implants. These are obviously related to the systemic effects already described, since some decomposition products have potential general toxicities.

Extensive work elucidating the relationship between the implants and tumor induction has been performed, mostly in rodents. Tumors at the sites of polymer implants (bakelite disks) in rats were first reported by Turner[44] in 1941. Subsequently, Oppenheimer et al.[45] investigated this field extensively. Having observed the development of sarcomas around cellophane films in this study, they later embedded several other plastics in rats (Dacron, glass coverslips, nylon, polyethylene, polystyrene, poly(vinyl chloride), Silastic, and Teflon). All induced malignant tumors within 1 to 2 years after implantation.[46] However, there is no report in the literature of a malignant tumor induced in primates or dogs by embedding plastics.[47,48]

At first it was thought that chemical impurities were responsible for tumorigenicity, but pure cellophane and polyethylene were then also shown to be tumorigenic.[49,50] Obviously, any common chemical mechanism for tumor induction by these diverse substances is obscure. A plain film appears to induce more tumors than other forms such as perforated films, textiles, or powders.[49] One fact emerged from these studies: the incidence of subcutaneous tumors in rodents is related to the size and configuration of the implant.

Alexander and Horning[51] showed that the use of larger films (2.0 cm^2) in rats resulted in a more rapid development and a higher frequency of tumors than smaller films (0.5 cm^2). Oppenheimer et al.[52] also tested metal foils in rats (silver, steel, tantalum, tin, and vitallium), and all but tin induced tumors; there was no appropriate explanation of the exception. Russell et al.[53] embedded thin films in rats [cellophane, polyethylene, poly(vinyl alcohol) sponge, poly(vinyl chloride), Silastic, Teflon, and glass]. Tumors developed with poly-(vinyl alcohol) (1 in 10), Silastic 250 and Silastic 2000 (both 1 in 17), and Teflon (2 in 45); the lower percentage of occurrence here may be attributed to the smaller size of the implants.

Hueper[54] implanted Silastic, benzoyl peroxide (a vulcanizing agent for Silastic), and 6 different types of rigid and foam polyurethane in rats and found that only benzoyl peroxide did not induce tumors. He felt that these results should provide a warning against indiscriminate use of polyurethane and Silastic in medical practice because of the possibility of delayed carcinogenic sequelae.

Oppenheimer et al.[55] pointed out the significance of pocket formation around embedded plastic films. No tumors developed if implants of subcutaneous purified cellophane and polystyrene were removed within 6 months, or if both implants and pockets were removed even as late as 10 months.

It can therefore be seen that the tumorigenicity of plastics attracted the attention of pathologists, who investigated the problem using rodents. However, surgeons focused their attention on the reactions of tissue to embedded plastics and used dogs as their experimental animals. Originally they were interested chiefly in plastics as suture material, but as plastics came to be used with increasing frequency in fabricating internal devices, surgeons became aware that interaction of these materials with body tissue was a problem. Basic materials have rarely been implanted for observation experimentally but a number of experimental and clinical papers have been published which deal with tissue reactions, particularly in relation to the healing process during the actual application of formed materials such as prosthetic grafts and valves.

LeVeen and Barberio[56] tested celluloid, Lucite, nylon, and Teflon in dogs; none contained plasticizers or color. After periods ranging from 36 hours to 6 months, microscopic studies showed adsorption of

protein on the surface of all the plastics with the exception of Teflon. Further, all but Teflon produced a proliferative foreign-body reaction. It was concluded that chemically inert plastics which are not wettable produce the least tissue reaction. They also emphasized that the greatest possible surface area of the material should be exposed to the greatest possible amount of tissue and suggested injecting a fine suspension of the material into the peritoneal cavity. In this way, one could hope to achieve maximum sensitivity to minor differences and the method would also provide a base line for comparison.

Dettinger et al.[57] compared several suture materials with the natural fibers, cotton and silk. The synthetic fibers (Dacron, monofilament surgical nylon, and Orlon) proved to be far less irritating to tissues than cotton silk; Dacron was the least reactive of the plastic fibers.

Harrison et al.[58] implanted plastics in dogs which were sacrificed at periods ranging from 1 week to 1 year. Ivalon sponge caused the greatest reaction, followed in order of decreasing reaction by nylon, Dacron, Orlon, and Teflon.

Usher and Wallace[59] added a new plastic to the list of materials tested. Marlex 50 polyethylene has a highly crystalline molecular structure, which affords unusually high tensile strength compared with the conventional materials. In a comparison study in dogs, Marlex and Teflon showed considerably less foreign-body reaction in the abdominal cavity than Dacron, nylon, and Orlon. Following further experimental studies by Usher and Gannon[60] using Marlex as a surgical prosthesis, Usher et al.[61] and Graham et al.[62] used Marlex clinically and concluded that Marlex mesh is admirably suitable as a prosthetic material in the repair of thoracic wall defects.

Little and Parkhouse[63] subcutaneously implanted disks of polyethylenes, poly(vinyl chlorides), nylons, latex rubbers, and silicone rubbers in guinea pigs, which were killed after 6 weeks. The silicones and the polyethylenes of low and medium density produced consistently good results, but the results of the other materials were not at all consistent. The study offers a method for determining particle size above which a fibroblast reaction is likely to occur, but leaves unsolved the problem of harmful chemical additions—it is easier to determine the limiting particle size by x-ray diffraction (and thereby eliminate polymers with crystallites) than to char-

acterize the reactions caused by chemical additives. According to Atlas and Mark,[64] macromolecules can be tailor-made for specific purposes, but this is still a development of the future.

Atsumi et al.[65] studied several materials implanted subcutaneously in mice. Tissue reactions were observed by measuring the ratio of gamma globulin to albumin and by studying local histological changes. Polyurethane, silicone rubber catalyzed with benzoyl peroxide, sulfur-cured rubber, and nylon caused strong foreign-body reactions, but only weak reactions were induced with Dacron, polyurea, medical grade silicone rubber, silicone rubber without benzoic acid, and deproteinized natural rubber crosslinked by gamma ray or by organic peroxide.

Mirkovitch et al.[32] reported that although abdominal wall implants of polyurethane films in dogs were enveloped by fibrous tissue and completely degraded into fragments, microscopic inspection showed inflammatory foreign-body reaction to be very slight.

Johnson[47] reported a striking growth of fibrous tissue into the Ivalon sponge which had been implanted in a human female breast for cosmetic purposes. The specimens had to be removed after 1 or 2 years either because of ulceration of the overlying skin or because of the formation of hard lumps.

In summary, there appear to be 3 mechanisms of polymer carcinogenic activity: (*1*) direct chemical interaction, (*2*) microphysical effects, and (*3*) macrophysical effects.

In the case of direct interaction, degradation products may be the carcinogenic agents. The polymers may be degraded in the presence of biological free radicals produced by oxidation and enzymatic reactions; then the free-radical fragments arising from degradation may inhibit the enzymatic free-radical process, effect the depolymerization of nucleic acids, and produce tumors. Also, the reactive centers in the polymer itself which are created by the degradation would be capable of binding basic tissue constituents, thereby impairing the metabolism of adjacent cells.

Second, the microphysical effect is seen in metabolically rather inert macromolecules. Excessive intracellular and extracellular storage of them may interfere with cellular functions in the long run, thereby causing cellular degeneration, death, and further reactive, regenerative cell proliferation.

In the third case, the macrophysical effect, the size and configura-

tion of implants as well as the formation of pockets have been demonstrated to affect the rapidity and frequency of tumor induction.

However, all of the work describing tumor induction associated with metal or plastic implants has been done in rodents; no case of malignancy due to a polymer implant has been reported in dogs or humans.[46,47,66] Thus, while no evidence exists to relate the prosthetic use of polymers to an increased incidence of cancer in the exposed tissues, oncologists remind us that if it takes 1 to 2 years for a malignant tumor to appear in a rodent, a similar result may take 10 to 15 years in a human being. This may well be a warning against the indiscriminate use of plastics in clinical use, for none of the available materials has been tested long enough to determine carcinogenicity.[54]

On the other hand, there are obvious and unexplained differences in tumor induction between rodents and higher species. Where cancerous change is concerned, it is impossible to draw conclusions that are applicable to man from results observed in mice. Thus, since no malignancies due to polymers in clinical implantations have appeared so far, there is perhaps no cause to exclude their use in man.[57]

Of the plastics tested so far, Silastic is most inert, followed in descending order by Teflon, Marlex, Dacron, Orlon, polyurethane, Ivalon, nylon, and Lucite. Of the metals, stainless steel has been accepted by the human body, and titanium is also a promising metal. Titanium has been used as a bone substitute[68] and as frame material for prosthetic heart valves.[69] It is recommended as being biologically neutral, and no unfavorable tissue reaction has been noted. However, it should be noted that perfect inertness is not always a desirable quality. Depending on the use of the material, it could be advantageous to have tissue ingrowth or even for the material to be completely ingested and disappear once it has served its role as a supporter (as in the case of suture materials). Szilagyi et al.[30] pointed out that Teflon grafts yielded the most consistently fine pseudointima, but that the degree of connective tissue incorporation was distinctly inferior to that of Dacron, which allowed the best tissue ingrowth and a more uniformly perfect intima. Of course, connective tissue ingrowth depends upon certain textile characteristics of the material (such as porosity) as well as the chemical reactivity. Also, biological reactivity is not an important limiting factor of a synthetic material used as a vascular graft.[67]

Blood Compatibility

Systemic and local effects of materials are indeed important, but as is the case with the mechanical and biological durability, critical defects may take some time to occur. However, the compatibility of materials with blood is immediately apparent. At the present stage of artificial heart research, this is the most important problem.

Thrombus formation on the surface of prostheses in the cardiovascular system is not merely a matter of the surface properties of the materials used. The blood flow rate (which implies blood velocity) and the internal configuration of implanted devices (which create a pocket, for example, in which blood could stagnate) are obviously responsible for thrombus formation.[34,70] One must also consider the effects on red blood cells among those not directly related to the surface properties of the materials themselves. Acute hemolysis, a self-limited syndrome common to all pump-oxygenator procedures,[71] does not appear to be more serious in implantations than in other open-heart procedures. On the other hand, chronic severe hemolytic anemia has also occurred, perhaps rarely, following intracardiac surgery.[72–79] In some cases, this has followed repair of ostium primum defects,[72–75] in others the implantation of aortic valve prostheses.[76–79] Irreversible mechanical damage to the cells and intravascular hemolyses occur only when high pressure jet streams pointing at an area of prosthetic material or irregular endocardium exists.[80] Nevertheless, such defects are more a matter of prosthesis design, or when incomplete or faulty repair of a cardiac defect was associated with the problem of re-operation. Therefore, this section will be limited to a discussion of the surface properties of materials themselves which are directly related to thrombus formation.

While many investigators were studying aortic grafts made primarily of textile materials (nylon, Dacron, Teflon, etc.), Dreyer et al.[81] implanted aortic grafts of polyurethane sponge and smooth polyurethane in the abdominal aorta of dogs. On the basis of their experience that the smooth grafts usually thrombosed while the rough ones stayed open, Kolff and others from the same group made several types of prosthetic heart valves using rough surfaced materials (collagen, polyurethane sponge, and Teflon).[82] After having overcome the technical problems of insertion and obtaining a sufficient

series of survivors, they found all of the valves coated with fibrin. Contrary to their experience with the aortic grafts, this fibrin became dislodged, disrupted, and reformed in many layers until the valves were eventually occluded. The moving and rubbing of the leaflets against each other disrupts the fibrin, which would have remained intact in a structure such as the aorta.

In other prosthetic valve experiments, the majority of dogs died from thrombi whether rough or smooth valves were used.[33,83–85] The thrombus always started at the insertion line and propagated further onto the valve leaflets. An important difference was observed in the behavior of the same material when used as a graft as when used as a prosthetic valve. In order to study the origin of intracardiac thrombosis and possibly to find the best material for constructing prosthetic heart valves, they inserted various plastics (collagen, knitted Teflon, Marlex, polyurethane, and Silastic) into the heart chambers of dogs.[82,86,87] On the basis of this experience, they concluded that the surface of valve leaflets should be smooth. However, this conclusion is only a rough indication of likely materials, not a final solution—as is shown by the results of prosthetic valves made from smooth materials.[34,83]

It became increasingly important to understand the relationship between the chemical structure of the compounds and their biological behavior, i.e., the relationship of surface properties to thrombus formation. Although it has been known for some time that blood clotting time could be prolonged by coating glass vessels with paraffin, and many investigators have studied the effects of the coating materials in this, the specific characteristics of the surfaces responsible for these effects have not been reported.

Ross et al.[88] studied 30 commercially available polymers or purified monomers polymerized by gamma or ultraviolet radiation. They measured wettability and surface charge by a streaming potential technique which made it possible to calculate the zeta potential, an index of the ability of the test surface to attract ions present in the adjacent conductive fluid. Having measured the rapidity and extent of intravascular clot formation for each polymer as well as the coagulation time in test tubes made of each polymer, they found that nylon, polystyrene, and dextran probes promoted clot formation. Teflon showed the same results as siliconized glass, and the majority of the remaining compounds showed clot formation

of an intermediate degree. Only 4 compounds—crosslinked heparin-like polysaccharides, poly(vinyl pyrrolidone), carbon rubber, and silica-filled silicone rubber—were found to retard clot formation to a greater degree than siliconized glass. The test tube clotting times were generally long for those compounds promoting little intravascular thrombosis. The contact angles bore no absolute correlation with the effects of compounds on blood, and the zeta potential also failed to show a relationship to clotting. The presence of ionic groups per se did not seem to influence clotting behavior. They concluded that (*1*) the extent of clotting promoted or inhibited by a substance appeared to be more dependent upon the chemical nature of the surface than upon the physical nature, and (*2*) non-ionic surfaces with highly negative charges or surfaces ionized by sulfate radicals inhibited clot formation to the greatest degree.

Mirkovitch et al.[89] and Leininger et al.[90] have also reported on the relationship between zeta potentials and blood compatibility characteristics of plastics. Plastic surfaces were found to have constant and reproducible zeta potentials generally in the range of −8 to −25 mv against saline solutions. When whole blood was substituted for saline, they found that the zeta potential changed rapidly with time and approached zero. The rate of change in blood potential and its magnitude were found to depend on the nature of the plastic surface, the blood fraction used (gamma globulin, fibrinogen, albumin, etc.), and its concentration. The findings were interpreted as the result of rapid adsorption of one or more blood components on the surface of the material. This work may lead to valuable information on the interaction of blood with plastic surfaces and thereby point the way toward new and improved materials for prostheses.

Lyman et al.[91] also pointed out that the adsorption of some molecular species on the plastic surface seems to be the determining factor and emphasized that it is the chemical nature of the surface and its related surface free energy that must be considered and not the polymer surface per se. They showed how their concept of surface free energy could be applied to existing blood coagulation data.

In the construction of a butterfly-type prosthetic heart valve which has a hard ring, Gott et al.[92] developed a process of coating the ring with colloidal graphite, a coating chosen for its extreme non-wettability, conductivity, small negative surface potential, chemical inertness, and very smooth surface. Their results with prosthetic

valves implanted in the mitral and pulmonary valve areas in dogs were better than other workers in the same area.

However, Mirkovitch et al.[93] reported discouraging results with graphite cloth and gold-plated polyurethane inserted in a canine right atrioventricular area with the same technique described earlier.[89] Electroconductive graphite patches showed the same thrombosis as other materials with a rough surface.

Gott et al.[94] later developed a new type of antithrombogenic coating, a combination of graphite, benzalkonium, and heparin (GBH). Graphite can bond a cationic surface active agent which in turn can bind the heparin. They also proved experimentally that intravascular prosthetic surfaces coated with graphite and benzalkonium are able to adsorb heparin from the blood stream, probably by anion exchange.[95] Thus, if the heparin in the GBH coating is slowly eluted or destroyed after being placed in the vascular system, there exists a mechanism whereby it might be replaced by endogenous heparin. This is a very promisng breakthrough in the knotty problem of thrombus formation on plastic surfaces.

Although GBH coating cannot be applied to all materials which could be used in constructing artificial heart devices, it does make possible the use of some materials which have been abandoned because of poor blood compatibility. For example, polyurethane (which proved to have an unsatisfactory surface in the sac-type artificial heart[18]) is being used once more, and there have been successful results in the patency experiments with auxiliary ventricles.[3] Lexan, the housing material in Gott's valve,[92] cannot be used in the cardiovascular system without the GBH coating.

At the present time, most investigators are using medical grade Silastic 372 for constructing the blood-handling parts of artificial hearts.[2,3,23,96,97] However, there are no grounds for optimism when calves with artificial hearts have not died from thrombosis[5,98] (which was also true of dogs with polyurethane devices[18]), for the experimental animals have survived only a little more than a day. Dogs with auxiliary ventricles, however, have been alive for 18 months, as reported by Grädel et al.[3] The ventricles were made of 2 materials, Silastic 372 and polyurethane treated with a GBH coating, and were implanted for patency studies. After 2 dogs died on the 104th and 390th day, respectively, from rupture of the ascending aorta at the silk tie, examination of the ventricles revealed no thrombus forma-

tion. In experiments yet to be reported, we have also found no thrombus formation in dogs sacrificed after 19 months.

Leininger et al.[99] devised a method of bonding heparin chemically to a number of surfaces such as cellophane, natural rubber, polyethylene, polystyrene, poly(vinyl chloride), and silicone rubber. Thus, we are again reminded that materials with shortcomings should continually be reconsidered in the light of new developments.

Despite encouraging results here and there, much remains to be done. No single physical property of a surface appears to determine its coagulant effect, and attempts at relating smoothness, wettability, conductivity, or the zeta potential directly to thrombus formation have failed to date. The definition of wettability is uncertain, and once a surface is wetted, the concept may be of no significance. Conductivity alone cannot be the controlling factor, for metals are generally both conductive and thrombogenic. The protein adsorbate on plastics, however, has been shown to be conductive, so any plastic in contact with blood will probably have a conductive surface. The zeta potential of a surface provides a convenient determination with which to study the adsorption of blood components by different plastics,[100] but it also fails to indicate blood–plastic compatibility directly. Possibly, however, studying these adsorption phenomena, particularly with the use of various blood fractions in relation to time, may eventually lead to better understanding of the interaction of blood with plastics.[101]

Polymer chemistry is far from being capable of duplicating natural vascular structure, but two findings are nonetheless encouraging. First, heparinization of the surface definitely increases compatibility and thereby gives up an immediate working direction towards fabricating compatible surfaces. (Although Gott's technique of heparinizing a graphite-coated surface is promising, poor results have been reported as well.[102]) Second, different polymers reveal varied patterns of blood factor adsorption. This finding may lead us to a theoretical understanding of the mechanisms involved in blood–plastic interaction; we would then be in a better position to define the ideal surface.

CONCLUSION

In reviewing the physical, chemical, and biological properties of many of the available materials, we find none which appear to fulfill

all of the criteria that would be desirable for the devices used in implantable mechanical heart assist devices or heart substitutes. At the present time, we can take advantage of the best materials available and fabricate systems that give reasonably satisfactory results by attempting to eliminate the shortcomings of the materials through design. However, design criteria may not have to be so stringent when newer materials are developed. More complete, more efficient pumping devices will then be possible. Thus, the medical investigators in this field look to the polymer and physical chemists for major contributions toward the ultimate development of the implantable total artificial heart.

The authors wish to thank Dr. Frank Hastings for permission to use material from "Studies Basic to Consideration of Artificial Heart Research and Development Program," which was prepared for the National Heart Institute, and to thank Eugenie Hatschek and Dale S. Cunningham for assistance in preparing the manuscript.

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Received December 7, 1966