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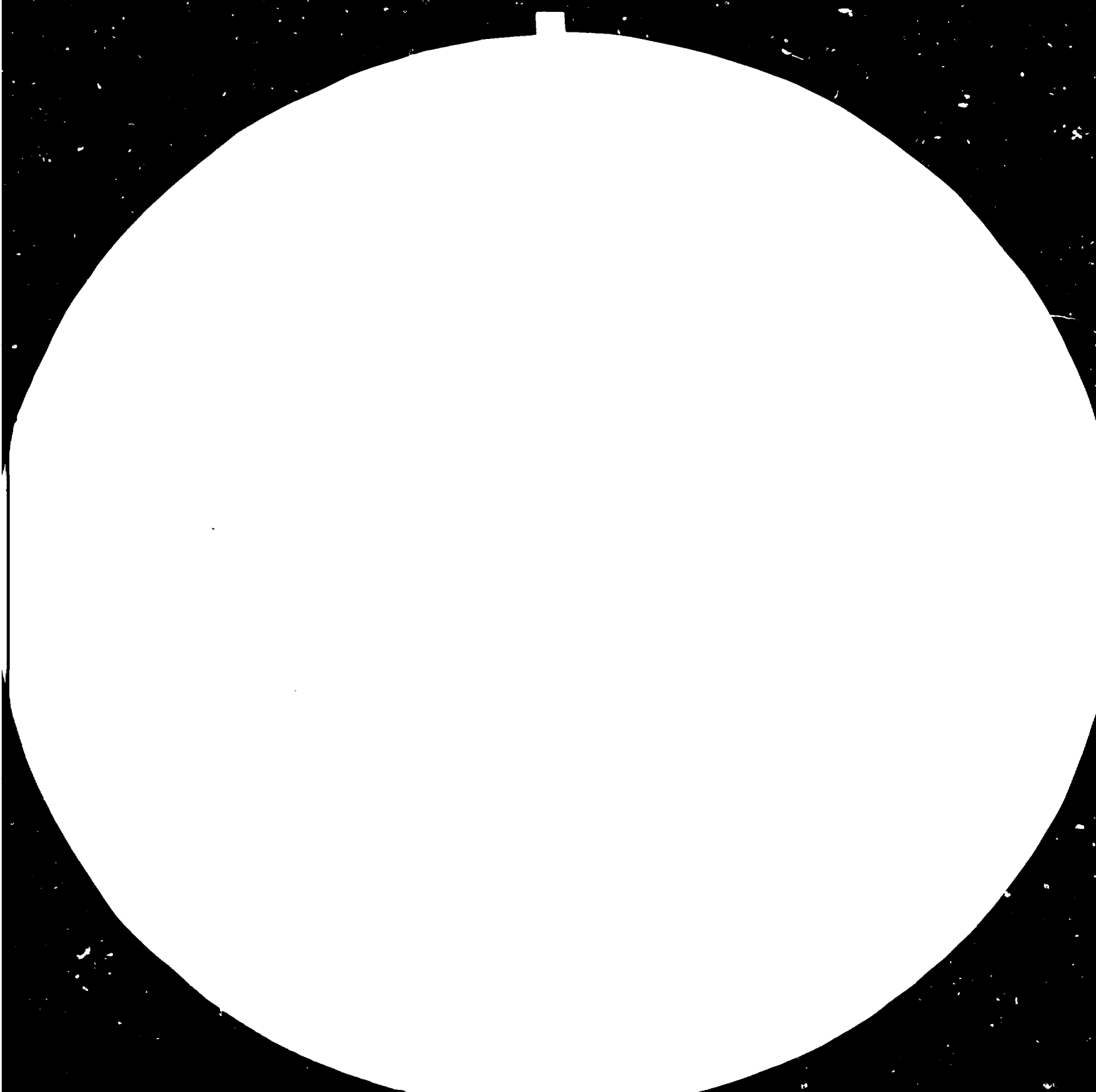

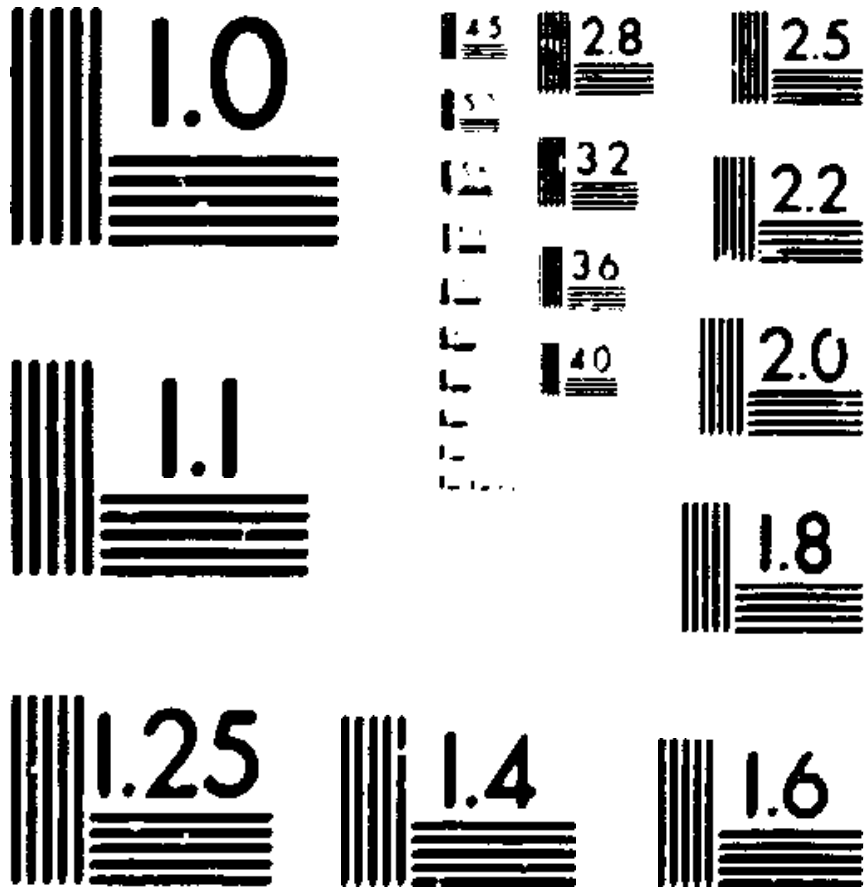

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PROSPECTS FOR PLASTICS IN MEDICAL APPLICATIONS*

by

G.W. Hastings**

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** Principal Lecturer, Biomedical Engineering Unit, North Staffordshire Polytechnic, Hartshill, Stoke-on-Trent, ST4 7NY, United Kingdom

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PROSPECTS FOR PLASTICS IN MEDICAL APPLICATIONS

G. W. Hastings, DSc, PhD, CChem, FRSC, FPRI,
Bio-medical Engineering Unit,
Medical Institute,
Hartshill,
Stoke on Trent,
Staffs,
England

INTRODUCTION

Advantages of Plastics in Biomedical Applications

The attraction of plastics materials for biomedical uses lies in the diversity of types and properties available. In theory it should be possible to tailor the material used to each particular application, but in general it is not either because other important properties are sacrificed or for economic reasons.

In practice, certain materials have become prominent in use because they are completely satisfactory or because they offer the most acceptable compromise. Satisfactory as a judgement on a material will include consideration of end-use properties and user acceptance, processability including sterilisation where necessary and availability at an acceptable cost. Other considerations will be whether the product is a relatively low cost high volume article or a low volume product with a high mark up. The high volume group are represented by the disposable items - syringes, infusion sets, storage containers, tubes, the latter by surgical implants.

However, the fact remains, that either by a change in basic molecular structure, or by different compounding a wide range of properties can be achieved.

For medical use, change in compounding is not always possible, because toxicity considerations are of prime importance. Many additives used commercially are not acceptable for medical use. Since modifications to polymer structure change manufacturing processes of the base polymer, this is also a problem since many manufacturers are unwilling or unable to consider this. There may well be a place for a specialist manufacturer making a wide range of polymers in small batches to specific requirements, although the market requirements would need to be researched very carefully.

Additives may be bad news and this is instanced in the example of pvc. The common phthalate plasticisers have been used in medical tubing, storage containers and administration devices. In certain cases the leaching of these into the body tissues may have a harmful effect and in an already ill patient may be just the final insult. Concern has arisen over this in Special Care Baby Units. However, newer polymeric plasticisers will change this situation.

It is essential for medical use to guarantee that a product does not change in formulation as well as in properties. The same properties are attainable with different formulations but this is often unacceptable for medical use. For example, polyacetal has a very large number of additives permitted for food-contact use and a given product may show considerable batch-batch variations . When used inside the body, as this material is, the user must know that the same additives are always present, or tissue reaction studies become meaningless and possibly dangerously misleading.

Standardisation and Good Manufacturing Practises

The use of International and National Standards is of prime importance. Not only does this ensure international acceptance and application of one company's or one country's products e.g. in connectors for anaesthetic tubing, an important marketing factor, but it helps to ensure that only satisfactory materials are used.

This extends to many aspects of manufacture. In the UK there are requirements of good manufacturing practise laid down by the Dept. of Health for medical products. These, and the Standard requirements, are very necessary.

A clean. controlled environment is necessary for production of medical devices. This may extend to rigorously controlled aseptic environments in certain cases, but this is not always so. Sterilisation will generally be necessary, and this requires that

a. materials should be sterilisable by one of the accepted methods, generally heat, ionising radiation, ethylene oxide gas
b. packaging should be adequate to protect the device and to provide for sterile transfer in an operating room where required
c. clean handling is essential to avoid dust, pyrogenic organisms, finger prints, processing materials (oils, mould release agents), or other contaminants being present.

Provision of different sizes for adults and children will also need to be considered as the latter may impose special requirements for fixing a device in position on very small children (neonates).

Design

Some of the comments above imply that attention should be given to design. However, this must be a direct consideration. Design is not just for ease of manufacture, although this is important. It must be related closely to the intended use and should take into account patient and doctor needs. This applies both to external and to implantable devices. Design considerations include

a. material properties

b. manufacturing and sterilisation

c. body-device interactions - mechanical

d. body-device interactions - chemical

e. short or long-term use requirements

f. limitations on size or shape imposed by site of use, method of application

g. functional requirement e.g. load bearing, fatigue properties, flex life.

Evaluation of Medical Devices

One of the problems in developing a new device is that the only suitable testing model for man is man himself. It is not always possible, for ethical or for other reasons, to test new devices or materials in the human body.

Toxicity studies in tissue culture in animals are the first step and details of these are found in the National Pharmacopaeia (e.g. US, British) and in Standards Specificaitons.

It is, however, functional testing that provides the main problems. Simulation of physical and physiological conditions is a time-consuming and costly exercise when carried out in laboratory designed machines. Furthermore, the environment provided is not controllable to the same extent as that which the body is able to achieve.

Many of the tests for disposable or short-term use products will be related to toxicity and pyrogenicity. Patient acceptability and ease of use will then be the determining factors.

It is the longer-term implants which require the next stage of testing for function. Heart valves and orthopaedic joint replacements illustrate this well.

Heart valves	- blood compatibility
	flow characteristics
	wear
	durability
Joint Replacements	- Wear properties
	frictional properties
	fatigue life
	bone compatibility
	load bearing capability
	mechanical compatibility

In spite of this seemingly alarming catalogue, plastics materials have a considerable history of use in medicine as implants and it is true to say that the concepts of treating human joint disease have changed dramatically with the inception of plastics.

Disposable Devices

The main uses of plastics materials encompass syringes, tubing for various uses, storage containers and packaging. Bottles for pharmaceutical preparations and graduated spoons or measures are other items used in large quantities.

Items associated with anaesthetic equipment are an important area and have been referred to in the studies presented already. There is a wide range of connectors, endotracheal and tracheostomy tubes and airways which use PVC, EVA.

Prostheses and Orthoses

The use of plastics and rubber materials in artificial limbs and helps for disabled people represents another major use. Cosmetic appearance as well as function is important but the main requirement is for adequate mechanical strength and fatigue life. Composite materials of different types are used and recent development in carbon fibre composites have shown the use that this, in a resin matrix, can bring advantages in terms of good strength to weight ratios.

The main problem is that, in general, each item is made individually to the requirements of the patient. However, the same methods of manufacture are used, and it is possible to standardise on a range of sources.

Prosthetic replacements for soft tissue following cancer surgery may be included.

Contact Lenses and Artificial Eyes

Acrylic polymers have dominated this field. The hard polymethyl methacrylate is still used in both applications but the soft type of contact lens based on poly (hydroxyetnyl methacrylate) is in widespread use. It offers a potentially better material in that oxygen and fluid transmission takes place through the water-swollen hydrogel structure. Protein deposition and clouding of the lenses is the subject of considerable research. Silicone rubbers have been studied as an alternative.

Dentures

Using dough moulding techniques acrylic based dentures are made in specially equipped dental laboratories. Breakage is common and reinforced materials are being examined. With a properly controlled manufacturing system it represents a ready use for plastics materials, using mainly acrylics.

Surgical Implants

Current Materials

Following two or three decades of experience, it is now possible to identify generally acceptable materials. These cover the whole range of metals, plastics and ceramics and can be considered from their clinical application.

Load bearing materials are those used primarily in orthopaedics, although there is an overlap into dental use because very large forces can be generated during mastication. Metallic alloys have attained a position of eminence because there was nothing else available to stand

the dynamic loads imposed by physical activity and to give rigid structural support. This concept of an implant as a strong, supporting item has been modified as a understanding of bio-mechanics developed (see below).

There is now substantial international agreement on the desired composition for stainless steel (International Standards Organisation, 1977). Other metallic alloys have been used to meet some of its deficiencies, particularly with regard to corrosion and fatigue resistance. Titanium, particularly a titanium-6-aluminium-4 vanadium alloy have seen increasing use for highly stressed components. A range of alloys based upon cobalt-chromium-molybdenum alloy (Sulzer Protasul 10) that since 1972 no case of failure by various means has been reported, for the implantation of more than 120,000 hip prostheses using this alloy.

The use of plastics materials has been a major factor in the advances of joint replacement surgery. The earlier uses of an acrylic cup as a spacer by Harmon and an acrylic femoral prosthesis by Judet have now passed into the history books. The real advance began in 1958 when Charnley first investigated ptfe and then abandoned this for ultra-high-molecular-weight polyethylene, UHMWPE (RCH 1000). Although acrylic cement had been investigated previously the consequences of Charnley's combination of UHMWPE for the acetabular component with a small diameter head steel femoral component and with acrylic cement to achieve firm fixation have dominated joint prosthesis development since that time.

It was not until the use of polyacetal by Poli and its clinical application by Christiansen that there was an introduction of a new polymer Two forms of material are available, a homopolymer and a copolymer.

Christiansen used the former and there do not appear to be adverse reports on biocompatibility. Mathys et al appear to have overcome problems in the use of copolymer for their prosthetic replacements for the shoulder, but a clear decision on choice of polymer must await further work.

It is not surprising, therefore, that the study of new materials has continued. High purity alumina (Al_2O_3) appears to be attractive and there is now considerable short-term clinical expertise in France and Germany. The apparent advantages are low rate of wear, a low coefficient of friction and lack of chemical reactivity, leading to excellent biocompatibility.

Various ceramic systems have been studied in addition to alumina, including carbon andapatite ceramics. There is increasing experience related to carbon and it appears to be very biocompatible. Apatite ceramics are being investigated in dental surgery, but it is not yet an established material.

Soft tissue. The materials which continue to dominate here are silicone polymers. Applications are well documented (e.g. Bloch and Hastings, 1973). Since they are available in fluids gels and rubbers, they appear to be ideal materials for soft tissue implants. Fluids have a very limited useage and the rubber is the most important of the group. Even this is not problem free and lipid absorption in cardiac valve components and fibrosis around mammary prostheses are reported complications. Newer types of silicone elasomter based on different monomers and using other polymerisation and vulcanisation techniques (gamma radiation) give more internally reinforced structure and may not show the same deficiencies.

A reinforced polyurethane elastomer has been used to support bone graft material in the craniofacial and manidbular regions. These elastomers offer a wide variation in molecular structure and properties and should see increased application. A urethane-type reaction can be applied to sulphur-containing pre-polymers to give a series of elastomers yet to be examined as biomaterials. Bioplasts based upon fibrin, originally studied for orthopaedic use have been developed further and are an attempt to utilise the biocompatible potential of natural materials. (This concept is discussed further below).

Cardiovascular. Polyester fibre (Dacron$_R$) has a continuing history of acceptance in vascular prostheses and valve components and the problems have been in the form of the material and the properties of the graft e.g. knitted or woven fabrics, porosity, kinkability. The pulsatility of the arterial system presents a special challenge and the use of elastomeric materials, in which polyurethane fibres wound onto a rotating charged mandrel give the porosity needed for tissue ingrowth has been an important application both of new materials and of technology of fabrication. The biocompatibility of carbon has been applied to valve prostheses with considerable success.

Requirements for Implanted Biomaterials

There have been various definitions of the ideal biomaterial, some general, some specific to a particular site or mode of use e.g. Park has discussed requirements for burn wound coverings.

Talbe I lists some characteristics of general application. When proposed they seemed to give an adequate statement but experience shows them to be too simplistic. Each surgical area presents its peculiar demands and each suffers the overriding potential for disaster brought by movement (implant loosening), infection and material failure.

TABLE 1

Characteristics of an Ideal Biomaterial

Sterilisable

Ease of fabrication at low cost

Resistant to mechanical strains

Not to produce allergy or hypersensitivity

Noncarcinogenic

Not to incite inflammatory response

Not physically modified in vivo.

TABLE 2

Problem Areas in Biomaterials Development

Fatigue failure

Surface wear

Corrosion/degradation

Deformation - creep

Adverse tissue effects

ion sensitisation

wear debris

Structure-Property Relationships in Implants

The mismatching of properties between implants may be one of the main reasons for implant failure. Composites offer a way of retaining adequate mechanical strength yet reducing the rigidity of the material by choice of matrix - fibre combinations. The author's own work on

carbon reinforced epoxies used in fracture treatment and subsequently in joint replacements is an example of this more recent approach.

A better understanding of structure in relation to properties both of plastics and of living materials makes possible better choice and use of available products.

Prospects for Plastics in Medical Applications

Carbon

One important derivative of the plastics and resin industries is the production of various forms of carbon. Pyrolysis of polymers under carefully controlled conditions leads to a range of products finding increasing medical use.

Types of Carbon

a) Electrographite

Calcined coke is bonded with pitch and after baking is graphetised at above 2500°C. Highly porous blocks are made.

b) Impregnated Electrographite

Following impregnation with pitch or polymers under pressure, the electrographites can be further carbonised to produce strong materials with improved wear properites. Ring and disc heart valves have been made from this material.

c) Coated Electrographite

By suspending the material in a fluid bed activated by a hydro-carbon gas mixture, pyrolytic carbon coatings can be deposited on the surface (low temperature isotropic, LTI carbon). These coatings can be highly polished.

d) Glass-like Carbons

Organic polymers can be pyrolised under controlled conditions to make a glass-like product. Phenolic resins are typically used and are pyrolised at temperatures above 1200°C forming a black glass-like material. Several applications include pacemaker electrodes and heart valve components.

e) Carbon Fibre

Widely used in composites in the leisure industry there is considerable use in aerospace, for example, for rotor blades and control surfaces. Medical applications of both fibres and composites have been reported. The fibres are made from organic polymer precursor fibre (polyacrylo nitrile). By controlled low temperature pyrolysis this is changed from a thermoplastic to a thermosetting fibre and futher pyrolysis with controlled stretching at higher temperatures converts it to carbon. There are two types: high modulus and high strength, depending on the pyrolysis temperature. Composite materials are made using a matrix of epoxy resin, high stiffness polyimides or thermoplastic resins, e.g. polysulphone. Carbon itself is also used as the matrix material. To improve strength pyrolytic carbon coatings have been given to the fibres. Another source of carbon fibre is mesophase pitch, but the properties of these fibres do not approach those of the PAN based fibres.

f) Carbon Fibre Reinforced Carbon (CFRC)

If a carbon fibre organic polymer composite is carbonised, a CFRC composite can be produced. Pitch impregnation of carbon fibres and chemical vapour deposition from hydrocarbon gases have been used. The same techniques as for laying up resin based composites can be used. The high strength, low modulus combination of this material is very attractive for medical uses and it is being actively investigated for the stem of a hip prosthesis in Germany.

Applications

Glass-like carbon is very well accepted by living tissue and has the important property of not initiating blood clotting processes. It has become increasingly used as heart valve components and complete prosthetic valve assemblies have been made from controlled carbonisation of poly furfuryl alcohol or phenolic resins. The reasons for blood compatibility are not fully understood but it is related to the ability of a surface to bind proteins in a form such that they are not denatured and hence present a "natural" surface to the blood stream.

A potentially more important future lies with composites. Carbon-carbon composites possess the excellent tissue acceptability of glass-like carbon and have good mechanical strength for load-bearing uses. A future in joint prostheses is under investigation.

Carbon-epoxy composites are well advanced in clinical evaluation as orthopaedic implants and the author has been involved with this for several years. Bone plates for fracture fixation offer significant advantages in terms of improved fatigue life (capacity to stabilise a less than ideal situation) and lower rigidity (giving more physiological load patterns in the bone). Joint prostheses are under active investigation and may include other resin matrix systems.

Carbon fibre composites also have potential as external devices for prostheses and arthroses (artificial limbs and supports). In light weight transport systems they may be attractive for carrying or supporting injured people in rough terrain.

Carbon fibre itself has been used directly for repair of tendons and ligaments but this is not generally accepted. Wherever the capacity exists for manufacture of polymers in bulk or fibre form (in particular poly-acrylonitrile fibre PAN) there is the possibility for secondary development of carbon. Although mesophase pitch fibres have also been investigated for high performance advanced composites, the PAN based fibres are superior in properties. Economic considerations have not so far justified the expectations of pitch based fibres but where a cheap readily available supply was obtained it would be worth consideration for lower performance applications.

Aerospace is becoming the main area for advanced composites but there is a big growth potential in automotive and leisure industries.

Polymers and Drugs

The capacity of polymers for adaptation to widespread uses is especially shown by developments in drug therapy.

Inert Carriers: Polymers are used as encapsulants for therapeutic agents and these are distributed in the polymer matrix by various means. The drug is released either by diffusion out of an unchanged polymer (e.g. antibiotic-loaded acrylic bone cement) or out of an increasingly swollen hydrophilic matrix. Alternatively, a degradable polymer is used and drug release is controlled by the rate of degradation. The rate of release can be controlled to give the required profile of drug administration and the main advantage is in avoiding the cyclical peaks in concentrations provided from the customary four times per day oral routine.

Active Carriers: If a drug is chemically attached to a polymer molecule and the macromolecular drug given to a patient, the whole complex will be taken up by the cells. When the bonds are degradable the drug can be released inside the cell. If the macromolecule also contains groups which are specific for certain cells the drug can be targetted to defined body sites, and the drug released where it is needed. Systemic effects and undesirable side reactions can be avoided by this means. This is one of the most important and exciting areas of polymer chemistry at present and has diagnostic as well as therapeutic potential. Monoclonal antibodies, enzymes and other active moieties can be attached to macromolecules and the form of the system can be ad pted e.g. microcapsules, artificial micules, to meet a range of requirements.

A more detailed description is beyond the scope of this paper but readers are referred to papers resulting from the Prague IUPAC Congress on Biomedical Applications of Polymers, July 1984.

The Way Forward

The final stage of production of medical plastics for use as disposable therapeutic devices or as implants must involve high standards of manufacture incorporating clean room or sterile assembly. This should be assessed in terms of market potential and it is probably preferable to start with relatively large volume devices which can be made on conventional equipment.

Polyethylene is likely to remain one of the main implantable plastics for some time and the emphasis should be on clean consistent quality high molecular weight material (MW 4×10^6). However, an implant industry is needed to support this unless implant grade polymer is to be supplied to other places.

Thermoplastic materials are the basis of several items such as dialysers and oxygenators but designs of component parts e.g. membranes, are very advanced. However, given the supply of advanced components, a secondary assembly using locally made housings may be possible.

A considerable potential exists in the area of aids for handicapped both for congenitally disabled and those who are so resulting from disease or injury. These aids range from devices to help turning taps, or holding domestic appliances to seats, splints, braces, frames and transport aids. The restraints of clean/sterile manufacture do not apply. A high level of engineering design and manufacture are needed however. It is frequently a neglected area but one which the plastics, rubber and related industries (composites) are well placed to serve.

Whatever the project, close collaboration between health care personnel and scientists/technologists is vital. It is best achieved by development of units in which the close contact is a daily routine experience. Communication between initially disparate groups needs to be learned often patiently, but is the essence of any significant progress.

References

Proceedings International Conference Biomedical Polymers and Symposium on Contact Lenses. Durham, 1982. Organised by Biological Engineering Society and the Plastics and Rubber Institute. (Biological Engineering Society, College of Surgeons, Lincolns Inn Fields, London, England).

Various articles in "Biomaterials" published by Butterworths Scientific, Westbury House, Bury Street, Guildford, England.

Plastics Materials in Surgery. B. Bloch and G. W. Hastings. 1972. pub. Charles C. Thomas, Springfield, Ill, U.S.A.

Series "Structure Property Relationships in Biomaterials". G. W. Hastings and P. Ducheyne (Editors). 1983. In press. CRC Press Inc., 2000 Corporate Blvd., NW, Boca Raton, Florida, U.S.A.