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ADVANCES IN MATERIALS TECHNOLOGY MONITOR

VOLUME 1, NUMBER 2, 1994

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna, 1994

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UNIDO's *Advances in Materials Monitor* is established as a mechanism of current awareness to monitor developments in the materials sector and to inform governments, industry and academia, primarily in developing countries.

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Published in 1994 by the United Nations Industrial Development Organization (UNIDO)
Vienna International Centre
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TO OUR READERS

To many of our readers, the area of biomaterials may seem to be somewhat inappropriate for this *Monitor*, finding that its place would be better in the *Genetic Engineering and Biotechnology Monitor*. The subject, however, is so vast and spreads into so many areas that we can but touch briefly on them in this overview of the subject. Professor Williams, who has prepared the feature article, has provided us with an excellent digest of biomaterials and we would welcome any comments and suggestions to expand on the subject.

It will have come as a surprise to many that after all these years the *Monitors* now have a "new look". We decided that in the light of UNIDO's new structure, it was time to change our image as well. For those who may not know, these quarterly newsletters first appeared in the early 1980s in response to a recommendation from a group of experts who were of the view that the new and emerging technologies hold significant potential for developing countries, and as such, asked UNIDO to collect and disseminate information on these technological developments. The concept of monitoring technological advances stems from the Vienna Conference on Science and Technology for Development held in the summer of 1979 and further considered by the General Conferences and meetings of the Industrial Development Board, UNIDO's governing body. Consequently UNIDO is engaged in implementing a programme of technological advances in which activities related to the new and emerging technologies form an important part. The aim of this programme is to sensitise developing countries and help them strengthen their technological capabilities, as appropriate. In this respect, readers will note on page 10 of this issue details of the Organization's assistance in the setting up of an international centre for materials evaluation technology in the Republic of Korea. Another activity worth mentioning is the advanced materials component of the International Centre for Science and High-Technology located in Trieste (Italy), which is supported and administered by UNIDO. We intend to expand on this subject in a later issue of the *Monitor*.

We began the task of producing the *Monitors*, first with the *Microelectronics Monitor* in December 1981, followed by the *Genetic Engineering and Biotechnology Monitor* in February 1982 and later on with the *Advances in Materials Technology Monitor* and the *Marine Industrial Technology Monitor*. The series will now be expanded to include the *High Technology Spin-Offs Monitor* and *Environment Technology Monitor*. The *High Technology Spin-Offs Monitor* will basically follow the established standard of the others in the series, with a compilation of information on new materials, processes, markets, etc., latest information on contracts and related venture capital transactions worldwide, success (or disaster) case histories, news from different countries relating to changes affecting technology transfer (education, laws, centres of excellence, etc.), publications, events – and of course, feature articles. For those who would like to receive the new *Monitor* in future, there is a form enclosed at the back of this issue that we would ask you to kindly complete and return to the address indicated. As yet, this publication will be distributed free of charge, unlike the *Genetic Engineering and Biotechnology Monitor*, the *Microelectronics Monitor* and the *Advances in Materials Monitor*, which impose an annual handling fee of US$ 40 on readers located in the industrialized world.

Vladimir Kojamovich
Technical Editor

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1. FEATURE ARTICLE

THE SCIENCE AND APPLICATIONS OF BIOMATERIALS

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Introduction

Surgery in the late twentieth century places heavy demands upon sophisticated technology, ranging from functional imaging equipment that assists in diagnosis, to lasers and robotics to improve accuracy and reliability. One of the most important areas in which technological advances have significantly enhanced surgery involves the use of synthetic materials for reconstruction of the body. These materials are generally referred to as "biomaterials" defined as materials intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body.

It is important to recognize that biomaterials have rarely been designed specifically for this use. Instead, they are generally materials developed for other applications in mind, but which have been found to be appropriate for medical use, often being modified or optimized for these applications. Thus these materials are generally no different in structure and properties to materials used in chemical, aerospace or nuclear industries. It is the matching of the properties of materials specific and, indeed, unique requirements of surgical reconstruction, that is the key to biomaterials science.

Surgical applications of biomaterials

Biomaterials are implanted into the body for many different reasons but these can be broadly grouped as follows. This listing takes into account the progression through life and the problems encountered that may require surgical intervention.

(a) **Congenital deformities**. Children are often born with a physical deformity which results in functional or aesthetic impairment. In some cases the consequences may be life-threatening, as with certain deformities associated with spina bifida, while in others they are more psychological, as in the case of facial disfigurement. The treatment and precise usage of the materials will vary from one situation to another.

(b) **Developmental defects**. A child apparently healthy and normal at birth may develop in an abnormal way, perhaps through impaired hormonal function leading to defects that require correction. Procedures such as leg lengthening and spinal curvature come into this category.

(c) **Trauma**. At any time in life, injuries may be sustained which require surgical intervention as part of the treatment. This may involve the use of materials and devices to assist the body to repair itself, such as sutures to close soft tissue wounds and fracture plates, nails and screws to facilitate bone repair, or may involve structures that replace or augment damaged tissue, such as artificial skin, bone substitutes, ligament prostheses and nerve guides.

(d) **Disease**. The human body is clearly subjected to many diseases of varying origin, the majority of which can be treated non-surgically. However, there is a significant number that can affect tissues, leading to either pain, loss of movement or loss of vital functions, so that surgery becomes essential. Specific examples, which involve the use of biomaterials in reconstruction include osteo- and rheumatoid arthritis, which may be treated by total joint replacement; atherosclerosis within the vascular system, which may be treated with artificial arteries; dental diseases such as caries and periodontitis; and cataracts of the eye, which require removal of the lens and its replacement. It is important to recognize here that the preferential order of treatment is first the use of non-surgical methods (e.g. using drugs), secondly the use of minimally invasive procedures in which the lesion is treated remotely or endoscopically, thirdly reconstruction involving natural tissues, preferably by using a graft of the patients' own tissues, and only finally the reconstruction using biomaterials and implanted devices. In other words biomaterials are only used when other treatments are inappropriate or ineffective.

(e) **Psychological factors**. As an extension to the developmental defects described above, there are many occasions in which adults find their shape or appearance cause them psychological problems. Under such circumstances, even when there is no medical or physical disability at all, and when few others would agree that there was anything that needed correction, it may be necessary to carry out some form of surgical restructuring of the relevant part of the body.

(f) **Tissue atrophy**. As part of the ageing process, tissues may change their shape and consistency resulting in either loss of cosmetic appearance, as covered above, or in some disturbance of function. This particularly concerns bone loss in localized or generalized osteoporosis and may necessitate some degree of reconstruction. With this set of generalized reasons, we may consider some of the most relevant clinical disciplines and describe specific examples of devices that utilize biomaterials.

Orthopaedic surgery

This is the surgical speciality which historically has been the most significant user of biomaterials. It is concerned with the musculoskeletal system and the treatment of diseases and disturbances of its components, particularly bones, cartilage, ligaments, muscles and tendons. It is this system that produces movement and responds to forces, and it is therefore very susceptible to injury and stress-related diseases, the consequences of which are very significant since they affect the ability to move. Of equal importance is the fact that any replacement of these tissues has to perform in the same mechanical environment, and attainment of the relevant mechanical performance is not a trivial matter.

The most significant application of biomaterials in orthopaedics is that of joint replacement, necessitated by the twin diseases of osteo- and rheumatoid arthritis. The former condition is essentially a mechanical disruption to the cartilage and underlying bone, while the latter is a painful inflammatory disease which causes destruction of

the tissues. Pain relieving drugs and anti-inflammatory agents may be reasonably effective but the diseases are progressive and in very many cases excision of the affected tissue and replacement with total joint prostheses provides the only long term solution.

In the hip, which was the first joint to be replaced in this way, it is usual to replace both the head of the femur and the socket within the acetabulum in this way. In the knee, which is affected just as much but which is more difficult to replace, the lower end of the femur, the upper end of the tibia and the patella are all involved. Since the main requirements for these joints are the ability to transmit forces under sliding conditions with the facility for permanent attachment to bone, combinations of materials that give low friction and high wear resistance for the articulating surfaces, high fatigue strength for the main structural components and a system to permit fixation to the bone are utilized in these prostheses. The articulating surfaces usually consist of a hard metal or ceramic bearing against a polymer, today, almost invariably, the latter being ultra high molecular weight high density polyethylene. The main structural components, such as the femoral stem, are usually made of high strength alloys. Fixation to bone may be achieved by the use of a so-called bone cement, this nearly always comprising an *in-situ* curing polymethylmethacrylate, or alternatively by the use of some system that permits bone attachment, either through a bioactive coating such as a calcium phosphate ceramic, or through specially introduced porosity that facilitates tissue ingrowth.

Joint replacements are not without their problems but are generally able to provide pain-free movement for patients for a reasonable length of time. While at some stage it was common for hip replacements to give 15 to 20 years performance, as the age range of patients fitted with the prostheses gets larger, overall performance today is generally not so good and it is an increasingly common problem for the devices to become loose. The principle architects of this loosening are the tissue reactions to the wear debris produced at the articulating interface and the difficulty of attaining and retaining an acceptable stress distribution in the prosthesis-bone system.

A second problem within orthopaedics that is relevant to biomaterials is ligament repair and augmentation. Ligaments are dense bundles of collagenous tissue that are attached to the bones within a joint and which provide stability and constrain movement. While ligaments rarely suffer disease *per se*, damage to them severely comprises this stability, such damage often occurring with sporting injuries. This is particularly relevant with the cruciate ligaments of the knee, injury to which severely compromises the ability to walk. Surgical treatment can take several different forms. It is possible to attempt reconstruction by totally replacing the damaged ligament with a prosthetic replacement, although matching the elastic characteristics of the natural ligament and producing a reliable anchorage to the bone are difficult objectives. The alternative is to use an augmentation device in which an implant is added to the damaged tissue and works with it to transmit the forces.

The third orthopaedic area to be considered is that of fracture fixation. Bone is quite a remarkable tissue, possessing an extremely efficient mechanism for self repair. When bone fractures, it is able to heal spontaneously, provided there is proper alignment and the fracture surfaces are held together in close apposition during the healing process, which may take a few months.

With the long bones, the correct alignment may be achieved through the use of an external support but there are many occasions when this is not possible, perhaps because there are multiple fragments, in which case, surgical intervention is necessary. The purpose is to achieve the correct juxtaposition of the bones and to hold them in this position. This may be done with plates, screws, rods or other fixtures. Although there have been a few attempts to use other materials, the vast majority of these devices are made from metals, which clearly need to combine the properties of strength, especially fatigue strength, with corrosion resistance and biocompatibility. Because bone is a dynamic tissue that requires the stimulus of mechanical stress for maintenance of its internal structure, problems do arise if rigid metal plates are retained within the bone after healing has taken place. Ideally, all fracture plates should be removed once the healing is complete and because of the slight risks of any operative procedure, much attention has been paid to the development of degradable plates to avoid this necessity. This is not an easy task since the requirements for degradability and inherent strength are almost mutually exclusive.

Maxillofacial surgery

Closely allied to the problems that relate to orthopaedics are those that concern the structural tissues of the head, mostly involving the bone but also the associated soft tissue. Three of the major areas are covered here.

First, there is the case of dental implants, used to replace missing teeth. The loss of natural teeth, through disease or trauma, has for many years been compensated by the provision of artificial teeth in the form of bridges or dentures. These essentially provide an aesthetic replacement of the crown of the tooth but do nothing to replace the root and its attachment to the bone of the jaw. While these are quite satisfactory in many patients, they do have a few disadvantages and it has been the ambition of dentists for a long time to use implants that replace teeth in their entirety. This is not easily achieved because the implants have to be in contact with a number of different types of tissue, including an epithelial barrier, they have to reside in the microbiologically hostile region of the mouth, and are exposed to a complex stress system without too much support. For many years, a poor success rate with the dental implants then available reflected this difficulty, but during the last decade improvements to design, materials and technique have led to far better performance, and dental implants now represent a very respectable alternative to traditional prosthodontic devices. The materials of choice are titanium alloys and alumina, often coated with a porous surface or a bioactive material such as calcium phosphate.

Secondly, there are traumatic events in the facial skeleton, traditionally treated conservatively but now increasingly being assisted by surgical intervention and the application of implantable devices. Fractures of the face are usually simple without too much distortion of shape and the requirements for stability are quite easily satisfied. However, it is becoming increasingly recognized that better results and far more convenience to the patient can be achieved through the use of internal fracture plates rather than the traditional interdental wiring. Small titanium plates for the fixation of mandibular or maxillary fractures are now in common use.

Thirdly, reconstructive maxillofacial and orthognathic surgery is becoming more popular as it becomes possible to treat a variety of diseases and deformities of the connective tissues of the head and neck. These range from inflammatory conditions of the periodontium to extensive hard and soft tissue tumours. In the former case the treatment of advanced periodontitis may involve the implantation of thin strips of material such as expanded polytetrafluoroethylene (PTFE) around the root of the tooth, which facilitates the regeneration of the connective tissue. Tumours of the head and neck present considerable problems of reconstruction. This partly arises because prior irradiation treatment may make wound healing extremely difficult, but there are also problems of attachment to the remaining part of the facial skeleton.

Cardiovascular surgery

Diseases of the circulatory system occur as frequently as those of the musculoskeletal system, but they are more life threatening than immobilizing. The diseases can affect the heart itself, the major circulatory system and the microvasculature, the main consequence of all being a perturbation to the rate and characteristics of blood flow. A few of the more significant situations requiring surgical treatment are briefly mentioned here. Because of the seriousness of operative procedures within the cardiovascular system, they are avoided whenever possible and it should be recognized that surgical reconstruction using synthetic devices is usually considered only when there are no less invasive procedures available.

The first aspect to consider is the failure of one of the valves of the heart. The mitral and aortic valves particularly are susceptible to disease and malfunction. For example, stenosis is an obstruction of the valve orifice which disturbs the pattern of blood flow, causing a raising of the blood pressure, while incompetence is a failure of the valve to close properly, allowing a retrograde flow of blood. When valvular disease has progressed to such an extent that it compromises the ability of the heart to maintain the circulation, it becomes necessary to remove the offending structure and replace it with a prosthesis. Mechanical valves, in which a poppet such as a ball or a disc opens and closes within some cage or strut system, have been used for over 30 years. Generally they work extremely well, although there have been some well-documented cases of mechanical failure in a few situations. However, because of their susceptibility to initiate thrombus formation, all patients in whom these heart valves are fitted require chronic anticoagulation, a generally undesirable situation. There have therefore been attempts to produce valves that are more compatible with blood and indeed able to open and close in a more physiological manner. This has resulted in the development of the so-called bioprosthetic valves, derived from animal tissue, either the muscle wall of cows' hearts or the valves of pigs. These do not necessitate anti-coagulation but the tissues do slowly deteriorate, requiring periodic replacement.

Moving on to the blood vessels, these are frequently affected by atherosclerosis, a condition in which deposits build up on their inner lumen, especially the arteries. The resulting stenosis again disrupts blood supply, placing the heart under considerable strain and causing damage to the deprived tissues. When it is the coronary arteries that are involved, the blood supply to the heart itself is affected, leading to a heart attack. If it is an artery in the lower leg, for example the femoropopliteal artery, the result is restricted circulation to the feet, which eventually causes gangrene. The deposit that forms consists of a collection of cells and proteins and it is sometimes possible to break this up using drugs. More usually, by the time that the condition is diagnosed, it is not treatable in this way, but may be relieved by one of the endoscopic techniques such as angioplasty, where the deposit is removed mechanically by use of a radiological guided balloon catheter or by laser ablation. If these angioplasty techniques fail, or if the problem recurs, then reconstruction may be the only option. Ideally, a vein or artery graft will be used, in which a vessel such as the saphenous vein or internal mammary artery is transposed to the damaged site. This works very well, and indeed is currently the only option for vessels smaller than 4 mm in diameter but in many patients it is impossible to obtain a suitable source. Under these circumstances, artificial arteries may be used. Without exception, the successful artificial arteries are microporous polymeric tubes, typically with expanded PTFE or polyester textiles. Their mechanical characteristics, such as compliance and kink resistance, and their compatibility with blood are critical.

In addition to these major areas of reconstruction, there are several other applications of materials within the cardiovascular system, very often for short but very critical periods. Examples here include catheters and cannulae, used to convey fluids into and out of the system, measuring devices such as sensors and extracorporeal equipment such as haemodialysis machines and oxygenators.

There are also some devices which are not concerned at all with the mechanics of blood flow but deal with the electrical activity of the heart. This is particularly important if there is discontinuity in the conduction of stimuli to the heart, in which case an implantable pacemaker may be used to supply and deliver signals to the heart muscle. Pacemakers consist of a package of microelectronics, usually hermetically sealed inside a welded titanium casing, connected to the wall of the heart by an insulated lead, terminating in an electrode.

Ophthalmology

The structure of the eye is conceptually very simple, consisting of a collection of tissues and fluids that direct and focus incident light onto the retina, where the light energy is transduced into electrical signals that are passed to the brain via the optic nerve. Blindness or partial loss of sight can arise from either disruption to the light pathway, an inability of the retina to capture the light with appropriate fidelity or a failure within the nervous system. While problems of the latter nature can rarely be remedied, there are procedures for reconstituting a light pathway that has been disturbed through disease.

For example, cataracts are an area of the lens that become cloudy, treatment of which involves removal of the lens, resulting in a severe visual defect. This is difficult to adequately compensate using spectacles and the treatment of choice involves the intraocular lens. This is usually made of poly(methyl methacrylate). Although at one stage there were problems of damage to the surrounding area with inflammatory responses, improvements to the surface quality and surgical technique have led to very considerable success for this simple procedure. The cornea is also affected by disease, most notably glaucoma, which again

disturbs the light pathway through changes in tissue structure. Corneal grafting, with tissue derived from cadavers, is very effective, but on some occasions is not possible, in which case artificial corneas, or keratoprostheses, are used, again usually being made of the clear poly(methyl methacrylate).

Other ophthalmological conditions which sometimes require the use of biomaterials include the traumatic detached retina, in which materials such as silicones are used to physically reattach this layer, and the very common use of contact lenses, used for the correction of minor vision abnormalities.

The nervous system

This is an area likely to increase in significance in the future. Intuitively, the brain and the nerves appear to be far too sensitive to accommodate invasion by foreign materials and devices, but there are several circumstances in which this is desirable and it is clear that materials can be placed within the central nervous system without apparent effect. One simple but very important application within the brain is the insertion of a catheter into the lateral ventricles to allow the drainage of cerebrospinal fluid in cases of infants with hydrocephalus, a potentially fatal condition associated with spina bifida. Also, after most neurosurgical procedures it is necessary to place some covering on the dura and a wide variety of materials have been used, apparently successfully, showing the surprising level of tolerance of this tissue.

A few very specific but important areas within the nervous system can be mentioned. The first concerns the regeneration of damaged nerve tissue. The capacity for repair is extremely limited, especially within the central system. Peripherally, however, some repair is possible and this may be facilitated by the use of nerve guides, tubular structures placed around the ends of severed nerves allowing the nerve tissue to regenerate and reconstitute the nerve pathway.

Secondly, there is the treatment of chronic severe pain. It is known that electrical impulses can be applied to nerves to block the impulses to the brain that give rise to the sensation of pain and implantable pain relief stimulators are now being introduced for this purpose. Finally, implantable devices may be used in the treatment of hearing loss. The middle ear, involving the three ossicles (stapes, incus and malleus) conducts sound waves through to the tympanic membrane. The disease of otosclerosis causes inflammation and eventual fusion of these bones, such that their ability to vibrate is compromised. These bones may be excised and replaced by quite simple structures which can themselves vibrate to produce sound. If it is the inner ear that is affected by disease, then the treatment is far more difficult, but some progress has been made in the conversion of sound waves into electrical signals and delivering these directly to the cochlear.

Criteria for materials selection

It will be obvious from the above that a wide variety of functions is required from surgical materials and that no single material or even small group of materials can satisfy all of the conditions. It is necessary, therefore, to consider generically the requirements of biomaterials and to identify the key elements of materials selection. These may be divided into those properties which determine suitability to perform the function and those which determine acceptability of the materials within the body.

Functional performance

Although biomaterials are intended to replace, both in structure and function, the diseased or damaged tissues, the performance required at this stage is generally quite limited and largely restricted to space filling or mechanical performance, either structural or fluidic. There are some areas where physical properties are relevant and in other cases we are now seeing the need for biological properties.

With respect to mechanical performance, we cannot specify a generalized requirement since the needs of a material in soft tissue reconstruction will clearly be different to those for materials in hard tissues. There are, however, a few general points. First, strength is always important and it is crucial that stress systems within the material-tissue complex are established and performance specifications determined with respect to both yield and fracture strengths. The body is a dynamic medium, and both viscoelastiv and fatigue behaviour are crucial. Nevertheless, these mechanical considerations *per se* should not be serious limiting factors, since with a few exceptions, there are sufficient materials off-the-shelf to satisfy these needs. Secondly, the matching of elastic constants and deformation behaviour of devices to the requirements of the body is critical. Ideally the rigidity, flexibility, compliance or any other characteristic of elastic deformation should be such as to enable the device to participate in the transfer of load and movement exactly as if it were a natural component. Failure to do so can have serious consequences on both the device and the tissues. Thirdly, since the mechanical performance has to be carried out within the chemically hostile environment of the body, conjoint mechanical-environmental failure modes such as stress corrosion cracking, corrosion fatigue, composite delamination, stress crazing and so on, are all possible.

Physical properties that have to be addressed include electrical properties and optical properties. The latter are straightforward as there are so few optically clear materials and it is rarely necessary to move away from the excellent poly(methyl methacrylate). On the other hand the choice of conducting or insulating materials for the various parts of implantable electronic devices is not so easy, especially as it is the long-term electrical performance in the wet tissue environment that is so critical.

Biocompatibility

The interactions between biomaterials and their host are the most significant factors determining their performance, especially in the long term. These interactions may be discussed under the general heading of biocompatibility, defined in terms of "the ability of a material to perform with an appropriate host response in a specific application". At the outset of this discussion it must be emphasized that the range of materials in use today has been based on the assumption that biomaterials have to be inert and have no effect on the tissues. Whilst this may be appropriate under many circumstances, and while we never wish there to be adverse effects, it is now considered that the total lack of interaction implicit in that concept is not appropriate to the use of many of the devices that are intended to become fully incorporated into the body and that distinctive and positive interactions are far better.

Biocompatibility is concerned with all of the reactions and effects that take place between a material and the body, these being of several different groups. The initial phase of contact between the material and the body is associated with an interaction with a fluid, such as blood, saliva, tears or just extracellular fluid, such that there will be an adsorption of macromolecules from that fluid onto the surface. This will usually involve proteins, the adsorption of which at this interface plays a crucial role in many biocompatibility mechanisms. The main components of biocompatibility concern the direct interactions at the interface, in which the environment of the body influences the material causing it to change its characteristics in some way, principally through corrosion and degradation processes, and the presence of the material causes the tissue to change its characteristics, through inflammatory or repair processes. The final component involves the response of the whole body to the presence of the device. Because of their direct relevance to material selection, we shall primarily discuss here the two central themes, space precluding any detailed discussion of adsorption or systemic aspects.

Corrosion and degradation

The environment of the body is surprisingly hostile to synthetic materials. It is an isotonic saline solution with a variety of added anions and cations, and a range of biological macromolecules, free radicals and cells, all of which have the potential to be biologically as well as chemically active. As far as metallic materials are concerned, the saline electrolyte ensures a highly corrosive environment, although it is known that the proteins present are also able to influence corrosion processes, especially if the metal concerned is able to bind to proteins. Because of this aggressiveness, it is only the noble metals and those that are passive under physiological conditions that are able to be used, accounting for the current selections enumerated below.

With ceramics, the behaviour varies considerably. On the one hand, the oxide ceramics such as alumina and zirconia are extremely stable, as expected. On the other hand, some calcium based ceramics are used which are degradable over a relatively short period of time. This is partly a natural dissolution process but is also assisted by active cellular processes under some circumstances.

Polymeric materials are the most difficult to judge from the degradability point of view. Polymers are normally degraded by physical agencies such as heat, light and ionizing radiations, which are absent in the body, so that they should be largely protected. However, some are degraded by hydrolysis and it is known that active molecular species within the tissues, particularly free radicals and enzymes are able to participate in degradation processes. We therefore have a spectrum of behaviour, at one end of which are some homochain, non-hydrolysable and hydrophobic materials such as PTFE, which appear to be non-degradable and at the other end are the hydrolysable and rapidly degradable polymers, such as the aliphatic polyesters. In the middle are a selection of polyamides, polyurethanes, polyesters and many others, which degrade slowly, often unpredictably, over a few years.

Soft tissue biocompatibility

It is still uncertain exactly what device characteristics determine the host response, but some general principles may be described. It is convenient to consider these on a temporal basis and to consider the response as a perturbation to wound healing, repair and remodelling processes that occur in response to tissue damage. If we consider that the surgical implantation of a material into an area of soft tissue constitutes an injury, we may analyse the effects of the material itself as a superimposition onto the effects of the surgery. Inflammation results whenever tissue is damaged and has to be considered as an inherently desirable response under these circumstances since it is designed to eliminate the source of the irritation. It involves changes to the microvascular network and the infiltration into the area of large numbers of cells. If the source of the injury can be eliminated and any debris removed, both being brought about by the activity of these inflammatory cells, then a repair process will be initiated, and the inflammatory cells will slowly withdraw. In soft tissue, the repair process is normally controlled through fibroblasts which synthesize collagen, the protein that constitutes scar tissue.

If, at the site of a surgical incision, a biomaterial is placed, it has the potential to interfere with either or both inflammatory or repair processes. With a totally inert material, these opportunities are minimal and it is likely that the inflammation and repair processes will continue as normal, the only influence of the material being that the device acts as a physical barrier to regeneration. Classically, the implantation of an inert biomaterial into soft tissue results in the formation of a thin layer of fibrous tissue that surrounds or encapsulates it. If, however, the material is not inert, which is usually the case, the reactions that take place at the interface will influence the events in the tissue. They may aggravate and extend the initial inflammatory response; more importantly, the continuation of the interfacial reactions means that there remains a persistent stimulus to inflammation; indeed a chronic inflammatory response, merging with a delayed and continuous fibroblastic response will be the manifestation of the continued reactions. Their effect on the performance of the device and the well-being of the patient vary quite considerably, but if uncontrolled are likely to be the determinants of failure, culminating in cell and tissue death. Of considerable importance here is the fact that these interfacial reactions will usually initially involve the release of some component from the material into the tissue, either a corrosion or degradation product or some reachable residue. The development of the inflammatory response, in which large numbers of cells are attracted to the area, where they are activated to release large quantities of potent chemicals such as superoxide ions and oxidative enzymes, rapidly increases the aggressiveness of the tissue, causing further and enhanced degradation of the material. The process is therefore catalytic in nature.

The precise features of the host response will, as noted above, depend very much on the individual circumstances. Material circumstances will obviously influence events, particularly with respect to bulk and surface chemistry, rates of degradation and the nature of the degradation products and surface features such as topography, size and shape. Of equal importance are the host variables such as location of the device and the age, sex, general health and activity and pharmacological status.

Hard tissue biocompatibility

Interactions with bone are extremely important with any orthopaedic or maxillofacial device and the ability to

attain and maintain good apposition and preferably adhesion to this tissue is crucial to their performance, especially joint prostheses. If a prosthesis is loose, or becomes loose, then it will fail. In contrast to the general situation outlined above where materials are naturally encapsulated in soft fibrous tissue, it is essential that no such soft tissue forms at the bone-material interface so that this inherent mechanism of fibrous encapsulation has to be avoided or suppressed. This has largely been attempted through the use of materials of maximal inertness, such as titanium, alumina and polyethylene. More importantly for the future, however, are the approaches involving materials that are positively attractive to bone, the so-called bioactive materials, such as calcium hydroxyapatite, which will encourage the preferential formation of bone at the interface.

It is also important to maintain this interface, two major factors contriving to destroy it. First, as noted earlier, bone is a dynamic tissue which is dependent on the appropriate level of mechanical stress for it to maintain its normal structure and architecture. Without stress, bone will resorb. With the wrong type of stress, bone will also resorb. It is vital for the stress distribution within the bone-prosthesis system to be optimized in order to maintain healthy bone. Secondly, should there be any restimulation of the inflammatory response, bone could be resorbed as a consequence of this associated cellular activity. The main culprits here are the wear particles generated at the bearing surfaces in joint replacements. Depending on their rate of release and the particle size, a significant chronic inflammatory response can arise, some of the cells involved having the capability of destroying bone, or stimulating other cells to do this. This is the ultimate limitation to orthopaedic prostheses.

Blood Compatibility

The interactions between materials and blood clearly underpins all of the applications of devices within the cardiovascular system, whether of short or long term duration. The initial event when blood flows over a surface is that plasma proteins are adsorbed onto the surface. The nature of the protein layer that is established will vary from one material to another and with time. A thin layer of protein on a surface is not necessarily undesirable in itself, but it is this layer which will determine whether blood will clot on the surface, primarily through its effect on the clotting cascade proteins and platelets.

The clotting cascade involves a sequence of enzymes catalysed reactions in which various circulating proteins are sequentially transformed into fragments, the end result of which is the conversion of prothrombin into thrombin, which catalyses the conversion of fibrinogen into fibrin and its subsequent polymerization. For reasons which are not entirely clear, some surfaces are far more likely to activate this sequence of events than others. Platelets, the smallest of blood cells, normally do not interact with the surface of blood vessels; they only do so when that vessel is damaged and the interaction is then very valuable in the process of haemostats. Unfortunately, the conditions which arise when a foreign surface is exposed to blood are similar to those of a damaged vessel, and the platelets react in the same way. A few platelets are initially attracted to the surface and become activated, a process involving the release of reactive substances from the platelet granules, which cause the attraction of large numbers of other platelets to that site and the formation of an aggregate. The combination of polymerized fibrin and platelets constitutes a blood clot, which is both damaging to device performance and compromises the safety of the patient.

The selection of blood contacting biomaterials is determined by the need to minimize this tendency, where several approaches are possible. First, extreme inertness may yield relatively non-thrombogenic surfaces, as with PTFE, although this is no guarantee. The second approach is the use of materials that inhibit or prevent the above reactions from taking place. This usually involves treating a surface with some substance that interferes with the clotting process, for example heparin, or with the platelet adhesion process, perhaps with prostacyclin. Thirdly, the surfaces can be prepared so that they mimic the natural surface, as with the attachment of phospholipids to polymer surfaces, or which actually provide a natural surface such as those covered with a layer of endothelial cells.

At this stage there is no universally blood compatible material or surface, but approaches such as these provide a promising future.

Materials in current use

It is convenient to discuss contemporary biomaterials in terms of the broad material categories metals, polymers, ceramics and composites and also to introduce the concepts of surface design appropriate to maximizing the usefulness of these materials.

Metals and alloys

Metals are primarily employed in situations requiring their unique combination of mechanical properties, particularly fatigue strength, toughness and ductility, although occasionally it is physical characteristics which are important. Then mechanical and physical specifications, however, are such that many alloy systems would be suitable and it is considerations of biocompatibility, and especially corrosion resistance and toxicity, that determine the final choice. It is possible to use the corrosion resistance of the noble metals—and indeed platinum group metals are employed in electrical applications, and gold in dentistry—but generally these do not have suitable mechanical properties for structural applications and are too expensive. Engineering alloys based on passivated metals are therefore generally preferred, titanium and chromium usually providing the passivity.

Titanium is undoubtedly the most corrosion resistant non-noble metal in physiological fluids. It does not have sufficiently good mechanical properties to be used as the pure metal in most circumstances and so alloys are usually chosen. For many years it has been the alpha-beta structure of Ti - 6%Al - 4%V that has dominated the scene, but more recently a few others have been introduced. The rationale for this has been a concern over the adverse effects of aluminium and vanadium, but these are speculations rather than objective decisions and there is no evidence of such adverse effects. Indeed, for many applications, the Ti - Al - V alloy has the best combination of mechanical, corrosion and biological properties. Two points should be made about the orthopaedic uses. First, it has a lower elastic modulus than the alternative metallic systems and is therefore more closely matched to bone with respect to rigidity. On the other hand, its wear resistance is considerably inferior to these alternatives and its use as a bearing surface in joints is not recommended.

On the other hand, some cobalt alloys provide very good behaviour in respect of this latter property. For over 60 years, alloys of the Stellite variety have been used in dentistry and surgery. Initially, these alloys, based on cobalt and chromium with varying amounts of molybdenum, nickel and carbon, gave a good balance of properties but the very restricted ductility limited their uses and processing. Variations in alloying procedures then produced far more versatile materials and today's selection of alloys provide some extremely good properties. The main limitations lie in the putative toxicity of chromium and nickel, although the significance is questionable.

Stainless steels provide the third example of structural alloys used for implants. They rely on chromium for their passivity, but the corrosion resistance is only marginal and only a small group of austenitic steels are suitable.

Ceramics and glasses

Until a decade ago, the inherent brittleness of ceramics precluded their use in critical structural applications within the body. However, advances in ceramic processing technology have enabled significant improvements to be made to fracture strengths and toughness to be made and now ceramics, with their amorphous counterparts of the glasses and glass-ceramics, are frequently used in these applications. There are three qualities of ceramics which underpin these uses, the inertness of certain oxide ceramics, their hardness and, within a small group of materials, a degree of bioactivity.

Some of the simplest ceramics, combining a metal with a non-metal, provide the best properties. In particular, when the non-metal is oxygen, a small series of extremely inert and hard ceramics may be identified. Of these, aluminium oxide is the most widely used in surgery. The long term biocompatibility in most situations is very good and its exceptionally high hardness accounts for its major use in orthopaedic joint replacements. Toughness is still only marginally acceptable, however, and there have been problems of brittle fracture. Because of this there is a growing interest in tougher ceramics, especially those involving transformation toughening phenomena such as the partially stabilized zirconias.

Calcium compounds are not renowned for their mechanical properties nor for their hardness, but some do have a special characteristic, which is attractive for certain medical uses. This is the chemical and structural similarity between certain calcium compounds and the mineral phase of bones and teeth. In particular, the substance calcium hydroxyapatite very closely resembles this phase and it has been known for some time that this material can be placed in contact with bone and stimulate bone regeneration. This is also true for some other calcium phosphates and indeed, calcium carbonates. The two main phosphates of interest are in fact the hydroxyapatite, which is essentially chemically stable in tissues and tricalcium phosphate, which is degradable. Both appear to possess this bioactivity and may be used in either particulate form or as a surface coating on tougher (e.g. metal) substrates. It is therefore possible to use these materials as alternatives to bone grafts in regeneration or as a means to achieve bone-bonding in major joints or dental implants. Apparently it is not only the phosphates which have this ability, but also carbonates, in particular the naturally occurring corals being very effective in stimulating bone reconstruction.

Polymers

Metals and ceramics are generally so much more rigid than hard tissues that their use for most tissue replacement or augmentation is counter-intuitive. It is far more logical to use polymers for these purposes because of their greater similarity to natural structures. Furthermore the wide variety of features, ranging from chemical reactivity to mechanical characteristics that can be developed within the family of polymers, allows far better tailoring of these materials to meet precise specifications.

A few general points should be made. First, polymers have the inherent capacity to display good biocompatibility, since the macromolecules themselves are usually non-toxic. However, only rarely are these macromolecules used as the sole component of the material, most of which contain a variety of other substances, ranging from intentional additives such as plastisizers and anti-oxidants to undesirable contaminants or residues, which tend to control the features of biocompatibility. Secondly, polymers can be produced in a variety of forms ranging from elastomeric to highly cross-linked structures, and from viscous fluids to high molecular weight solids, often within the same chemical family, providing a variety of properties. A few of the major classes of polymer are listed below.

Polyethylene is chemically the simplest of all polymers and as a homochain polymer is essentially stable and suitable for long-term implantation under many circumstances. Moreover it is amenable to a variety of production technologies, is relatively inexpensive and has good general mechanical properties, so that it has become a versatile biomedical polymer with applications ranging from catheters to joint replacements. After several decades of use it is still the material of choice for the acetabular component of hip replacements. It performs adequately in this capacity although there are problems with the tissue response to the wear debris that is produced. This is in fact one of the more controversial aspects of biomaterials at the moment.

Closely related is polypropylene, which is widely used in medical devices ranging from sutures to finger joints and to oxygenators.

The extreme inertness of some fluorocarbon polymers is responsible for the widespread use of materials such as PTFE. However, the relatively poor mechanical performance limits their applications to soft tissue reconstruction. This is an important factor since clinical experience shows that these materials cannot be used in any joint replacement. In recent years, most interest has been displayed in the microporous expanded material "Gore-Tex", which is successfully used in artificial arteries, periodontal surgery and elsewhere.

Poly(methyl methacrylate) has been mentioned several times. It is a hard brittle polymer that appears to be unsuitable for most clinical applications, but it does have several important characteristics. First and foremost is the fact that it can be prepared under ambient conditions so that it can be manipulated in the operating theatre or dental clinic, explaining its use in dentures and bone cement. The relative success of many joint prostheses is dependent on the performance of the PMMA cement, which is prepared intraoperatively by mixing powdered polymer with monomeric methyl methacrylate, which forms a dough that can be placed in the bone where it then sets. Although suffering a number of deficiencies in this respect, including the

exotherm of polymerization, the toxicity of the volatile methylmethacryate and the poor fracture toughness, no better material has been developed to date.

Polyesters have also been mentioned several times, since they have several features that make them attractive for medical uses. It is important to match the properties to these uses, particularly recognizing that the chemical structure of polyesters is intrinsically hydrolysable. Whether or not a polymer based on any particular molecule is degraded under conditions found in the body will depend on the accessibility of the carboxyl groups to water.

At one end of the spectrum we have a series of aliphatic polyesters based on naturally occurring substances such as lactic acid, which are biodegradable with residence times ranging from a few weeks to over a year. These materials, particularly copolymers of lactic and glycolic acid can be used as absorbable suture materials and drug delivery systems. The fibre forming capabilities of polyesters, which allow this fabrication of sutures, also permits the preparation of fabrics and textiles. Aromatic polyesters such as terephthalate are extensively used as woven or non-woven structures in artificial arteries and ligament regeneration.

Polyurethanes have had a variable history of use in medical applications, partly arising from the wide range of materials that can be prepared with the urethane group. Bearing in mind the fact that the precursors of polyurethanes, such as toluene di-isocyanate, have well known toxicities, and the fact that the structures generally are susceptible to degradation, it is not surprising that these do display varying biocompatibility characteristics. On the other hand, certain polyurethanes have excellent mechanical properties, especially as thermoplastic elastomers, and are very suitable for areas of soft tissue reconstruction. Furthermore, for reasons not entirely understood, polyurethanes often have excellent blood compatibility. For these reasons, some of these polymers, especially the polytether urethanes) have been used in critical blood contacting applications, including intravascular catheters. However, their inherent susceptibility to degradation has resulted in a number of difficulties, for example the stress cracking of pacemaker lead encapsulation.

Although the vast majority of synthetic polymers are based on the carbon-carbon bond, a small number are based on silicon. Specifically, a linear chain of alternating silicon and oxygen atoms yields the family of siloxanes. Depending on the nature of the side groups attached to the silicon, a range of substances may be produced, ranging from oils to elastomers. It has long been thought that the inherent strength and stability of the Si-O bond should result in biologically stable polymers. Thus, over several decades, substances such as polydimethylsiloxane have enjoyed widespread medical and dental use, ranging from intravascular catheters, dental impression materials and contact lenses to a variety of soft tissue augmentation devices. In the latter case, silicones has been surrounded by controversy in recent years, largely associated with the unsubstantiated claims that they activate the immune system and cause a variety of auto-immune diseases in their hosts. This has been particularly associated with the use of certain silicones in breast implants.

Finally, in the section of polymers, mention must be made of the growing interest in naturally occurring biopolymers and their analogues, which should be able to possess characteristics much more similar to the tissues of the body. We have already seen that polymers of lactic acid and similar molecules are degraded into metabolizable moieties, which improves the prospects of good biocompatibility. In other situations the polymers themselves may be analogous to those occurring naturally.

One important example here involves the use of collagen, which is the main component of several tissues, including tendon. It is possible to use such tissue as a biomaterial or extract collagen from them and reconstitute it. Collagen is only weakly antigenic and should not provoke an immune response, although if collagenous tissues are used, such as bovine pericardium that is used in bioprosthetic heart valves, it is necessary to cross-link the material, usually with glutaraldehyde, in order to ensure it is not antigenic. It is not only proteins that may be considered in this context—polysaccharides may also be appropriate. One such substance receiving widespread interest is hyaluronic acid, which may be modified in many ways to produce materials of varying properties, including excellent biocompatibility and biodegradability.

Carbons

It is perhaps unusual to consider carbons as a separate class of material, but this is appropriate in the context of biomaterials. Carbon, as the major elemental constituent of organic molecules would appear to be intrinsically safe to use within the body and it is on this basis of putative inertness and biocompatibility that attempts have been made to use carbon, in several of its forms in implantable devices. The major deficiency of this element is that it is not possible to prepare it as a structural material and it is difficult to fabricate it into useful artefacts. It has been used as a monolithic solid, but relatively unsuccessfully when in stressed situations. Minute components in non-stressed situations, such as pacemaker electrode tips on the other hand, can be very successful. The more usual approaches to incorporate carbon into medical devices involve either surface coatings or fibres. For example, pyrolytic graphite may be deposited onto tough metallic substrates in components of heart valves while there is a growing interest in the new diamond-like carbons. Carbon fibres have occasionally been used by themselves, but more frequently they are used as the basis of composites, such as carbon-carbon or carbon fibre reinforced polymers.

Surface modifications and coatings

It will be clear from the above discussions that it is extremely difficult to satisfy all of the demands of surgical applications in single materials. Although the traditional materials scientists' approach to this type of problem, involving the development of composites which attempt to produce the best compromise, has been used in the biomaterials field, it is unlikely to solve all of the problems because composites tend to have greater rather than less biocompatibility deficiencies. More appropriate to the use of medical devices is the approach where the functional properties are provided by an appropriate engineering material as a substrate while the appropriate biocompatibility properties are provided by the surface, specially designed for that purpose. There are already several examples of this approach in clinical practice. For example, corrosion resistance and tribological characteristics of metals can be improved by the application of ion-implantation or ion-assisted coatings. Superior bio-

compatibility of some polymers may be achieved through processes which render the surface more hydrophilic. Polymers may also be rendered biologically active through the use of agents, such as anti-coagulants, immobilized on their surfaces, or through the attachment of natural tissue components such as phospholipids. Finally, and as an indication of the future direction of biomaterials, it is possible to modify some surfaces to make them attractive to specific cell types. Thus materials used for artificial arteries can be treated so that they become attractive to the patients own endothelial cells. Indeed, such materials can be placed in cell cultures where the endothelial cells form as a surface lining, thereby greatly increasing the prospects of good blood compatibility.

The situation with biomaterials is clearly in a state of rapid change. There is still a wide range of opportunities for conventional materials and improvements are urgently needed. However, it is the imaginative use of the whole spectrum of natural, synthetic and hybrid structures, no doubt encompassing developments in molecular biology as well as materials science, that will lead to more effective, more reliable and more significant implantable medical devices.

Market opportunities in biomaterials and medical devices

There is no doubt that the numbers of medical devices in production is increasing on a world-wide basis. The industry is highly competitive and is one of relatively high cost/low volume. Medical devices of the type discussed in this report are naturally dependent on the supply of appropriate materials. This does present a problem, however, as volumes of material required, in contrast to other industrial sectors, are low and although manufacturers can command reasonably high prices, the materials supplier to the medical device manufacturer is not in such a strong position. In many cases, it is ideal if the device manufacturer is also the supplier of the specialist material but this is rarely possible. Some important figures for medical device supply in various parts of the world are given below.

Selected bibliography

The reader is referred to the following journals which deal with biomaterials or medical devices:

Journal of Biomedical Materials Research, Wiley, New York
Journal of Materials Science; Materials in Medicine Chapman and Hall, London
Biomaterials, Butterworth, Oxford
Clinical Materials, Elsevier, Oxford
Medical Device Technology, Advanstar, Chester

The following textbooks and monographs cover aspects of the subject:

Black, J. *Biological Performance of Biomaterials*, Dekker, New York, 1981
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(Figures for 1991)	Market (US$ million)	% GDP on health care	Per capita spent on devices	Pop (millions)
Europe	18 600		34	554
Germany	5 000	8.2	64	7
France	2 700	8.9	48	56
UK	2 100	5.9	38	55
Italy	2 000	7.7	34	58
Spain	1 000	6.3	26	39
Netherlands	800	7.7	53	15
Switzerland	600	7.7	86	7
Remainder	4 575		14	210
USA	29 900	12.5	120	250
				120
Japan	12 000	6.5	100	3 700
Rest of World	10 400		3	

In terms of product groups, the following figures (in US$ million) provide an indication of market sizes

	World	European
Bone fracture plates	250	60
Hip replacements	1 000	250
Knee replacements	400	< 100
Other bone implants	250	90
Tendon/cartilage	< 100	< 40
Dental implants	200	< 50
Heart valves	350	150
Vascular grafts	200	< 50
Cardiovascular catheters	700	250
Drug delivery catheters	300	100
Controlled drug delivery	3 000	1 000
I.O.L.'s	450	180
Membranes	1 400	600
Pacemakers	1 300	400

2. NEWS AND EVENTS

Establishment of an International Centre for Materials Evaluation Technology (ICMET)

One of the latest achievements of the UNIDO Programme on Technological Advances is the preparation for the establishment of the International Centre for Materials Evaluation Technology in the Republic of Korea.

Background

As we enter the mid-1990s, the world's economy is increasingly being driven and shaped by the development and application of three major technology families, namely new, improved and advanced materials, microelectronics and biotechnology. Materials technology is a key enabling technology for a wide range of industrial sectors which will have a major influence on economic and industrial competitiveness—and new and advanced materials constitute one of the key trends in the technology of engineering industries, leading to major qualitative changes in the production cycle, from the processing of raw materials to the obtaining of finished products.

In future, both the new materials and those with improved properties will play an essential role in the development of advanced technologies such as electronics, mechatronics, new energy, aerospace, etc. In addition, the technological impact of new materials on related industries will be very significant and this is a more important point than the market size of new materials itself.

Innovation in engineering materials has been responsible for major technological advances in recent years and the trends are set to continue into the next century. World-wide demand for advanced materials production has been increasing rapidly within the last decade and it forecasts to rise by the year 2000 and beyond. Between 1985 and 1988, the number of companies involved with advanced materials grew from 302 world-wide to more than 1,800. The global market is expected to reach US$ 72 billion to US$ 95 billion by the year 2000, almost an order of magnitude growth from 1987. The demand for advanced ceramics alone will increase 8.5 per cent a year world-wide between 1990 and 2000 to reach a US$ 25 billion market in the year 2000, up from US$ 11 billion in 1990.

It is also widely acknowledged that reliable methods for testing and evaluation of new and advanced materials are crucial for their successful development and efficient incorporation into competitive industrial products. Reliable and appropriate methods of materials evaluation and specification are, in fact, vital for the development of new materials, materials selection, product design, process selection, quality control and assurance, and the prediction and assessment of in-service performance.

Strategy

Having recognized the vital importance of these issues and the need for international cooperation in this area, the seven most industrialized countries of the world in the 1980's initiated a multilateral programme on advanced materials known as the Versailles Project on Advanced Materials and Standards (VAMAS). This programme provides a focus for cooperation amongst the industrialized nations in developing common technical bases from which harmonized standards can be produced with considerable benefits for all parties involved.

At present, many developing countries are also preparing strategic plans for building-up/strengthening their technological capacity in the area of materials design, processing, evaluation and utilization. It includes the establishment of testing facilities and implementation of R&D work programmes in characterization and certification of new and advanced materials. For instance, the Government of Mexico is planning to establish a national centre aimed at strengthening capacity and implement a national programme in this particular area. A plan of actions on building up capacity in the area of advanced materials has recently been developed for the Arab region by UNESCWA in cooperation with UNIDO, where the establishment of testing facilities is considered to be a main component of the overall programme. Several African countries, which are carrying on R&D in the area of new materials, have included the establishment of testing laboratories/centres in their strategic plans.

Present or on-going programmes

Taking this into account, and as a part of its on-going promotional programmes in the area of materials science and engineering, UNIDO has undertaken some steps to

support the industrialization process in developing countries through building up awareness among policy makers, scientists and industrialists dealing with materials issues and the introduction of new materials' testing and evaluation issues as a key factor in improving the quality of products and meeting the environment control and energy requirements.

Since the development of widely recognized evaluation methods are slow and dispersed in the developing countries, there is a genuine need to develop a concerted activity in this area. Therefore, a concept of an International Centre to Materials Evaluation Technology (ICMET) was developed and discussed with the Korea Research Institute of Standards and Science (KRISS), which expressed an interest in hosting this centre.

It was in particular proposed to set up an International Centre which would provide the basic organizational support to develop and maintain multilateral cooperation. Necessarily, this would include an element of networking for laboratories with overlapping interests. It was designed that the centre may assist developing countries in both frontier science and engineering research as well as in information gathering, monitoring and dissemination, and the generation of materials properties databases, which would provide the basis for national industrial and economic development and strategic planning.

The Regional Workshop on Testing and Evaluation of New Materials in Asia, organized by UNIDO and held in Taejon, the Republic of Korea, 25-28 March 1991, emphasized the importance of these issues and urged UNIDO to assist the developing countries in building up the adequate technological capability in this particular area. The participants of the meeting also strongly supported the preparatory work undertaken by the Republic of Korea and UNIDO in establishing ICMET, which would provide a framework for international cooperation with synergistic benefits for developing countries.

In order to verify the concept of ICMET and secure support to its establishment from the international community, a mission of experts was organized and led by UNIDO in order to visit and consult leading institutions and experts in nine Asian and American countries. The project was financed by the UNDP Office in Seoul and the Government of the Republic of Korea on a cost-sharing basis. The mission found considerable interest in the creation of an international centre (or regional centre during its start-up phase). The findings of the mission were reflected in the feasibility study prepared by the experts. It was recommended that a preparatory and pilot activities phase over two years should start as soon as possible to lay the basis for the establishment of ICMET and the development of a longer term plan and work programme.

As a part of its ongoing efforts to promote the establishment of ICMET further, UNIDO organized the Consultative Group Meeting on Collaboration in Testing and Evaluation of New Materials in Asia, held from 22 to 24 March 1994 in Taejon, the Republic of Korea. After reviewing the background document for ICMET, the participants fully supported this initiative and considered the Centre as an appropriate institution for international cooperation in the area of materials evaluation for the benefit of developing countries.

Based on the feasibility report the participants also elaborated the detailed programme of activities for the preparatory/pilot phase of the Centre and undertook to explore ways of supporting it, including in-kind contributions. The meeting considered it essential to establish a network as a complement to ICMET and participants agreed to undertake initially the role of national focal points.

Institutional framework

While preparing the feasibility study on the Establishment of ICMET, the UNIDO mission found that KRISS enjoys a high reputation amongst scientists and technologists in the developing world and is seen as a credible organization to lead the initiative to host the proposed Centre. The concept of the Centre was almost universally welcomed and appreciated, as was the selected venue for its location. It was also noted that the Republic of Korea had made considerable progress in economic development and that it would be very useful for other countries to learn from its experience. The country's resources and growing capabilities were seen as vital for the success of the international centre, particularly in the formative stages when a strong driving force and momentum is needed.

A substantial measure of support has already been received by UNIDO for the organization of training courses to improve manpower skills of developing countries in the materials field. Various centres of excellence, such as the Standards and Industrial Research Institute of Malaysia (SIRIM), the Singapore Institute of Standards and Industrial Research (SISIR), etc., exist in different countries and would be prepared to share their facilities for cooperative R&D on materials evaluation. Some countries have already offered to host workshops, training events, etc. with some financial support to meet local costs of delegates. Other forms of in-kind support, such as contribution of materials, are to be sought.

Problem to be addressed

To transform new and advanced materials into competitive industrial products successfully, it is widely acknowledged that the evaluation technology is important. Materials evaluation technology is known as the method of measurement, testing or analysis used to determine the physical, mechanical or chemical characteristics and properties of materials. Reliable and appropriate methods of materials evaluation and specification are, in fact, vital for the development of new materials, materials selection, product design, process selection, quality control and assurance, and the prediction and assessment of in-service performance.

In fact, what industry requires is a set of consistent and widely recognized evaluation techniques for common use by both the producers and users of new and advanced materials. Ideally, these techniques should be standardized, but the technical bases from which reliable standards can be developed are lacking in many areas, with the consequence that often there are large disagreements on evaluation techniques and even on results obtained from the same technique. Much underpinning work is required to resolve basic but complex issues.

For example, testing needs for advanced composites are driven by user requirements—each user tries to develop his own set of test methods to characterize and qualify a material, and to establish design allowables. Thus, while the need to know basic materials properties is essentially the same for all users, methods used to determine these properties are different. Therefore, to assess composites performance under compression, one can find 15-20 dif-

ferent test configurations. Multiple test methods are clearly inefficient, not just for the materials suppliers, but also for the materials users and test houses. Key factors are:

- It is costly to purchase and maintain different test facilities;
- Training to develop expertise for each method can be expensive;
- It is difficult or even impossible to combine test results into a database.

However, new and advanced materials, especially those manufactured in developing countries and based on local resources, often require a new approach and more sophisticated and systematized techniques for characterization, testing and evaluation, which are not generally available. This acts as a serious barrier to the wider diffusion of the technology and poses significant problems for the developing countries.

In these countries, progress on materials measurement and evaluation technology is slow because of the heterogeneity of the activities concerned, the amount of necessary work compared to the available resources, and the diverse bodies involved (industrial federations, users, test laboratories, government authorities, individual firms, international organizations, etc.). Often in the developing countries there is no focus for materials evaluation work and some lack a critical mass at present, making it difficult for them to undertake this work efficiently.

In addition, trade in advanced materials and products made from them is global in character and there is therefore a genuine requirement for international cooperation in the development of characterization and evaluation techniques that are accepted across national boundaries. Cooperation amongst developing countries who share common problems and whose perspectives are similar is believed to be vital and of significant importance if their needs are to be properly met. Indeed, similar technological capabilities and requirements can provide an excellent basis for fruitful and effective partnership amongst them and facilitate their entrance into the market.

A bridge should also be established between developing and developed countries in this important area of materials science and engineering. In spite of the fact that some countries have bilateral arrangements with one or two developed countries, these are far from adequate.

It is also acknowledged that both financial and human resources in developing countries are limited and there is a shortage, with the exception perhaps of India, the People's Republic of China and one or two Latin American countries, of trained materials scientists and technologists. Therefore, the developing countries are keen and consider it essential to have avenues for international exchange and cooperation to combat part of this deficiency.

Target beneficiaries

The establishment of an International Centre for Materials Evaluation Technology (ICMET) will have a number of important wider benefits:

(a) It will provide a basis for developing countries to gain access to engineering and processing of new materials and their characterization. That would assist the development and strengthening of general technological capabilities in the materials evaluation technology area, vital for future competitiveness of industry. It would also raise the level of understanding of the importance of specifics in test methods throughout the materials related industry.

(b) Cooperative international programmes will enable the developing countries to address materials evaluation issues within their own national institutions in a more coordinated and effective manner.

(c) Collaborative work on materials evaluation will provide a strong platform for materials research communities in the developing countries to build closer contacts on wider topics.

(d) The Centre will have a better scope for interactions and linkages with established centres and other related initiatives of the developed countries than individual institutes or even countries of the developing world would on their own.

(e) International standards are of crucial importance to industry and business, and through ICMET's work, the developing countries will be in a better position to contribute and influence their standards development more positively.

(f) ICMET will assist accredited laboratories to perform to a higher standard and ease the laboratory accreditation process as a whole in the developing countries.

Such an international nodal point can assist developing economies in both frontier scientific and engineering and research and in information gathering, monitoring and dissemination, and the generation of materials properties databases to provide the basis for national industrial and economic development and strategic planning. It would also have the advantage of providing access to instrumentation to those research institutions in developing countries that cannot afford such instrumentation.

We invite all institutions, enterprises and R&D centres to participate in the project. Requests for further information should be addressed to: Mr. V. Kojamovitch, UNIDO, Vienna International Centre, P.O. Box 300, A-1400 Vienna, Austria.

Techmart

After its successful beginning in China in December 1991, Technology Market (Techmart) was held in Zimbabwe and India in 1992 and 1993, and is to continue in up to two different locations each year. For 1994 Techmart is planned for Viet Nam in November and India in 1995, which will be concentrating more on the investment side of TT.

Techmart is a business forum where the rights to manufacture and upgrade existing products and processes can be bought and sold through direct contacts between technology seekers and technology suppliers from developed and developing countries, with special emphasis on the needs of small- and medium-scale industries (SMIs).

The rights offered may cover machinery, tools, patents, designs and the use of recognized trade marks and names to promote the business, or it may involve finding a source of expertise, investment opportunities and capital to stimulate business activity. The technologies for sale will include both well-tried and newer technologies, especially where their application may bring economic or environmental benefits or improve the quality and acceptability of a product or process.

Techmart, which is specifically aimed at the needs of SMIs in developing countries, also serves to market the technologies produced by SMIs themselves. It is a unique forum organized by the United Nations Industrial Development Organization (UNIDO) and associated

national development authorities and financial institutions, with the assistance of consulting firms specializing in technology transfer. The experience gained in many developing countries, through modifying and adapting technologies to suit local conditions, has resulted in the creation of many sources of low-cost but well-tried systems of manufacture that closely match the needs of entrepreneurs in developing countries.

Techmart permits the display of technologies by means of sample products, drawings, process flow diagrams, photographs and product catalogues covering various industrial sectors. A comprehensive, indexed compendium of the technologies offered and requested by companies and organizations world-wide is always available in advance of the event to enable potential customers to select and compare technologies of interest. The entrepreneur who purchases this compendium of technologies and examines its contents before attending Techmart may be able to transform his or her business to achieve faster growth through technical collaboration arrangements. Expert legal advice on technology acquisition and the negotiation process, one-to-one prearranged business meetings, plant visits and seminars on emerging technologies and the UNIDO technical assistance programme are essential components of each Techmart.

Techmart is aimed at the business person, the manufacturer and the buyer or seller of technology who wishes to generate productive new business. It represents an important opportunity for technical universities and research institutes to seek outlets for the results of their work and to identify new areas for research and development. Techmart will also able them to highlight their ability to provide training resources needed by industry. Investors should likewise attend Techmart to promote their interest in financing new business opportunities. Manufacturers' associations, trade associations, chambers of commerce, development banks and agencies and national governmental organizations responsible for implementing economic, industrial and technology policies should attend Techmart together with leaders in the development of new and existing manufacturing operations in their own countries.

Techmart is a meeting place where technological resources and the latest developments in manufacturing industry are brought together and new business opportunities are offered to the leaders of manufacturing businesses in both developed and developing countries. It provides a unique setting for the conclusion of practical business arrangements focusing on technologies and including the financial, legal and investment advice required to produce a powerful solution to technical and entrepreneurial problems. More than this, Techmart is the only event that enables entrepreneurs to identify required technologies before deciding to attend. To facilitate the process of matching technologies with needs, UNIDO compiles and publishes a technology compendium that describes thousands of technologies currently available for transfer to developing countries. Technologies may be offered and requested by completing the attached compendium entry forms. A copy for dispatch immediately on publication can then be purchased to enable the entrepreneur to indicate which offers or requests he or she would like to discuss at the Techmart.

Companies and organizations offering licensing opportunities may reserve an exhibition booth at the Techmart to display their technologies by means of sample products, drawings, process flow diagrams, photographs and product catalogues. The normal sizes of the display booths are 6 and 9 square metres, and the cost of renting a booth is quoted on each Techmart leaflet, which will be forwarded upon receipt of the attached order form, duly completed.

Companies, organizations and individuals seeking technologies or partners for cooperation may register their interest in Techmart. Potential visitors can order and pay in advance for a copy of the technology compendium by using the attached order form. They will be dispatched by airmail prior to the event.

Purchasers of the technology compendium will be encouraged to visit Techmart and to participate in the seminars on technology transfer, industrial cooperation and emerging technologies that are scheduled to take place at that time.

Attendance at Techmart will generally be at the participants' expense. However, UNIDO may offer limited financial assistance to selected entrepreneurs from developing countries to attend Techmart, provided they initiate business contacts with technology suppliers and requesters before the event, and can show a serious interest in cooperation by meeting the concerned parties at Techmart. Similar assistance may also be sought from the development banks, industries and international, regional and national development agencies willing to sponsor participation in Techmart.

Offers of, and requests for, technology may be submitted by companies, organizations, exhibitors, visitors and others for inclusion in the technology compendium (entry form attached), which will contain only entries that describe a specific product or process. General offers of service, manufacturing, consultancy etc. will not be included. Each entry should clearly describe what is being offered, its potential uses and the claimed advantages.

The assistance rendered by UNIDO during Techmart will enable entrepreneurs to select and compare alternative technologies offered by developed and developing countries to improve or refine products and processes in various industries to meet specific technological needs.

As a condition of participation in Techmart, detailed information on the results of contacts made through Techmart must be submitted to UNIDO to enable it to plan and provide follow-up project support.

Subject to the availability of funds, follow-up assistance to Techmart participants may include prefeasibility and feasibility studies for selected projects, continued expert advice on technology negotiation and the investment process, identification of high-level technical expertise for projects, as well as agency support for project implementation and equipment procurement. On the basis of specific requests for follow-up assistance, the involvement of other UNIDO departments may be required to satisfy demand and to ensure cost-effective project implementation.

Further Techmart are planned for 1995 in Lusaka, Zambia in March or April, and Sao Paulo in November. More information about Techmart events may be obtained from: Technology Service, Investment and Technology Promotion Division, United Nations Industrial Development Organization (UNIDO), Vienna International Centre, P.O. Box 300, A-1400 Vienna, Austria. Fax: 43-1-232156 or 2307584; Telex: 135612 uno a; Tel.: 43-1-21131, Ext. 3693; Cable: unido vienna; E-mail address: GE QUIK-COMM:AAQ00118@UNIDO.

Viet Nam Techmart '94

Since 1986, when Viet Nam began an ambitious reform programme, the country has been making a steady transition from a centrally planned economy to a market-based system. The main elements of this reform include opening the economy to foreign investment and technology and encouraging the development of the private sector; the equitable distribution of wealth and income; and rural reforms.

UNIDO, in cooperation with Viet Nam's Ministry for Science, Technology and Environment (the National Centre of Science and Technology Information and Documentation), is organizing VIET NAM TECHMART in Hanoi from 1 to 4 November 1994.

At VIET NAM TECHMART technologies will be displayed by means of sample products, drawings, process flow diagrams, photographs and product catalogues. The following industrial sectors will be represented:

- Food processing, including food preservation;
- Light industry (plastics and textiles);
- The electronics industry (microcomputers, electronic equipment and household electrical appliances);
- Chemicals and pharmaceuticals;
- Advanced materials.

The business opportunities available at VIET NAM TECHMART will be of interest to individuals and organizations, such as:

- Manufacturers, buyers and sellers of technology;
- Manufacturers' associations, trade associations, chambers of commerce;
- Investors;
- Development banks and agencies;
- Technical universities and research institutes.

Companies, organizations and individuals looking for technologies or offering partnership for cooperation can register their participation in VIET NAM TECHMART. The programme will include technology displays; prearranged business meetings, plant visits, technology information, negotiation and acquisition seminar; seminar on technology legislation in Viet Nam; advisory services on technology negotiations and sectoral seminars.

More information about VIET NAM TECHMART may be obtained from the Technology Service, Investment and Technology Promotion Division, UNIDO, Vienna International Centre, P.O. Box 300, A-1400 Vienna, Austria. Tel.: 00431 21131 ext. 3693; Fax: 00431 232156 or 2307584; Telex: 135612 uno a; E-mail: EARN:S568568@UNIDO1.BITNET

A few examples of technologies offered and requested by participants in VIET NAM TECHMART are described below.

Offers

Natural latex products—A 68 metre long, fully automatic process to produce high grade latex medical goods. Raw material is natural latex available in Viet Nam. Capacity estimated at 90 million items per year. The technology is commercialized. Technical assistance and production equipment is offered.

Further details are available from Mr. Pham Xuan Mai, Director, Medical Rubber Enterprise, 38 Truon Quoc Dung Dist., Phu Nhuan Ho Chi Minh City, Viet Nam. Tel: 84-8-440187; Fax: 84-8-441398; Telex 811 287 VIMEX VT.

Cyanoacrylate adhesives and anaerobic sealants—Manufacturing technology for a complete range of cyanoacrylate adhesives and anaerobic sealants. The products are suitable for use in the automotive, engineering and electronic industries. The technology is commercialized and is available for manufacture under licence.

Further details are available from Dr. W. P. Millrine, Adaptove Technologies Ltd., Companies House, Tower St., Ramsey, Isle of Man, United Kingdom. Tel: +44-624-815544; Fax:+44-624-815548.

Methyl methacrylate (mma) manufacturing plant—Technology is available for the manufacture of methyl methacrylate (MMA), which is used for optical lenses, oven windows, headlight covers, artificial marble, etc. It is also widely used in adhesives and pigments. This C4-based technology is more economically and environmentally sound than the aceton-cyanohydrin based process currently used world-wide. The technology is available for manufacturing under licence.

Collagenase (collagenolytic proteinase) from hepatopancreas of kamchatka crabs—A low waste biotechnology is available for production of high purity collagenase from hepato-pancreas of Kamchatka crabs. Collagenase is used in medicine to heal wounds and burns, in cosmetics as a bioactive agent in skin care and in biotechnology for the isolation of viable cells from tissue. The technology is commercialized and is available under licence or joint venture.

Further details are available from Mr. Vadim Kotelnikov, Asian and Pacific Centre for Technology Transfer (APCTT), Adjoining Technology Bhavan, Off New Mehrauli Road, Post Office Box No. 4574, New Delhi 110 016, India. Tel: +91-11-685-6276; Fax: +91-11-685-6274; Telex: 31-73271 APCT IN.

Requests

Boat building using fibreglass plastics—Technology requested to build boats of plastic strengthened by fibreglass. Fibreglass plastics needed for producing the boat body, canoes, basins, stairs and other consumer goods. The products should have high mechanical strength, low weight, heat resistance, insulating, and be efficient and easy to make. The technology should be commercialized and available under joint venture agreement.

The request comes from Mr. Dan Cong Ngon, Director, Company for Technology Development and Supply of Sea Products of Da Nang City, 134 Trung Nu Vuong, Da Nang City, Viet Nam. Tel: 84-51-23154; Fax: 84-51-25714.

Powered drill for geological exploration—Technology for machine drill, as substitute to hand drilling, in order to drill, sample and describe geological strata. The hole depth should be 30 metres and a diameter of 130 millimetres. The technology should be in current production and available as a turnkey operation.

The request comes from Mr. Luu Van Hai, Deputy Director, Irrigational Work Design and Investigation Enterprise, Van Khe Village, Ha Dong Township, Ha Tay Province, Viet Nam. Tel: 84-34 24412.

Foundry, metal transformation and processing—Designs, formulations and technical assistance are needed. The Technology should be commercialized.

The request comes from Mr. Bipin K. Paliwal, Technical Manager, MITTAL Appliance Pvt. Ltd. 338 Sihvaji Nagar Indore, M.P., India. Tel: +91-731-37375/37376; Fax: +91-731-431444

Production of knitted fabric—Technology and equipment are requested to produce knitted fabric. Low

noise technology and a small production acreage to be covered. Expected productivity to be 200,000 metres per year. Own investment of $100,000 can be afforded. The technology should be commercialized and available under joint venture.

The request comes from Mr. Tran Tri Binh, Director, Mac Dinh Chi Private Enterprise for Woven and Printed Fabric, 4 Tan Hoa Don, Ward 14, Precinct 6, Ho Chi Minh City, Viet Nam. Tel: 84-8-443603.

19th Annual Meeting of the Society for Biomaterials in Conjunction with the 25th International Biomaterials Symposium

These two meetings, held 28 April–2 May 1993 in Birmingham, Alabama, USA, were preceded by a one-day workshop on Biotechnology Applications Biomaterials. The workshop, the first of its kind, was sponsored by the Food and Drug Administration Center for Devices and Radiological Health. With over 11,000,000 users of biomaterial implants, the necessity of improving the compatibility between the implant and the host is of primary importance. Therefore, the workshop was organized to focus on research aimed at designing biotechnology derived biomaterials that have the potential to achieve homology with the host. Structuring of hybrid artificial tissues and organs is one of the most promising strategies for improving implant/host compatibility.

Lura J. Powel (Chief, Biotechnology Division, National Institute of Standards and Technology/NIST) discussed NIST's biomaterials programme. For many years, NIST has maintained a joint research programme with the American Dental Association. The major thrust of the NIST programme is new monomer systems that shrink less, are more resistant to oral fluids, and have the potential to bond to teeth and other materials. These monomers are expected to find applications in improved dental composite restoratives, adhesives, cements, and maxillofacial prostheses. (Extracted from *Materials Technology*, Vol. 8, Nos. 7 & 8, July/August 1993)

3. RECENT DEVELOPMENTS

Micro-organisms degrade aliphatic polycarbonate

The National Institute of Bioscience and Human Technology, Agency of Industrial Science and Technology (AIST) JSP Corp., and a research team headed by Professor Y. Yoshida at the Department of Applied Chemistry, Faculty of Engineering, Tokyo University, have discovered micro-organisms that degrade aliphatic polycarbonate (PC), a plastic material. The research is attempting to degrade types of aliphatic PC with very high molecular weights. The micro-organisms, however, have already proved able to degrade an aliphatic PC with a molecular weight of 2,000.

Aliphatic PC, a new type of plastic material, is produced from carbon dioxide (CO_2), which causes global warming. However, there is only one biodegradable plastic material, aliphatic polyester. The new PC is another biodegradable material, and the design of biodegradable plastics will become more flexible.

The seven micro-organisms were found by the clear zone method. Diluted samples were applied individually to an agar containing emulsified and suspended PC. Each medium was kept at 30° C for two weeks and then examined to see whether a clear zone exists or not, which is caused by a colony decomposing the PC around. The samples were collected from lakes and rivers in the Kanto Area, Japan. The species and genera have yet to be identified. The highest performance achieved was to reduce 80 mg of aliphatic PC (molecular weight: 2,000) to about a quarter in 200 hours. The research will continue with aliphatic PC of greater molecular weights.

Aliphatic PC can be used as plastic, but may be a source of polyurethane. Biodegradable polyurethane may therefore be developed. Unlike aromatic PC, a conventional engineering plastic material, aliphatic PC has the advantage of being produced from CO_2. Applications range widely from an intermediate product in the polyurethane process, to films and fine chemicals. With a melting point higher than those of polyesters, aliphatic PC may be exploited in industries.

Aliphatic PC decomposes in rats. The biodegradability of the polymer by micro-organisms, however, has been established for the first time. All biodegradable plastic materials previously known were aliphatic polyesters, such as polyhydroxybutyric acid (PHB) and polycaprolactone. Information may be obtained from the National Institute of Bioscience and Human Technology, AIST, 1-1, Higashi, Tsukuba City, Ibaraki Pref., 305; Tel.: +81-298-54-6089, Fax: +81-298-54-6009. (Source: *JETRO*, May 1994)

Functional reconstruction of membrane fusion protein

The National Institute of Bioscience and Human Technology, the Agency of Industrial Science and Technology (AIST), is developing new technology for artificially fusing lipid membranes using hemaglutinin glycoprotein on the surface of influenza virus to fuse the virus to a target cell allowing introduction of chemical substances such as drugs and DNA into the cell.

Membrane fusion protein taken from the virus is incorporated into liposome as glue, with the pH change in the ambient environment controlling the fusion functions.

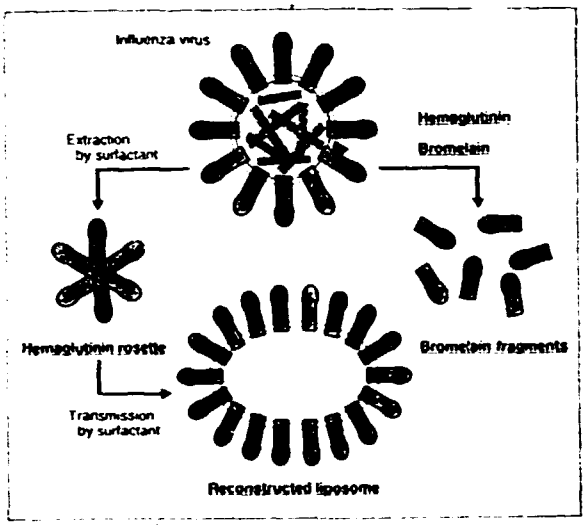
The new technology will be the basis for Japanese industrial-government R&D projects on microcell reactors to develop a proposed new material production system that imitates the efficient material production of the cell from intake of raw materials and energy to output of the final product, in contrast to existing bioreactors which use a single enzyme. The institute plans to use the new technology in the exocytosis process for final product extraction.

In the technology, the viral membrane is dissolved into lipid and protein in surfactant and is purified by sucrose density gradient centrifugal separation to isolate the protein. Phosphatidylcholine and lipid cholesterol are then added to the isolated protein to form a submicron-diameter liposome with hemaglutinin molecules embedded on the surface.

In the experiments, the resultant liposome was mixed with the membrane of red blood corpuscles to investigate the membrane fusion mechanism. The fusion occurred in a slightly acid environment with 70–80 per cent of the liposome working, while no fusion occurred when the acidity was neutral. This indicates the possibility of effective membrane fusion control.

A capsule can be produced by mixing the liposome with a drug agent and incorporating in another lipid membrane. The resulting capsule releases the drug, controlled by the acid change in the environment, so no release

occurs when the environmental acidity is neutral. In the acid environment, the membrane fusion functions are activated to fuse the inner membrane with the outer for drug release, so the capsule can be used for the intelligent drug delivery system (DDS). More information available from National Institute of Bioscience and Human Technology, AIST, 1-1, Higashi, Tsukuba City, Ibaraki Pref., 305; Tel.: +81-298-54-6053, Fax: +81-298-54-6005.



(Source: *JETRO*, April 1994)

Biomaterials combine performance and economy

The pressures on the medical community to curb the spiraling cost of health care are being reflected in a host of resins and devices designed to cut the length of hospital stays and shift treatment to the home. Some of these new biomaterials, which come into prolonged contact with body tissues, include wound dressings that speed healing, surgical sutures that do not require follow-up visits for their removal, artificial organ parts that resist degradation in the body, and ultrathin but strong catheters to make diagnostic procedures less invasive and less traumatic to patients.

Despite these opportunities, a number of key players have recently exited the biomaterials field. Their stated reasons for leaving include competitive pressures and small markets. But industry observers say that negative publicity about alleged harmful effects of some products, together with liability concerns, have also prompted departures.

Allegations of adverse effects in the body have involved such materials as silicone breast implants, thermoplastic polyurethanes (used in vascular grafts, artificial heart valves, and drug-delivery devices), and ultra-high-molecular-weight polyethylene for knee and hip joints.

Exxon Chemical, for instance, has developed a series of microporous polyolefin films that are said to be highly breathable (allowing air and water vapour through), yet possess potent barrier properties (keeping out microorganisms and liquids such as water, alcohol and blood). The films, tradenamed Exxaire, have already been applied in composites (with polyesters or non-woven polyolefins) for surgical gowns, where they are challenging more expensive materials such as the widely used Gore-Tex product, an expanded polytetrafluoroethylene film. They are being developed for wound dressings, diapers and feminine hygiene products.

In the wound dressing area, the porous film's high breathability (a feature known to hasten healing) would be a plus. By contrast, current dressing fabrics made of non-woven polyolefins, polyesters, wood pulp and nylon have breathable properties that are "virtually nil".

The film itself, which is sold to converters in gauges ranging from 25 to 64 micron, can be made from high density polyethylene, low-density PE, linear-low-density PE, polypropylene, and polyolefin copolymers. To create the micropores, polymers are filled with minerals such as calcium carbonate, titanium dioxide, talc, barium sulphate, or glass beads, and fabricated on standard cast film equipment. The stretching that accompanies the processing creates the micropores (around 10 micron in diameter) around the filler particles. The pores become connected by channels less than a micron thick. Breathability can be tailored by adjusting polymer composition and processing, which affect the number and sizes of pores and channels.

Exxaire films are being evaluated for wound dressing applications by an unidentified device fabricator. Tests on the material are said to show little toxicity. As for the form of any dressings made from the porous materials, they might be composites or consist of the bare film. (Current dressings are composites of films and a backing fabric, typically polyester.)

Meanwhile Elf Atochem's Pebax line of amide-based thermoplastic elastomers, already used as catheters in angiographic procedures and as transdermal drug-delivery patches, is being investigated by some customers for several applications. Pebax TPEs can be made breathable by adding functional groups to their polymer chains. Potential applications include surgical drape (a fabric placed over incisions to allow surgeons to operate underneath) and wound dressings. The resin has a high degree of melt stability that allows it to be extruded into strong, uniform, flexible films as little as 13 micron thick. Adding functional groups permits tailoring of other properties as well; the film can be made hydrophilic in this way, for example. Processing is done on conventional extrusion equipment. USP Class VI certified grades are offered.

As a raw material, the breathable film would be costlier on a per-pound basis than competing drape materials like polyesters, polyurethanes, and polyolefins. It could be cost competitive in finished products because the film has a specific gravity that is some 20 per cent lower than the competing materials.

Tests on the drape and dressing applications are primarily in the laboratory stage.

Another group of TPEs is being investigated for the implant market by a small device manufacturer called Corvita. The materials, tradenamed Corethane, can be fabricated into elastomers with properties similar to the aromatic polyether urethanes widely used in implant materials. Corvita claims that the materials do not undergo the degradation in the body, induced by enzymes, which has hampered the effectiveness of polyether urethanes.

Despite the degradation problems with some thermoplastic PURs, they are still used as implants because of their excellent flexural fatigue resistance, high tensile strength (compared to silicones), and ability to bond to themselves.

Another materials supplier, PolyMedica Industries, has developed an implantable urethane, tradenamed Chronoflex, that resists enzyme-induced degradation. The polyurethane material is being developed with three partners: Medtronics (Minneapolis, MN, USA), Vygon (Ecouen, France), and an undisclosed company. Intended uses include components for artificial hearts, vascular grafts and vascular ports.

PolyMedica markets several thermoplastic polyurethanes for medical applications in the US and Europe. These include wound dressings and films that can be stretched over surgical incisions to close them, replacing sutures or staples. The latter materials, tradenamed Spyroflex, can be peeled off by patients four days after surgery, eliminating hospital visits for removal.

Corvita, meanwhile, is developing a class of polyurethane copolymers, along with urethane composites with other polymers, for implants. One of the products is a copolymer of polycarbonate and polyurethane. The material lacks the polyether segments in the polymer chain that are responsible for degradation in the body. In Corvita's *in vitro* tests of durability, the copolymer soaked in nitric acid for a month at 70° C and showed no loss of tensile strength. Standard implant-grade polyurethanes, by contrast, lost 60 to 90 per cent of tensile strength. Potential applications for the copolymers include insulators for pacemaker leads, long-term in-dwelling catheters, and pump diaphragms for artificial hearts.

Another developmental Corvita product is a composite of the PUR/PC grade and a silicone polymer. The material is being tested by two undisclosed device manufacturers as a potential replacement for silicone in breast implants. Claimed advantages of the composite in this application are a lower tendency to rupture and tear (due to its higher tensile strength than silicone alone) and its ability to transmit X-rays. (Silicone implants, which are partially opaque to X-rays, can mask tumours during examinations.)

Aside from the movement away from traditional implant materials, another trend benefiting materials producers is the increased use of catheters and tubing in diagnostic and therapeutic procedures where surgery was once the only recourse. Amoco, for example, is capitalizing on the advantages of its Udel line of polysulphones in the thin-wall tubing and catheter area. Claimed benefits include dimensional stability, rigidity, heat stability and ease of processing.

One Amoco customer, Microspec Corp., Rindge, NH, USA, produces a thin-wall polysulphone tube with an inside diameter of 0.96 mm, wall thickness of 0.07 mm, and dimensional tolerances of 0.013 mm and 0.0064 mm, respectively. This tube is said to be tough enough to protect delicate fibre optic and electronic components inside, and to insulate the patient from the heat and current passing through it. Uses include endoscopy, laproscopy, electrodiagnostics and laser surgery.

Miles (represented by Bayer) has also been focusing on thin-wall tubing materials made of its Texin line of polyether-based PUR elastomers. The materials are said to exhibit a combination of toughness, flexibility, biocompatibility, and resistance to heat, chemical and radiation sterilization methods. Applications include central vein catheters, extension tubes for catheters, and coatings for wire guides used in the catheter systems. Microspec extrudes custom tubing and profiles from the Miles product with outside diameters as small as 0.020 mm and inside diameters to 0.064 mm.

The entire range of biomaterials may eventually benefit from ongoing work to modify existing materials by plasma technology. Researchers at Himont's Plasma Science Division have been experimenting with plasma-applied, biocompatible organosilicon and fluorocarbon coatings on thermoplastics. Plasma offers great opportunities to impart specialized properties—biocompatibility and water wettability, for instance—to low-cost resins. As a result, such surface-modification techniques will play a role in future biomaterials production processes.

More data can be obtained from companies mentioned in this article from the list below.

Amoco Chemicals (Europe) S.A., 15 rue Rothschild, CH-1211 Geneva 12, Switzerland.

Bayer AG, D-W5090, Leverkusen-Bayerwerk, Germany.

Corvita Corp., 8210 N.W. 27th St., Miami, FL 33122, USA.

Elf Atochem, La Defense 10, Courbevoie Cedex 42, F-92091 Paris la Defense, France.

Exxon Chemical International Inc., Mechelsesteenweg 363, B-1950 Kraainem, Belgium.

Himont Italia SpA, Via Rosselini 19, I-20124 Milan, Italy.

PolyMedica Industries, 2 Constitution Way, Woburn, MA 01801, USA.

Sampling of biomaterials from producers

Material	Producer	Claimed properties	Applications	Status
Polyolefin film	Exxon	Highly porous, good barriers	Wound dressing	Customer testing
Polyurethane/silicone composites	Corvita	Resists degradation in body	Organ implants	Customer testing
Amide elastomers	Elf Atochem	High flexural modulus, hydrophilic	Surgical drape, wound dressing, catheters	Customer testing
Thermoplastic polyurethane	PolyMedica Industries	Resists degradation in body	Organ implants	Customer testing

(Source: *Modern Plastics International*, February 1993)

IKV has process for polymer bone screws

Recently completed work in Germany has resulted in process technology that could make polymer surgical screws feasible for mending broken bones. The screws would degrade in the body once the break heals.

The Institute for Plastics Processing (IKV) in Aachen and Boehringer Ingelheim, located in Ingelheim, have developed technology to injection mould the screws. The team has overcome initial structural flaws, including a tendency for heads on the plastic screws to rip off.

Boehringer, which makes the polylactide resin for the screws, is setting up a 220-kN press in Ingelheim that will be used to demonstrate the technology to interested processors.

The resin used to make the screws is expensive—about $1800/kg. Shot weights for the parts are about 1.2 g. The system at IKV makes eight screws per cycle; a single screw weighs about 0.05 g.

IKV says that by placing the polylactide resin under pressure in the presence of carbon dioxide, the glass transition and processing temperatures can be reduced drastically. The amorphous resin, which turns to lactic acid in the body, can be processed at 32° C when in the presence of "supercritical" CO_2 at 74 bar. Normal processing temperatures for the resin are 130–240° C, and such high heats preclude the employment of many protein-based additives that the body can absorb.

The testing has been done in an autoclave, and the technology is still at the research stage. The process, which sinks viscosity by diffusing the supercritical CO_2 into the resin, can be used for all amorphous polymers. Currently under study are polylactide foams to treat burn victims. IKV is attempting to gauge the volume of CO_2 that seeps into the parts, which can determine how the part will change once pressure on the CO_2 is removed. (Source: *Popular Plastics & Packaging*, March 1994)

Bioactive glass granules to coat bone implants

Scientists in Turku, Finland, have developed bioactive glass granules that can fill the gaps between bone and living tissue. The glass can be used either to coat inert implants or as a bulk filler.

The non-reactivity of implants made of inert materials, such as titanium or alumina, can make bone bonding difficult and limit the success of the treatment. To overcome this problem, scientists at the Department of Prosthetics, the Institute of Dentistry, Turku University in Finland and the Department of Chemical Engineering at the Abo Akademi in Turku, have developed the implant material.

The granules made of glass in the system SiO_2-Na_2O-CaO-P_2O_5, can attach to living bone by chemical bonding by a sequence of reactions within the glass and at its surface. By altering the chemistry of the glass, it has proved possible both to increase the strength of the implants and to control the level of bioreactivity.

The bioactive glass granules have many uses. They can act as a filler to replace missing bone or bone which has become infected or cancerous. In addition, they are useful for repairing the damage caused by periodontal disease in which the membrane and bone around the teeth are gradually eaten away.

Where a load-bearing implant is needed, the glass can be used to coat metal implants. The Turku team are now working to improve the loading characteristics of the glass, so that metal implants will not be needed. For further information, contact: Dr. Antti Yli-Urpo, Institute of Dentistry, University of Turku, Lemminkaisenkatu 2, SF-20520, Turku, Finland; Tel.: +358-21-63381; Fax: +358-21-6338356. (Source: *Advanced Ceramics Report*, Oxford, June 1993)

Medical technology

Absorbable plastics are soon to spare many patients a second operation. Plastics have already won a place for themselves in the medical technology field. For a long time now, syringes, probes and catheters have been made of polymer materials. A variety of implants, ranging from artificial lenses to joints, are now made of plastic. Researchers in Aachen, Germany, are currently working on a new and promising variant of this material, absorbable plastic. This material involves polymers that will dissolve after a specific time inside the body. A process of this kind could save patients with broken bones from having to undergo a second operation to remove screws, pins or other linking elements from their limbs. At the moment, however, the material developed in Aachen is still only suitable for use on "unburdened bone", for example, in the skull, which includes sections of very thin bone material. The material is not yet strong enough for use in broken limbs. Some time in the future, however, fibre-reinforced polyester could change this. There is no need to worry about plastic waste inside the body—the absorbable material breaks down into lactic acid. (Source: *Deutschland*, 2 April 1994)

Polymer lipid membranes: production, properties and applications

The increasing use of the simulation method in the science of membranes, which traditionally employs model membranes—liposomes, monolayers on the water-gas surface, and "black" lipid membranes as well as biological membranes that are highly labile, thus limiting the selection of research methods, and reports on the high stability of polymer liposomes used, *inter alia*, to study the mechanical interaction of liposomes with the cells and fix enzymes in the lipid membranes, prompted a review of the preparation of polymer membranes from polymerizable lipids—the closest analogues of natural phospholipids—and using these membranes in simulating membrane-dependent biological processes. Various methods of initiating polymer reactions in lipid bilayers are considered, and the stability of polymer membranes from diacetylene-, dien-, styrene-, methacryloyl-, and thiolipids is analysed and compared. The issues of polymer membrane applications in simulating the intercellular recognition processes and examining phase transitions are addressed. In particular, the general approaches to producing polymer lipid membranes, the types of polymerizable phospholipids and the properties of polymer membrances, and biological process simulation using polymer membranes are examined in detail. Special attention is focused on protein incorporation in polymer membranes and polymer liposome interactions with the blood component cells (hemocompatible materials). (Source: *Biologicheskiye Membrany*, Vol. 10, No. 3, May/June 1993) (Abstract of article by V. V. Chupin, A.V. Anikin, G.A. Serebrennikova, Moscow Institute of Fine Chemical Engineering imeni M. V. Lomonosov; UDC 577.352)

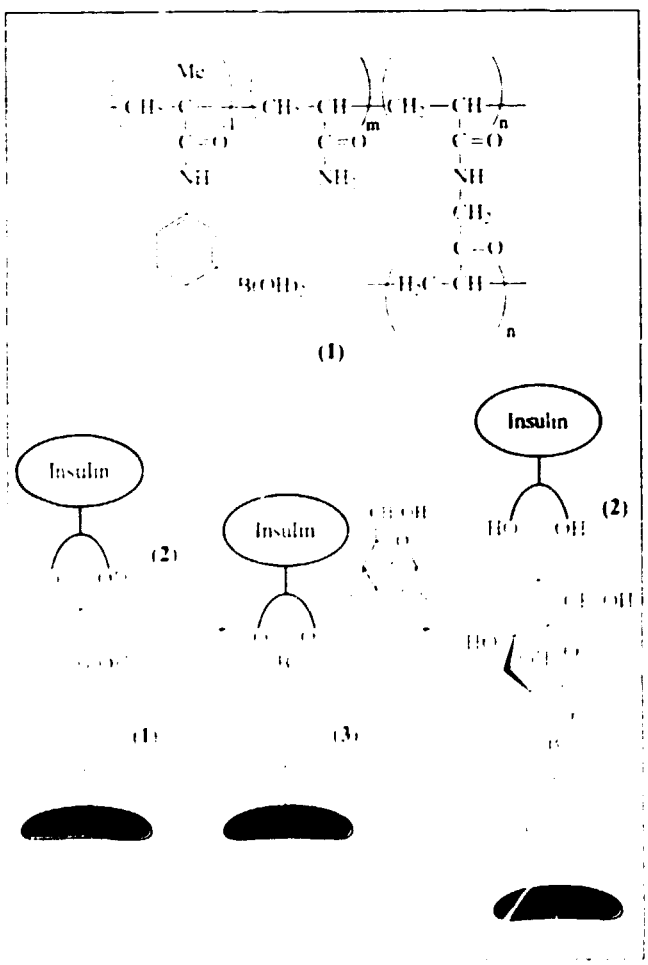
New polymer for surgery

Organoapatites are made by combining A Indomethycin (anti-inflammatory drug) + tyrosine (protein from sea mussels) + biocompatible polymers polyhydroxymethyl methacrylate + hydroxyapatite: they are connected by covalent bonds while keeping their individual chemical identities intact. The material is used to repair soft tissues like nerves or skin. The material is reliable for repairing damage to the human skeleton. (Source: *Chemistry & Industry*, No. 24, 20, December 1993)

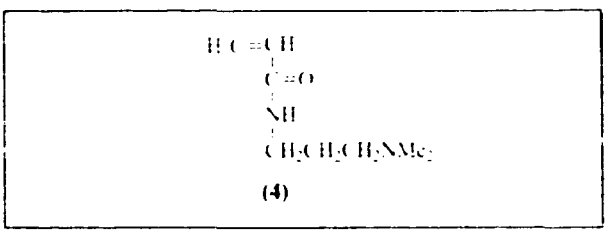
Glucose-responsive insulin-releasing polymer devices

Levels of blood sugar are mainly controlled by two hormones, insulin and glucagon, both secreted by the pancreas. Insulin depresses blood sugar levels, glucagon raises them. Insulin deficiency results in diabetes mellitus. In quite a number of cases, treatment of diabetes requires that the diabetic checks the glucose concentration in his or her blood and injects insulin before every meal to prevent undesirable excesses in the blood sugar level. Though still a long way from any clinical application stage, several groups have recently published their initial results on glucose-responsive insulin-releasing polymer devices. One example used the polymeric hydrogel (1) which was obtained by reverse phase suspension polymerization of a methacrylamidophenylboronic acid, acrylamide and a cross-linker. As a result of the binding ability of phenylboronic acids with hydroxylated molecules, polymer (1) has a high affinity to glucose and its derivatives. Hence, an insulin derivative (2) with a gluconic acid side chain can be bound onto the copolymer gel. The resulting polymer (3) was filled into a column for further elaboration. Upon washing the column alternately with buffer and 200 mg/dl glucose-buffer solutions, a quick response of insulin release, varying from 4 to 11 µg/ml, was observed at pH 8.5 and above. The mechanism of glucose-responsive insulin release from polymer (3) was attributed to competitive en gluconated insulin (2) and glucose (D. Shiino *et al.*, *Biomaterials*, 1994, 15, 121). An improved version of the copolymer used acrylamide (4) as an additional comonomer. The amino groups in the side chain of (4) raise the association constant of the copolymer with glucose and allowed insulin release under physiological pH conditions (*J. Controlled Release*, 1994, 28, 317).

A glucose-sensitive insulin-releasing protein device has been made of glucose oxidase linked to insulin by a disulphide bridge. To aid detection, the insulin was further esterified with a coumarin derivative which served as a fluorescent marker. Following the addition of aqueous glucose to a solution of the insulin-glucose oxidase hybrid (5), glucose was oxidized to gluconolactone. At the same time, the disulphide link was cleaved and the modified insulin was released. (D-J Chung *et al.*, *Bull. Chem. Soc. Jpn.*, 1994, 67, 1468).



(1)



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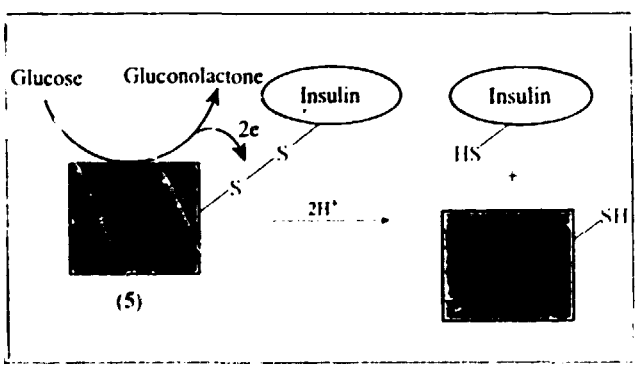
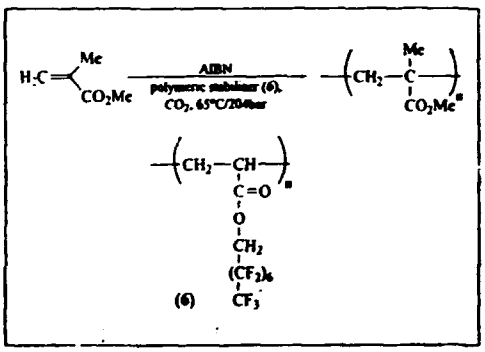


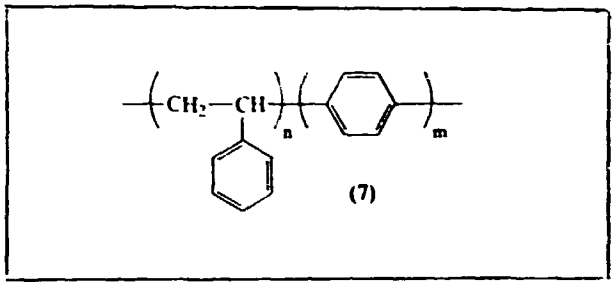
(5)

Reactions in supercritical carbon dioxide have become increasingly popular (G. Kaupp, *Angew. Chem. Int. Ed. Engl.*, 1994, 33, 1452). Polymerization in supercritical fluid-swollen polymers might provide a new route to polymer blends. While CO_2 is a poor solvent for most polymers, it swells them considerably. Diffusion rates in supercritical fluid-plasticized polymers are dramatically increased over non-swollen samples. After soaking polymers, such as poly(chlorotrifluoroethylene), polyethylene, nylon or poly(oxymethylene), in a mixture of supercritical carbon dioxide, styrene and azobis(isobutyronitrile) (AIBN) at 40° C and 103 bar for several hours, polymerization of styrene within the swollen substrates can be initiated by increasing the temperature to 80° C (J. J. Watkins and T. J. McCarthy, *Macromolecules*, 1994, 27, 4845).

J. M. DeSimone and co-workers have now accomplished the dispersion polymerization of methyl methacrylate in supercritical carbon dioxide (*Science*, 1994, 265, 356). Though methyl methacrylate is soluble in CO_2, poly(methyl methacrylate) is not. The trick is to add the CO_2-soluble surfactant (6). This ensures high molar masses for poly(methyl methacrylate), with M_n up to $3x10^5$ g/mol, and a relatively narrow size distribution for the polymer particles. After venting of the CO_2, the polymer is isolated as a free-flowing powder. Residual monomer and stabilizer can then conveniently be removed from the polymer using a supercritical fluid extraction process to give a highly purified product. This should be compared with conventional dispersion polymerizations in aqueous media, where the stabilizer is usually left in the polymer and the waste water is contaminated with leftover monomer and initiator.



Polymer chemists have long envied the zeolite community which had no problems in preparing porous materials of defined structure with a controlled distribution of cages and channels. This has now been achieved with the block copolymer (7). The right conditions were, however, crucial. When (7) was spread as a thin (10–30 μm thick) film from a CS_2 solution, the solvent had to be allowed to evaporate under a flow of moist air. A closer look at the structure of these films by means of scanning optical micrographs revealed a regular array of empty spherical cells, about 0.2–10 μm in diameter. This honeycomb morphology of a polystyrene-type polymer is quite remarkable as the size of the cells is at a scale two or three orders greater than the polymer molecules. The mechanism for their formation is still speculative. The authors suggest that rapid evaporation of CS_2 increases the superficial concentration of the polymer; simultaneously, the cooling of the solution leads to condensation of water. These factors provoke a gelation process and a phase separation, possibly around water droplets, which leave behind the porous structure after drying (B François *et al.*, *Nature*, 1994, 369, 387).



(Source: *Chemistry & Industry*, 3 October 1994. Article by Arno Kraft, University of Düsseldorf, Germany.)

4. APPLICATIONS

Novel materials in biomedical and environmental protection applications

Today improved qualities of food supplies and medical care have prolonged life, thus generating an increasing demand for "human spare parts" and medical supplies. Polymers are key components in medical packaging, e.g., blood bags, disposable syringes, gloves, tubes, dental fillings, implants, heart valves, blood vessels, artificial skin, artificial kidneys as well as diagnostics. The 1986 market for 800,000 tons is expected to exceed 1.5 million tons in the year 2000. PVC consumption amounts to more than 200,000 tons. This is a good indication that PVC matches the tough medical product requirements. For political reasons, the expected increase in PVC consumption may decline. Some of the key polymer applications in packaging, structural human spare parts and functional polymer systems for diagnostics are highlighted below.

Most of the engineering resin product requirements encountered in automotive applications are also highly desirable in structural medical applications, i.e., property combinations of high stiffness, strength, toughness, abrasion resistance, dimensional stability, durability and chemical resistance. Many materials that have survived in space for several years are completely destroyed within a few months in the presence of normal human body fluids. Upon degradation, no toxic fragments should be formed. Also, all materials should be biocompatible to prevent undesirable reactions with blood, causing blood clotting. Ultra-high molecular weight polyethylene, known to exhibit unusually high abrasion resistance, has met all these requirements and is being used successfully as a component of artificial hips. In recent advances, high pressure has been applied to enhance polyethylene crystallinity by orientation of the polyethylene chains. This feature is shown by atomic force microscopy for extruded polyethylene with parallel zig-zag chains. Surface modification with plasma-induced hydroxyapatite ceramic deposition substantially enhances biocompatibility to improve adhesion between polyethylene and bone tissue. Highly oriented gel-spun polyethylene fibres are used as reinforcing fibres, e.g., in disposable gloves. As a result of recent advances in materials sciences, surface treatment and processing, including computer-assisted design (CAD) to custom-fit spare parts, the average life time of artificial hips improved substantially in recent years.

In medical applications, novel generations of resorbable plastics are being developed. Polyactides, known for years

as resorbable sutures, are now extruded to form bio-resorbable plates and nails, used in bone surgery. Resorption rates and bulk property are being controlled by polymer microstructures, in particular the sequence distribution of the asymmetric carbon atoms. While the poly-(D,L-lactide) is amorphous, flexible and readily resorbed within a few weeks or months, the corresponding poly-(L-lactide) is crystalline, rigid and degrades at a much lower rate over some years. Using stereoblock copolymers containing amorphous and crystalline segments or blending the different stereosiomers has led to new classes of materials with controlled resorption. At present, several groups are evaluating fibre reinforcement in order to enhance the stiffness. In a number of cases, the biocompatible fibre components, e.g., bioglass fibre or polylactide fibres have adversely affected biocompatibility of biocomposites.

In medical packaging, we find an increasing amount of the typical high performance thermoplastics such as polysulphones, polyetherimides, polyimides and polyetherketones. As a result of the high temperature and chemical resistance such containers can be sterilized and reused without losing their dimensional stabilities. In contrast to many typical engineering applications, the biomedical applications are rather attractive with respect to the price-performance ratio.

In addition to packaging and structural applications, diagnostics represents a very attractive market for functional polymer systems. The new glucometer system developed by Bayer to measure blood glucose concentration is vital in the treatment of diabetes. This computerized test is based on films coated with a polyurethane membrane. Glucose is oxidized in the presence of glucodeoxidase to yield gluconolactone and hydrogen peroxide. Subsequently, hydrogen peroxide oxidizes tetramethylbenzidine to form a dye, which is used as a probe for the quantitative determination of glucose concentration.

This is a good illustration of how polymers, as inert structural parts and packaging, as well as biofunctional membrane, are combined to produce highly sophisticated medical products. As human beings grow older, the market for innovative biomedical materials and functional systems is likely to continue its rapid growth.

Polymeric materials of controlled porosity are key components of separation and membrane technologies being used in a wide range of applications, e.g. water desalination, food processing, filtration, gas separation, biotechnology and dialysis. Microporous polymer and polymers with tailor-made pore architecture give excellent flux and selectivities. Today artificial kidneys based upon semi-permeable membrane materials are being used extensively to purify blood by removing urea and ureic acid. Biocompatible polyethercarbonate block copolymers containing polyethylenoxide segments are the materials of choice for dialysis membrane applications. (Excerpt from *Popular Plastics & Packaging*, March 1994)

Small beads make big medicine

Microscopic monosized plastic beads have revolutionized the cleansing of bone marrow and opened new paths to the treatment of several severe forms of cancer.

In 1979 Professor John Ugelstad at the Norwegian Institute of Technology (NTH) in Trondheim discovered the first batch of monosized polymer particles ever made, but had no idea of what to do with them. He did not know that these beads, when magnetized, would become a vital means of separating cells in bone marrow ten to fifteen years later, thus providing medical scientists with a tool now widely used with good results in tissue typing for transplants, treating several forms of cancer, AIDS research, fighting plagues and syphilis, and in pregnancy tests. The beads are also used in microbiology to detect and analyse bacteria and viruses and in molecular biology. To date, the most important application of the monodisperse (i.e. single-sized) beads has been in chromatography of biological compounds, e.g. in blood and urine. The liquid is forced through a column filled with porous monodisperse beads, i.e. proteins are separated. The monodisperse character of the particles results in a fast and efficient separation never achieved before. As with so many things in basic research it was an academic challenge that set us going, explains Professor Ugelstad.

Scientifically speaking, the challenge was an old one. Since the early 1950s polymer scientists all over the world had been trying to make microscopic monosized polymer beads. However, it had long been universally accepted that it was unlikely that anyone could make such beads, which may be as small as one thousandth of a millimetre in diameter, on earth. It was thought that gravitation would affect the formation of the beads and make production impossible. So it was assumed that the only way they could be produced was under conditions of weightlessness, that is, in space.

Indeed, American scientists and NASA had plans for experimental production of microscopic monosized particles in space in the early 1970s, even though the manufacturing costs would have been enormous. To manufacture a single gram, or about 15 billion beads, would have cost some $30,000. There were also practical problems which, for one thing, made it possible to manufacture only one kind and one size of beads.

The initial Norwegian breakthrough in 1979 was followed by another success three years later. Further research had enabled the beads to be magnetized. This opened up enormous opportunities in biomedicine.

The beads can also be coated with specific antibodies, or "glue", which makes them selective to a specific antigen. They can therefore find and bind themselves selectively to specific types of cells, including malignant cells, or to parts of cells, viruses, bacteria, specific proteins or other components, which for various reasons have to be isolated from other biological material. And because each tiny ball contains magnetic iron oxide the particles can be separated from body fluids with the aid of a magnet, together with the cell or component to which they have become bonded.

As it turned out, these qualities make the beads very useful in current experimental treatments of some forms of cancer where the tumour has spread to the bone marrow. These include cancer of the lymph, cancer of the breast, some forms of lung cancer and some forms of leukaemia.

The first to realize the potential of the magnetic beads in the treatment of cancer was Dr. John T. Kemshead, now Head of Research at the Imperial Cancer Research Fund's Paediatric and Neuro-Oncology Group at Frenchay Hospital in Bristol, England.

"The problem with cancer is that we do not yet know if we really manage to isolate and kill all the tumour cells in a person's body during treatment. But thanks to Professor Ugelstad's beads, we can at least remove all the

tumour cells that we find in the bone marrow", says Dr. Kemshead.

The magnetic beads were used for the first time to treat a patient with neuroblastoma in 1983. A that time treatments for quite a number of different types of childhood cancers had made a big step forward, but not, unfortunately, those for neuroblastoma. The usual treatment for this particular type of cancer included high doses of drugs and radiation, in fact, doses so great that as well as eliminating the tumour, they destroyed all the patient's bone marrow.

Because the patient's bone marrow would be destroyed, the doctors used to remove some of it before treatment.

After therapy was complete it would be reinfused into the patient. However, the problem was that there might still be cancer cells in the reinfused and untreated bone marrow since this had not been exposed to medication and radiation.

"In many ways, the treatment is the same today, except for the use of magnetic beads. By introducing them as part of the treatment we were able to remove cancerous cells from the bone marrow that had been removed from the patient and reinfuse 'clean' bone marrow" says Dr. Kemshead. He has now treated more than 200 children with this particular form of bone marrow manipulation with, as he puts it, "Extremely encouraging results".

The results of an experimental treatment of cancer of the lymph that started at the Norwegian Radium Hospital in Oslo in 1987 are also encouraging. Some 60 selected patients with this dreaded disease have undergone treatment very much like the one Dr. Kemshead is using on his neuro-blastoma patients. Of the 60 Norwegian patients, 35 are without cancer symptoms today.

"These results are very promising. But we cannot, at least not yet, say for certain that the results are due to the beads alone. Only selected patients have undergone treatment, and there have been general improvements in bone marrow transplants during the last years", says Chief Physician Dr. Gunnar Kvalheim at the Norwegian Radium Hospital's Department of Tumour Biology.

"It could therefore be a combination of factors that have led to today's promising results," he said, adding that some of the patients have been under observation for too short a period to say anything quite certain about how the results of this method of treating cancer patients will turn out in the long run.

Using magnetic monosized polymer beads is not the only way of cleansing bone marrow. Indeed, quite a number of methods are being used today. "But no other method is as thorough as the beads," agree Dr. Kemshead and Dr. Kvalheim.

Their thoroughness also makes the beads quite versatile in the search for a universal treatment of several forms of cancer that have spread to the bone marrow.

"One way to search for such a cure is to reverse today's use of the magnetic beads. Instead of looking for an antibody that will bind the beads to specific tumour cells, which will then be removed from the bone marrow and killed, we look for an antibody that will bind the beads to healthy, not yet mature cells. That way we can 'pull out' the healthy cells and kill the rest, including all the tumour cells", says Dr. Erlend Smeland, acting Head of Research at the Radium Hospital's Immunology Laboratory.

This reversed process has already been successfully carried out in the laboratory, but Dr. Smeland says he will need at least two more years of laboratory testing before it can be carried out clinically. However, a similar method of isolating healthy cells is currently being tried out on selected cancer patients in a hospital in Seattle, USA.

The ability to attach themselves to specific cells as long as they are coated with the right antibody or "glue" make the magnetic beads versatile in a number of other fields of microbiology. In conjunction with AIDS research for instance, one can extract the specific cells one wants to have a closer look at. The beads are therefore used both by European and American AIDS researchers alike. And because using the beads is both quick and simple, one is now able to diagnose HIV much quicker than before.

The same is true with bacteria. By using magnetic beads coated with the right antibodies, contagious diseases can be diagnosed sooner, and subsequent measures can be taken to stop them from spreading. Cholera is one example for which researchers at the American Health Department's Centers for Disease Control in Atlanta, Georgia, used the beads to monitor the spread of cholera through shellfish and crabs to the Gulf of Mexico during the cholera epidemic in South America that peaked in 1992. The researchers' findings resulted in a temporary ban on oyster fishing from the seabed off Mobile, Alabama.

The magnetic beads are also being used in conjunction with transplants, for example, to determine whether a donor's kidney will be accepted by the body of the receiver. In Scandinavia all tissue-typing laboratories use magnetic beads as part of their determination process, compared to some 70 per cent of laboratories in the rest of Europe. In Scandinavia the survival rate of transplanted organs such as kidneys has increased by some 15 per cent since the introduction of the beads in tissue typing.

There is also a business side to the microscopic beads. In Norway, Dynal, a limited liability company, was founded to market magnetic beads for biomedicine. The company's turnover 1992 was more than NOK 60 million.

Dynal has established offices and sales teams in the UK, Germany, France and Japan. The company is also represented in the USA where it collaborates with Baxter, the world's largest producer of medical equipment related to blood products.

The beads themselves are being produced by another Norwegian company, Dyno Particles, which like Dynal was founded as a direct result of Professor Ugelstad's invention. Both Dynal and Dyno Particles are part of the large Norwegian consolidated group Dyno, which is primarily concerned with polymer products. (Source: *GEMINI*, Norway 1993)

Therapeutic applications

A significant problem in the radiation treatment of cancer is the serious side-effects. Localization of radiation at the site of the tumour decreases the radiation dosage required to kill the cancer cells and therapy minimizes such side-effects. An innovative approach to the localized delivery of radioactive yttrium-90 to treat liver cancer has been developed at the University of Missouri-Rolla using glass microspheres.

In this approach, a yttria-aluminosilicate glass, containing ^{89}Y is made in the form of 25-mm microspheres. The microspheres are first bombarded by neutrons, which

creates ^{90}Y, a radioactive isotope with a short half-life and short-range emission. The radiated microspheres are then injected through a catheter placed in an artery and the blood stream carries them to the liver where a high proportion goes to the cancerous part. Clinical trials so far look promising. The glass-microsphere radiation delivery vehicle can also be modified with different radioactive isotopes to achieve various ranges and is being tested preclinically for treatment of kidney cancer and arthritis.

Still another therapeutic application of bioceramics is delivery of various steroid hormones from aluminium calcium phosphate porous ceramics. The advantage of this method is sustained delivery of a potentially toxic substance over long periods of time, again inhibiting systemic side-effects caused by large dosages. (Source: *American Ceramic Society Bulletin*, Vol. 72, No. 4, April 1993)

Shape memory polymer has biomedical applications

A shape memory polymer (SMP) that can change its shape and hardness, and on cue return to its original state has reportedly been developed by Mitsubishi Heavy Industries Ltd., Japan. It is said to allow these transformations at user-friendly, biocompatible temperatures—even body temperature. SMP also has exceptional damping characteristics, and in a thin-film form has a vapour permeability that changes with temperature. These changes are virtually instantaneous, and can be programmed to occur under specified conditions.

Applications being considered include a catheter that becomes soft inside the body but remains stiff externally for accurate manipulation, as well as orthopaedic and rehabilitation devices that can be customized to fit the individual. Customization is also the key for sports applications, such as a child's bicycle helmet that is tailored to the head after purchase, and may be remoulded as the child grows.

SMP is available in pellet, solution, or liquid form, and can be easily compounded. It can be formed by extrusion, injection moulding, coating, or casting processes in conventional manufacturing environments. Semifinished products are also available, including foam and microbeads. Independent bio-compatibility analysis has been conducted, including USP Class VI and cytotoxicity testing.

For more information: Richard F. Gordon, Memry Corp., 57 Commerce Drive, Brookfield, CT 06804; Tel.: (203)740-7311; Fax: (203)775-2359. (Source: *Advanced Materials & Processes*, March 1994)

Biosensors

Scientists at Dublin City University have been developing biosensors to study the release of neurotransmitters during different types of behaviour. Robert O'Neill, whose team is working on a glutamate sensor, became interested in neurochemistry while at the physiology department in Oxford, and since then he has been developing electrochemical technology to investigate processes in the brain.

Dr. O'Neill is particularly interested in using biosensors to investigate what happens when the chemical message systems go wrong. One example of this is in epilepsy, where an over-release of glutamate leads to convulsions and brain damage. Glutamate is also associated with the "Chinese Food Syndrome" in which headaches may be caused by vast amounts of glutamate crossing the blood-brain barrier.

Micro electrode sensors have been used to measure vitamin C concentrations in the brain, and Dr. O'Neill said that there is evidence that fluctuations in this vitamin reflect changes in glutamate release. "One needs to have as much evidence as possible that vitamin C is a good reflection of glutamate release and we hope to measure vitamin C and glutamate release simultaneously", he said. "Not only is glutamate a fast acting substance, it is the most widely used excitory chemical message in the brain", he added.

In the long term, Dr. O'Neill's team expects to be in a position to study the release of glutamate in stress, anxiety, depression etc., and they could be in a position to understand how the drugs used to treat these conditions interact with the brain.

In the shorter term the team is working on the development of a glutamate sensor—an 8 micron carbon fibre which is to have an enzyme, glutamate oxidase, trapped on the sensor tip. The sensor, protected by a polymer film, will be implanted in specific regions of the brain.

Other laboratories throughout the world are also attempting to develop a glutamate sensor, but the approach of the team is considered unique. Dr. O'Neill commented that the basic research awards from Forbairt had provided a great incentive for post-graduates working on the project. "It is a very encouraging aspect of the Irish education system", he said, "and a scheme we need to keep." (Source: *Lab-Tech*, A quarterly supplement to *Technology Ireland*, Vol. 2, No. 1, April 1994)

Some biosensor components and detection modes

Biological element	Transducer	Measurement
Enzymes	Solid electrodes	Amperometry
Micro-organisms	Ion selective electrodes	
Whole cells (animal and vegetable)	Gas-sensing electrodes Field effect transistors	Potentiometry
Antibodies	Photodiode Photomultiplier (and fibre optic)	Optical
Antigens	Thermistor Piezoelectric crystal	Calorimetry Mass change

(Source: *Lab-Tech*, a quarterly supplement to *Technology Ireland*, Vol. 2, No. 1, April 1994)

Bioceramics: from concept to clinic

Ceramic materials are becoming a natural choice for replacing bone and teeth, as well as for other applications. Although many materials are already used in the medical and dental communities, their long-term reliability still remains a question.

The discovery of fire, and consequently the discovery that it would transform clay into ceramic pottery, helped to drastically improve the quality and length of human life. Within the last four decades another revolution has occurred in the use of ceramics to improve the quality of life. This revolution is the innovative use of specially designed ceramics for the repair and reconstruction of diseased or damaged parts of the body, otherwise known as bioceramics.

Bioceramics come in a wide range of materials: single crystal, polycrystalline, glass, glass-ceramics and composites. Conventional ceramics and glasses have been used for a long time in the health-care industry for eye glasses, diagnostic instruments, chemical ware, thermometers, tissue culture flasks, and fibre optics for endoscopy. Insoluble porous glasses have been used as carriers for enzymes, antibodies and antigens since they have several advantages. These advantages include: resistance to microbial attack, pH changes and solvent conditions; resistance to temperature; and resistance to packing under high pressure, which is required for highflow. Ceramics are also widely used in dentistry as restorative materials, gold porcelain crowns, glass-filled cements, and dentures, among others.

Although dozens of ceramic compositions have been tested as implants to repair various parts of the body, few have achieved human clinical application. It is now known that clinical success requires the simultaneous achievement of a stable interface with connective tissue and a match of the mechanical behaviour of the implant with the tissue to be replaced. Researchers continue to make progress towards reaching this goal.

Type of tissue attachment

The mechanism of tissue attachment is directly related to the type of tissue response at the implant interface. No material implanted in living tissues is completely inert; all materials elicit some type of response. The four types of response allow different means of achieving attachment to the musculo-skeletal system. These responses depend on the type of material.

If the material is toxic, the surrounding tissue dies. On the other hand, if the material is non-toxic and biologically inactive (nearly inert), a fibrous tissue of variable thickness occurs between the implant and the tissue. Because this tissue is not chemically or biologically bonded, it can easily move, leading to loosening of the implant and eventual failure.

If the material is inert and porous, an interfacial bond forms because of ingrowth of tissue into pores on the surface or throughout the implant. The increased interfacial area between the implant and the tissues results in an increased resistance to movement of the device in the tissue. Therefore, this implant can withstand more stress than the inert dense type.

However, the pores in this type of implant must be greater than 100 to 150 μm in diameter to provide sufficient blood supply to the ingrown tissue. If the blood supply is cut off, the implant can become unstable and eventually fail. In addition, porosity weakens the material; thus, porous coatings applied to metal implants have been a partial solution to this problem.

If the material is non-toxic and dissolves, the surrounding tissue replaces it. Known as resorbable bio-materials, these are designed to degrade gradually over a period of time and be replaced by natural tissue. This leads to a very thin or non-existent interfacial thickness. Such materials are based on the same principles of repair by the body which have evolved over millions of years. However, it is still difficult to match the resorption rates to the repair rates of body tissues, as well as to maintain the strength and stability of the interface until the natural tissue replaces the bioceramic.

If the material is nontoxic and biologically active or bioactive, an interfacial bond forms between the tissues and the implant. There are now a large number of bioactive materials with a wide range of rates of bonding and thickness of interfacial bonding layers. They include glasses, glass-ceramics, hydroxyapatite, and composites. Although all of these materials form an interfacial bond, the rate of bonding, the strength of the bond, the mechanism of bonding, and the thickness of the bonding zone differ for the various materials.

Nearly inert crystalline bioceramics

High-density, high-purity (>99.5 per cent) alumina was the first bioceramic widely used clinically. It is used in load-bearing hip prostheses and dental implants because of its combination of excellent corrosion resistance, good biocompatibility, high wear resistance, and high strength. Although some dental implants are single-crystal sapphire, most alumina devices are very fine grained polycrystalline α-Al_2O_3. A very small amount of magnesia (>0.5%) is used as a sintering aid and to limit grain growth during sintering.

The success of these materials as implants depends on their properties of strength, fatigue resistance and fracture toughness. These properties are a function of grain size and purity, and alumina with an average grain size of <4μm and >99.7 per cent purity displaying the optimum properties. Careful control of grain size during sintering is, therefore, critical. In addition, alumina implants must be produced at the highest possible standards of quality assurance, especially if they are to be used in patients over 50 years of age.

Alumina has been used in orthopaedic surgery for nearly 20 years, motivated largely but its acceptance by the body and minimal scar formation (which permits cementless fixation of prostheses) and in its exceptionally low coefficients of friction and wear rates. However, the latter are only achieved when the grains are very small and have a very narrow size distribution.

Alumina on alumina load-bearing wearing surfaces, such as in hip prostheses, must have a very high degree of sphericity produced by grinding and polishing the two mating surfaces together. The alumina ball and socket in a hip prosthesis are polished together and used as a pair. Wear of such a device is ten times lower than that of metal and polyethylene hip sockets.

Such low wear rates have led to widespread use in Europe of alumina noncemented cups press-fitted into the socket of the hip. The cups are stabilized by bone growth into grooves or around pegs. The mating femoral ball surface is also of alumina, which is bonded to a metallic stem. Though long-term results in general have been excellent, it is essential that the age of the patient, nature of the disease of the joint, and biomechanics of the repair be considered carefully before any prosthesis is used.

In the USA, the primary use of alumina is for the ball of the hip joint, with the socket component being made of ultra-high molecular weight polyethylene (PE). Other clinical applications of alumina implants include knee prostheses, bone screws, jaw bone reconstruction, middle ear bone substitutes, corneal replacements, segmental bone replacements, and blade, screw, or post-type dental implants.

Porous ceramics

The potential advantage offered by a porous ceramic is its inertness combined with the mechanical stability of the highly convoluted interface developed when bone grows into the pores of the ceramic. Mechanical requirements of prostheses, however, severely restrict the use of low-strength porous ceramics to low-load or non-loadbearing applications. Studies show that, when load bearing is not a primary requirement, nearly inert porous ceramics can provide a functional implant.

When pore sizes exceed 100 μm, bone will grow within the interconnecting pore channels near the surface and maintain its blood supply and long-term health. In this manner the implant serves as a structural bridge and model or scaffold for bone formation. The microstructures of certain marine corals make an almost ideal casting material for obtaining structures with highly controlled pore sizes. Several types of coral are promising, with pore-size ranges of 140-160 μm and 200-1000 μm. After the coral shape is machined, it is fired to drive off CO_2 from the limestone, forming a porous structure of calcia, or transformed directly into hydroxyapatite ceramic.

Porous ceramic surfaces can also be prepared by mixing soluble metal or salt particles into the surface. The pore size and structure are determined by the size and shape of the soluble particles that are subsequently removed with a suitable etchant. The porous surface layer produced by this technique is an integral part of the underlying dense ceramic phase. Materials such as alumina may also be made porous by using a suitable foaming agent that evolves gases during heating.

Porous materials are weaker than the equivalent bulk form. As the porosity increases, the strength of the material decreases rapidly. Much surface area is also exposed, so that the effects of the environment on decreasing the strength become much more important than for dense, non-porous materials. Permeation of certain body fluids into the micropores of seemingly dense alumina has been shown to result in marked reductions in strength.

Bioactive glasses and glass-ceramics

Certain compositions of glasses, ceramics, glass-ceramics and composites have been shown to bond to bone. These materials are called bioactive ceramics. Some even more specialized compositions of bioactive glasses will bond to soft tissues as well as bone. A common characteristic of such bioactive materials is a modification of the surface that occurs upon implantation. The surface forms a biologically active hydroxycarbonate apatite (HCA) layer which provides the bonding interface with tissues. The HCA phase that forms on bioactive implants has the same chemical structure as the mineral phase in bone and is therefore responsible for interfacial bonding.

This bonding results in an interface that resists substantial mechanical forces. In many cases the interfacial strength of adhesion is equal to or greater than the cohesive strength of the implant material or the tissue bonded to the bioactive implant. Bonding to bone was first demonstrated for a range of bioactive glasses which contained specific amounts of SiO_2, Na_2O, CaO, and P_2O_5. These glasses contained less than 60 mol% SiO_2, high contents of Na_2O and CaO, and had a high CaO/P_2O_5 ratio. Such a composition produced a surface that was highly reactive when exposed to an aqueous medium.

Many bioactive silica glasses are based upon the formula called 45S5, which signifies 45 wt% SiO_2, S as the network former, and a 5 to 1 molar ratio of Ca to P. Glasses with substantially lower molar ratios of Ca to P (in the form of CaO and P_2O_5) do not bond to bone. 45S5 glass implants have been used successfully for replacement of ear bones and maintenance of the jawbone for denture wearers for up to eight years, with nearly a 90 per cent retention rate. This glass is also used for the restoration of the bone next to teeth that might otherwise be lost because of gum disease. Other research has shown that a range of low-alkali (0 to 5 wt%) bioactive silica glass-ceramics also bond to bone. Known as Ceravital, this composition has been successfully used for 10 years as implants in middle-ear surgery to replace bone damaged by chronic infection.

Several other compositions have been developed that are bioactive. Researchers in Japan have developed a two-phase silica-phosphate glass-ceramic (composed of apatite ($Ca_{10}(PO_4)_6(OH,F_2)$, wollastonite ($CaO.SiO_2$) crystals, and a residual glassy matrix). Known as A/W glass-ceramic, this material has been successful in hundreds of patients for replacing part of the pelvic bone and in vertebral surgery. A German university has developed an easy-to-machine silica-phosphate glass-ceramic containing phlogopite (a type of mica) and apatite crystals. Additional compositions of bioactive glasses have been developed in Finland for use in repair of the jawbone and cranium.

The ability of the material to bond to bone is dependent on the composition, although substitutions in the 45S5 formula of 5-15 wt% B_2O_3 for SiO_2 or 12.5 wt% CaF_2 for CaO (used for converting the material to a glass-ceramic) do not affect the bonding ability. However, other materials will: for example, the addition of as little as 3 wt% Al_2O_3 does prevent bonding. Small additions of Al_2O_3, Ta_2O_5, TiO_2, Sb_2O_3, or ZrO_2 were found to inhibit bonding in Ceravital compositions. Similarly, Al_2O_3 and Ti_2O_2 additions were found to inhibit bone bonding for the A/W glass-ceramic.

Consequently, it has been concluded that bioactivity occurs only within certain compositional limits and very specific ratios of oxides in the Na_2O-K_2O-MgO-P_2O_5-SiO_2 systems; however the extent of these compositional limits and the reasons for these limits are still not well understood. However, it is now known that for a bond with tissues to occur, a layer of biologically active HCA must form. The bond will not form if the rate of HCA formation is too slow.

Calcium phosphate ceramics

Calcium phosphate-based bioceramics have been in use in medicine and dentistry for nearly 20 years. Applications include dental implants, skin treatments, gum treatment, jawbone reconstruction, orthopaedics, facial surgery, ear, nose and throat repair, and spinal surgery. Different phases of calcium phosphate ceramics are used depending upon whether a resorbable or bioactive material is desired. These include dicalcium phosphate ($CaHPO_4$) and hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$(HA)).

The mechanical behaviour of calcium phosphate ceramics strongly influence their application as implants. Tensile and compressive strength and fatigue resistance depend on the total volume of porosity. Because HA implant have low reliability under tensile load, such calcium phosphate bioceramics can only be used as powders, or as small, unloaded implants, as in the middle ear, dental implants with reinforcing metal posts, coatings on metal implants, low-loaded porous implants where bone

growth acts as a reinforcing phase and as the bioactive phase in a composite.

Composites and coatings

One of the primary restrictions on clinical use of bioceramics is the uncertain lifetime under the complex stress states, slow crack growth and cyclic fatigue that arise in many clinical applications. Two solutions to these limitations are use of bioactive ceramics as coatings or in composites. Much of the rapid growth in the field of bioactive ceramics is due to development of various composite and coating systems.

Composites have been composed of plastic, carbon, glass, or ceramic matrices reinforced with various types of fibres: including carbon, SiC, stainless steel, HA, phosphate glass and ZrO_2. In most cases the goal is to increase flexural strength and strain to failure and decrease elastic modulus. The strongest composite achieved to date is a A/W glass-ceramic containing a dispersion of tetragonal zirconia, which has a bend strength and fracture toughness of 703 MPa and 4 $MPa.m^{1/2}$ respectively.

A bioceramic coating, which has reached a significant level of clinical application, is the use of HA as a coating on porous metal surfaces for fixation of orthopaedic prostheses. This approach combines biological and bioactive fixation. Though a wide range of methods have been used to apply the coating, plasma spray coating is usually preferred. Such a coating enhances the early-stage interfacial bond strength of implants; however, the long-term durability of these coatings is still being debated.

Towards standardization

Bioceramics has evolved to become an integral and vital segment of today's modern health-care delivery system. The full potential is only beginning to be recognized. In future years, the composition, microstructure and chemistry of various types of bioceramics will be tailored to match the specific biological and metabolic requirements of tissues or disease states. This "molecular-based pharmaceutical" approach to the design of bioceramics should couple with the growth of genetic engineering, sensor technology, and information processing, resulting in a range of products and applications not even imagined at present, but potentially beneficial to millions of people annually.

However, at present there is a critical need for standard test methods to determine the long-term lifetime performance of bioceramics under real conditions. Too many materials are introduced into clinical use without proof tests or lifetime prediction tests. Standards do not currently exist for bioactive ceramics or coatings, although the American Society for Testing and Materials has a subcommittee involved with such materials, with the goal of achieving such standards.

Standardization of test methods also needs to be established. At present, there is no way to compare interfacial bonding strength data for the various materials. Likewise, there is no basis to compare fatigue life for any of these materials or establishing the relative importance of grain-boundary attack or slow crack growth under standardized conditions. These deficiencies must be corrected within this decade because there is a rapidly growing number of failures of load-bearing metallic prostheses, which requires traumatic and expensive surgery. Though bioceramics offer one of the few alternatives for solving this problem, their long-term reliability must be proved before clinical use is expanded.

Table 1. Classification of Bioceramics

Type of bioceramic	Type of fixation	Description of attachment	Materials
Nearly inert	Morphological	Bone grows into surface irregularities by cementing the device, or by press fitting into a defect	Single crystal and polycrystalline alumina
Porous ingrowth	Biological	Bone ingrowth occurs, which mechanically attaches the bone to the material	Porous polycrystalline alumina, hydroxyapatite-coated metals
Surface reactive	Bioactive	Attaches directly by chemical bonding with the bone	Bioactive glasses or glass-ceramics, hydroxyapatite
Resorbable	Resorbable	Ceramics are slowly replaced by bone	Calcium sulphate, tricalcium phosphate, calcium phosphate salts

Figure 1. Comparison of interfacial thickness of reaction layer of bioactive implants or fibrous tissue of inactive bioceramics in bone

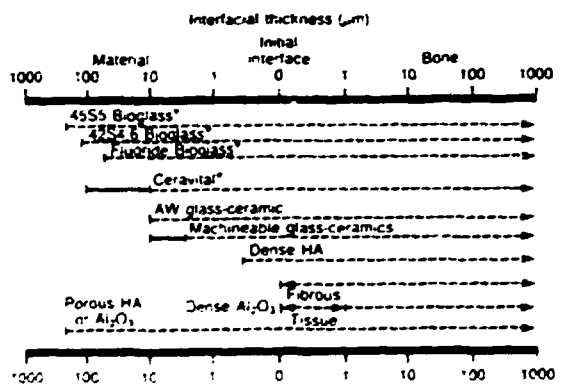
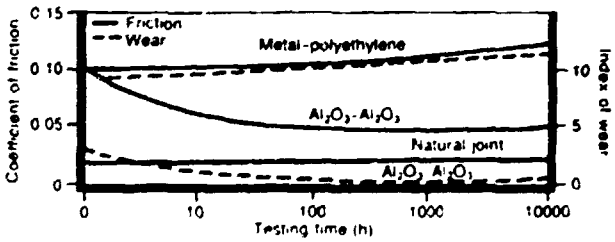


Figure 2. Time dependence of (-) coefficient of friction and (---) index of wear of alumina—alumina versus metal—PE hip joint (*in vitro* testing)



(Source: *American Ceramic Society Bulletin*, Vol. 72, No. 4, April 1993; Article written by Larry L. Hench, Department of Materials Science and Engineering, University of Florida, Gainesville, Florida 32611)

Proceedings of the National Science Council, ROC
Part B: Life Sciences
Vol. 18, No. 2, 1994, pp. 58-63

(Scientific Note)

The Use of Collagen Polymer Tube and Fibrin Clot in Peripheral Nerve Repair

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(Received 20 September 1993;
Accepted 14 February 1994)

ABSTRACT

Following extensive or multiple nerve injury, repair by nerve graft is the treatment of choice. In recent years, nerve repair using tubes made of synthetic material has yielded satisfactory results in experimental animals. Previously we have demonstrated that fibrin clot formed within an impermeable silicone tube promoted nerve regeneration. In the present study, we evaluated the applicability of a nerve graft fabricated out of autologous collagen and agarose. The copolymer collagen tube, 1 cm long and filled with autologous fibrin clot was implanted between transected rat right sciatic nerve and the left sciatic nerve was similarly transected and repaired with silicone tube. After one, two, and four months the regenerated nerves were removed and processed for light microscopic and morphometric analysis. We demonstrated that both types of tubes supported extensive nerve regeneration across the gap to reach the distal segment. The collagen tubes provoked a slow foreign body response with infiltration by macrophages and foreign body giant cells which became abated after two months. After four months, the nerve regenerate was encapsulated and separated from the collagen tube by a fluid exudate. The number of myelinated axons at midpoint in the nerve regenerate in the silicone tube was 9117 ± 282 while that in the collagen tube was 8589 ± 137. This preliminary study has demonstrated that collagen polymer tube may have potential use in peripheral nerve repair.

Key Words: *nerve graft, collagen, nerve regeneration, biomaterial*

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Injury to the peripheral nerve initiates a potent regenerative process which may result in significant restoration of motor and sensory functions (Cajal, 1928; Lie, 1981; Varon *et al.*, 1981). It has been shown that neurotrophic factors including nerve growth factor (NGF) produced by Schwann cells in the distal segment play a major role in the promotion of peripheral nerve regeneration (Liu *et al.*, 1978; Lundborg *et al.*, 1982; Politis *et al.*, 1982; Heumann *et al.*, 1987; Scarvelli, 1984). Consequently, the primary objective of surgical intervention is to restore the continuity between the proximal and distal stumps and to direct the regenerating axons into the distal segment.

Primary anastomosis using epineurial sutures usually yields satisfactory results, except when a gap is present between the ends of severed nerves due to extensive damage. For decades, entubation repair using autologous nerve or vein grafts has yielded good results (Sunderland, 1991). In recent experimental studies, tubes composed of various types of synthetic materials and with various degrees of permeability have been evaluated. Nerve repair using an impermeable silicone tube has yielded satisfactory results as it allows growth of axons and non-neural cells into a fibrin clot which forms in the tube during the first two days (Aebischer *et al.*, 1988; Knoops *et al.*, 1990; Liu, 1992). Others maintained that porous or semipermeable tubes are superior to the impermeable tubes as they allow the entrance of growth factors and nutrients from the surrounding tissues into the tubes (Jeng *et al.*, 1987). The questions of biocompatability and degradation of the implants are also matters of concern. A silicone tube is relatively inert; it is nevertheless a foreign substance and can eventually lead to nerve compression. In the present study, the feasibility of using a polymer tube made of autologous collagen and agarose and filled with autologous fibrin clot was evaluated to bridge an 8 mm gap in transected rat sciatic nerve.

(1) Preparation of the collagen tube

A collagen solution was prepared by soaking a rat tail tendon in 0.3 per cent acetic acid with constant stirring for three days at 4° C. The undissolved material was sedimented and the clear supernatant was brought to pH 7 with 10 per cent NaOH (5 per cent by volume). The precipitated collagen was washed several times in distilled H_2O and redissolved in 0.3 per cent acetic acid to achieve a protein concentration of 2 mg/100 ml and stored at -20° C. A "collagen–agarose mixture" was prepared by quickly mixing equal volumes of the collagen solution with 1 per cent agarose in 2 X concentrated Eagle's minimal essential medium (Flow Lab). To bring the pH of the mixture to 7.6, 10 per cent NaOH (5.8 per cent by volume) was added. The mixture was then poured into a mould and it solidified in 15 minutes. A soft tube which formed in the mould was removed and dried at room temperature for one day. The external diameter of the tube measured 2.2 mm and the internal diameter was 1.4 mm. It was sterilized by gaseous ethylene oxide and cut into 10 mm segments.

(2) Operative procedure

Twelve male Sprague-Dawley rats weighing 300-400 g were anaesthetized with intraperitoneal injections of pentobarbital (40 mg/kg). Under aseptic conditions and using microsurgical technique, the right sciatic nerve was transected and sutured to a 10 mm long collagen tube by an epineurial suture using 10-0 nylon suture leaving an

8 mm gap between the nerve stumps. A fibrin clot made by rapidly mixing 200 ul of autologous plasma and 20 ul of thrombin solution (50 U/ml) was injected into the lumen of the collagen tube just before suturing.

For comparison, the left sciatic nerve was similarly transected and sutured to a 10 mm long impermeable silicone tube (Mentor Co., Colleta, CA) with an external diameter of 2.2 mm and an internal diameter of 1.4 mm. The tube was likewise filled with fibrin clot before being sutured to the nerve stumps.

(3) Sample collection and preparation

After one, two, and four months, groups composed of four rats were anaesthetized and the tubes containing the nerve regenerates were removed with proximal and distal stumps attached. The specimens were fixed in 10 per cent buffered formaline for 16 hours and embedded for paraffin and epon sections. For paraffin embedding, the entire length of the nerve was embedded in one piece and longitudinal sections were made and stained with H&E hematoxylin and eosin (H&H) and silver stain for the neuraxon. For the epon sections, 3 cross-sections were taken from each nerve (a) from the proximal stump at 2 mm proximal to the transection line, (b) midpoint at the nerve regenerate and (c) from the distal stump at 2 mm from the transection line. The epon sections were cut at 1 micron and stained with 1 per cent toluidine blue.

(4) Data analysis

The cross-sections of the epon-embedded sciatic nerve were photographed with a Leiz microscope and prints were made with 25 X magnification. Montages were constructed and the number of myelinated axons were counted manually. Each figure represented an average of counts taken from four nerve specimens. A student's *t*-test was used for comparison between the two groups.

One month postimplantation

The outer surface of both collagen and silicone tube were encapsulated by a thin fibrous membrane. The gap in both the collagen tube (group A) and the silicone tube (group B) was occupied by a cable containing groups of new myelinated and unmyelinated axons. As shown in table I and figure 1, the number of myelinated axons in the proximal stump was 7839 ± 704. In the gap, myelinated axons numbered 1328 ± 123 in group A and 1541 ± 87 in group B ($P < 0.01$). In the distal segment, the number of myelinated axons was 1028 ± 107 in group A and 1492 ± 143 in group B ($P < 0.01$). In group A, the surface of the cable was covered by a small number of mononuclear cells and multinucleated giant cells indicating a foreign body reaction (figure 2c).

Two months postimplantation

The nerve regenerate was encapsulated by a thin epineurium and the overall number of myelinated axons had increased (figure 2b, c). In the gap, there were 5792 ± 279 myelinated axons in group A and 5984 ± 103 in group B ($0.01 < P < 0.05$). In the distal segment, there were 3156 ± 194 myelinated axons in group A and 6136 ± 115 in group B ($P < 0.01$).

Four months postimplantation

The nerve regenerate in the collagen tube appeared to be thicker than that in the silicone tube due to a thicker epineurium (figure 2a). Histologically, the foreign body reaction had lessened. The number of myelinated axons in the gap was 8589 ± 137 in group A and 9117 ± 282 in group B ($P < 0.01$). In the distal segment, there were 6714 ± 732 myelinated axons in group A and 9780 ± 871 in group B ($P < 0.01$).

In this preliminary study, it was demonstrated that a polymer tube fabricated from autologous collagen and agarose and filled with autologous fibrin clot can successfully support nerve regeneration across an 8 mm gap. There was a mild inflammatory response with a foreign body reaction on the surface of the nerve regenerate in the collagen tube during the first two months. This foreign body reaction abated after two months; and resulted in a thicker epineurium. By the end of four months, the number of myelinated axons in the collagen tubes (group A) was almost the same as that in the silicone tubes (group B). However, the number of regenerated axons in the distal segment of group A was consistently lower and amounted to approximately 78 per cent of those in group B. The reason for the poorer results obtained in the collagen tube group could be due to the foreign body reaction directed against the collagen and/or agarose. The weak tensile strength in the collagen tube may have caused sagging of the tubal wall and inadequate immobilization of the nerve regenerate inside the tube.

Previous studies have shown that the permeability of the tubes makes little difference as fluid can enter the impermeable tube through small openings between the inner tubal wall and the nerve stumps even when the tubal wall is impermeable. After the first week, all tubes will be sealed off by a fibrous capsule and become impermeable. The fluid which accumulated in the impermeable silicone tube is a mixture of exudated plasma proteins and locally synthesized growth factors which promote cell and nerve growth (Longo *et al.*, 1984; Liu, 1992; Liu *et al.*, 1993).

There has been an increasing interest in the use of collagen copolymers in the replacement of tissues and organs (Nimni *et al.*, 1988; Rao *et al.*, 1988). In view of its biocompatibility and inertness, collagen can be modified in many ways to make it suitable for biomedical applications such as skin and bone grafts, heart valves and sutures. Despite untoward responses such as foreign body reactions and cell-mediated immunity to implanted bovine collagen (Ellingsworth *et al.*, 1986), collagen-based biomaterial has found widespread clinical application such as sutures. Pure collagen cannot be used in nerve repair because it yields a soft gel which could not hold its shape and is rapidly absorbed. Therefore agarose was added to collagen in order to increase its strength and resilience. After drying, the collagen tube was a thin-walled tube showing good mechanical strength, excellent handling, mild foreign-body response and reproducible results. This preliminary study has demonstrated that the collagen tube can successfully support nerve regeneration across an 8 mm gap between transected peripheral nerves. Future studies should be directed towards making collagen tubes with an increased tensile strength and decreased foreign body reaction.

Acknowledgements

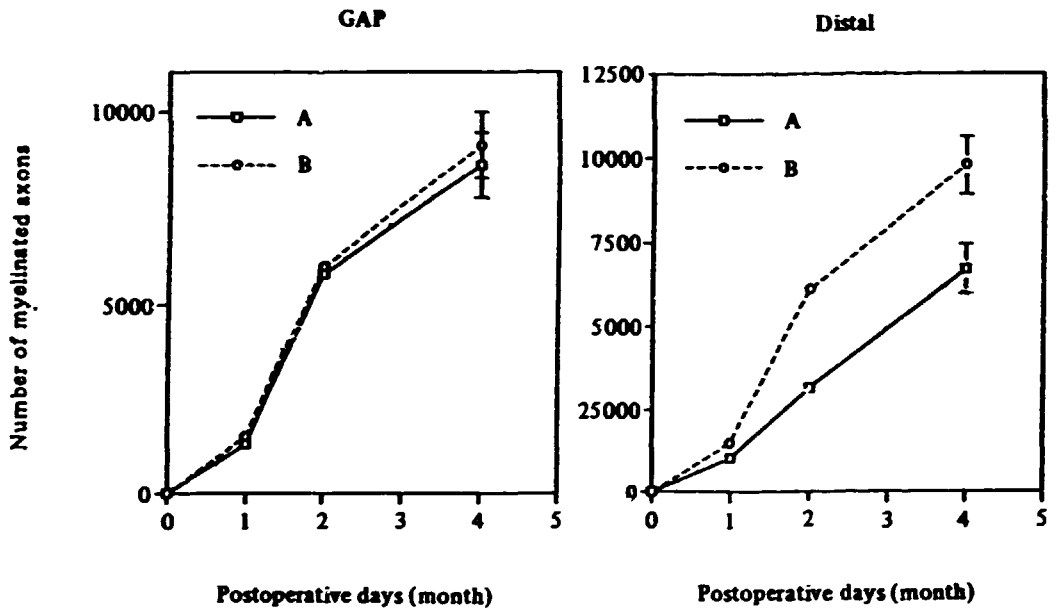
The authors thank Ms. Shou Chih Lin for her assistance in animal experimentation, Ms. Shu Chuan Yen and Ms. Shing Chih Tsai for histological preparation and morphometric analysis. This work was supported by a grant from the National Science Council, Republic of China (NSC-81-0412-B006-544).

Table 1. Number of Myelinated Axons in Nerve Regenerates

1 month		2 months		4 months	
Gap	Distal	Gap	Distal	Gap	Distal
A: 1328 ± 123	1028 ± 107	5792 ± 279	3156 ± 194	8589 ± 137	6714 ± 732
B: 1541 ± 87	1492 ± 143	5984 ± 103	6136 ± 115	9117 ± 282	9780 ± 871
*$p<0.01$	$p<0.01$	$0.01<p<0.05$	$p<0.01$	$p<0.01$	$p<0.01$

Proximal stump: 7839 ± 704
A: Collagen tube B: Silicone tube
*Statistics: Student's *t*-test

Figure 1



A: Collagen tube, B: Silicone tube

a. The number of regenerated myelinated axons in the gap at 1, 2, and 4 months after implantation with (A) collagen tube, and (B) silicone tube.
b. The number of regenerated myelinated axons in the distal segment 1,2, and 4 months after implantation with (A) collagen tube, and (B) silicone tube.

Figure 2
Collagen Tube in Nerve Repair

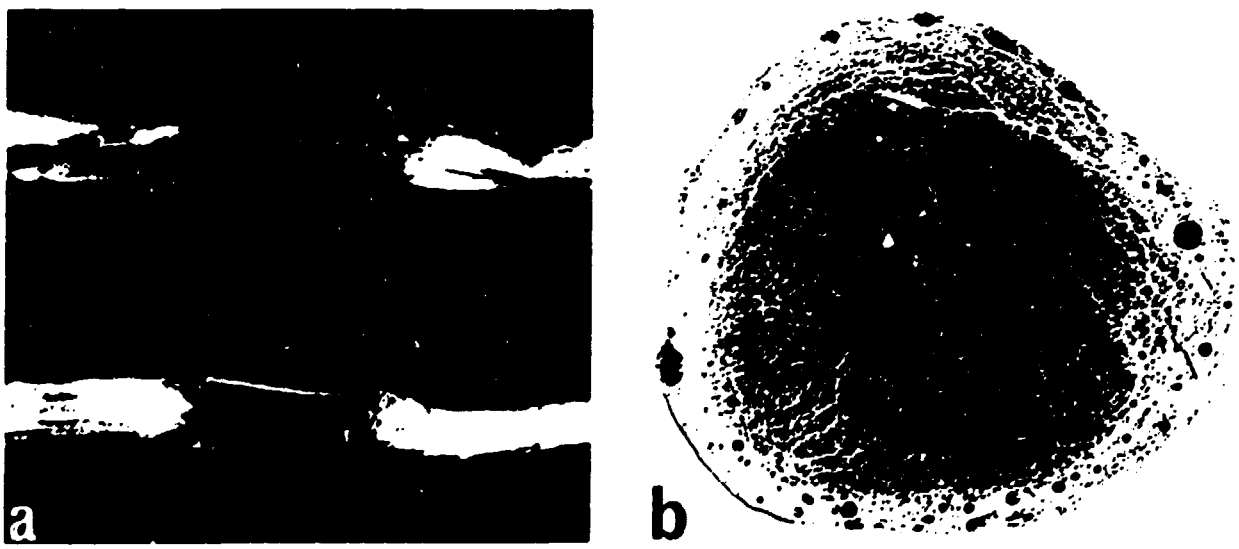
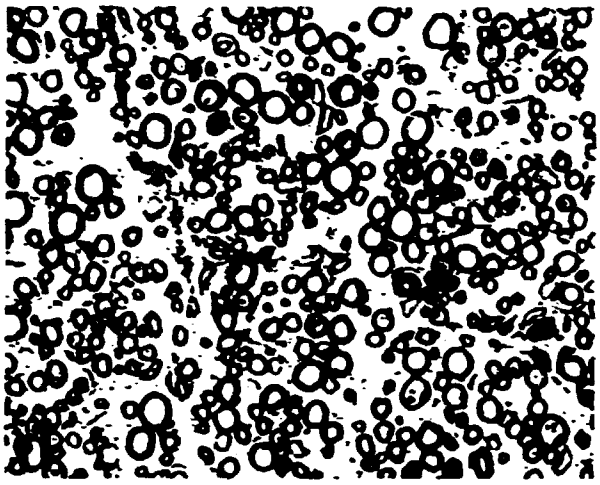


Figure 2 *(continued)*



a Nerve regenerate within (A) collagen tube, (B) silicone tube 4 months postimplantation. The nerve regenerate in the collagen tube is thicker due to fibrosis in the epineurial wall (magnification × 10).

b. A well formed nerve regenerate in the collagen tube 2 months postimplantation showing many myelinated and unmyelinated axons. (Epon section, toluidine blue stain, × 6).

c. Nerve regenerate in collagen tube 1 month post-implantation showing scattered foreign body giant cells between the nerve and the tubal wall (magnification × 100). H&E stain.

d. A close view of the regenerated nerve with myelinated and unmyelinated axons in the collagen copolymer tube 2 months after implantation. (Epon section, toluidine blue stain, × 120).

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Developments in dental cements

Repairing or replacing teeth takes up over half a dentist's working day.(1) The success of this work depends, at least in part, on the properties and performance of the materials available for use. When talking about a filling most people think of the silver-coloured mercury amalgam alloy or gold. However, the use of tooth coloured fillings (often referred to as white) is becoming more widespread and the chemistry and technology used in their formulation has become more sophisticated. Recent developments in the area of dental materials have concentrated on tooth-coloured restorative materials. In the past there were two distinct classes of these materials, the glass-ionomer and the composite resin, but over the past five years these boundaries have blurred with the formation of hybrid materials.

Glass-ionomer cement

Glass-ionomer cement (GIC), or more correctly glass polyalkenoate cement, is an acid-base reaction cement formed by the action of an aqueous solution of a poly-(alkenoic) acid on an ion-leachable basic glass.(2) The glass is a base in the sense that it is a proton acceptor, even though it is not soluble in water. The principal setting reaction of a GIC is the slow neutralization of the acidic polymeric solution to form a polysalt matrix.(3) The setting begins as soon as the components are mixed, and the material quickly becomes hard enough to allow the dentist to shape it. A set GIC is a very complex composite material—micrographs of its structure have shown the residual glass particles embedded in interconnected polysalt and silica matrices.(4)

From the dentist's point of view, a set GIC is a translucent material with a high compressive strength, which in the mouth is bland, adhesive and resistant to acid and aqueous attack. The GIC has the additional advantage that it releases fluoride thus protecting the remaining tooth around the filling.(3) The fluoride is available because calcium fluoride is in the glass and the fluoride level in the filling is replenished after brushing with a fluoride toothpaste.

In some GICs the strength and wear properties have been improved by including finely divided silver alloy or by fusing the glass with silver alloy before mixing, forming a ceramic metal hybrid known as a cermet.(5) These approaches, endeavouring to find a material with properties such that it could replace amalgam, are the subject of continuing research.

A disadvantage of GICs, is that the immature cement is sensitive to moisture. This vulnerability continues as long as any cement-forming ions from the glass are in soluble form and capable of being washed out of the cement by saliva. Alternatively, patients who breathe through the mouth can inhibit the cement's setting reaction by desiccation. To overcome these sensitivities clinicians tend to cover freshly placed cement with an impervious layer of varnish or petroleum jelly.

Composite resin cement

The setting reaction of a composite resin (CR) cement is a free-radical polymerization of the resin monomer rather than an acid-base reaction, but the major difference between GIC and a composite material is the filler's role in the setting reaction. For a GIC, the presence of the glass particles is fundamental to the reaction mechanism, as the source of cross-linking ions, whereas the filler particles of a CR are not involved in the setting mechanism and do not undergo any chemical change during the reaction.(6)

The monomer is usually a large molecule aromatic or urethane dimethacrylate. If the monomer is large, then the polymerization shrinkage will be small compared with the molecular size. However, in some formulations smaller diluent monomers, with high shrinkage values, must be included to decrease the system's viscosity. Possible diluent monomers include ethylene glycol dimethacrylate (EGDMA) and triethylene glycol dimethacrylate (TEGDMA).

Commercial dental CR materials are supplied as either one- or two-paste systems. The one-paste system is a visible light-cured formulation (generally blue light, 470 nm). The initiation system used in these light-cured materials is an α-diketone with an amine reducing agent. The setting reaction is then a photopolymerization initiated by the radicals formed when the initiator is exposed to light of particular wavelength and intensity. The two-paste systems either undergo self-cure when the two pastes are mixed (chemical cure), or a dual cure mechanism involving both chemical (self-cure) and light cure. The initiator in the chemical cure systems is usually benzyl peroxide with a tertiary amine accelerator.

The fillers, silica, lithium aluminosilicate or barium alumino borate glasses,(7) are chosen with thermal expansion coefficients similar to that of the tooth material itself, and refractive indices similar to that of the matrix. If the refractive index of the filler matches that of the matrix, then the composite will have similar translucency to the tooth. The particles are 0.04-8 μm in size and filler loadings vary from 25-86 per cent.(8) The amount of filler present and its particle size distribution affects cement properties such as compressive strength, stiffness and abrasion resistance.

When CR cements are set by polymerization of the monomer, they are made up of filler particles embedded in a polymer matrix. These particles are bonded to the matrix by silane coupling agents. The dimethacrylates become extensively cross-linked on polymerization, but the set cement still contains considerable unsaturation, about 25-45 per cent.(9) The unpolymerized methacrylate groups exist as residual monomer or alternatively as pendant side chains, these species can act as plasticisers causing a reduction in mechanical properties. The extent of the polymerization in a light-activated material depends on the cure regime: the light intensity and the length of exposure. Care must be taken to ensure that the maximum depth of light-penetration (depth of cure) is not exceeded.

Resin-modified glass-ionomers

The most exciting recent development in dental materials is the introduction of the resin-modified glass-ionomer cement (RMGIC). This combines the technologies of CR cement and conventional GIC. RMGICs were introduced to overcome the moisture sensitivity problems associated with GICs, increasing their ease of use with a light-cure facility while at the same time preserving the clinical advantages of the parent materials. RMGICs are actually marketed as light-cured (or curable) GICs, though this nomenclature has caused some confusion. The underlying reaction in a GIC is an acid-base reaction. The light-cured set does not apply to this reaction, but instead to a reaction taking place in addition to the conventional set.

Consequently, resin-modified is a more accurate description.

Conventional GICs have working times of 6-90s but more importantly the setting time is 4-7 minutes. During this time, and for up to 1 hour afterwards, the cement must be protected from contamination. The resin-modified materials have much longer working times but much shorter setting times (a 30-40s cure), with the benefit of the command set facility, and are protected from moisture by the photopolymerization matrix.

The first commercially available RMGICs were liner/base grade materials. More recently restorative grade materials have been introduced. The RMGICs are available as both two component powder/liquid and encapsulated formulations.

The original concept for a RMGIC depended on the addition of 2-hydroxyethyl methacrylate (HEMA) to a conventional GIC formulation.(10) Some initiators/activators were also included. This idea has been extended to other methacrylates, usually those used in composite resin formulations. RMGICs have been further developed in systems where the polyacid has been modified by adding unsaturated groups pendant to the polymer backbone.(11) In these compounds the polyacid is involved in both the acid-base and the polymerization reactions. Despite the modification of the acid, the formulation still includes some monomer, usually a methacrylate, to ensure an effective photoreaction.

The first commercial RMGICs introduced in the late 1980s were about 80 per cent acid-base (conventional GIC) and 20 per cent polymerizable resin.(12) The more recent restorative grade formulations have a higher percentage of acid-base reaction, quoted as around 90 per cent.(13) The commercial cements are formulated as both the mixture and modified-acid materials.

The RMGIC has two possible setting reactions, a light-initiated polymerization and the acid-base reaction of a GIC.(12) The acid-base neutralization reaction starts as soon as the components of the cement are combined. The rate of this ion-transfer reaction is lowered by the inclusion of organic species and a reduction in the level of water in the composition. Consequently, the working time of the unirradiated cement is extended beyond that of GIC. A true RMGIC must be capable of setting without being photocured, thus demonstrating that the acid-base reaction is still active. However, it should be noted that in most systems, failure to photocure will result in inferior properties for the set cement.

In most situations the initial set of the cement will be caused by the formation of a photopolymerization matrix. In the systems where the two reactions are separate, the photoinitiated reaction is the polymerization (or copolymerization) of the included methacrylates. Where the polyacid has been modified to undergo further polymerization, the photoinitiated reaction has different forms since it involves polymerization of the methacrylates and cross-linking of the polyacid chains. Consequently, it would seem that in each of the possible formulations, the set cement will have two interpenetrating matrices, the ionic matrix from the acid-base reaction and the polymerization matrix from the photo reaction.

However, the setting reaction is not that simple. The nature of the species involved means that the two reactions cannot take place independently. The organic methacrylate species slow down the ionic acid-base reaction and the ion transport required for matrix formation will be impeded by the presence of a polymerization matrix. The effect of the polar species on the polymerization reaction is not clear.

RMGICs have improved aesthetics compared with the conventional materials (see above). This means that they are the cements preferred for use in any situation where the restoration's appearance is important. The major limitation when using a photocured material is the need for illumination, so the curing light must have access to the restoration. In a similar vein, the depth of penetration of the curing light is generally quoted as between 2-3 mm depending on cure time and material. Obviously if a large restoration is being prepared, it cannot be cured in bulk, but rather a layering technique with the photocured material or a conventional material must be used.

The RMGICs have a fluoride release rate equivalent to that of the conventional cements.(14) The shear bond strength of the materials to bovine dentine is larger than that of conventional materials,(15) and the inclusion of resins has improved their fracture toughness compared with their conventional counterparts.(16) Similarly, RMGICs have higher compressive strengths after 24 hours than conventional materials. In fact, the resin-modified materials have achieved the 24 hour measured compressive strength of the conventional materials at 1 hour.(17) These comparisons must be treated with caution because of the difficulty in preparing standard compressive specimens of the resin-modified materials.

A recent addition to the RMGIC range, known as "tri-cure" material, has been introduced to address the problem of depth of cure on illumination.(18) This, like some composite materials, has both photocure and self-cure polymerization reactions. It is called tri-cure because the system has the acid-base reaction, photopolymerization and chemical polymerization. The acid-base and chemical polymerization reactions start as soon as the two components are mixed, the photopolymerization occurs on illumination. The name tri-cure could be regarded as a misnomer, because the two polymerization reactions involve the polymerization of the same species, but with different means of initiation. However, a photopolymerization has a faster rate than a self-cure reaction, thus the nature of the species produced may differ. The advantage of a tri-cure system is that cure can be achieved beyond the penetration depth of the curing lamp.

The introduction of RMGICs has blurred the distinction between the composite resin and glass-ionomer cements, but the differences between the child and its two parents have not always been appreciated. An unirradiated RMGIC cannot be regarded as a conventional GIC. The situation has been further complicated by the introduction in 1993 of a new material, which the manufacturers, DeTrey Dentsply, have christened "compomer". It is described as combining both the CR and GIC technologies.(19) However, it is not a straightforward combination, the acidic component of the reaction is not a polymer, instead it is an acidic monomer derived from HEMA and, unlike any other GIC or RMGIC, it is supplied as a one-paste system that requires no further mixing. For this to be achieved water, a vital ingredient of the acid-base reaction, has been excluded from the formulation. The setting reaction used on the clinical timescale is a pure photopolymerization. The manufacturers claim that the set cement will then take up water from its oral environment and that this will facilitate the acid-base reaction. This reaction will take place over a period of

weeks. The converse of this claim, that an uncured cement, when placed in water, should set by the acid-based reaction alone has been greeted with some scepticism. Nevertheless this material is an interesting addition to the range of available dental materials.

These recent developments in dental cements are chemically interesting and have the potential to become very significant in clinical dentistry. As with all advancements in any field there have been some initial problems with the use of these materials, but if these are resolved and the long-term durability of the restorations live up to expectations, then they will represent a major advance, bringing closer the dream of a dental material that is indistinguishable from the original tooth structure and which lasts just as well.

Dental cements

Material	Components
Glass-ionomer	Ion-leachable glass, poly(acrylic acid)(or copolymers with itaconic/maleic acids), water
Composite resin	Various monomers (usually methacrylates), filler (non-reactive glass and/or silica, initiator system
Resin-modified-glass-ionomer	Ion-leachable glass poly(acid)(or modified poly(acid) with pendant unsaturated groups), various monomers (usually methacrylates), water, initiator system
Compomer	Methacrylate monomer, acidic monomer, ion-leachable glass, initiator

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(Reprinted from *Chemistry & Industry*, 21 November 1994)

5. MARKET TRENDS

Advances in biomedical composites

The medical device industry is currently in a position to present significant new opportunities for manufacturers of advanced composites. With the greater need for prosthetics that are lightweight and comfortable and materials used in surgical implants that are inert and do not react with biological tissue, the composites industry is in a unique position to fill these demands. Some companies have been producing products to fit these niches and some are now developing less expensive methods and materials in anticipation of changes such as limitations on cost reimbursements. Although plastics are used in many types of medical devices from catheters to tissue adhesives, this article presents a brief background of the biomaterials industry and then primarily focuses on orthopaedic and prosthetic applications in which devices are used to correct or prevent deformities or to replace missing parts of the body such as limbs.

Markets and materials

World-wide consumption of medical devices increased by 7 per cent to $70.9 billion in 1991, according to the Health Industry Manufacturers Association (HIMA) review of health-care technology market trends. The US trade surplus in medical devices is projected to be $8.4 billion for 1995, which is a 24 per cent increase per year based on US Department of Commerce data. The US production of medical devices is projected at an annual growth rate of 7.4 per cent. The US market for prosthetic knees and hips is approximately $1 billion per year, according to ICI Americas (Wilmington, Delaware). The total US market for polymeric biomaterials is at approximately $3.2 billion per year, $2.5 billion of that in medical disposables. The Biomaterials Industry Subpanel of the National Research Council estimated that more than two million prosthetics are implanted each year in the United States and Europe. Silicone accounts for approximately 10 per cent and polyurethanes for 5 per cent of that figure.

During the 1960s, surgical implant devices were made mostly of metal. Manufacturers used materials that were available from other higher volume product lines. Today, biomaterials are synthesized and manufactured for specific use in particular devices. Surgical implants have been an important part of improving the quality of life for patients to reduce pain and to improve and increase function. The Biomaterials Industry Subpanel, commenting in 1989 in its final report on the needs and issues in the biomaterials industry, reported that total joint prostheses have demonstrated success ratios greater than 90 per cent after 10 years

of use for patients who are more than 65 years old. Use of implants in 45- to 65-year-old patients significantly decreases the relative success ratios to 90 per cent for four years. New systems developed to serve this younger group may require new biomaterial designs and clinical reconstructive procedures. Many of the available biomaterials and devices have lifetimes of 20 years when used by patients, whereas the subpanel suggests a lifetime of 80 years would be a worthwhile objective. Basic research on new substances could provide completely new systems for reconstructive surgery. (Extracted from *Advanced Composites*, July/August 1993)

New study on polymers

Global demand for polypropylene (PP) reached 15 million tons in 1992, up 9.8 per cent over 1991. At the same time, the world demand for LDPE (including LLDPE) reached about 20 million tons, HDPE reached about 13 million tons, polystyrene reached 9 million tons, and PVC reached 18.2 million tons. These conclusions were reached in a new multiclient study recently published by Kuhlke and Associates, Houston, TX. In 1992, the Asian Pacific region accounted for 35.5 per cent of this polypropylene demand. In the base case presented in the study, the world demand for polypropylene is forecast to rise to over 20 million tons by 1997 with HDPE demand rising to over 16.5 million tons. For the polypropylene demand to be in balance with capacity by 1997, the demand will have to increase by 9.5 per cent per year. With only a 4 per cent growth rate per year, the current oversupply situation would remain essentially unchanged through 1997 (see chart 1).

The current imbalance in the polypropylene supply demand equation is the result of a major construction boom from 1989 to 1993, which saw the building of new poly propylene plants at a faster rate than the demand was increasing (see chart 2).

Because of this construction boom, the PP industry is now in a period of waiting for the demand to catch up with capacity. To hurry this along, prices will remain weak to encourage the high-cost plants to shut down. At the same time, new grades will be introduced to stimulate growth in demand.

The major growth markets for polypropylene in the mid-1990s are expected to be medical applications, and in some applications as a replacement for polystyrene and PVC. Improved grades are forecast to improve the clarity of polypropylene containers and possibly allow it to compete successfully with PET. New filled grades are expected to allow polypropylene to compete with ABS in automotive interior parts and in appliances. Speciality filled grades are expected to successfully compete with filled nylon and other engineering resins. In textiles, new markets are still expected to offer substantial growth opportunities, such as gloves, thermal underwear, cigarette tow, and geotextile membranes. These are just a few of the new developments expected in the mid-1990s to foster high growth for PP resins.

Similar conclusions were reached for the other volume polymers also studied in this report. The polymers studied were polyethylene, polypropylene, polystyrene and PVC. A study of the world capacity to produce ABS was also included. The 686-page report includes a country-by-country analysis of these polymers with summaries by the six major regions of the world. These individual country reviews include a detailed analysis of the capacity by plant location, production and consumption per capita by country over the period 1989 to 1997. Further information can be obtained from W. C. Kuhlke at Kuhlke & Associates, 14519 Cindywood, Houston, TX 77079.

Chart 1

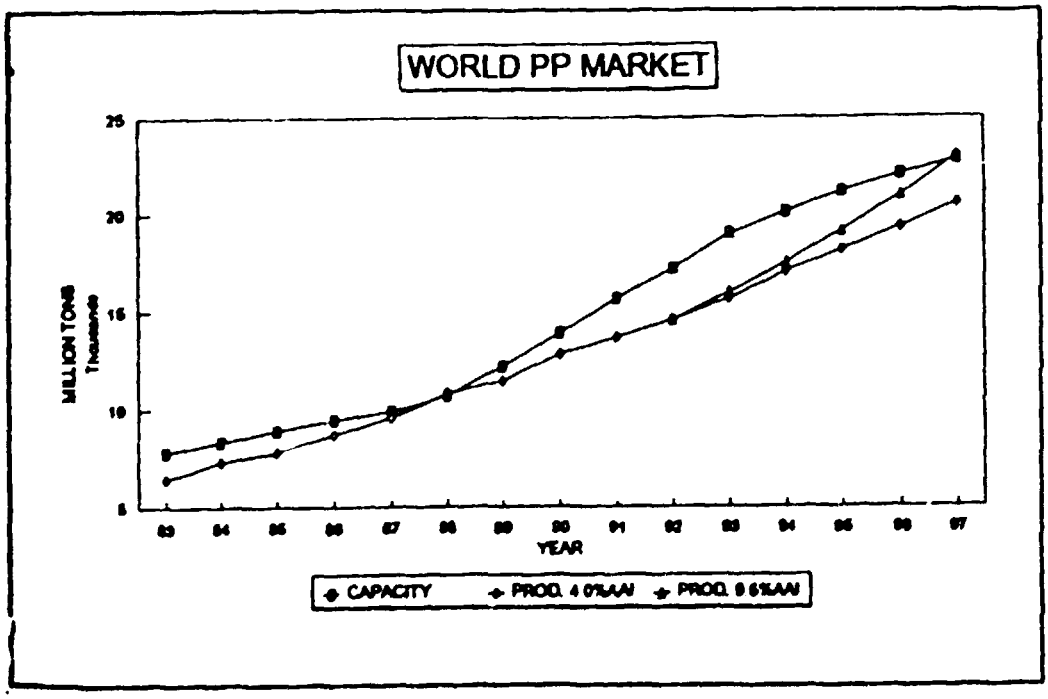
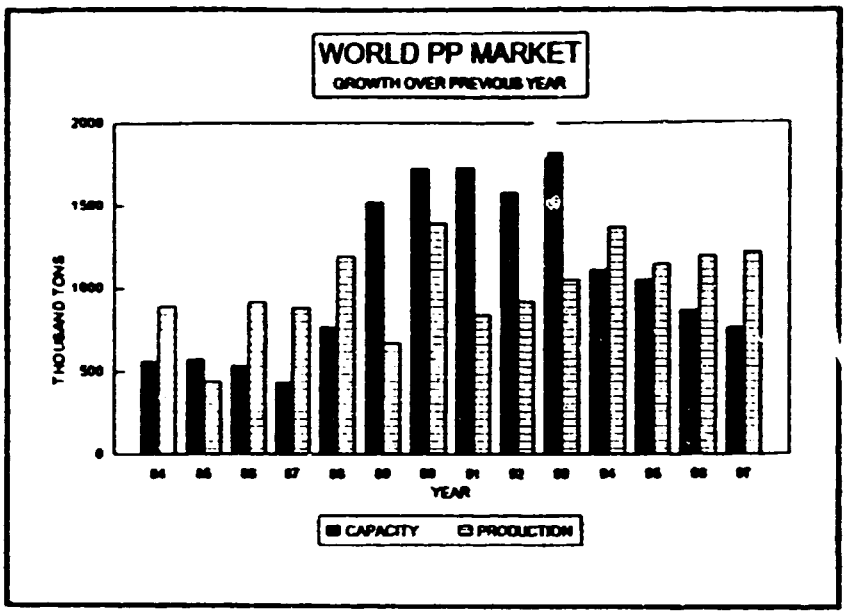


Chart 2



(Source: *Popular Plastics & Packaging*, December 1993)

6. PUBLICATIONS

Biomaterials Dictionary from Technomic

In the field of biomaterials, you encounter terminology from a wide range of disciplines every day.

You have to understand terms from polymer chemistry, medicine, pharmacology, metallurgy, organic chemistry, physiology, biochemistry, and more.

At last, a new book eliminates the need for numerous dictionaries and provides a handy reference specially for those working in the biomaterials industry.

Szycher's Dictionary of Biomaterials and Medical Devices contains over 2,700 definitions of terms used in the biomaterials field. This new book is an indispensable reference that combines language from a multitude of disciplines and defines them as they apply to biomaterials.

Developed and written by a well-known biomaterials expert, Michael Szycher, Ph.D., PolyMedica Industries, Inc., USA, this dictionary presents terms frequently sought by biomaterials scientists in the usual pursuit of research, developments, or manufacture of medical devices.

Plus, the book includes three useful appendices:

Polymers in Medical Applications, Drug-Related Devices Classification, and Critical Device (Class III) listing.

Defining everything from AAMI to zymogen, this new dictionary fills the gap in reference materials on biomaterials and helps scientists understand and assimilate the terms needed for successful communication in this new field. (Available from Technomic Publishing AG, Missionsstrasse 44, CH-4055 Basel, Switzerland)

New book on advances in polymers in medicine

New developments in polymers in medicine provide the means for controlled delivery, site specific delivery, and a variety of administrative routes.

Now, a new book, *Polymers in Medicine: Biomedical and Pharmaceutical Applications*, provides a broad presentation of polymer utilization in medicine.

Edited by Raphael M. Ottenbrite, Virginia Commonwealth University, and Editor, *Journal of Bioactive and Compatible Polymers*, USA and Emo Chiellini, University of Pisa, Italy, the book contains the 16 reports presented at the recent Fourth International Conference on Polymers in Medicine, September 1990, Riva del Garda, Italy.

Developed by leading specialists from around the world, the reports present advances in polymer drug chemistry, pharmacology and processing, polymer-drug interaction, controlled and site specific release, and pharmacological action.

Reports include: Microencapsulation of Mammalian Cells in Biocompatible Polyacrylate; Methacrylic Polymers Obtained by Radiation Induced Polymerization for the Slow Release of Peptide and Protein Drugs; Wound Dressings Made of N-Carboeybutyl Chitosan; Development of *In Vitro* Evaluation of an Oral formulation for Monosialoganglioside GM1; Synthesis and Pharmacological Action of Some Cholestryamin Analogs; Muramyl Dipeptide Polymer Conjugates; Antitumour and Antiviral Activities of Certain Polyoxometalates; and Lipopeptide Based Biomaterials for Cosmetology and Dermatology.

(Available from Technomic Publishing AG, Missionsstrasse 44, CH-4055 Basel, Switzerland. Motan expands in USA)

The following 12 Books/Journals announcements were read in the "John Wiley & Sons Ltd., Baffins Lane, Chichester, West Sussex PO19 1UD, UK", Book Announcement 1994 Catalogue

Polymer Surfaces

From Physics to Technology

F. Garbassi, Istituto Guido Donegani, Novara, Italy

Polymer Surfaces is a state-of-the-art work presenting a comprehensive approach to all aspects of polymer surfaces, therefore providing a necessary link between scientists and technologists. Despite increasing interest in the subject, existing literature remains fragmented amongst journal articles, review volumes and conference proceedings, until now!

Never before has such a thorough treatment of the subject been published, particularly with emphasis on application aspects. Patented literature has also been considered in what will prove to be an invaluable work.

Contents: Part I—Introductory remarks: The Origin of Surface Properties: Dynamics of Polymer Surfaces: Part II—Characterization methods: Spectroscopic Methods: Surface Energetics and Contact Angle: Other and Emerging Methods: Part III—Modification techniques: Physical Modifications: Chemical Modifications: Bulk Modifications: Part IV—Applications: Wettability: Adhesion: Barrier Properties: Biomedical Materials: Wear and Friction. (0471938173, 474 pp. 1993. £60.00/$96.50)

High Resolution XPS of Organic Polymers

The Scienta ESCA300 Database

G. Beamson and D. Briggs, ICI Wilton Materials Research Centre, UK.

A practical handbook containing a unique collection of high resolution XPS spectra of over one hundred organic polymers, recorded on the Scienta ESCA300, the world's best commercially available XPS spectrometer. An introductory section gives background material relevant to the database whilst the database itself is presented in the form of easy-to-use double-page spreads of spectral data.

This will prove an invaluable and high-quality source of practical information to those working in the fields of surface analysis, polymer science and biomaterials in both industrial and university laboratories.

Contents: Introduction: Description of the Spectrometer: Performance on Conducting Samples: Performance on Insulating Samples: Performance Testing of the Spectrometer: Experimental Protocol: Curve Fitting: Lineshapes: Shake-up Structure: Valence Bands: Impurities: X-ray Degradation: Organization of the Database: List of Polymers and Acronyms: The Database: Appendices. "This is a remarkable text by any standards and clearly represents an extraordinary body of work." (0471935921, 306 pp. 1992. £69.00/$120.00)

Inorganic Materials

Edited by D.W. Bruce, University of Sheffield, and D. O'Hare, University of Oxford, UK.

With recent expansion in materials chemistry this book addresses several of the vigorous areas of research in which inorganic materials are central. Each chapter provides an introduction to the subject under discussion and then develops the field to provide a sensible, but critical, overview, with certain topics being developed.

Written by an international team this volume will be suitable for researchers, both industrial and academic, with a direct or peripheral interest in materials chemistry.

Each chapter provides an introduction to the subject under discussion and then develops the field to provide a critical overview, with certain topics being developed.

Contents: Molecular Inorganic Superconductors: Molecular Inorganic Magnetic Materials: Metal-Containing Materials for Nonlinear Optics: Inorganic Intercalation Compounds: Biogenic Inorganic Materials: Clay Chemistry: Polymeric Coordination Complexes: Metal-containing Liquid Crystals, Precursors for Electronic Materials. (0471928895, 558 pp. 1992. £58.00/$90.95)

The Wiley Static SIMS Library

Project Directors: J.C. Vickerman, Surface Analysis Research Centre, UMIST, UK, and D. Briggs, ICI Materials Centre, Wilton, UK.

Wiley are pleased to announce the launch of a major new looseleaf publishing project in the field of materials characterization. Static SIMS is rapidly emerging as a very powerful technique for the surface chemical characterization of materials.

As a surface mass spectrometry it has a unique capacity to investigate materials with complex surface chemistry. As in the case of conventional organic mass spectrometry, the effective application of the technique requires a large data bank of standard spectra with which to compare spectra derived from unknown materials.

This project will, for the first time, compile a comprehensive Static SIMS Library which will enable users to interpret SSIMS spectra, thereby benefitting from the power of the technique.

The hard-copy core manual will feature the following:

1000 pages in two updateable looseleaf binders: Positive and negative ion spectra from each material with brief details of the preparation and analysis conditions: Spectral interpretation of the principal peaks as provided by the contributors: Detailed analytical protocols and standard spectra from each of the instruments used in producing the library spectra: A guide to spectral interpretation: A status guide on the use of chemometrics: A guide to the use of MS/MS techniques.

The electronic version will be packaged with the hard-copy version and will feature:

Simple scrolling, overlaying, zooming facilities for the screen access of the spectra: All the spectra featured in the hard-copy version at the spectral resolution provided by the contributing laboratory but without the spectral interpretation: Additional options available for the file export in VAMAS format as ASCII files: PC Windows and Mac versions will be available: Instrument manufacturers may incorporate the database in their data systems under a licence agreement.

The broad material areas to be covered are: Polymers: Natural Products: Polymer Additives: Pharmaceuticals: Surface Active Agents: Organic Coatings: Inorganic Materials: Metals and Alloys: Electronic Materials. (0471938181, Approx. 1000 pp. Publication in Autumn 1994. Price to be announced)

Occupational Biomechanics
Second Edition
D.B. Chaffin, The University of Michigan, USA and Gunnar B.J. Anderson, Rush-Presbyterian-St. Lukes Medical Centre, USA.

Understanding how to prevent musculoskeletal disorders and improve manual working conditions is a concern for employee and employer alike. This landmark text, the fruit of over 45 years' research experience in various industries, reveals how to work and design work tools and workplaces for optimal productivity and safety. Gathering in a single volume what was previously only available in scattered journals and technical papers, this book represents a significant step forward for professionals and students in engineering, medicine and occupational health.

Contents: Occupational Biomechanics as a Speciality; The Structure and Function of the Musculoskeletal System; Anthropometry in Occupational Biomechanics; Mechanical Work-Capacity Evaluation; Bioinstrumentation for Occupational Biomechanics; Occupational Biomechanic Models; Methods of Classifying and Evaluating Manual Work; Manual Materials Handling Limits; Guidelines or Seated Work; Biomechanical Considerations in Machine Control and Workplace Design; Hand Tool Design Guidelines; Guidelines for Whole-Body and Segmental Vibration; Worker Selection and Training Criteria; Summary. (0471601349. 538 pp. 1991. £49.50/$68.95)

Silica Gel and Bonded Phases
Their Production, Properties and Use in LC
R.P.W. Scott, University of London, UK and Georgetown University, USA

Silica gel is probably the most important single substance involved in modern chromatography. This book deals comprehensively with the subject of silica gel from the perspective of both the analyst and chromatographer. It aims to provide the reader with a basic understanding of the physical and chemical properties of silica gel and bonded phases and how those properties impact on the quality of the separations that are achieved by them.

This book will be a valuable reference to a broad spectrum of scientists as a result of the increasing popularity of chromatography in such diverse fields as biotechnology, environmental science, forensic science and in pharmaceutical production control.

Contents: Silica Gel—Its History and formation; The Manufacture of Silica Gel; Test Procedures and LC Column Packing; The Silica Gel Surface; The Exclusion Properties of Silica Gel; Solvent/Solute Interactions with the Silica Gel Surface; An Introduction to Bonded Phases; The Synthesis of Bonded Phases; The Characteristics of Reverse Phases; Solute/Solvent Interactions with the Surface of a Reverse Phase; The Mechanism of solute Retention; Appendix 1: Grinding Mills Available for Silica; Appendix 2: Classifiers Available for Silica; Appendix 3: Test Equipment for Silica; Index. (Separation Science Series (0471939854. 274 pp. 1993. £35.00/$56.50)

Spectroscopy of New Materials
Volume 22
Edited by R.J.H. Clark, FRS, University College London, and R.E. Hester, University of York, UK.

This is the 22nd volume in the Advances in Spectroscopy series, companion to Volume 19, "Spectroscopy of Advanced Materials" which was published in 1991. Topics covered include solid state NMR, studies of electronic properties of materials, non-linear optics and photochromism. As with all previous volumes in this established series, the aim of the book is to integrate theory and practice and to bring together different branches of both academic and industrial research through the presentation of critical review articles in fundamental and applied spectroscopy.

Contents: Chromophores for Non-linear Optical Materials; Photochromic Materials; Optical and Infrared Spectroscopy of Phthalocyanine Molecular Assemblies; Solid State NRM Studies of Aluminophosphate-based Molecular Sieves; Electronic and Spectroscopic Properties of Conducting Langmuir-Blodgett Films; Spectroscopy of Proton and Electron Cooperation Systems. (*Series: Advances in Spectroscopy. 0471939110. 360 pp. 1993. £110.00/$176.00*)

Structural and Chemical Analysis of Materials
X-Ray, Electron and Ion Spectrometry
J.P. Eberhart, Louis Pasteur University, Strasbourg, France

Provides, in a single volume, a comprehensive and coherent survey of the theoretical and practical aspects of the more important techniques used in materials analysis.

Includes essential information on techniques commonly used whilst avoiding heavy mathematical formalism so that it is neither oversimplified nor incomprehensible.

Contents: Introduction: Interaction of X-rays and Particle Beams With Materials; Radiation, Generation and Measurement; Diffraction Techniques Applied to Materials Analysis; X-ray, Electron and Secondary Ion Spectrometry Applied to Material Analysis; Techniques of Electron Microscopy. (*0471929778. 576 pp. 1991. £117.00/$200.00*)

Journal of Biomedical Materials Research
An Official Journal of the Society for Biomaterials and the Japanese Society for Biomaterials
Editor-in-Chief: James M. Anderson, Case Western Reserve University, Institute of Pathology, USA
(Volume 28, 1994. Monthly. US$1,215)

Biopolymers
Editor M. Goodman, University of California at San Diego, USA (Volume 34, 1994. 12 Issues. US$1,860)

Polymers and Biomaterials
Edited by Hanbao Fang, Yafang Han and Liji Huang

Polymers and Biomaterials is a compilation of symposia on Advanced Engineering Plastics, Functional Polymers, and Biomedical Materials, and is the third volume of the five-volume Proceedings of the Chinese-MRS International Conference held in Beijing, China in 1990. Although these proceedings are from an international conference, the great majority of papers presented in this volume are by Chinese authors and thus represent the state-of-the-art efforts in the areas of advanced engineering plastics, functional polymers, and biomedical materials. This volume contains a total of 88 papers with 31 papers on advanced engineering plastics, 16 papers on functional polymers, and 41 papers on biomedical materials. Of the 88 papers, 74 were authored by Chinese scientists.

The largest group of papers is in the biomedical materials section and includes studies on polymer systems, ceramics, bioactive glasses, carbon films, and polyelectrolytes. Studies on materials for orthopaedic, plastic, cardio-

vascular, and drug sustained release applications are also included. The manuscripts range from fundamental synthesis and characterization to bio- and blood-compatibility studies to *in vivo* studies of the respective materials. As such, this section presents and excellent state-of-the-art capability of efforts by Chinese investigators.

To obtain: Elsevier Science Publishers, P.O. Box 211, 1000 AE Amsterdam, The Netherlands. Phone: 31 (20) 586 2911. Fax: 31 (20) 586 2726. *Or:* Elsevier Science Publishing Co., 655 Avenue of the Americas, New York, NY 10010. Phone: (212) 633-3650. Fax: (212) 633-3680.

Medical and Dental Materials
Edited by D.F. Williams
Volume 14 from the series *Materials Science and Technology*, edited by R. W. Cahn, P. Haasen and E. Kramer. 1992. XX, 469 pages with 132 figures and 55 tables. Hardcover. DM 430.00. ISBN 3-527-26827-8

This volume deals with medical and dental materials that are available or are under development. Materials topics included are: biofunctionality and biocompatibility; bone and joint displacement; cardiovascular system; artificial organs; skin and nerve regeneration; dental restorative materials; oral and maxillofacial surgery; medical and dental adhesives; polymeric encapsulants; implantable electrodes; drug delivery; ophthalmology.

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7. MEETINGS

1993

1-3 September Noordwijkerhout The Netherlands	7th International Conference on Polymers in Medicine and Surgery (Organized by the Polymer Industry Division of The Institute of Materials, 1 Carlton House Terrace, London SW1Y 5DB, UK. Fax: 071 839 3576)

1994

1-3 June New Orleans, USA	The Third World Congress on Biosensors Elsevier Advanced Technology, Mayfield House, 256 Banbury Road, Oxford OX2 7DH, UK. Fax: 44865-310-981
8-10 June Alfred, NY	Second Annual Workshop on Ceramics in Biomedical Applications Institute of Bioceramics, McMahon Building, New York State College of Ceramics at Alfred University, Alfred NY 14802, USA. Fax: 607-871-3469
19 June-2 July Chania, Greece	Materials Science and Implant Orthopedic Surgery Dr. Nir Kossovsky, Dept. of Pathology, UCLA Medical Center, 10833 Le Conte Ave., Los Angeles, CA 90024-1732, USA. Fax: (310) 206-5178
7-9 September Lausanne, Switzerland	PerAc '94—a State-of-Art Conference on Perceptive Processing, Artificial Life, Autonomous Agents and Microrobotic Systems Laboratoire de Microinformatique, LAME-EPFL, CH-1015 Lausanne, Switzerland. Fax: (021)693-5263
12-16 September Smolenice Castle Slovak Republic	6th International Conference on Artificial Intelligence and Information-Control Systems of Robots Slovak Academy of Sciences, Dubravska cesta 9, 842 37 Bratislava, Slovak Republic.
27-29 September Baden-Baden Germany	IFAC Conference on Integrated Systems Engineering VDI/VDE Gesellschaft Mess- und Automatisierungstechnik P.O. Box 10 11 39, D-40002 Dusseldorf, Germany. Fax: (0211) 6214-575
3-7 October Greece	ICNM-2: Second International Conference on Nanostructured Materials Universitat des Saarlandes. Fax: +49 681-302-5222
4-7 October Golden, Co.	Conference on Renewable Energy (Contact: Dr. F. Abulfotuh, NREL, 1617 Cole Blvd., Golden, Colorado 80401, USA. Fax: (303)231-1196.
6-7 October Aachen, Germany	37th International Colloquium on Refractories (Forschungsgemeinschaft Feurerfest eV, An der Elisabethkirche 27, D-53113 Bonn, Germany. Fax: 49 228 91 508 55)
9-14 October Sao Paulo, Brazil	International Congress on Metallurgy and Materials Technology Brazilian Metallurgy and Materials Society, Rua Antonio Comparato, 218, 04605-030 Sao Paulo, Brazil. Fax: (11) 240-4273
18-20 October Mons, Belgium	Ceramic-Ceramic Composites (Belgian Ceramic Society, Ave Gouverneur Cornez 4, B-7000 Mons, Belgium. Fax: 32 0 65/34 80 05)
19-21 October Mexico City Mexico	The Technologies of Plastics: Materials, Processes and Applications (Seminars and Conference Group, Freehold Executive Center, 4400 Route 9 South, Suite 1000, Freehold, NJ 07728, USA. Fax: +1 908 409 1431)
19-21 October Amsterdam The Netherlands	The recycling of Metals ASM Int'l Europe, rue de l'Orme 75, 1040 Brussels, Belgium. Fax: 32/2-733.43.84

25-28 October Nagoya, Japan Tokyo	International Symposium on Electromagnetic Processing of Materials Iron and Steel Institute of Japan, Keidanren Kaikan, 3rd floor, 1-9-4 Otemachi, Chiyoda-ku, 100, Japan. Fax: (81) 3-3245-1355
1-5 November Düsseldorf, Germany	Glastec '94 (Glastec Office, Düsseldorfer Messegesellschaft mbH, Nowea, Postfach 32 02 03, D-4000 Düsseldorf 30. Fax: 02 11 45 60 668)
2-4 November Würzburg, Germany	New Materials Symposium Forschungszentrum Jülich, PO Box 19 13, D-52425 Jülich, Germany. Fax: +49 2461 612398.
7-10 November Dearborn, Michigan	10th Annual ASM/ESD Advanced Composites Conference Exposition ASM International and The Engineering Society (ESD). ASM International, Materials Park, Ohio 44073-0002, USA. Fax: 216/338-4634
11-15 November Beijing, China	Chinaplas '94 (Adsale Exhibition Services Ltd., 14/F Devon House, Taikoo Place, 979 Kings Road, Quarry Bay, Hong Kong. Fax: +852 516-5024)
14-18 November Los Angeles, California	20th International Symposium on Testing and Failure Analysis ASM International Electronic Materials and Processing Division; Materials Park, Ohio 44073-0002, USA. Fax: 216/338-4634
14-18 November Los Angeles, California	Electronic Materials and Processing Symposium ASM International, Electronic Materials and Processing Division, Materials Park, Ohio 44073-0002, USA. Fax: 216/338-4634
15-17 November Warwick, UK	3rd International Conference on the Behaviour of Materials in Machining - solutions to your Machining Problems The Institute of Materials, 1 Carlton House Terrace, London SW1Y 5DB, UK. Fax: 071 823 1638
28-30 November Malaysia	Conference on Renewable Energy Prof. B. Yatim, Faculty of Physical and Applied Sciences, Universiti Kebanagsaan Malaysia, 43600 UKM Bangi, Selangor Darul Ehsan, Malaysia. Fax: 6 03 8256086
6-8 December Brussels, Belgium	R&D on Industrial and Materials Technologies Preliminary Programme of the 5th EC Conference; DG XII - Science, Research and Development
8-10 December Greece	Symposium on Solar Energy and Buildings Prof. N. Chrysochoides, President CRES, 19th Km Marathonos Ave., 19009 Pikermi-Attikis, Greece. Fax: 0030 1 6039904

1995

19-20 January Dublin, Ireland for	European Workshops on Eco-Products Research Projects—New Materials Impacts on the Environment (cleaner technologies) - Design Health and Waste Management (European Foundation for the Improvement of Living and Working Conditions, Loughlinstown House, Shankill, Co. Dublin, Ireland. Fax: +353 1 282 6456
26-31 March Orlando, Florida	Corrosion/95 Symposium Controlling the Decaying Infrastructure (Symposium Chairman Victor Chaker, Port Authority of NY and NJ, One World Trade Center, 72-S, New York, NY 10048, USA. Fax: (212) 435-4593).
27-30 March Karlsruhe, Germany or Hawaii, USA	International Conference on Intelligent Autonomous Systems Topics will include: Smart Sensors, System Design Tools, New Applications, etc. (Center for NDE, 102 Maryland Hall, The Johns Hopkins University, Baltimore, MD 21218, USA)

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