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The Challenge for High Polymers in Medicine, Surgery, and Artificial Internal Organs

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SUMMARY

High polymers are used in medicine, surgery, or artificial organs in three ways: 1) to construct complete artificial replacements for human organs, 2) to repair, sustain, or augment function of normal organs, and 3) to provide a biochemical function.

Artificial hearts, heart lung machines, and artificial kidneys are examples of artificial organs that man is designing and building to replace natural organs. Plastics are used widely in their construction. Plastics offer a variety of properties needed for these applications, including ease of fabrication, chemical inertness, and nontoxic properties, and a wide range of physical properties in hardness, flexibility, and permeability.

Externally, as adjuncts or assists to natural organs, there are many applications of plastics in present use from clothing to glasses to dentures. Internally, the applications include vascular prostheses, check valve balls for heart valves, encapsulating resins for pacemakers, meshes and foams for reconstructive surgery, drainage tubes, and cannulae for hemodialysis. The plastics most widely used in surgical implants are polytetrafluoroethylene, polypropylene, saturated aromatic polyesters, and polysiloxanes. Growing use is being made of segmented polyurethanes, acrylics, and epoxy resins. Experimental work is under way on polyelectrolytes and various hydrogels based on polyhydroxyl compounds.

The newest class of applications of high polymers is that wherein the polymer has a definite and specific chemical interaction with the biochemistry of the body, i.e., it plays a pharmaceutical role. Examples of this include: 1) synthetic ion exchange resins for absorbing metabolites from the blood; 2) synthetic polyelectrolytes capable of absorbing specific viruses; 3) synthetic polymers such as (a) polyinosinic-polycytidylic acid (a synthetic ribonucleic acid) or (b) a copolymer of vinyl pyran and an undisclosed comonomer which promotes the production of interferon, a chemical substance normally produced by cells as an antiviral agent; and 4) synthetic natural-like polypeptides, enzymes, and chemical modifications of these with enhanced biologic activity.

The future of the use of high polymers in these applications appears to be in the earliest stages. Half a million Americans die each year of heart disease and 60,000 die of kidney disease, hence the potential for artificial versions of these organs is very large. The use of surgical devices is growing steadily. The use of polymers as drugs has not yet been tapped. In 50 years, biochemists will have a battery of synthetic polymer drugs which will cure many diseases, prevent cancer, speed wound healing, and eventually, it is hoped, provide a chemical regime for regeneration of lost limbs and organs.

INTRODUCTION

The technical challenges presented the polymer chemist by aerospace, hydrospace, and a myriad of industrial applications are well known. They have involved the development of lightweight, high-strength materials for service from cryogenic temperatures to temperatures above 600°C. Materials with high structural strength and adhesive properties and resistance to exotic chemicals have been the focus of interest. Revolutionary advances have occurred in cost reduction and product improvement. The opprobrious adjective "cheap" is fading from common usage as a generic modifier for the noun "plastic." In short, today's plastics are more and more assuming the character of known and understood materials, like steel and concrete, where their successful application is merely a function of proper engineering design.

Yet a far more challenging field than any of these has scarcely been touched by the polymer chemist—the design of high polymers for use in medicine, surgery, and artificial internal organs.

This field is still in its infancy, but enough progress has been made to indicate how sophisticated the polymers of the future will have to be and how rewarding will be their successful development.

Most applications for plastics not concerned with medical applications usually have four or five critical or mandatory requirements – usually tensile strength, compressive strength, adhesion, thermal shock resistance, and chemical resistance. Properties such as cure rate, viscosity at time of application, vapor pressure, and gel stage solubility are not of great concern, since curing ovens can always be run at different operating conditions, cure times can be extended to overnight, selection of solvents for application can be varied, etc.

However, for medical and surgical applications, the requirements become more and more complex the more one attempts to have the high polymer or plastic composition assume a natural role within the living body. Thus, the requirements on a plastic tube to carry blood during blood donation are not as complex as those required by a long term in-dwelling catheter, which again are not as demanding as those for a plastic artificial blood vessel, etc., which are not as demanding as those of a bone adhesive intended to cure in the body.

This paper is intended to outline some of the problems that face medical science, to indicate how high polymers have provided some solutions, and to indicate what challenges lie ahead.

The principal use of polymers in surgery and artificial organs is as structural plastics.

Plastics are used because they are:

1. Light weight.
2. Readily available and low in cost.
3. Easy to form, mold, cut, thread, and otherwise fabricate.
4. Relatively strong (on a strength-to-weight basis) and mechanically durable.
5. Relatively inert and chemically stable; they do not corrode or set up electrolytic cells.
6. Nonconductors of heat and electricity.
7. Transparent.

The plastics which enjoy the greatest use in this field today are:

1. Silicone rubber.
2. Teflon.

3. Polypropylene.
4. Polyvinyl alcohol.
5. Polymethylmethacrylate.
6. Aromatic polyesters (Dacron).

The structure of these polymers is shown in Figs. 1 and 2.

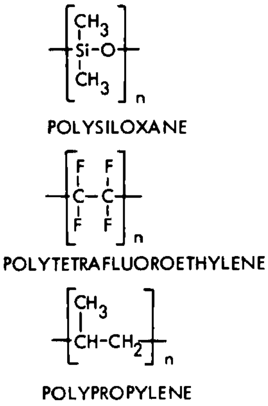

Fig. 1. Polymers most commonly used for surgical implants.

The structure of natural polymers in the body are shown in Fig. 3, wherein the highly complex side chains, ring structures, and stereospecific nature have been reduced to simplicity to show the backbone of these polymers as being those of polyamides, polyethers, and polyesters.

Comparison of the structure of the popular surgical plastics allows several conclusions to be drawn.

1. The popular plastics are generally fully polymerized before implantation or use.
2. Their monomers are either very volatile or very soluble or otherwise capable of being extracted before implantation.
3. The general chain composition is composed of generally stable chemical bonds, rather different than those found in the natural polymers, so that the body's hydrolyzing conditions and chain breaking enzymes find it difficult to degrade the polymer chain.

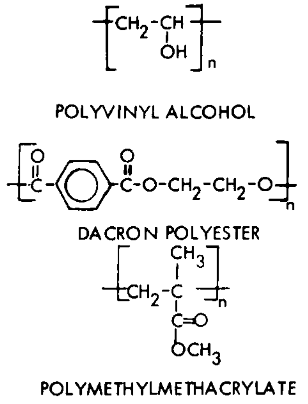

Fig. 2. Polymers used in some surgical applications.

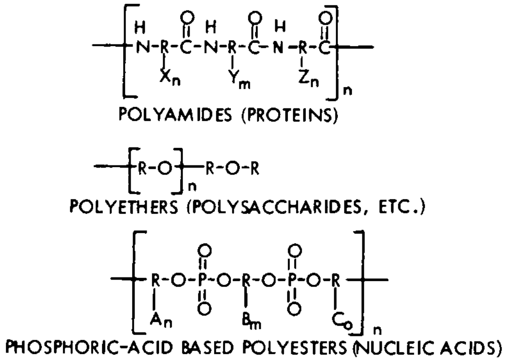

Fig. 3. Natural polymers in animal tissue, classification.

These plastics and other plastics are used for a variety of applications:

1. Sutures.
2. Tubing for handling blood.
3. Heart valves.
4. Components for artificial kidneys and blood oxygenators.
5. Artificial skin and covering for prosthetic devices.
6. Plastic artificial corneas.
7. Maxillary-facial reconstructions after surgery.
8. Artificial blood vessels.

9. Hip socket prostheses.
10. Drainage tubes.
11. Reconstructions of the trachea, larnyx, and other passageways.
12. Insulation of implanted electrical devices.

By far the most dramatic uses to date are their uses in the construction of artificial organs.

MEMBRANES

One of the most important structures in the living body is the membrane. Not only are cell walls highly specialized membranes, but the primary functioning member of numerous organs such as the lungs, kidney, and brain membrane is to provide membrane type functions [1].

At the present stage of the technology the largest single use for membranes in medicine concerns the artificial kidney. Here, membranes are used to filter metabolic waste products from the blood of uremic patients. Cellophane is the material of choice and has been for the last 20 years.

Medical grade cellophane contains pore sizes of about 25 Å, permitting the indiscriminate passage of molecular weights below about 4,000 and excluding all the larger species. When ultrafiltration is used, passage of molecules as large as insulin (MW 6,000) occurs [2]. Pore sizes can be increased to permit passage of solutes with molecular weights of at least 134,000 but again without specificity [3]. This indicates the general limitation of present synthetic films. Being semipermeable, interchange reactions follow pressure gradients, with transportation limited to molecular volumes smaller than the size of the pores.

Looking into the future, one can envision sophisticated systems which discriminate on the basis of selected characteristics, such as stereospecific structure, electrical polarizability, or solubility characteristics of the molecules, so that the efficiency of artificial kidneys would be much enhanced. To date, a very limited selectivity has been encountered with films of block copolymers where a hydrophobic block portion provides strength and a hydrophilic portion swells to permit some degree of diffusion transport [4].

On the basis of present research, it appears that hollow fibers will permit marked advances in the size, at least, of artificial kidneys [5].

For very small molecules, films are presently available which provide transportation rates which are a function of solubility and diffusion of these solutes in the membrane material. Silicone rubber films are the most widely investigated of this type, and thin films of silicone rubber are presently used in some designs of heart lung machines to provide O_2/CO_2 transport [6], but the disadvantages of such equipment continue to make bubble oxygenators, which contain no membranes at all, the devices of choice at most facilities in spite of the problems arising clinically because of the gas-blood interface.

These are the challenges in the field of artificial kidneys and artificial lungs for membranes, but needs exist for better synthetic skin substitutes for use as wound dressings, especially in the case of burns. Membranes are needed which can be used to envelop enzymes and drugs so that they can be buried under the skin to provide a long-time biochemical function.

BLOOD COMPATIBLE INTERFACES NEEDED FOR ARTIFICIAL HEARTS AND ARTIFICIAL BLOOD VESSELS

A major need exists for materials that are compatible with blood. Such materials would be useful in artificial blood vessels–to correct athero-sclerotic shrunken passageways or to eliminate aneurisms–and in cardiac assist devices and in artificial hearts–to replace or augment the function of the natural heart.

There are two main problems encountered when plastics and other foreign bodies are exposed to flowing blood in the body. First, the blood clots, and second, red blood cells are damaged, either mechanically or chemically, such that they lose their oxygen carrying capacity and the patient becomes anemic.

Research on producing plastics that do not cause clotting is proceeding along a number of empirical lines since the clotting mechanism, despite a large amount of work, is not yet fully understood or characterized. Approaches to date have been to synthesize polymers with a variety of specialized surfaces, such as low surface energy so as to prevent wetting, or with negative charges so as to resemble natural blood vessels [7]. To achieve low wetting, various block polymers, various hydrocarbon, and fluorinated and silicone based polymers have been used. To achieve negative surfaces, synthetic polyelectrolytes have been studied; surfaces and polymers have been prepared containing heparin, a naturally-occurring negatively charged low molecular weight polymer providing anticoagulant action; and surfaces containing cholesterol and sialic acid, as do the cell membranes of the endothelial cells lining the blood vessel.

Synthetic work to date has been conducted on the problem of red blood cell damage, because of the difficulty of measuring it and because clotting problems must first be eliminated.

BLOOD COMPATIBILITY ACHIEVED BY IN-GROWTH OF NEO-INTIMA

To date, the best compatibility with blood is achieved by permitting the body to deposit multiple layers of what is essentially new tissue on the prosthetic device in contact with the blood, which is, under optimum conditions, ultimately organized into a neoendothelial lining [8]. The depositions may be adhered within the loops of a delicate velour fabric of nylon or Dacron so that they do not come loose and lodge at distant sites to restrict or entirely block circulation in some part of the vascular tree; or the depositions may be quite thick, vascularized, and nourished by ingrowing tissue that invades fenestrations or interstices in the Teflon or Dacron prosthetic segment.

Reliance on natural tissue creates design problems with the fabrics involved and does not appear to guarantee against late complications as a result of continuing instability at the tissue-plastic interface. The concept, however, does represent the first tentative steps along the road of forcing the tissue to do what might normally be considered alien to its response pattern.

Conceivably some of the best current nonthrombogenic systems might be satisfactory if atraumatic techniques for prosthetic installation are assumed, along with optimum hemodynamics, but sufficient uncertainty in the literature exists to preclude a definitive assessment of the present art. The researchers appear to be some distance from their ultimate goal, and it seems quite unlikely that the goal will be met with off-the-shelf materials or by experimental products in search of markets.

In the design of blood vessels and artificial hearts or cardiac assist devices such as the intraaortic balloon, the need also exists for polymers possessing long-time fatigue life when exposed to the possibly degrading environment of the physiological environment. This requirement, added to requirements of being nonthrombogenic and nonhemolytic, compound the problem markedly. Dacron-reinforced silicone rubber bags appeared preferred to date [9].

BLOOD SUBSTITUTES

Another use of polymers which still poses a challenge is a suitable substitute for blood plasma. A hundred years ago physicians had not perfected blood transfusions, but even then they were looking for blood substitutes. One substance which had a short-lived vogue was whole goat's milk.

In more recent years efforts have been made to develop polymers that would provide the necessary osmotic and viscous properties to act as a plasma or blood extender. Polyvinylpyrrolidone was used extensively for this purpose toward the end of World War II for the treatment of German casualties. Subsequent investigations in the United States revealed that the material is retained for indefinite periods in the spleen, lymph nodes, liver, bone marrow, and adrenal cortex, leading to physiological and pathological alterations [10]. Another material, a natural-occurring polymer, high molecular weight Dextran–still used to some extent in diluting blood passing through the heart-lung machines to prevent sludging of the red cells–has the disadvantage of prolonging clotting time, which can create serious complications if its administration is connected with surgery. The inability of the body to metabolize the plasma substitute, or the undesirable side effects produced by it, have precluded the use of present materials in any large-scale manner. But if such a material were available that the body would accept unhesitatingly, it would substitute for the present pooled plasma–which is always in uncertain supply–and which directly contributes to the alarming extent of infectious hepatitis encountered in hospitals.

TISSUE ADHESIVES

Another challenging area for the polymer chemist is that of tissue adhesives. Adequate tissue adhesives would eliminate the trauma to tissue of sutures, and could permit better operations on various organs where suturing is very unsatisfactory.

The principal experimental tissue adhesive to date has been the alkyl cyanoacrylates (Fig. 4). These function well as adhesives because of their very high polymerization rates in the presence of nucleophiles and the absence of an inhibitor (SO_2 is used in the container and evaporates when the adhesive is applied), but still possess problems of toxicity to tissues. As indicated in Fig. 4, various alkyl chains have been studied in attempts to develop less toxic versions [11].

Polyurethanes have also been investigated, but with less success to date.

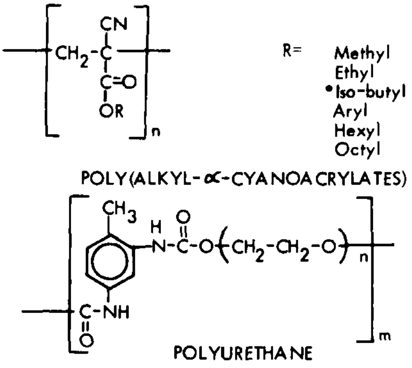

Fig. 4. Bone and tissue adhesives, experimental.

PHARMACEUTICAL POLYMERS

Up to this point, this article has discussed the use of plastics primarily as structural members in artificial organs or in reconstructive surgery. It would now be appropriate to discuss the new pharmaceutical polymers—synthetic high polymers that serve a biochemical or pharmaceutical need in the body.

Synthesis of Proteins and Enzymes

Such a discussion can be initiated by pointing to the recent synthesis of various proteins (insulin) and enzymes (ribonuclease) in their entirety, using monomeric starting materials and automatic chemical processing equipment [12, 13]. More recently, the complete determination of the amino acid sequence of the polypeptide gamma globulin—the key molecule of immunity—has been accomplished [14]. In regard to the synthesis of proteins, one can also point to less elaborate synthesis efforts wherein a suitable mixture of amino acids and catalysts are heated in a reactor at a suitable temperature for a suitable time. The resulting fragments of polypeptides and proteins have been found to display certain types of biologic activity, e.g., melanocyte-stimulating activity [15].

Composition of Antibiotics

Consider bacteriological agents a moment. Nearly all of the antibiotics developed in the period 1928-1968 have turned out to be peptides:

penicillin, gliotoxin, tyrothricin, tyrocidine, gramicidin A, and actinomycin [16].

Although comparatively few of these have had their structure fully elucidated by synthesis or analysis, enough has been done to learn that in most cases these are peptides which are cyclic, contain a percentage of D-amino acids in addition to the common L-amino acids, but they also contain a number of uncommon amino acids in place of certain of the 20 common amino acids.

The challenge inherent in producing antibiotics of known structure and use, and then producing further chemical modifications, is one which opens vast fields for research, especially for visionary syntheses polymer chemists and for theoretical reasoners who can lay down general principles of structure to guide synthesis work through the maze of infinite possibilities.

Thus, once one has demonstrated that large, complex molecules can be synthesized in their entirety, the natural challenge is to:

1. Go on to even longer more complex proteins.
2. Attempt to synthesize only portions of proteins and enzymes so as to fully determine exactly which parts of the molecule impart the biochemical activity.
3. Once it has been determined what structures and substructures impart the biological activity, it is natural to attempt to augment the biological activity by substituting more polar or less polar groups, or large or smaller steric groups into the molecule.
4. Or to attempt to incorporate the biologically-active groups into a polymer chain of different compositions, or different solubility, so that the function of the enzyme can be modified by virtue of changing its transport or retention within the body.

Polymeric pharmaceuticals could be thus longer lasting, instead of being excreted in 12 or 24 hr clearance times, or they could be held within certain types of tissue selectivity, etc., or they could be fabricated into films and membranes for uses not yet thought of.

Antiviral Polymers

There is also another side to the coin. Besides synthetic versions or modifications of natural-occurring types of proteins, enzymes, etc., there is the possibility of polymers which are completely synthetic and completely strange to the biochemist, but which because of their size, shape, and composition serve a biochemical role. Let us examine mankind's fight against viruses in this regard.

For decades, researchers have been developing vaccines to prevent many of the most serious virus-caused diseases. They have had great success in stamping out polio, and in controlling smallpox, measles, mumps, and most recently in development of a rubella (German measles) vaccine. But there is a host of viral diseases for which vaccines do not exist, ranging from the common cold to hepatitis and possibly even to certain forms of cancer.

Mankind needs medicines that will fight off the common cold, flu, eye infections, and cold sores, and drugs that will work against the viruses that are believed to cause hepatitis, uterine cancer, infectious mononucleosis, leukemia, and other diseases.

At least 200 viruses are known to infect humans. They float in the air and usually enter the body through the nose and throat. When the body has no resistance to them, the viruses take over the machinery of human cells and proliferate. The effect can be just a runny nose—or it can be the irreversible destruction of nerve tissue that is caused by the polio virus.

Vaccines protect against some viruses by building up a supply of antibodies in the human system. The drugs fight viruses two ways: by setting up a chemical barrier against them in the system, and by prompting the body to produce interferon, a protein which blocks the action of viruses.

Production of Interferon

It has been found that various synthetic polyelectrolytes are efficacious in causing the body's cells to increase their production of interferon.

Thus, polymers from maleic anhydride (Fig. 5), from maleic anhydride and ethylene, and from vinyl pyran and methacrylic acid (Fig. 5) can cause an increase in interferon production [17]. This is an exciting discovery because 1) it allows synthesis of a series of molecules of predetermined structure and molecular weight so that tools are available to investigate the biochemistry of the cell, and 2) the possibility of producing antiviral polymeric vaccines exists.

Absorption of Viruses by Polyelectrolytes

In addition, the possibility also exists that polymers can be synthesized that can selectively adsorb viruses and deactivate them and hold them until they are eliminated by the body's normal clearance mechanisms.

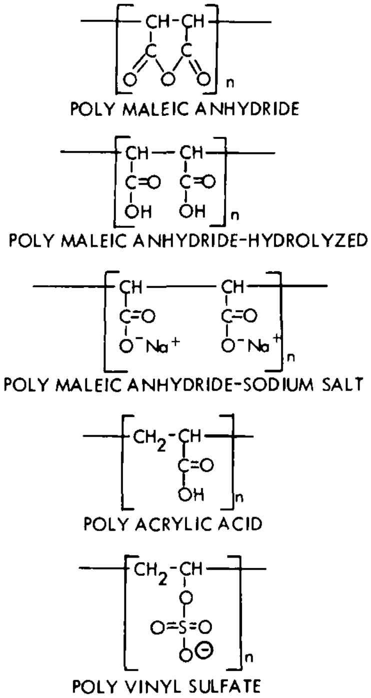

Fig. 5. Synthetic polyelectrolytes evidencing biological activity in causing production of interferon on changing course of embryonic cell differentiation.

Natural Monomers Polymerized in New Ways

In the fight against viruses, however, the chemist is not limited to nonnaturally-occurring polymers, but rather can use naturally-occurring monomers and rearrange them in different ways along the polymer chain so as to produce a nonnatural protein or a nonnatural nucleic acid, for example, and thus induce interferon production [18]. One such synthetic polymer has already been produced (Fig. 6).

Use of Synthetic Polymers to Cause Changes in Cell Growth

However, going deeper into cytology, it appears that not only can polymers cause the cell's production of chemicals to alter, as in the case of production of interferon, but polymers can be used to change the very nature of the cell itself.

Looking at growing embryological tissue, or at wound repair growth,

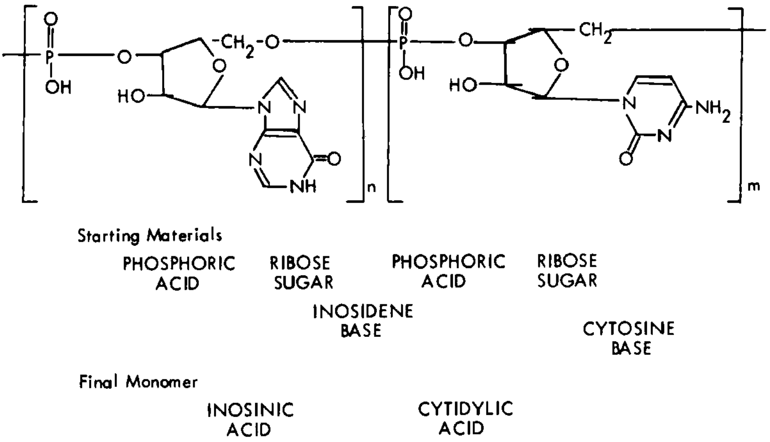

Fig. 6. Synthetic polymer made from naturally-occurring monomers found to induce production of interferon.

various cells go through various growth phases. In the earlier phases they are general types of cells, but at some point the cells differentiate, that is, they become specialized nongeneral cells. There are now clues that polymers can be used to control this differentiation.

In our own work, we have found that wound repair epithelium, growing in contact with certain charged polymers, i.e., polyelectrolytes (Fig. 7), appears to produce giant hair follicles as opposed the normal-sized hair follicles to be expected in skin wound repair [19].

Another investigator has found that exposure of the embryo of certain low phylum animals to polyvinyl sulfate causes a change in the differentiation of the ectoderm so that marked changes in the neural tissue and forebrain occur [20].

Another investigator has found that certain cells, when in contact with some but not other polymer surfaces and exposed to microampere direct currents, will dedifferentiate and then redifferentiate to another type of cell, opening up a whole new field of chemical physics [21].

Thus, the biomedical challenges to the high polymer chemist are greater in number and complexity and in inherent interest than those presented him from any other single area of human endeavor.

Even in the immediate future, the need for his services is acute, and the possibility of solid contributions, on the nonspeculative level, virtually guaranteed. Half a million Americans die every year of heart disease and

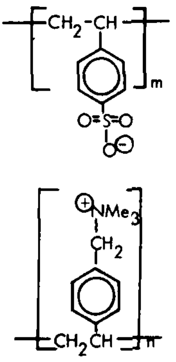

Fig. 7. Synthetic anionic-cationic polyelectrolytes found to cause growth of giant hair follicles.

60,000 of kidney disease, and liver and lungs falter and fail, and take their continuous toll among us.

Not only is the research challenging, but the potential commercial market, although varied, is huge, not only for artificial internal organs but for all forms of surgical prostheses. And the use of polymers as drugs has not been tapped. Drugs to correct underlying health problems would be in larger demand, surely, than the present market for materials to conceal the symptoms or to make physical reality less painful.

In 50 years biochemists will have a battery of pharmaceutical polymers which will cure many diseases, prevent cancer, speed wound healing, and eventually, it is hoped, provide a chemical regime for regeneration of lost limbs and organs. Depending on how well chemists respond to this challenge, it may even occur within our lifetimes, which, in turn, might be much longer as a result of this endeavor.

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