Chapter 15

BIOMATERIALS FOR MEDICAL PURPOSES PROGRESS PARALLEL WITH THE DEVELOPMENT OF CIVILIZATION

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INTRODUCTION

The main feature of today is the desire to increase the quality and duration of human life. A significant role in achieving this is played by successes in the development and use of new biomaterials, which are increasingly and more often used in medicine to support life and normal functioning of the body. Over the past 50 years, more than 40 different materials (ceramics, metals, polymers) have been used to treat, repair, and replace various parts of the human body, including skin, muscle tissue, blood vessels, nerve fibers, bone tissue, and more. The relevance and necessity of developing new biomaterials is due to the existing high demand for polymer materials for various fields of activity, primarily biomedical. The development of new materials for medical purposes, necessary for the contact of a living organism with the environment, is a task of high complexity. Specialized biocompatible materials are especially in demand for the new direction of medical materials science, formed in recent years – cell and tissue engineering, related to reconstructive surgery and the development of bioartificial organs. These studies are implemented at the intersection of the chemistry of high-molecular compounds, biotechnology, biophysics, molecular and cellular biology, and medicine and contain a complex of interconnected fundamental tasks. As a result of the rapid progress of various constituent parts of physico-chemical biology, a new direction in science and production emerged, which was named biotechnology. This direction has been formed over the last two decades and has already gained strong development. Knowledge about life processes, which is rapidly expanding, allows not only to adapt these processes for practical purposes, but also to manage them, as well as to create quite promising in practical terms new systems that do not exist in nature, although similar to existing ones.

In the 21st century, biomaterials are widely used in medicine, dentistry and biotechnology. Only 60 years ago, biomaterials, as we think of them today, did not exist and even the word "biomaterial" was not used. There were no manufacturers of medical devices (except for external prostheses such as limbs, fracture fixation devices, glass eyes and dental devices), no formalized regulatory approval procedures, no understanding of biocompatibility, and no academic courses on biomaterials. However, "raw" (ie, simple, untreated) biomaterials have been used with poor and mixed results throughout history. We trace the history of biomaterials from the earliest times of human civilization to the beginning of the XXI century. Therefore, it is appropriate to divide the history of biomaterials into the following key eras: biomaterials and civilization; the era of the "hero-surgeon" (the period before and after World War II); creation of biomaterials / engineering devices; the modern era leading to the new millennium[1].

The growth of the biomaterials market is mainly due to such factors as increased funds and grants from government bodies around the world for the development of new biomaterials, increased demand for medical implants, increased cardiovascular diseases, and increased research in the field of regenerative medicine. In addition, a significant increase in plastic surgery and wound healing is expected to drive the growth of the biomaterials market in the coming years. In recent years, orthopedic implants with a porous coating and completely or partially porous have gained immense popularity. This is explained by the fact that porous structures reduce the modulus of elasticity and stimulate bone growth around the implant. Powder metallurgy, 3D printing, and additive manufacturing are among the potential methods for producing porous metal and ceramic implants. Rising demand for smart biomaterials that generate and transmit bioelectrical signals similar to native tissues for precise physiological functions is also expected to drive market growth. Piezoelectric scaffolds are smart materials that play an important role in tissue engineering. They stimulate signaling pathways and, therefore, improve tissue regeneration in the affected area. The polymer products segment dominates the market and is expected to continue to lead during the forecast period owing to its wide range of product applications. The widespread availability of biopolymers and advanced polymers for bioresorbable tissue fixation and other orthopedic applications is also expected to accelerate revenue generation in the segment. Polymeric biomaterials are one of the cornerstones of tissue engineering. Continuous advances in technologies such as microfabrication, surface modification, drug delivery, nanotechnology, and high-throughput screening play an integral role in expanding the use of polymeric materials in tissue

[1] Biomaterials Science. An Introduction to Materials in Medicine / B. D. Ratner, A. S. Hoffman, F. J. Schoen, J. E. Lemons. 3rd edn. Academic Press : Elsevier Inc. 2013. 1519 p.

engineering. Natural biomaterials are expected to witness lucrative growth rates during the forecast period owing to various product benefits on synthetic biomaterials from the point of view of biodegradability, biocompatibility and remodeling. Due to these advantages, they are mostly used to replace or restore the structure and function of damaged organs or tissues. The size of the global biomaterials market is driven by factors including an increase in the elderly population susceptible to diseases such as cardiovascular, dental, orthopedic and neurological. Biomaterials are widely used in hip and knee replacement operations. High demand for implantable devices, which are widely used for chronic degenerative diseases such as orthopedic and cardiovascular, has accelerated market growth. The orthopedic applications segment dominates the biomaterials market. The use of metal biomaterials in orthopedic surgery due to their high load-bearing capacity is one of the factors driving the growth of the segment. In addition, the continuous development and introduction of advanced orthopedic implants by market vendors will also be a significant driver.

1. "Biomaterials" and civilization

The introduction of non-biological materials into the human body occurred throughout history. Human remains found near Kennewick, Washington, USA (often referred to as "Kennewick Man") have been dated (with some controversy) to 9000. Described by archaeologists as a tall, healthy, active man, this individual roamed the region (now known like southern Washington), with a spearhead embedded in the thigh. It probably healed and did not significantly hinder his activity. This "unintentional" implant illustrates the body's ability to cope with implanted foreign material. The tip of the spear was supposed to be similar to modern biomaterials, but it was an implant of an alien material that was "portable". Another example of the introduction of foreign material into the skin, dating back more than 5,000 years, is tattooing. Carbon particles and other substances probably caused the classic foreign body reaction.

Dental implants in early civilizations date back to the ancient world, and some of the earliest attempts at dental implantation were attempts to fill gaps left by missing teeth in individuals both living and dead[2]. In China 4,000 years ago, bamboo pegs were used to fill gaps left by missing teeth. In Egypt 3,000 years ago, a king had a copper peg in the gap left by a missing upper tooth. This brass peg was put up after his death. Even 2,300 years ago, an iron false tooth was found in a corpse in a Celtic grave in France. Again, it is assumed that this tooth was placed after the person died. In countless

[2] Historia de los Biomaterialeshttps [Electronic resource]. Access mode : https://www.timetoast.com/ timelines/historia-de-los-biomateriales-09d9d538-857e-40b4–9645-672e72642506.

civilizations 2,000 years ago, animal and human teeth (often from slaves or poor people) were used to replace missing human teeth. The Mayans made mother-of-pearl teeth from seashells around 600 AD and apparently achieved what we now call osseointegration, that is, seamless integration into bone[3]. The basis of these procedures was not a scientific understanding of material science, biological understanding or medicine[4]. However, their success and longevity is impressive and highlights two points: the "farewell" nature of the human body and the persistent desire to overcome the loss of physiological / anatomical functions with the help of an implant. Thousands of years ago, there is some evidence that seams could be used even in the Neolithic period[5]. At the beginning of history, large wounds were closed mainly by one of two methods – cauterization or suturing. Linen seams were used by the early Egyptians, and catgut (from the English catgut – "calf entrails") – in the Middle Ages in Europe. Metal sutures are first mentioned in early Greek 40 literature. Galen of Pergamon (c. 130–200 AD) described gold wire ligatures. In 1816, Philip Physick, a professor of surgery at the University of Pennsylvania, suggested the use of lead wire sutures, noting that there was little reaction. J. Marion Sims of Alabama commissioned a jeweler to make sutures from silver wire, and in 1849 he performed many successful operations with this metal. Despite the problems that appear to have arisen without knowledge of sterilization, toxicology, immunological response to foreign biological materials, inflammation, and biodegradation, sutures have been a relatively common manufactured biomaterial for thousands of years. Artificial hearts and organ perfusion In the fourth century BC. e. Aristotle called the heart the most important organ in a living organism. Galen suggested that veins connected the liver to the heart to circulate "vital spirits throughout the body through the arteries." English physician William Harvey in 1628 supported a relatively modern view of the heart's work when he wrote: "One role of the heart is to convey the blood and move it through the arteries to the extremities everywhere." Considering that the heart is a pump, it was logical to think about replacing the heart with an artificial pump. In 1812, the French physiologist Le Gallois expressed the idea that organs can be kept alive by pumping blood through them. From 1828 to 1868, a number of experiments on organ perfusion using pumps were conducted. In 1881, Etienne-Jules Marais, a brilliant scientist and thinker who published and invented photographic technology, motion studies, and physiology, described the artificial heart apparatus. In 1938, aviator and engineer Charles Lindbergh

[3] Bobbio A. The first endosseous alloplastic implant in the history of man. Bull. Hist. Dent. № 20. 1972. P. 1–6.

[4] . False teeth of the Roman world / E. Crubezy, P. Murail, L. Girard, J-P. Bernadou // Nature. Vol. 391. 1998. P. 29.

[5] Scott M. 32,000 years of sutures / M. Scott // NATNews. Vol. 20, No. 5. 1983. P. 15–17.

and surgeon and Nobel laureate Alexis Carrel wrote the visionary book Organ Culture. This book is a seminal document in the history of artificial organs and deals with pump design (called the Lindbergh pump), sterility, blood damage, nutritional requirements of perfused organs, and mechanics. In the mid-50s of the XX century. Dr. Paul Winchell, better known as a ventriloquist, patented an artificial heart. In 1957, Dr. Willem Kolf and a team of scientists tested an artificial heart on animals. Contact lenses Leonardo da Vinci developed their concept in 1508. In his essays, he noted that the optics of the human eye can be changed by placing the cornea directly in contact with water. In the archive of the great artist and scientist of the Italian Renaissance, there is a drawing of "eyes with a bathtub filled with water." The front surface of the bathtub is made in the form of a convex lens. Such "liquid glasses" appeared as a prototype of modern contact lenses. In the manuscripts of René Descartes from 1637, there are drawings of another interesting device that is directly related to contact vision correction. This device consisted of a tube that was filled with water, one end of the tube was covered with a lens, and the other was placed directly in front of the eye. Thus, the first optical system, similar in principle to modern contact lenses, was created. The use of lenses that are in direct contact with the eye was first theoretically substantiated in 1730 by De Lamur in his dissertation. Later in 1801, Thomas Jung conducted experiments with a short tube filled with water and equipped with a biconvex lens. This device was used to compensate for eye refraction defects. And in the works of the English physicist John Herschel, published in 1845, the contact correction of corneal astigmatism was theoretically substantiated. Based on the Descartes-Young tube, a hydroscope was created to correct vision problems associated with corneal deformation. This stage in the history of the development of contact correction must be considered intermediate, since these devices were uncomfortable, bulky, and also exhausted the skin around the eyes. This device was a geometric eyepiece system made in the form of a half mask. The infraocular space was filled with water, which was used to make contact with the eyes. Despite all the inconveniences, some patients still used hydroscopes due to the extreme need for contact vision correction. And one year later, in 1888, the Swiss ophthalmologist Adolf Gaston Eugen Fick (nephew of Adolf Eugen Fick from the famous "Fick's Law of Diffusion") publishes an article entitled "Contact Glasses" in the magazine "Archiv fur Augen Heilkunde". This was the first message about contact lenses. At first, Fick conducted experiments on animals, and only then dared to move on to the human eye. After first making plaster casts, Fick blew his first lenses. In the same year, the use of similar contact lenses was reported by the French ophthalmologist Eugene Kalt for the treatment of a patient with keratoconus. Further details on wearing contact lenses were published in August Müller's dissertation in

1889. The theory of contact vision correction developed by Muller was based on a series of tests conducted on his myopic eyes. Müller used contact lenses made by the optician Himmler without knowing anything about Fick's discovery. Therefore, August Müller is also counted among the pioneers in this field of optical vision correction. The first contact lenses were scleral, that is, they had a large diameter and were similar to single-wall eye prostheses. The optical part of such a contact lens rested on the sclera, the central optical part refracted the rays. A liquid with glucose or saline was used to fill the space under the lens. In the future, contact lenses were improved by various ophthalmologists and opticians (including D. Sulzer (1892), G. Dore (1892) and others). Müller, a famous glassblower from Wiesbaden (Germany), set up the first production of contact lenses. Although Müller's lenses remained only conventional ocular prostheses, they had a number of advantages over earlier designs. So, the scleral part was made of white glass, and the optical part was made of transparent. Between 1914 and 1924, contact lenses became more affordable thanks to mass production in Jena by the famous German optical company Carl Zeiss. To ensure the possibility of choosing the optimal shape of the lens for a particular eye, the company produced sets of contact lenses. After the "fitting" the most convenient lens was made an individual scleral lens. Also, unlike Muller lenses, Zeiss lenses provided better adaptation due to grinding. The production of scleral lenses from Muller's glass and the improvement of the optical forms of Zeiss' lenses culminated in the late 1920s of the 20th century. the first stage in the history of the development of contact lenses. The main achievement of this period is the development of serial production of optically flawless scleral lenses. The second stage (1929–1948) is marked by attempts to improve existing models in terms of form and adaptation. In 1929, István Czapody proposed a method of individually selecting the shape of the scleral lens based on casts of the eyes made with the help of special plastics. But the method did not become widespread due to danger, inconvenience and high cost. In the future, Hungarian ophthalmologists Istvan Czapody, Joseph Dallos, and I. Dyerfi (1938) made a great contribution to improving the methods of selecting and manufacturing contact lenses. They proposed a technique for manufacturing individual scleral lenses by pre-removal of casts from the eye and preparation of forms based on them. In the 30s of the 20th century, casting of lenses according to a template began to be actively practiced. This method of production was first used by the American optometrist Theodore Obrig, who discovered that the intolerance of contact lenses is due to their pressure on the limbus area. Thus, the third period of the history of the development of contact correction is characterized by the beginning of serial production of contact lenses, a significant spread of their use in optics, the beginning of use for diagnostic purposes, as well as as a

prolonged ophthalmic medicinal form in combination with saturation with pharmacological drugs. Until 1936, all scleral lenses were made of glass. Dierfi suggested plastic as a material for making contact lenses. One year later, V. Feinblum, an American ophthalmologist, began manufacturing lenses with a plastic scleral part and a glass cornea. In the same year, Dierfi and Obrig produced contact lenses entirely from plastic – polymethyl methacrylate. The central optical part of the scleral lens was placed in front of the cornea, the peripheral support or optical part was adjacent to the sclera and held the lens on the eyeball. The use of new material allowed to significantly improve the quality of products. Plastic has the same high transparency as glass, does not break, weighs less, does not interact with eye tissues, is harmless. Due to the excellent technological properties of the material, new, more efficient methods of manufacturing lenses have become available. Dierfi pressed contact lenses. Later, Dallos discovered the method of turning, which became widely used[6]. This method was perfected by Obrig in 1937. Lens selection methods have also been significantly improved. In 1938, Theodore Obrig proposed to use a fluorescein solution to assess the position of the lens on the eyeball, which fluoresced when illuminated in blue and allowed to assess the thickness of the sublens space in different areas of the lens. After that, the lens parameters were adjusted. Despite all the improvements, scleral lenses had many disadvantages − heavy weight, large size, immobility on the eye, difficult exchange of tears in the sublens space, limited access of oxygen to the cornea. All these factors affected the portability of the lenses and limited the time they were worn. In addition, the process of selecting and manufacturing scleral lenses remained expensive and time-consuming[7]. The wearability of the lenses could not be improved even by using polymethyl methacrylate (PMMA) or by using fenestration, a special treatment to increase oxygen access to the sublens space. In 1936, New York optometrist William Feinblum proposed scleral lenses made from a combination of glass and plastic that were significantly lighter than the old double-glazed lenses. In 1948, California optician Kevin Tuohy introduced the first contact lenses that resembled modern gas-permeable contact lenses. These all-plastic lenses were called "corneal" contact lenses because they were smaller in diameter than earlier contact lenses and covered only the clear front surface of the eye (the cornea). Early hard lenses were made of a non-porous plastic material called PMMA, these lenses were not gas permeable but were designed to move with each blink so that oxygen-deprived tears could "roll" under the lens to keep the cornea healthy. Correctly fitted PMMA

[6] Чиж І. Г. Теорія оптичних систем. Підручник. К. : КПІ ім. Ігоря Сікорського, 2021. 426 с.

[7] Born M., Wolf E. Principles of optics: electromagnetic theory of propagation, interference and diffraction of light. 7th ed. CUP, 1999. 952 p.

corneal contact lenses could be worn for 16 hours or more. Advances in lens manufacturing technologies and the knowledge of ophthalmologists led to a mass appeal to these rigid plastic contact lenses in the 50s and 60s of the XX century. The biggest event in the history of contact lenses was the invention of the first hydrophilic ("water") hydrogel soft contact lenses by Czech chemists Otto Wichterle and Dragoslav Lim in 1959. The first impetus to work on the development of soft contact lenses was his chance conversation on the train on the way from Olomouc to Prague in 1952. A partner (Dr. Poore) read an expert article on the possibilities of eye replacement surgery. Wichterle realized that plastic would be a better material for implants than precious metals. Therefore, he began to develop a theory of a three-dimensional hydrophilic polymer that would be well tolerated by the eye. The most suitable gel was polyhydroxyethyl methacrylate (PHEMG), which absorbed about 40% of water, was transparent and had good mechanical properties. Initially, the gel was poured into molds, but the lenses broke when the molds were opened and had irregular edges because there was a problem with its processing. However, in 1958, with Wichterle's dismissal from the institute, the study of hydrophilic gels and lenses was liquidated. In 1961, the scientist came up with a completely new method of processing the PGEMG gel-casting in open rotary molds, but since there was no opportunity to continue the development of the implementation of the invention in the Czechoslovak Academy of Sciences, Wichterle began to practice this method at home. Therefore, at the end of 1961, he managed to prove in his apartment that high-quality contact lenses can be produced at minimal cost by the method of monomer centrifugal casting in rotary molds. The first device for making contact lenses is very famous, because it was assembled from a set of children's constructors of the brand Merkur. After successfully testing these lenses, in a clinic with Dr. Dreyfuss, Wichterle thought that their production was connected with great economic interests, especially in the USA. Similar conclusions were reached by state institutions, and therefore Wichterle proposed to develop lens research within the framework of a state institution. But 49 he demanded forty workers to carry out work outside the institute, because he claimed that this study does not belong to the Institute of the Academy of Sciences[8]. Since 1963, when manufacturing methods improved, interest in contact lenses, as well as confidence in them, increased. A US response was also received, and after several months of negotiations, a license agreement was signed in Prague on March 12, 1965, with Robert Morrison and the National Patent Development Corporation (NPDC), represented by Martin Pollack and Jerome Feldman. They founded the 50 joint-stock company "Corporate Flexible Contact Lens", whose sublicense partner in 1966 was Bausch & Lomb − one of the most important manufacturers of

[8] Отто Віхтерле[Електронний ресурс]. https://en.wikipedia.org/wiki/Otto Wichterle.

contact lenses today. When the Food and Drug Administration granted a license to sell the lenses in the U.S. in March 1971, B&L's stock rose so dramatically that the company's equity grew by $250 million overnight. Because of their greater comfort, soft contacts soon became more popular than rigid PMMA contact lenses. Today, despite the presence of rigid gas-permeable contacts, which often provide clearer vision than soft lenses and extremely good oxygen permeability, more than 90% percent of contact lenses prescribed in the United States are soft lenses. In 1981, lenses for long-term wear appear in the USA and Western Europe. In 1987, contact lenses that allow you to change the color of your eyes appear for the first time. In 1996, for the first time, lenses with a filter that protect the eyes from the effects of ultraviolet light appeared on sale. The 2000th year was marked by the appearance of the first contact lenses made of silicone hydrogels with high gas permeability, intended for long-term continuous (up to 1 month without removal at night) wear. Since the appearance of soft contact lenses, their design has been improved, which has made it possible to improve performance. The first lenses had a large thickness, which caused distortion of visual perception. As the lens design and manufacturing process improved, visual perception and wearability improved. The PHEMG polymer is still the basis of most soft contact lens materials, although various manufacturers use some modifications. The development of soft lenses gave a powerful impetus to the development of the contact lens industry, which is comfortable to use and requires almost no adaptation, thanks to which many of those who used glasses are switching to contact lenses.

Most implants prior to 1950 had a low probability of success due to poor understanding of biocompatibility and sterilization. Factors that contribute to biocompatibility include implant chemistry, leachability, shape, mechanics, and design. Early research, especially with metals, focused mainly on ideas from chemistry to explain the response to the implant. Perhaps the first study evaluating the bioreactivity of implant materials in vivo was conducted by H. S. Levert (1829). Gold, silver, lead and platinum have been studied in dogs, and platinum in particular has been found to be well tolerated. In 1886, bone fixation plates made of nickel-plated sheet steel with nickel-plated screws were investigated. In 1924, A. Zierold published a study of the reaction of tissues to various materials in dogs. Iron and steel were found to corrode rapidly, leading to resorption of adjacent bone. Instead, copper, magnesium, aluminum alloy, zinc and nickel discolored the surrounding tissues. Gold, silver, lead and aluminum were allowed, but the mechanical properties were insufficient. Stellite, a Co-Cr-Mo alloy, was well tolerated and durable. In 1926, M. Larg noted the inertness of stainless steel 18-8 containing molybdenum. By 1929, a vitalium alloy (65% Co – 30% Cr – 5% Mo) was developed and successfully used in dentistry. In 1947,

J. Cotton from Great Britain discussed the possible use of titanium and alloys for medical implants. Biocompatible materials should have several characteristics. First, they should not be toxic to cells. If a medical implant is placed and kills the surrounding cells, this will obviously cause complications for the patient. Second, the material should not cause an immune response. A common problem with medical implants is rejection, when the immune system identifies substances in the implant as foreign and tries to fight them. This leads to inflammation and infection and can affect the function of the implant. Biocompatible materials should also not cause chemical reactions that lead to injuries in the body.

The history of the development of plastics as materials for implantation is not as old as that of metals, because by the 40s of the XX century. there were few plastics. Perhaps the first article about the implantation of a modern synthetic polymer – nylon in the form of a seam – appeared in 1941. Already in 1939, articles were published about the implantation of cellophane, a polymer made from plants, which was used as a wrapping for blood vessels. The reaction to this implant was described as a "pronounced fibrotic reaction". At the beginning of the 40s of the XX century. articles appeared discussing the reaction to implanted PMMA and nylon. The first publication about polyethylene as synthetic material for implants dates back to 1947[9]. The production of polyethylene using a new technology of high-pressure polymerization, which was carried out as early as 1936, is described. This process made it possible to produce polyethylene without fragments of initiators and other additives. Ingraham et al. demonstrated good results during implantation (i.e. mild foreign body reaction) and attributed these results to the high purity of the polymer they used. In 1949, research was conducted that additives to many plastics have a tendency to "sweat", and this fact may be responsible for the strong biological response to these plastics. Scientists Livin and Barberio found a vigorous foreign body reaction to cellophane, Lucite, and nylon, but an extremely mild reaction to the "new plastic" Teflon[10].

2. The era of the "hero-surgeon"

During World War I, and especially at the end of the war, newly developed high-quality metal, ceramic, and especially polymer materials moved from wartime limitations to peacetime availability. The possibilities of using these strong inert materials immediately interested surgeons in the need to replace diseased or damaged body parts. Materials that were

[9] Ingraham F. D. Polyethylene, a new synthetic plastic for use in surgery / F. D. Ingraham, E. Jr. Alexander, D. D. Matson // JAMA. Vol. 135, No 2. 1947. P. 82–87.

[10] LeVeen H. H. Tissue reaction to plastics used in surgery with special reference to Teflon / H. H. LeVeen, J. R. Barberio // Ann. Surg. Vol. 129, No 1. 1949. P. 74– 84.

originally made for airplanes, cars, watches, and radios have been used to solve medical problems. These early biomaterials included silicones, polyurethanes, Teflon, nylon, methacrylates, titanium, and stainless steel. Historical context helps us appreciate the contributions made primarily by physicians and dentists. Immediately after World War II, there were few cases of surgeons collaborating with scientists and engineers. Doctors and dentists of this era saw fit to invent (improvise) where the life or functionality of their patient was at stake. In addition, there was minimal government regulatory activity and the protection of human subjects as we know it today was non-existent. The doctor was directly entrusted with the life and health of the patient, he had much more freedom than today for heroic actions when other possibilities were exhausted. These doctors read about the wonders of materials science after World War II. Looking at the patient opened up on the operating table, they could imagine replacements, bridges, canals and even organ systems based on such materials. Many materials were tested instantly. Some managed to do it by accident. These were high-risk trials, but they usually took place where other options were unavailable. The term "hero surgeon" seems justified because the surgeon often put life (or quality of life) at stake and was willing to make a huge technological and professional leap to fix a person. This era of biomaterials quickly ushered in a new order characterized by scientific/technical input, government quality control, and decision sharing before attempting new high-risk procedures. However, the foundation of ideas and materials for the field of biomaterials was built by courageous, dedicated, creative individuals, and it is important to look at this foundation to understand many of the views, trends, and materials that are prevalent today.

After World War II, Sir Harold Ridley, M.D., inventor of the intraocular lens (IOL), had the opportunity to examine pilots who had inadvertently had plastic shards implanted in their eyes from the broken canopies of Spitfire and Hurricane fighters. Debris from the dome of a Spitfire aircraft was the source of inspiration for the creation of intraocular lenses. At that time, it was believed that the human body does not perceive implanted foreign objects, especially in the eye – the body's reaction to a fragment or a bullet was cited as an example of the difficulties of implanting materials into the body. The eye is an interesting implant site because you can look inside through a clear window to observe the reaction. When Ridley did this, he noted that the shards healed in place with no further reaction, by his eye's standard. Today, we would describe this stable healing without significant ongoing inflammation or irritation as "biocompatible." This early observation of "biocompatibility" in humans may be the first using criteria similar to those used today. Based on this observation, Ridley traced the source of the plastic domes to ICI Perspex polymethyl methacrylate. He used this material to make

implantable lenses (IOLs) that, after some experiments, function well in humans as replacements for surgically removed natural lenses that have been clouded by cataracts. The first human implantation took place on November 29, 1949. Over the years, Ridley has been at the center of fierce controversy as he challenged the dogma against implanting foreign materials into the eye – it's hard to believe that the implantation of a biomaterial has caused such a stir. Due to controversy, this industry did not emerge immediately – it was the early 1980s, before IOLs became a major force in the biomedical device market. Insightful observations, creativity, perseverance and surgical talent of Ridley in the late 40s of the XX century. have grown into an industry that currently applies more than 7 million such lenses annually to people. Throughout human history, cataracts have meant blindness or a surgical procedure that required the recipient to wear thick, unsightly lenses that did not correct vision well. Ridley's concept, using a plastic material recognized as "biocompatible", changed the course of history and significantly improved the quality of life of millions of people with cataracts[11].

The first hip replacement was probably performed in 1891 by German surgeon Theodor Gluck, who used a cemented ivory ball. This procedure was unsuccessful. In the period 1920–1950, many attempts were made to develop a prosthesis for hip replacement. Surgeon MN Smith-Petersen in 1925 investigated the use of a glass hemisphere for placement on the hip joint. It failed due to low durability. Chromocobalt alloys and stainless steel have improved mechanical properties, and many variations have been investigated. In 1938, Judet brothers from Paris, Robert and Jean, researched an acrylic surface for hip procedures, but it had a tendency to loosen. The idea of using fast-setting dental acrylics to bond dentures to bone was developed by Dr. Edward J. Haboush in 1953. In 1956 Mackie and Watson-Farrar developed a "complete" hip with a metal acetabular cup that was fixed in place. Metal products probably led to a high rate of complications. It was John Charnley (1911–1982), working in an isolated tuberculosis sanatorium in Wrightington (Manchester, England), who invented the first truly successful hip joint prosthesis. A femoral stem, ball head, and plastic acetabulum proved to be a reasonable solution to the problem of replacing a damaged joint. In 1958, Dr. J. Charnley used a Teflon acetabulum with poor results due to residual wear. By 1961 he was using a high molecular weight polyethylene cup and had much better success rates. Interestingly, Charnley learned about high molecular weight polyethylene from a salesman who was selling new plastic gears to one of his technicians. Dr. Dennis Smith made an important contribution to the development of hip replacements by introducing Dr. Charnley to dentally developed PMMA cements and optimizing these

[11] Apple D. J. Sir Nicholas Harold Ridley, Kt, MD, FRCS, FRS / D. J. Apple, R. H. Trivedi // Arch. Ophthalmol. Vol. 120, No. 9. 2002. P. 1198–1202.

cements for hip replacement. Total knee arthroplasty borrowed elements of hip arthroplasty technology, and successful results were obtained in the period 1968–1972, when the leading surgeons were Frank Gunston and John Insolly.

The history of dental implants has already been described, in 1809 Maggiolo produced a gold implant placed in fresh extraction sockets to which he attached the tooth after a period of healing. This is remarkably similar to modern dental implant procedures. In 1887, this procedure was used with a platinum pin. Gold and platinum gave poor results over time, so this procedure was never common. In 1937, Venable used the surgical alloy Vitallium (vitallium is a trademark of a cobalt-based stellite alloy containing, wt. %: 25–35 Cr, 4–6 Mo, 1.5–3.5 Ni, 0.2–0 .35 C and is corrosion-resistant in oxidizing environments) and Co-Cr-Mo for such implants. At Harvard he applied the Vitallium screw implant, it was the first successful dental implant. This was followed by a number of developments in surgical procedures and implant design (eg, the endosteal scapular implant). Per Ingvar Branemark, an orthopedic surgeon from Lund University (Sweden), implanted an experimental device – a titanium cylinder that was screwed into a rabbit's bone to observe healing reactions. After completing the experiment, which lasted several months, he tried to remove the titanium device and found that it was firmly embedded in the bone[12] [13]. Dr. Branemark called this phenomenon "osseointegration" and investigated the use of titanium implants for surgical and dental procedures. He also developed low-impact dental implant surgical protocols that reduced tissue necrosis and increased the likelihood of good outcomes. Most dental implants and many other orthopedic implants today are made of titanium and its alloys.

Kidney failure for most of history was a death sentence lasting about one month. In 1910, John Jacob Abel made the first attempts to remove toxins from the blood at Johns Hopkins University. Experiments were carried out with rabbit blood, and it was impossible to perform this procedure on humans. In 1943, in Nazi-occupied Holland, Willem Kolf, a doctor just starting his career at the time, built a drum dialyzer system from a 100-liter tank, wooden rails, and 130 feet of cellulose sausage casing as a dialysis membrane. Some successes have been seen in saving lives when there was only one unpleasant outcome − kidney failure. Kolf took his ideas to the United States and in 1960 developed the "artificial washing machine kidney" at the Cleveland Clinic. A major advance in kidney dialysis was made by Dr. Belding Scribner of the University of Washington. Scribner developed a method of regular access to the bloodstream for dialysis treatment. Before that, only after a few

[12] Віталіум [Електронний ресурс]. Режим доступу : https://uk.wikipedia.org/wiki/Віталіум.

[13] Regeneration of bone marrow / P. I. Branemark et al. // Acta Anat. Vol. 59. 1964. P. 1–46.

procedures, the blood access points were used, and further dialysis was not possible. After seeing the potential of dialysis to help patients with acute pain, Scribner tells the story of waking up in the middle of the night with the idea of getting easy access to blood − a shunt implanted between an artery and a vein that exited through the skin in a "U" shape. Through the open part of the shunt, blood could be easily accessed. When Dr. Scribner heard about the new Teflon® plastic, he envisioned how to get blood out of and into blood vessels. In 1960, he, Wayne Quinton and David Dillard invented a revolutionary device – the Scribner shunt. This device used Teflon tubing for vascular access, a transcutaneous Dacron® cuff, and silicone rubber tubing for blood flow. Subsequently, the device saved the lives of many people with end-stage kidney disease around the world. The first patient treated was Clyde Shields. Thanks to treatment using a new bypass technique, he lived with chronic kidney failure for more than eleven years and died in 1971. Interestingly, Dr. Scribner refused to patent his invention because of its importance to medical care. An additional important contribution to the creation of the artificial kidney was made by chemical engineering professor Les Bubb (University of Washington), who, working with Scribner, improved the efficiency of dialysis and invented a mixer for dosing the dialysis fluid. The first dialysis center was opened in Seattle using these important technological advances. Scribner's invention created a new challenge for clinical practice and a moral dilemma for physicians: who will be treated if possible treatments are limited? The ethical issues arising from this dilemma are known as the Seattle experience. Scribner's presidential address to the American Society of Artificial Organs (1964) discussed issues of patient selection, discontinuation of treatment, patient suicide, dignified death, and selection for transplantation. This experience of choosing those who will receive dialysis is often considered the beginning of bioethics[14].

Willem Kolff was also a pioneer in the development of the artificial heart. The first artificial heart in the Western Hemisphere was implanted in a dog by in 1957 (a Russian artificial heart was implanted in a dog in the late 1930s). Kolf's artificial heart was made of thermosetting polyvinyl chloride, cast inside hollow molds to prevent sutures from forming. In 1953, John Gibbon invented the heart-lung machine, but it was only useful for acute care, such as during open-heart surgery. In 1964, the National Heart and Lung Institute set a goal of creating an artificial heart by 1970. Dr. Michael DeBakey implanted a left ventricular assist device in a human in 1966, and Dr. Denton Cooley and William Hall implanted a fully artificial polyurethane heart in a human in 1969. Between 1982 and 1985, Dr. William de Vries implanted a series of Jarvik hearts based on designs by Dr. Clifford Kwan-Gatt and

[14] Blagg C. Development of ethical concepts in dialysis: Seattle in the 1960s / C. Blagg // Nephrology. Vol. 4, No. 4. 1998. P. 235–238.

Donald Lyman – patients lived up to 620 days with the Jarvik 7 device. In the 1960s and 1970s, mechanical hearts were developed by the National Institutes of Health, but were largely unknown to the public. Then, in 1967, Christian Bernard performed the first human heart transplant, an event that sparked worldwide interest: people suddenly realized that heart replacement was a way to treat heart failure. In 1969, Denton Cooley performed the first implantation of a temporary artificial heart, and the primitive device supported the patient for nearly three days until a donor was found with an urgent appeal to the press. After another decade and a half of NIH-supported research, the Jarvik 7 heart became the first artificial heart implanted as a permanent replacement for a terminally ill natural heart. At the University of Utah, on December 2, 1982, William Devries, MD, implanted the Jarvik 7 total prosthesis in Barney Clark, a Seattle dentist who volunteered to undergo the groundbreaking procedure because he wanted to contribute to medical science. Dr. Jarvik recalls that before the operation, Dr. Clark told the doctors that he did not expect to live more than a few days with the experimental heart, but that he hoped that what the doctors learned could one day save the lives of others[15].

Breast Implants The breast implant evolved to eliminate the poor results achieved by directly injecting substances into the breast for augmentation. Polyvinyl alcohol sponges were implanted as breast prostheses in the 1950s, but the results were also poor. In fact, in the 60s of the XX century. in California and Utah classified silicone injections as a criminal offense. Texas University plastic surgeons Thomas Cronin and Frank Giraud invented the first in the early 60s of the XX century. silicone breast implant – a silicone shell filled with gel. Many variations of this device have been tried over the years, including a polyurethane foam lining (Natural Y implant). This breast implant option was fraught with problems. However, the main humosilicon gel breast implant was generally accepted[16]. The first test operation was performed by surgeons on the dog Esmeraldi, who was transplanted with a silicone bag with gel. The implant was inserted under the skin and left for several weeks. Esmeralda chewed the stitches and had to remove the implants. Overall, the operation was a success and Giro 66's surgeon declared that the implants were "safe as water". Shortly after that, surgeons began searching for a woman who would agree to the operation. In the spring of 1962, mother of six Timmy Jean Lindsey lay on the operating table at Jefferson Davis Hospital in Houston, Texas. Ms. Lindsay did not plan to have breast augmentation, she came to the hospital to have her tattoo removed, and

[15] Jarvik R. The Jarvik-7 [Electronic resource]. Access mode : https://www.jarvikheart.com/history/robertjarvik-on-the-jarvik-7.

[16] Bondurant S. Safety of Silicone Breast Implants / S. Bondurant, V. Ernster, R. Herdman. Washington : National Academies Press, 1999.

the doctors offered her to volunteer for the first breast augmentation surgery. Surgeon Cronin spoke about the operation at the 1963 meeting of the International Society of Plastic Aesthetic Surgeons (ISAPS) in Washington County. From 1992 to 2006, silicone implants disappeared from the U.S. market due to FDA rulings due to too many complaints due to ruptures and leaks. Surgeons continued to use implants that were filled with a saline solution. After a series of investigations, the FDA concluded that silicone breasts are safe with a small risk of lymphoma[17].

Surgeons have long needed methods and materials to repair damaged and diseased blood vessels. At the beginning of the 20th century, Dr. Alexis Carrel developed methods of anastomosis (stitching) of blood vessels, for this achievement he received the Nobel Prize in Medicine in 1912. In 1942, Blackmore used metal tubes containing vitalium to close arterial defects in soldiers wounded in the war. Intern Arthur Voorhees (1922–1992) noticed during a post-mortem examination in 1947 that tissue had grown around a silk suture left inside a laboratory animal. This observation stimulated the idea that the tissue tube could also heal by "taking up residence" in the body's tissues. Perhaps this in vitro healing response could be used to replace an artery? His first experimental vascular grafts were sewn from silk handkerchief and then parachute fabric (Vinyon N) using his wife's sewing machine. The first human prosthetic vascular graft implant was delivered in 1952. The patient lived for many years after this procedure, which inspired many surgeons to copy the procedure. By 1954, another paper was published that established the obvious advantages of porous (fabric) tubing over rigid polyethylene tubing[18]. In 1958, the textbook on vascular surgery described the following technique: "Terilene, Orlon, or nylon fabric is bought in a drapery store and cut with pinking shears to the desired shape. Then it is sewn with a thread of similar material into a tube and sterilized by autoclaving before use"[19].

Partially blocked coronary arteries lead to angina pectoris, a decrease in the functionality of the heart, and, ultimately, in the event of an artery blockage (ie myocardial infarction) − the death of a portion of the heart muscle. During bypass operations, a section of vein is taken from another part of the body and the occluded coronary artery is replaced with a clean channel. Such operations are long-term, difficult for the patient and expensive. Synthetic vascular grafts with a diameter of 3 mm, corresponding to the

[17] Боуз К. Операції зі збільшення грудей – півстоліття [Електронний ресурс] / К. Боуз, К. Гебблсвейт. Режим доступу : https://www.bbc.com/ukrainian/entertainment/2012/04/120403_breasts_implants_dt.

[18] . Egdahl R. H. Plastic venous prostheses / R. H. Egdahl, D. M. Hume, H. A. Schlang // Surg. Forum. Vol. 5. 1954 P. 235–241.

[19] . Rob C. Vascular surgery / C. Rob // Modern Trends in Surgical Materials / L. Gillis (ed.). London : Butterworth & Co., 1958. P. 175–185.

anatomy of the human coronary artery, become thrombosed and therefore cannot be used. Another option is percutaneous transluminal coronary angioplasty (PTCA). In this procedure, a balloon is inserted through a catheter into the coronary artery and then inflated to open the lumen of the occluding vessel. However, in many cases, the coronary artery can spasm and close from the trauma of the procedure. The invention of the coronary artery stent, an expandable metal mesh that keeps the lumen open after PTCA, became a major revolution in the treatment of ischemic occlusive disease. In his own words, Dr. Julio Palmaz describes the origin and history of the cardiovascular stent. Instead of a spring or coil, Dr. Palmaz developed a stainless steel slotted metal tube with balloons. Experimenting with different designs and types of metal eventually led to the development of the Palmaz-Schatz stent, which was placed in coronary arteries in dogs in 1985 and, with financial support from Johnson & Johnson, in humans in 1987. This was hampered by delivery problems and high frequency complications[20].

In London in 1788, Charles Keith wrote "Essay on the Revival of the Apparently Dead" where he discussed electric shocks to the chest to resuscitate the heart. In the period 1820–1880, it was already known that electrical shocks could modulate heartbeats (and of course 70 consider the Frankenstein story from that era). The invention of the portable cardiac pacemaker, difficult to carry by today's standards, can be attributed almost simultaneously to two groups (1930–1931): Albert S. Hyman (USA) and Dr. Mark C. Leadville (working in Australia with physicist Major Edgar Booth). Canadian electrical engineer John Hopps, conducting research on hypothermia in 1949, invented an early cardiac pacemaker. Heaps' discovery was that if a cooled heart stops beating, it can be electrically restarted. This 71 led to Hopps' invention of the vacuum tube cardiac pacemaker in 1950. Paul M. Zoll developed a pacemaker with Electrodyne in 1952. The device, about the size of a large tabletop radio, was powered by an external current and stimulated the heart using electrodes placed on the chest. This therapy caused pain and burns, although it could speed up the heart. In 1957-1958 Earl E. Bakken, founder of Medtronic, Inc., developed the first wearable transistorized (external) pacemaker at the request of cardiac surgeon Dr. C. Walton Lillehey. Bakken quickly produced a prototype that Lillehei used on children with heart block after surgery. Medtronic commercially released this wearable transistorized device as the 5800 pacemaker. In 1959, engineer Wilson Greatbatch and cardiologist UM Chardak developed the first fully implantable pacemaker. They used two Texas Instruments transistors, a technical innovation that allowed small size and low power consumption. The pacemaker emulator was encased in an epoxy cage to prevent inactivation by body fluids.

[20] . Стент [Електронний ресурс]. Режим доступу : https://uk.wikipedia.org/wiki/Стент.

The development of the prosthetic heart valve took place in parallel in cardiac surgery. Until the heart can be stopped and blood flow can be controlled, valve replacement will be a difficult problem. In 1952, Charles Hufnagel implanted a valve consisting of a PMMA tube and a nylon ball in the beating heart, the Hufnagel heart valve, consisting of a polymethyl methacrylate tube and a nylon ball. A heroic and largely unsuccessful operation that inspired heart surgeons to believe that prosthetic valves are possible. The development of the cardiopulmonary machine in 1953 by Gibbon made it possible to carry out the next stage of the evolution of the heart prosthesis. In 1960, surgeon Albert Starr performed mitral valve replacement in humans using a valve design consisting of a silicone ball and a polymethyl methacrylate cage (later replaced by a stainless steel cage). The valve was invented by engineer Lowell Edwards. The heart valve was based on the design of the bottle stopper invented in 1858. Starr quotes it as: "Let's make a valve that works and don't worry about how it looks," referring to Edwards's design, which was radically different from the leaflet valve that nature had formed in mammals. Before the invention of the Starr-Edwards valve, no one lived with a prosthetic heart valve for more than three months. This valve has been found to provide good patient survival. The main problems with valve development in that era were thrombosis and durability. Warren Hancock began development of the first sheet tissue heart valve in 1969, and his company and the valve were acquired by Johnson & Johnson in 1979.

Drug delivery and controlled dosing, for most of the history, drugs were administered orally or by subcutaneous injection. In general, there were no attempts to modulate the rate of entry of the drug into the body. In 1949, Dale Wurster invented what is now known as the Wurster Method, which allowed pills and tablets to be encapsulated and thus slow their release rate. However, modern ideas about controlled release can be traced back to physician Jude Folkman. Dr. Folkman noticed that the dyes penetrated deeply into the silicone rubber, and based on this, he hypothesized that drugs could do the same. He sealed isoproterenol (a drug used to treat heart block) in silicone tubes and implanted them into the hearts of dogs[21]. Folkman noted the delayed release and later applied the same idea to the delivery of the steroid for birth control. He presented this patent-free development to the World Population Council. Entrepreneur and chemist Alejandro Zaffaroni heard about Folkman's work and in 1970 founded Alza (originally named Pharmetrics) to develop these ideas for the pharmaceutical industry. The company has developed a number of new polymers for controlled release as

[21] . Folkman J. The use of silicone rubber as a carrier for prolonged drug therapy / J. Folkman, D. M. Long // J. Surg. Res. Vol. 4. 1964. P. 139–142.

well as new delivery strategies. Alza was a leader in launching this new industry that is so important today[22].

3. New biomaterials and engineering devices

In contrast to the biomaterials of the hero-surgeon era, when mostly standard materials were used for the manufacture of medical devices, in the 60s of the XX century. In the 1990s, materials developed specifically for use as biomaterials were obtained. This part outlines some key classes of materials and their evolution from raw materials to synthesized biomaterials. Silicones are a class of polymers that have been studied for many years, only at the beginning of the 40s of the 20th century. Eugene Rohov pioneered the scale-up and production of commercial silicones by reacting methyl chloride with silicon in the presence of catalysts. In Rohov's 1946 book, The Chemistry of Silicones, he commented anecdotally on the low toxicity of silicones, but did not suggest a medical application. Perhaps the first report of implantable silicones was by Lahey (1946)[23]. The potential for medical use of these materials was realized shortly thereafter. In a 1954 book on silicones, McGregor has a whole chapter called "Physiological Response to Silicones." Toxicological studies have been cited that attribute to McGregor that the amount of silicones that people can ingest should be "completely harmless". He mentions the use of silicone rubber in artificial kidneys without references. Silicone-coated rubber grids were also used to support the dialysis membrane[24].

Polyurethane was invented by Otto Bayer and his colleagues in Germany in 1937. Polyurethane chemistry has always offered a wide range of synthetic options, hard plastics, flexible films or elastomers. Interestingly, this was the first class of polymers to exhibit the elasticity of rubber without covalent cross-linking. As early as 1959, polyurethanes were investigated for biomedical applications, in particular heart valves[25]. In the mid − 1960s, a class of segmented polyurethanes was developed that demonstrated both good biocompatibility and excellent durability in biological solutions at 37 °C[26]. Marketed as Biomer by Ethicon and based on DuPont Lycra, these segmented polyurethanes consisted of Jarvik 7 pump diaphragms that were

[22] . Hoffman A. The origins and evolution of “controlled” drug delivery systems / A. Hoffman // Journal of Controlled Release. Vol. 132, No. 3. 2008. P. 153–163.

[23] Lahey F. H. Comments (discussion) made following the speech “Results from using Vitallium tubes in biliary surgery”, by Pearse H. E. before the American Surgical Association, Hot Springs VA / F. H. Lahey // Ann. Surg. Vol. 124. 1946. P. 1027.

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implanted in seven individuals. Teflon DuPont chemist Roy Plunkett discovered the extremely inert polymer Teflon 76 (polytetrafluoroethylene) (PTFE) in 1938. William L. Gore and his wife, Viv, founded a company in 1958 to use Teflon to insulate wires. In 1969, their son Bob discovered that Teflon, when heated and stretched, forms a porous membrane with attractive physical and chemical properties. Bill Gore tells a story that while on a chairlift at a ski resort, he pulled a piece of porous Teflon tubing from his parka pocket to show a fellow passenger. The skier was a doctor and asked to test a sample of a vascular prosthesis. Porous Teflon Goretex and similar expanded PTFEs are now the leading synthetic vascular grafts and are used in surgery and biotechnology.

Hydrogels have been found in nature since the evolution of life on Earth. Bacterial biofilms, hydrated extracellular matrix components, and plant structures are ubiquitous, water-swollen motifs in nature. Gelatin and agar were also known and used for various applications early in human history. But the modern history of hydrogels as a class of materials intended for medical applications can be precisely traced. In 1936, DuPont scientists published an article on newly synthesized methacrylic polymers. Poly-2-hydroxyethyl methacrylate (polyHEMA) was mentioned in this work. It was briefly described as a hard, brittle, glassy polymer, and was apparently not considered important. After this paper, polyHEMA was essentially forgotten until 1960. Wichterle and Lim published an article in the journal Nature describing the polymerization of HEMA monomer and crosslinking agent in the presence of water and other solvents[27]. Instead of a fragile polymer, they got a soft, water-swollen, elastic, transparent gel. Wichterle developed an apparatus (created from a children's construction kit) for centrifugally casting hydrogel into contact lenses with the appropriate refractive power. The interest and application of hydrogels has grown steadily over the years. Important early applications included acrylamide gels for electrophoresis, porous polyvinyl alcohol (Ivalon) sponges as implants, many hydrogel formulations as soft contact lenses, and alginate gels for cell encapsulation. Polyethylene glycol (PEG), also called polyethylene oxide (PEO) in its high molecular weight form, can be classified as a hydrogel, especially if the chains are cross-linked. However, PEG has many other uses and realizations. The low reactivity of PEG with living organisms has been known since at least 1944, when it was investigated as a possible agent for the intravenous administration of fat-soluble hormones[28]. In the mid-70s of the XX century. Frank Davis and colleagues found that if PEG chains were attached to

[27] Wichterle O. Hydrophilic gels for biological use / O. Wichterle, D. Lim // Nature. Vol. 185. 1960. P. 117– 118.

[28] Friedman M. A vehicle for the intravenous administration of fat soluble hormones / M. Friedman // J. Lab. Clin. Med. Vol. 29. 1944. P. 530–531.

enzymes and proteins, they would have a much longer functional residence time in vivo than biomolecules that were not PEGylated[29]. Professor Edward Merrill of the Massachusetts Institute of Technology concluded, based on what he called "diverse evidence" from the literature, that surface-immobilized PEG would resist protein and cellular uptake. The experimental results of his research group in the early 80s confirmed this conclusion[30]. Developments in synthetic chemistry by Dr. Milton Harris at the University of Alabama, Huntsville, greatly accelerated the application of PEG to a wide range of biomedical problems.

Polylactic-glycolic acid was first discovered in 1833 by anionic polymerization from cyclic lactide monomer, in the early 60s of the 20th century. it became possible to create materials with mechanical properties comparable to dacron. The first publication on the use of polylactic acid in medicine may be Kulkarni et al. (1966)[31]. This group demonstrated that the polymer degraded slowly after implantation in guinea pigs or rats and was well tolerated by the organisms. Cutright et al. (1971) were the first to use this polymer for orthopedic fixation[32]. Subsequently, polyglycolic acid and copolymers of lactic and glycolic acids were developed. Early clinical applications of polymers in this series were for sutures, based on the work of Joe Frazz and Ed Schmitt of David & Geck, Inc.[33] Glycolic/lactic acid polymers have also been widely used for the controlled release of drugs and proteins. The group of Professor Robert Langer from the Massachusetts Institute of Technology is a leader in the development of these polymers in the form of porous frameworks for tissue engineering[34].

Hydroxyapatite is one of the most studied materials for bone healing. It is a natural mineral, a component of bone, and a synthetic material with wide medical uses. Hydroxyapatite can easily be made into a powder. One of the first to describe the biomedical applications of this material was Levitt et al. (1969). They used hot pressing of hydroxyapatite into a form useful for

[29] Abuchowski A. Effect of covalent attachment of polyethylene glycol on immunogenicity and circulating life of bovine liver catalase / A. Abuchowski, J. R. McCoy, N. C. Palczuk, T. van Es, F. F. Davis // J. Biol. Chem. Vol. 252, No. 11. 1977. P. 3582–3586.

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[31] . Polylactic acid for surgical implants / R. K. Kulkarni, K. C. Pani, C. Neuman, F. Leonard // Arch. Surg. Vol. 93. 1966. P. 839–843.

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[33] Frazza E. A new absorbable suture / E. Frazza, E. Schmitt // J. Biomed. Mater. Res. Vol. 5, No. 2. 1971. P. 43–58.

[34] Langer R. Tissue engineering / R. Langer, J. P. Vacanti // Science. Vol. 260. 1993. P. 920–926.

biological experiments[35]. From this early assessment of the materials science aspect of the natural biomineral, thousands of articles have appeared. In fact, the nacre implant described in the history section may owe its effectiveness to hydroxyapatite – it has been shown that nacre calcium carbonate can be converted in phosphate solutions to hydroxyapatite[36].

In 1791, William Gregor, an amateur chemist from Cornwall, used a magnet to extract the ore we now know as ilmenite from a local river. He then extracted the iron from this black powder with hydrochloric acid, and obtained a residue which was crude titanium oxide. After 1932, a process developed by William Kroll allowed the commercial extraction of titanium from mineral sources. At the end of World War II, titanium metallurgy methods and titanium materials went from military to peacetime use. By 1940, satisfactory results had already been achieved with titanium implants. The major breakthrough in the use of titanium for bone implants was Branemark's discovery of osseointegration, described above in the section on dental implants[37].

Among biomaterials, bioglass is one of the first fully synthetic materials that seamlessly bonds with bone. It was developed by Professor Larry Hench and his colleagues. In 1967, Hench was an associate professor at the University of Florida. At that time, his work was focused on glass materials and their interaction with nuclear radiation. In August of that year, he traveled to the Army Materiel Conference in Sagamore, N.Y., with a U.S. colonel who had just returned from Vietnam, where he had directed supplies to 15 Army Mobile Surgical Hospital units. The colonel was not very interested in the radiation resistance of the glass. He most likely challenged Hench in this way: hundreds of limbs a week in Vietnam were being amputated because the body was found to reject the metals and polymeric materials used to repair the body. "If you can make a material that will resist gamma radiation, why not make a material that the body won't resist?" Hench returned from the conference and wrote a proposal to the US Medical Research and Development Command. In October 1969, the project was funded to test the hypothesis that silicate-glass-ceramic glasses containing critical amounts of Ca and P ions would not be rejected by bone. 81 In November 1969, Hench produced small rectangles of what he called 45S5 glass (44,5 wt% SiO_2) and Ted Greenlee, associate professor of orthopedic surgery at the University of Florida, implanted them into femurs at the Veterans Affairs Hospital in Gainesville. Six weeks later, Greenlee called Hench: “Larry, what samples

[35] LForming methods for apatite prostheses / S. R. Levitt, P. H. Crayton, E. A. Monroe, R. A. Condrate // J. Biomed. Mater. Res. Vol. 3. 1969. P. 683–684.

[36] . Ni M. Nacre surface transformation to hydroxyapatite in a phosphate buffer solution / M. Ni, B. D. Ratner // Biomaterials. Vol. 24. 2003. P. 4323– 4331.

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did you give me? They did not leave the bone. I've stretched them, pressed on them, broken a bone, and they're still held in place". This is how bioglass was born. Later research by Hench, using surface analysis equipment, showed that the surface of bioglass in biological fluids changes from a silicate-rich composition to a phosphate-rich structure, possibly similar to hydroxyapatite[38].

Biotechnology in general is a system of techniques targeted use of life processes living organisms for industrial production valuable products. These technologies are based on usage catalytic potential of various biological agents and systems – microorganisms, viruses, plant and animal cells and tissues, as well as extracellular substances and cell components. Currently in development and development biotechnologies occupy an important place in the activity almost all countries.

Biotechnological processes are multifaceted in their own way historical roots and by their structure, they combine elements of fundamental sciences, as well as a number of applied industries such as chemical technology, mechanical engineering, economics. Modern biotechnologies are sharp need scientifically based processing technology and hardware design. Therefore it is necessary organic connection with technical sciences: mechanical engineering, electronics, automation. Social and economic sciences are also important in development ecological biotechnology, as they are solved by it practical tasks have a large socio-economic importance for any society.

CONCLUSIONS

It is likely that the modern era in the history of biomaterials developed to control specific biological reactions was initiated by the rapid development of modern biology (second and third generation biomaterials). In the 60s of the 20th century, when the basic principles and ideas of the field of biomaterials were laid, such concepts as cell surface receptors, growth factors, nuclear control of protein expression and phenotype, cell attachment of proteins and gene delivery were either contradictory observations, or undiscovered phenomena. Thus, pioneers in the field could not develop materials with these ideas in mind. To the credit of the biomaterials community, it has been quick to adopt and use new ideas in biology. Similarly, new materials science ideas such as phase distribution, anodization, self-assembly, modification, and surface analysis were quickly assimilated into the biomaterials scientist's toolbox and vocabulary. It is useful to list several important ideas in the biomaterials literature that laid the foundation for biomaterials science as we see it today: o protein adsorption;

[38] Clark A. E. The influence of surface chemistry on implant interface histology: a theoretical basis for implant materials selection / A. E. Clark, L. L. Hench, H. A. Paschall // J. Biomed. Mater. Res. Vol. 10. 1976. P. 161–177.

o biospecific biomaterials; o non-fouling materials; o healing and foreign body reaction; o controlled release; o tissue engineering; o regenerative medicine; o nanotechnology. However, it is important to appreciate the intellectual leadership of the many researchers who promoted these ideas that comprise modern biomaterials, a part of the recent history of biomaterials that will one day be completed. Today, we practice biomaterials by immersing ourselves in an evolving history. Thus, biomaterials has gone from hero surgeons sometimes working with engineers, to a field dominated by engineers, chemists and physicists, to our modern era with biologists and bioengineers as key players.

SUMMARY

The North American biomaterials industry has seen significant returns in the recent past, driven by the rise in popularity of plastic surgery and the funding of biomaterials-based research. At the same time, the Asia-Pacific region will become a profitable growth area for the global biomaterials market in the coming years, due to the increase in the prevalence of heart diseases, which will subsequently lead to an increase in the number of pacemaker procedures. North America accounts for the largest share of revenues since the beginning of the 21st century. thanks to the initiatives of several public and private organizations. These include the National Science Foundation and the National Institute of Standards and Technology, which provide knowledge and assistance related to the use of biomaterials in biomedical applications. This has led to the expansion of the use of biomaterials in this region. In addition, factors such as favorable government policies and the presence of several major market players in this region have contributed to the increase in the regional market share. The biomaterials market in India is growing at a rapid pace, with orthopedic, dental and cardiovascular biomaterials accounting for a significant share of the Indian biomaterials market. The increase in the number of orthopedic procedures, dental and cardiovascular surgeries is the reason for the high market share of orthopedic and cardiovascular biomaterials. Owing to the high prevalence of cardiac disorders and increasing number of pacemaker procedures in India, the pacemaker market is expected to witness steady demand and a steady growth rate over the forecast period. Today, Europe also takes over the palm of primacy among the use of biopolymers, this is connected not only with chronic or acquired diseases of the population of European countries, but also primarily with military actions in Ukraine. If since 2014, such cases took place mainly among conscripts, then since 2022, the civilian population has also joined them, which suffers more and more every year. Therefore, the latest directions of biotechnological science and practice; development of new biomedical materials, methods of their modification and processing into

specialized biomedical products; assessment of physico-chemical and medical-biological properties of biomaterials and their products; review and analysis of modern achievements in biomedical technologies have reached a new level and do not lose their relevance.

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