

Rubber Medicine

Material made from
the latex of the rubber tree
closes ulcers and rebuilds
the esophagus and the eardrum

DINORAH ERENO

Published in June 2003

The latex extracted from the rubber tree, the raw material, which during the 19th century placed Brazil as the major world exporter of rubber, is the basis of an innovative biomaterial with excellent results for the healing of chronic ulcers and in the reconstruction of perforated esophagi and eardrums. Developed at the School of Medicine in the town of Ribeirão Preto (FMRP), part of the University of São Paulo (USP), the biopolymer should initially be produced by the company Pele Nova Biotecnologia, in a pilot plant installed in the city of Campo Grande, in the state of Mato Grosso.

The company was founded by the Brazilian Academy for Advanced Studies, a non-government organization (ONG) maintained by the company Avamax Biotecnologia, which has amongst its members the ex-president of Embraer and Varig, Ozires Silva. "We make the connection between scientists and investors by showing products with a potential for fighting for a place in the market", Ozires explained, who has already promoted various meetings between the project's coordinator, Joaquim Coutinho Netto from the Biochemistry and Immunology Department of FMRP, and parties interested in knowing details of the new product.

The objective of these meetings, at which investors from Germany and Italy have already participated, is to raise the capital necessary to set up the pilot plant and later on an industrial plant. The pilot plant, scheduled to begin working this coming month of July in an old factory used for the industrialization of heart of palm, and belonging to Avamax, was projected according to the criteria demanded by the National Agency for Sanitary Vigilance (Anvisa in the Portuguese acronym). The plant will be installed in the industrial district of Ribeirão Preto, previously projected by the now Minister of the Treasury Department, Antônio Palocci, when he was the mayor of the town.





Dressings using a biopolymer based on vegetal latex show results on average within twelve days

Multinational competition - The biopolymer, which will initially be launched to treat chronic ulcers of the feet and legs, is going to compete with other products from large multinational companies such as Johnson & Johnson and Novartis. According to Coutinho, the formulae are different, but the results identical. "This is without saying that the treatment with our product will cost, at least, ten times less", he says. "One imported 15 gram tube of a healing ointment based on gel with human hormone costs US\$ 350 and lasts for only a few days", Coutinho compares.

The story that led to this biomembrane had its beginning in 1994 when the at that time master's degree student in the surgery area of FMRP, Fátima Mrué, from the state of Goiás who spent two years in Tokyo, Japan, and followed surgery patients with cancer, decided to work on her thesis with the prosthesis of Takimoto, which carried the name of the medical inventor, a compound of silicon and collagen and used to reconstruct the esophagus. Fátima got in touch with Coutinho in order to know how to obtain collagen from pigskin, a technique described in an article published during the decade of the 60s and which was to be used in the make up of the artificial substitute.

Today, Coutinho states that he had never imagined that that simple question concerning collagen would lead him to weekly meetings with people interested in investing in the biopolymer. In the end, in order to get rid of the student on that occasion – today Fátima Mrué is a surgeon at the Oncology Center of the Clinical Hospital of Goiânia –, Coutinho said to her that if she found the paper he could help her in the job of making a substitute material similar to Takimoto's. "A very difficult and painstaking task for that time since there was no Internet", as she herself recalls. Two days later, much to his surprise, Fátima returned with the paper in her hands. Coutinho, resigned to the fact, decided to help the persistent student in the preparation of collagen from pigskin.

However, on being mixed with silicone, there was no way of making the two materials combine together. "We couldn't reproduce the Japanese prosthesis", Coutinho recalls. "Takimoto didn't explain his patent what to do to fix the collagen in the prosthesis", Fátima even got in contact with the Japanese doctor to ask for help, but he did not reveal his well-kept secret.

Inspiration in the past - "It was then that I had the idea of making prosthesis from the latex of the rubber tree", recalls the doctor, probably inspired in memories of the large rubber tree plantations of the small town in the interior of the state of São Paulo where he was born, Guapiacu. He thought that it would be much easier to mix the collagen in the milk from the rubber tree. Fátima didn't place much faith in the proposed solution, but decided to respect it. As they were going to need someone who would make the experimental prosthesis, they found in the region of São José do Rio Preto the

chemist Antônio César Zabrowski, from the company Globbor, that sells rubber to Goodyear. Zabrowski offered to manufacture the prosthesis and built them making use of a ribbed glass mold, composed of vegetal latex and 0.1% collagen or polylysine.

The experimental prosthesis, a tube of 8 centimeters in length by 2 centimeters in diameter was implanted in the esophagus of eight dogs. However, an uncommon occurrence caught the attention of the researchers. Ten days after the implant, the prostheses were expelled together with the feces of the animal. They found this strange and decided to carry out an endoscopy in order to know what had happened, since none of the dogs appeared to be ill. By the end of the examination both Fátima and Coutinho were surprised with the revelation that, in such a short period of time, a new esophagus had formed in the separated fragment. In the histological analysis (an evaluation of the tissue under the microscope), it showed itself to be practically equal to the normal esophagus, with all the layers. "The-

re was practically no scarring and also there was not the formation of fibrosis at the repaired location, showing a process of structural neoformation", says Coutinho.

"The results were surprising and we decided to investigate the phenomenon in depth", he explains. As the histological cut of the material showed the presence of a large quantity of blood vessels at the locality where the prosthesis had been placed, this could explain the process of the accelerated repair (healing). However, this property of latex to stimulate angiogenesis (the formation of new blood vessels) was only discovered because the polymer was not obtained by the traditional method, known as vulcanization, using a temperature of between 110° C to 125° C. Zabrowski had made use of a technique of polymerization under special conditions, developed and patented by him, and later purchased by Avamax.

The proof that the method of obtaining the biopolymer was fundamental to the process of angiogenesis was done when the researchers carried out tests using surgical gloves and contraceptives that have the same raw material, namely latex, to see how they would behave in the process of healing. "But these materials didn't show any angiogenesis activity", Coutinho says. Tests were even done using embryonated chickens eggs to evaluate the formation of veins, and with rabbits' ears, to verify the speed with which the process of healing occurred. "The application of the biomaterial sped up a structural neoformation process, highly organized and without leaving a scar", the doctor concludes.

Quick healing - After completing the cycle of tests on animals, the moment arrived to begin an evaluation of the biomaterial based on vegetal latex on human patients. In 1997, Coutinho and Fátima submitted to the Medical Ethical Commission of the Clinical Hospital of FMRP a request to begin experiments on humans. "This authorization was only granted one year later, allowing the student Paulo César Grisotto, who was completing his doctorate degree at that time in Ribeirão Preto, to widen and to advance his studies, dealing with patients with chronic ulcers of difficult healing at the hospital in Itajobi (SP), a town in the region of São José do Rio Preto", Coutinho

The polymer was obtained under special conditions which has led to a patent



PHOTOGRAPH BY CYNTHIA BRITOPULSAR

Cut on the trunk of a rubber tree from which runs the latex, the raw material of the biopolymer

re from the anatomic point of view and 19% of re-perforation mainly caused by the lack of blood vessels in the graft.

On the other hand, the use of a biomembrane from latex showed intense vascularization, as indicated in the work of the otolaryngologists José Antonio Aparecido de Oliveira and Miguel Angelo Hyppolito from USP at Ribeirão Preto named "Myringoplasty Making Use of a New Biosynthetic Material", presented in 1998 during the 34th Brazilian Congress of Otolaryngology in Porto Alegre. The team won first place by describing the success of the grafts using the biopolymer. "We verified intense vascularization in 100% of the grafts, which is not usual when not using a membrane made from natural latex", states one of the parts of the prize-winning paper. The report refers to only nineteen perforated eardrums that received the biomaterial as a transitory implant during myringoplasty. Today the number of successes has reached five hundred.

Two doctorate theses, developed at the Surgery and Anatomy Department of FMRP, under the guidance of Professors Jesualdo Cherri and Carlos Eli Piccinato, and defended by the vascular surgeons Mário Augusto da Silva Freitas and Paulo Cesar Grisotto, respectively in August of 2001 and February of 2003, have pointed out, after tests done with animals, that it is possible to recover cardiovascular arteries by way of the use of latex prostheses. But as yet more experimental work is necessary before making tests on human patients, in order to evaluate the efficiency of this material that could substitute the current synthetic prosthesis or biological material of animal origin, such as the pericardium of the cow or pig.

These pieces of research show that the biopolymer based on vegetal latex could still give origin to many other products, with diverse applications. The dressings are only the first step for the company Pele Nova Biotecnologia to enter into dispute for a national market estimated at around 4.5 million people, who, most probably, could not pay the very high cost for the imported medicine. •

says. "On average, twelve days after starting to use dressings with the biopolymer on the patients, the chronic wounds, mainly with diabetes patients, began to show signs of evident granulation and epithelial formation, as against the six months necessary for traditional methods, that include interning in hospital", the doctor states. According to an epidemiological survey carried out in the town of Juiz de Fora in the State of Minas Gerais, by Marco Andrey Cipriani Frade, around 2.7% of the population has chronic ulcers on their feet or legs, a percentage that reaches as high as 10% in diabetes patients. These wounds represent the second highest reason for work absenteeism in Brazil.

Reconstructed eardrum - Six years after Dr. Grisotto had begun to carry out tests on humans, the number of patients stu-

died in the hospitals of Ribeirão, Itajobi, Juiz de Fora and others had reached 3,000 of whom 2,500 had ulcers and the remainder with a perforated eardrum by infection or trauma. All of the tests were carried out after approval by the Medical Ethics Commission of the respective institutions.

The surgeries to reconstitute the eardrum using a biomembrane of latex were carried out at the Otolaryngology Sector of the Ophthalmology and Otolaryngology Department of FMRP. This surgery, named myringoplasty, has as its objective the reconstitution of the mechanism of sound transmission. Various materials are used for this objective, a favorite being the fascia (a layer of fibrous tissue that covers the body under the skin) of temporal muscle, cartilage, placental tissue, among others, but the results showed up to 30% of failu-