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The Use of Biomaterials to Treat Abdominal Hernias

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1. Introduction

Hernia is the most frequent abdominal surgery. Although hernia is a highly prevalent disease, with serious risks and well-known anatomy, there were high rates of recurrence after treatment until the mid-20th century. With the advent of biomaterials, also called prostheses or meshes, the definitive cure of this disease is close to 100%. Using an appropriate surgical technique, following the appropriate postoperative care, with good integration of the prosthesis, a person can safely return to normal life with all the usual activities, including sports and physical efforts. Meshes are indicated for the treatment of all kinds of abdominal wall hernias, such as umbilical, epigastric, femoral and, mainly, inguinal and incisional hernias. Just as the surgical technique to treat this disease has evolved with a significant number of modalities, so also research and the prostheses market are taking up an increasingly outstanding position in the world (Usher, 1958; Penttinen & Grönroos, 2008).

2. Abdominal wall hernias

2.1 Definition

Hernia is derived from the Latin word for rupture. A hernia is defined as an abnormal protrusion of an organ or tissue through a defect, an opening, in its surrounding walls (figs. 1 and 2). This opening is called hernial ring. Its content may be any abdominal viscera, most frequently the small bowel and omentum. When protruding through the hernial ring, the herniated structure is covered by the parietal peritoneum, here called hernial sac (Malangoni & Rosen, 2007).

2.2 Classification

Although hernias can occur in various regions of the body, the most common site is the abdominal wall, particularly in the inguinal and ventral regions. **Hernias of the inguinal region** are classified as direct, indirect and femoral hernia, depending on where the hernia orifice is located in the fascia transversalis, in the deep inguinal ring and in the femoral ring, respectively. A **ventral hernia** is defined by a protrusion through the anterior abdominal wall fascia. These defects can be categorized as spontaneous or acquired or by their location on the abdominal wall: epigastric hernia occurs from the xyphoid process to the umbilicus; umbilical hernia occurs at the umbilicus; hypogastric hernia is a rare spontaneous hernia that occurs below the umbilicus in the midline; and acquired hernia typically occurs after
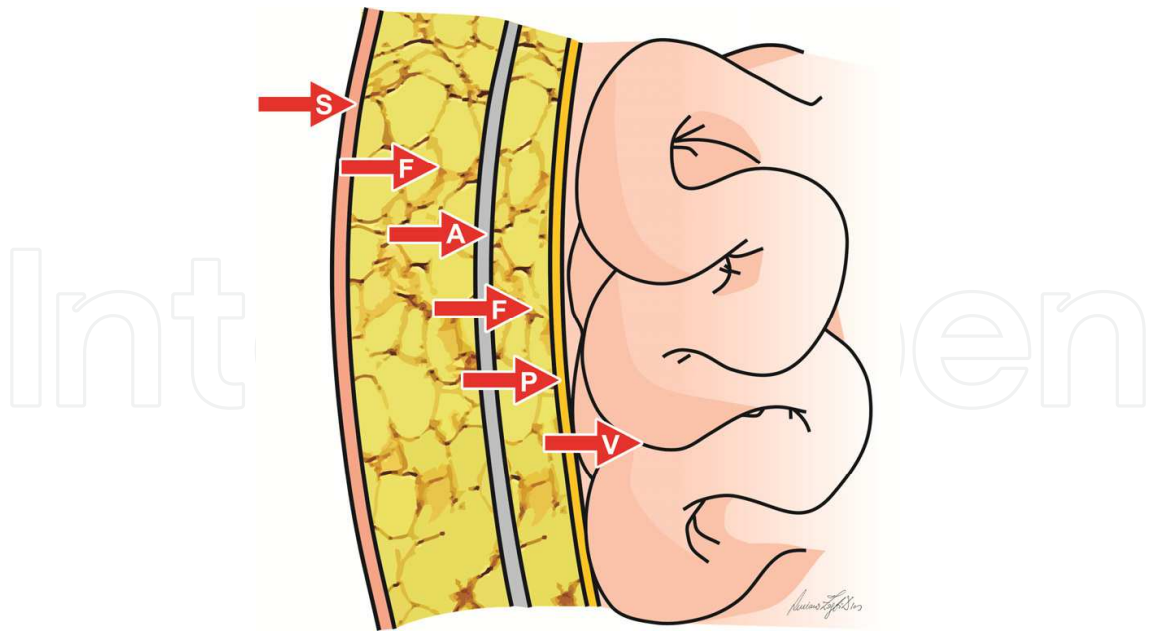
Fig. 1. Schematic drawing of a normal abdominal wall and their layers: Skin (S); Fat Tissue (F); Aponeurosis (A); Pre-peritoneal Fat Tissue (F); Peritoneun (P); and the abdominal viscera (V).
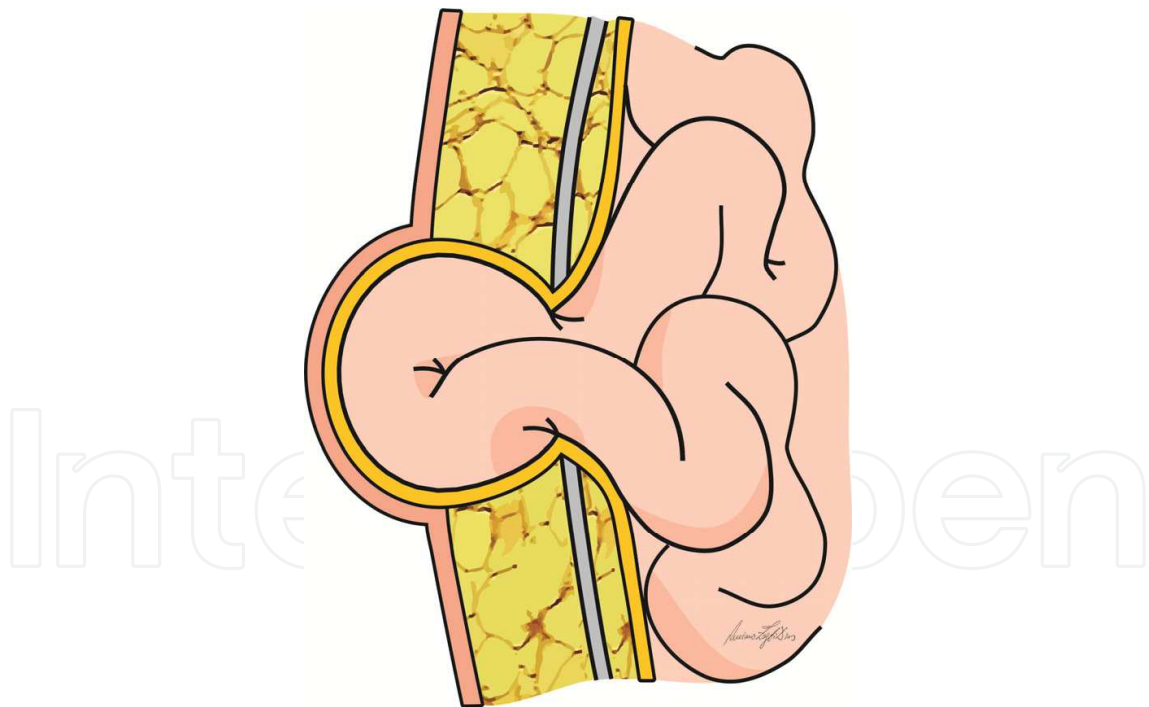

Fig. 2. Schematic drawing of a hernia. In this case, the bowel is the herniated viscera.

surgical incisions (figs 3 and 4). This is therefore termed *incisional hernia* and is the most common long-term complication after abdominal surgery (Franklin et al, 2003; Malangoni & Rosen, 2007; Penttinen & Grönroos, 2008).

Independently of the site, the principles of treatment are the same, only the surgical technique is different, according to regional anatomy.
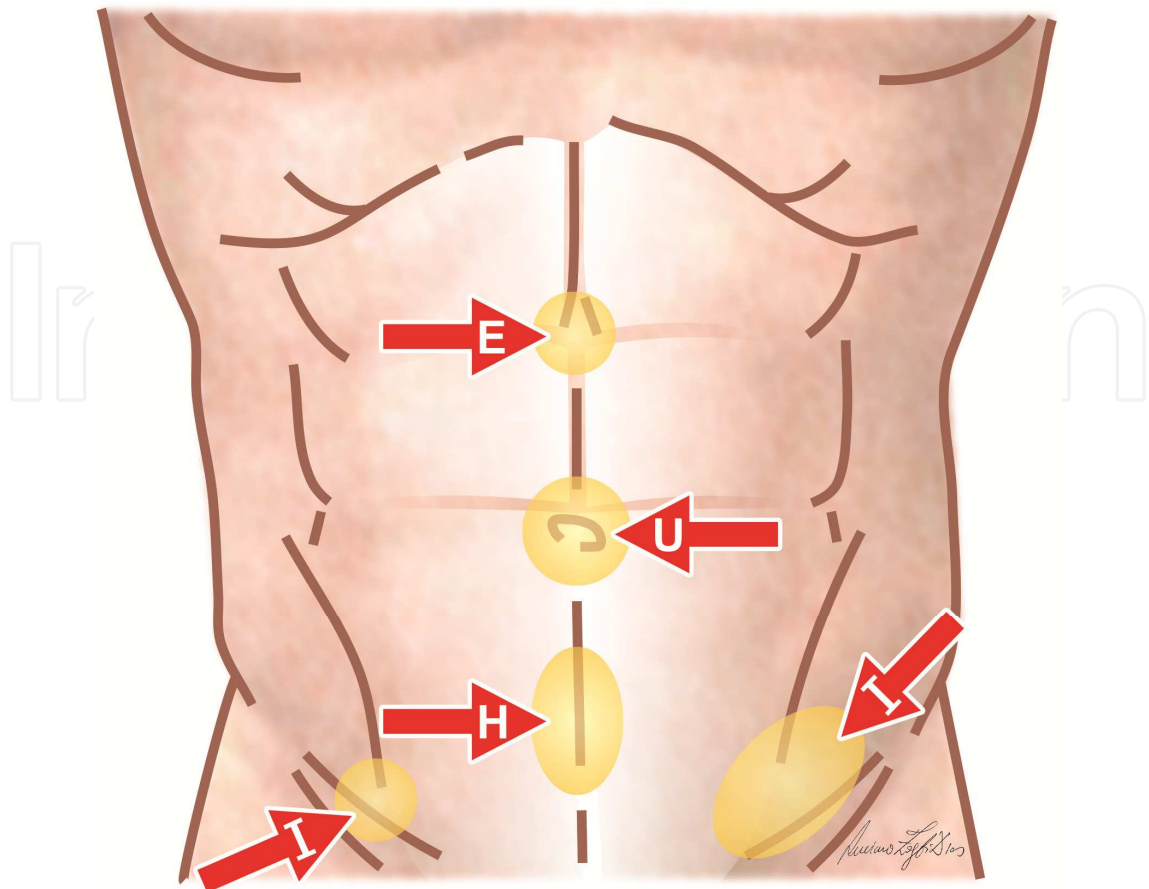
Fig. 3. Mainly places of abdominal wall hernia: Epigastric (E); Umbilical (U); Hypogastric (H); Inguinal (I).
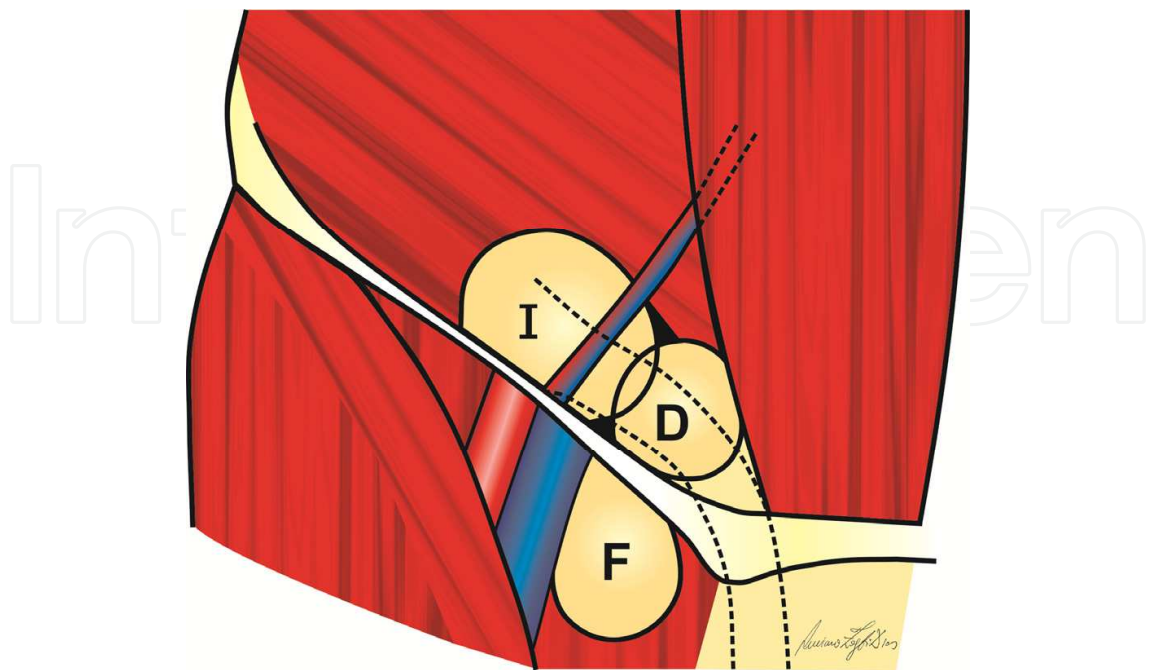

Fig. 4. Hernias of the groin area: Indirect (I); Direct (D); Femoral (F).

2.3 Epidemiology

Hernias are a common problem; however, their true incidence and prevalence are unknown. It is estimated that 5% of the population will develop an abdominal wall hernia, but the prevalence may be even higher. About 75% of all hernias occur in the inguinal region. Two thirds of these are indirect, and the remainder are direct inguinal hernias. The chance of a person having to undergo an inguinal hernia operation during his/her life is quite high, 27% in the case of men and 3% in the case of women. Men are 25 times more likely to have a groin hernia than are women. An indirect inguinal hernia is the most common hernia, regardless of gender. In men, indirect hernias predominate over direct hernias at a ratio of 2:1. Direct hernias are very uncommon in women. Although femoral hernias occur more frequently in women than in men, indirect inguinal hernias remain the most common hernia in women. About 3% to 5% of the population have epigastric hernias, and they are two to three times more common in men. The female-to-male ratio in femoral and umbilical hernias, however, is about 10:1 and 2:1, respectively (Malangoni & Rosen, 2007).

2.4 Risk factors

Hernias are characterized by the rupture of a wall that should be whole (incisional and inguinal direct hernias), or by the widening of a natural orifice (umbilical, femoral and direct inguinal hernias), generally due to excessive and sudden pressure on a fragile area. This weakening occurs because of biochemical and systemic changes in the collagen metabolism, weakening all the connective tissue. The best known risk factors are: old age, male sex, malnutrition, obesity, chemotherapy, radiotherapy, cortisone, sedentarism, decompensated diabetes mellitus, lack of vitamin C, anemia, smoking, chronic obstructive pulmonary disease, abdominal aortic aneurysm, long-term heavy lifting work, positive family history, pregnancy, appendicectomy, prostatectomy, peritoneal dialysis (Rodrigues et al., 2002; Wolwacz et al., 2003; Chan & Chan, 2005; Junge et al., 2006; Szczesny et al., 2006, Penttinen & Grönroos, 2008; Simons et al., 2009).

2.5 Complications if untreated

There is no spontaneous cure or medication to treat this disease. The only existing treatment is surgical correction. As long as it is not treated, the hernia defect will tend to become wider and increase progressively. Besides, herniated organs could be trapped by the hernial ring, and be unable to return to their usual site. When this happens it is called an **incarcerated** hernia. The risk of an inguinal hernia becoming incarcerated is less than 3% per year. The risk is greater in femoral hernias. The most serious risk of this disease is **strangulation**, which occurs when the incarcerated organ is deprived of a blood supply and becomes ischemic (fig.5). In this case, if the hernia is not treated urgently, its content may develop necrosis, infection, sepsis and death. When there is incarceration, the hernia must be reduced manually within 4 to 6 hours. After that, emergency surgery must be performed (Speranzini & Deutsch, 2001a).
Hernia surgery should ideally be performed electively, before these complications arise, making the procedure more effective and safe, since an emergency operation due to a strangulated inguinal hernia has a higher associated mortality (>5%) than an elective operation (<0.5%). Mortality increases about seven-fold after emergency operations and 20-fold if bowel resection was undertaken. After treatment, the risk of incarceration and/or strangulation disappears, as long as the hernia does not recur (Simons et al., 2009).
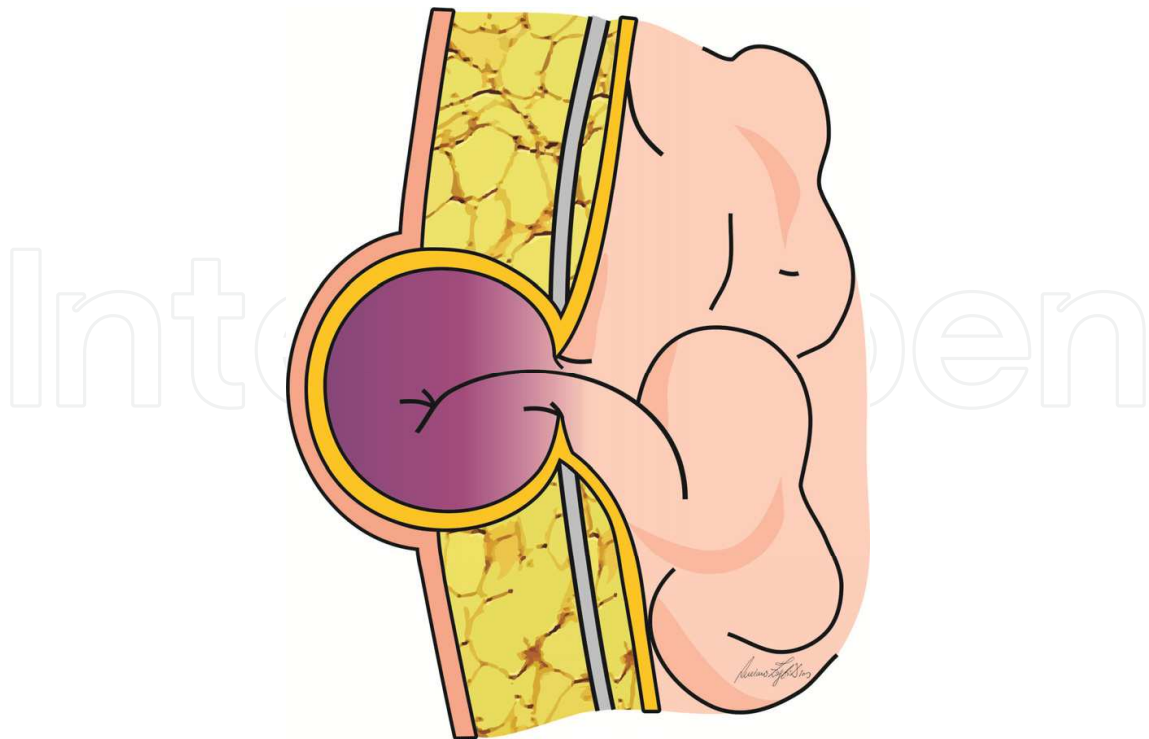
Fig. 5. Ischemic bowel due to strangulation

2.6 Treatment options

Although the only treatment is surgery, there are many effective surgical alternatives. However, merely correcting the hernia defect with sutures does not avoid the source of the problem, because the patient's tissues will still be fragile and predisposed to rupturing again at the same site. The recurrence rate for ventral hernia may be as high as 40–54% after open repair without meshes. Mesh repair is superior to suture repair, results in a lower recurrence rate and less abdominal pain. It does not cause more complications than suture repair (Burger et al. 2004; Penttinen & Grönroos, 2008).

For each type of hernia there are several techniques involving prostheses and different models of prosthesis. Surgeons in training, who see a variety of prosthetics in use, must recognize that the technique of prosthetic implantation is far more important than the type of prosthetic. To help the surgeon choose, it is helpful to look at the prosthetic landscape with a perspective based on (1) the prosthetic's raw material and design, (2) the implantation technique, and (3) the clinical scenario (Earle & Mark, 2008).

For treating inguinal hernia, the use of a polypropylene prosthesis is the best technique. Eighty-five percent of the operations, overall, are performed using an open approach and 15% are performed endoscopically. The surgeon should discuss the advantages and disadvantages of each technique with the patient. Endoscopic inguinal hernia techniques result in a lower incidence of wound infection, hematoma formation and an earlier return to normal activities or work than the Lichtenstein technique. When only considering chronic pain, endoscopic surgery is superior to open mesh. However, endoscopic inguinal hernia techniques need general anesthesia, result in a longer operation time and a higher incidence of seroma than the Lichtenstein technique (Simons et al., 2009).

Independently of the technique employed, after covering the hernia site adequately, the mesh must be fixed to the abdominal wall in order to prevent it from folding over or

(a)Intraperitoneal sublay   (b) Extraperitoneal sublay

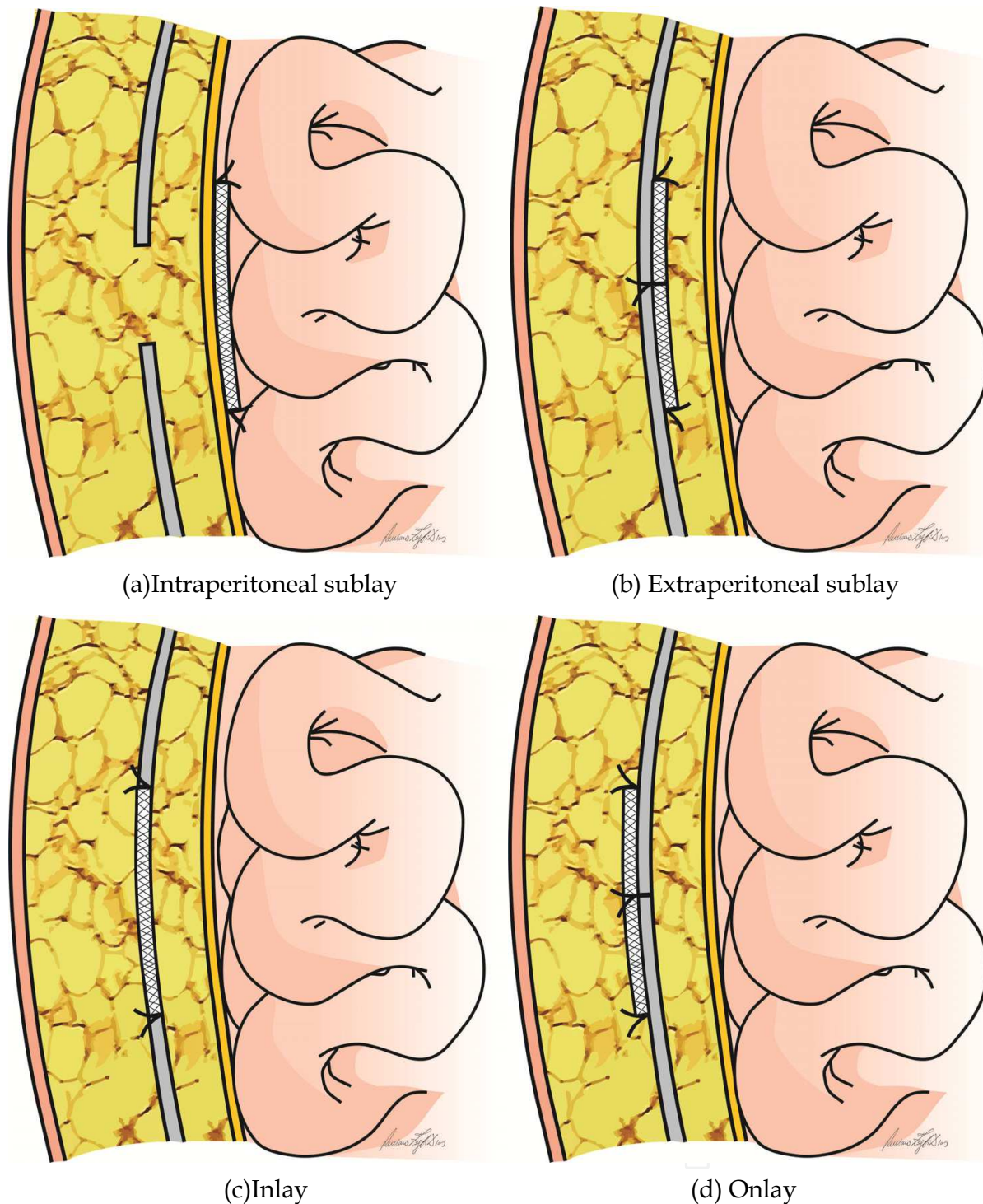(c)Inlay   (d) Onlay

Fig. 6. Possible plans of the abdominal wall to insert the prosthesis.

migrating. It may be fixed simply by physical principles of pressure between layers of the abdominal wall (Stoppa & Rives, 1984), by means of a suture with inadsorbable thread (Lichtenstein et al., 1989), absorbable thread (Gianlupi & Trindade, 2004), clips (Read, 2011) or fibrin glue (Agresta & Bedin, 2008; Negro et al., 2011). For fixation of the mesh in ventral hernia repair, most authors have used an extraperitoneal – but intraperitoneal is also possible (fig.6a) - sub-lay technique, in which the mesh is sutured into place on the posterior

rectus sheath with approximately 4 cm of fascia overlap (fig.6b). The other two repair options include an inlay technique (fig.6c), such that the mesh is sutured to the fascial edges, and an onlay technique whereby the mesh is placed and sutured onto the anterior rectus sheath (Fig.6d). The inlay technique has the advantage of minimal soft-tissue dissection thus reducing devascularized tissue, but the disadvantage of high rate of recurrences, while the onlay technique has the disadvantage of vast soft tissue dissection above the rectus layer (Penttinen & Grönroos, 2008).

3. History of biomaterials

Trusses have been used for the treatment of inguinal hernia for thousands of years. In the 19th century, several surgical techniques were proposed to treat hernia, but all of them limited themselves to the raphe of the hernia defect. Until then, the rate of occurrence was high, even surpassing 50%. Cooper already suspected of the degenerative nature of the disease and, Billroth, ahead of his time, perceived that even if he knew everything about anatomy and surgery, he still lacked something. Even before the meshes were created he said that: "If we could artificially produce tissues of the density and toughness of fascia and tendon, the secret for the radical cure of hernia would be discovered" (Amid, 1997; Franklin et al., 2003; Read, 2004; Earle & Mark, 2008).

The first biomaterials were described in 1900, when Oscar Witzel used a silver mesh (Witzel, 1900). Handley developed silk meshes in 1918, but they were no longer used because they did not tolerate the organism (Handley, 1963). In 1928, Goepel inserted stainless steel prostheses, of a fine, flexible, easily manipulated material (Goepel, 1900). Its drawback was the tendency to become fragmented, injuring tissue and blood vessels. The attempt to make celluloid-based materials, by Mandl, in 1933, did not meet with success, since, despite its flexibility and resistance to tension, it easily developed abscesses from infection (Mandl, 1962). In 1946, another metal material was described, vitalium, which was no longer used because of its rigidity (McNealy & Glassman, 1946). Amos Koontz adopted tantalum to treat eventrations in 1948, and it was widely accepted (Koontz, 1948). This was a resistant metal, with a low tendency to corrosion, appropriate to the synthesis of granulation tissue and very safe against infection. Its disadvantages were fragility and high cost, and therefore it was no longer used. The fragmentation observed in these metal substances over time is due to a principle of physics called *point of metal fatigue* (Sans,1986).

The era of plastics began in the manufacture of prostheses when nylon mesh was introduced in 1944 (Acquaviva & Bourret, 1944). Mersilene mesh, a polyester polymer, was widely known as an alloplastic material in 1946 (Adler & Firme, 1959). In 1951, Kneise described the use of the Perlon meshes (Kneise, 1953). In 1958, Francis Usher introduced the first generation of polyethylene mesh to correct abdominal hernias. Despite its good resistance and inertia, the clinical application of this material was limited because it could not be easily sterilized. In 1962 the same author fulfilled Billroth's dream and presented to the worldwide surgical community the material that, with Lichtenstein's encouraging results decades later, became the best known and most used: It is Marlex, a high density propylene; it cannot be affected by acids, alkalis, or organic solvents; it is highly resistant; inert to the infectious process; non-toxic; it cannot be absorbed; it can be cut and modeled without deforming; in other words, all of the benefits of polyethylene added to the virtue of being possible to sterilize in the autoclave (Usher, 1958, 1962; Lichtenstein, 1989). Mesh screens of other materials, also published at the time, such as chromed catgut (Schönbauer & Fanta, 1958),

Silastic, based on silicone (Brown et al., 1960), and Supramid (Rappert , 1963), were not successful (table 1).

Year	Author	Material
1900	Witzel	Silver
1918	Handley	Silk
1928	Goepel	Stainless steel
1933	Mandl	Celluloid
1944	Acquaviva & Bourret	Nylon
1946	Mc Nealy & Glassman	Vitalium
1946	Adler & Firme	Mersilene
1948	Koontz	Tantalum
1951	Kneise	Perlon
1958	Schönbauer & Fanta	Chromed catgut
1958	Usher	Polyethylene
1960	Brown et al.	Silastic
1962	Rappert	Supramid
1962	Usher	Marlex

Table 1. Development of synthetic prosthesis over the course of history.

4. Mechanism of biomaterial integration to the organism

4.1 Normal healing

After tissue injury, such as surgery, the healing process occurs. It takes place in three phases. It begins with the **inflammatory, substrate or exudative phase,** characterized firstly by vasoconstriction and platelet aggregation. Fibrin is formed as the coagulation mechanism continues, in order to diminish loss to hemorrhage, and it lasts approximately 15 minutes. Then the opposite phenomenon is observed,   with the consequent exudation of proteins and plasma cells in the zone affected. The cell response is processed 6 to 16 h after the onset of the lesion, when a large amount of polymorphonuclear neutrophils appear, as the *first wave of cell migration*. They stay from 3 to 5 days, with a peak within 68 h (Monaco & Lawrence, 2003). Already on the 1st day there is a monocyte incursion. These are macrophage precursors. Neocapillary growth and fibroblastic proliferation begin about 36 h after injury. The activated macrophages are the predominant leukocytes on day 3, when they peak and persist until healing is complete. This first phase lasts until the 2nd day (Castro & Rodrigues, 2007), and may last until the 4th day postoperatively (Pitrez, 2003).

Around the 3rd to 5th day the **proliferative or connective tissue phase** begins, in which angiogenesis and fibroplasia occur, from the proliferation of the endothelial cells and fibroblasts, respectively. They will build the *granulation tissue*. The lymphocytes appear around the 5th day, peaking on the 7th day , and they are mostly represented by T Lymphocytes. During the 2nd week, the fibroblasts become the dominant cells, especially on the 10th day. After this period they differentiate into fibrocytes. Fibroblasts synthetize collagen, which promotes repair resistance. Around the second week type III collagen is gradually replaced by type I collagen. The fibroblasts migrate into the wound from the surrounding tissue, differentiating into myofibroblasts, forming actin filaments, synthetizing a collagen that is periodically reabsorbed, and like the muscles, the scar tissue

has a centripetal movement, making the scar spheroid (Nien et al., 2003). Wound contraction is an essential aspect of healing. It diminishes the area of the defect making it easier to close. During this phase, tension resistance of the synthetized tissue is still low, no more than 25% to 30% of the original resistance (Junge et al., 2002; Klinge et al., 2002).

From the 21st day onwards, during the last phase of the healing process, called **molding, maturing, resolutive or differentiation phase,** tension resistance will reach its highest levels. The accumulation of collagen tissue peaks on the 21st day, and its value remains practically constant in the 3 following months. During this period, acute and inflammatory cells diminish, angiogenesis is suppressed, and fibroplasia ends. The balance between synthesis and degradation of collagen is restored, and *reformulation of collagens* is seen. In the mature matrix type I is 80% to 90%, and type III is 10 to 20% of the total collagen. This matrix undergoes continuous modification until a stable matrix is formed. The scar tissue takes on 40% of the tensile resistance around 6 weeks, 80% around 6 months, and its maximum resistance is achieved after many months, or even years, but it is not equal to the resistance of healthy tissue. (Monaco & Lawrence, 2003; Pitrez, 2003).

4.2 Healing with a prosthesis

The reinforcement given by the prosthesis does not occur due to the mere mechanical presence of the material at the surgical site. It is caused by the tissue that will be produced because it is there. After any prosthetic is implanted, an extraordinarily complex series of events takes place and the healing process described above will occur amidst the mesh. The architecture formed by its filaments and by its pores will act as a foundation for the deposition of connective tissue. The principle and phases of healing are similar, and on the mesh screen weave, a new tissue will be built similar to a dense aponeurosis (Zogbi et al., 2010).

Immediately after implantation, the prosthetic adsorbs proteins that create a coagulum around it. This coagulum consists of albumin, fibrinogen, plasminogen, complement factors, and immunoglobulins. Platelets adhere to this protein coagulum and release a host of chemoattractants that invite other platelets, polymorphonucleocytes (PMNs), fibroblasts, smooth muscle cells, and macrophages to the area in a variety of sequences. Activated PMNs drawn to the area release proteases to attempt to destroy the foreign body in addition to organisms and surrounding tissue. The presence of a prosthetic within a wound allows the sequestration of necrotic debris, slime-producing bacteria, and a generalized prolongation of the inflammatory response of platelets and PMNs. Macrophages then increasingly populate the area to consume foreign bodies as well as dead organisms and tissue. These cells ultimately coalesce into foreign body giant cells that stay in the area for an indefinite period of time (Earle & Mark, 2008). The histological examination of the mesh screens removed shows that all prostheses, independent of type of biomaterial, induce an acute and intense inflammatory reaction (Zogbi et al., 2010, whose quantity and quality depend on the type of material of which the mesh is made (Di Vita et al., 2000). The fibroblasts and smooth muscle cells subsequently secrete monomeric fibers that polymerize into the helical structure of collagen deposited in the extracellular space. The overall strength of this new collagen gradually increases for about 6 months, resulting in a relatively less elastic tissue that has only 70% to 80% of the strength of the native connective tissue. It is for this reason that the permanent strength of a prosthetic is important for the best long-term success of hernia repair (Earle & Mark, 2008).

Three aspects are valuable from the histological standpoint, in the interaction between the material and the organism: the size of the tissue reaction, the cell density and fibroblastic activity. The tissue reaction is 10mm on the 20th day and 20 mm on the 40th day. Cell censity is moderate to the 8th day and maximal after the 30th day. Fibroblastic activity begins on the 8th day on the intraperitoneal plane and 10th day on the extraperitoneal plane. It is maximal on days 30 and 35, respectively. The mechanical resistance of wall reconstruction is similar at the end of 30 days, independently of the material used. During the early postoperative period, between the first and second week, the permeable macroporous prostheses are significantly more resistant than the impermeable ones. This period, during which the prosthesis insertion zone is fragile, is called the Howes latency period (Sans, 1986; Zogbi et al., 2010).

5. Classification

Currently there are more than 70 meshes for hernia repair available on the market (Eriksen et al., 2007). They can be classified into different categories according to composition or type of material (Ponka, 1980), pore size (table 2) (Amid, 1997), density (Earle & Mark, 2008) and others. The classification below covers all these characteristics:

5.1 Synthetic nonabsorbable prosthesis
5.1.1 Type I: Totally macroporous prosthesis
The macroporous prostheses are characterized by a diameter larger than 75 (Amid, 1997) or 100μm (Annibballi & Fitzgibbons, 1994). Thus, they allow easy entry of macrophages, fibroblasts, collagen fibers, which will constitute the new connective tissue and integrate the prosthesis to the organism. They also allow more immunocompetent cells to enter, providing protection from infection-causing germs. The larger the pore diameter, the greater and faster will be the fibroplasia and angiogenesis (Gonzalez et al., 2005). On the other hand, there will also be a greater risk of adhesions when the screen is inserted in the intraperitoneal space, especially if it is in contact with the viscerae; it may also promote erosion and fistula formation (Hutchinson et al., 2004; Mathews et al, 2003; Melo et al., 2003). The main representative is **Polypropylene (PP)** (fig.7). Common brand names include **Marlex**® (Davol, Cranston, Rhode Island), **Prolene**® (Ethicon, Somerville, New Jersey), **Prolite**® (Atrium Medical, Hudson, New Hampshire), **Atrium**® and **Trelex**® (Erle & Mark, 2008). PP is the material most used to correct hernias, both anteriorly, retroperitoneally or laparoscopically (Bellón, 2009). PP is an ethylene with an attached methyl group, and it was developed and polymerized in 1954 by the Italian scientist, Giolo Natta. It is derived from propane gas. The position of the methyl groups during polymerization affects overall strength and it is at a maximum when they are all on the same side of the polymeric chain. This polymer is hydrophobic, electrostatically neutral, and resistant to significant biologic degradation (Earle & Mark, 2008). Since it is thermostable, with a fusion point of 335ºF, it can be sterilized repeatedly in an autoclave (Amid, 2001). Studies show that the tensile strength of PP implanted in organic tissue remains unchanged over time. Disposed in different makes and models, the mesh screens developed for use in hernioplasties are monofilamentary, rough, semi-rigid and allow elasticity in both directions (Speranzini & Deutsch, 2001b). The screen thickness varies according to the model. For instance, Atrium®, Marlex®, Prolene® are respectively, 0.048, 0.066 and 0.065 cm (Goldstein, 1999). It has a high tolerance to infection. When there is a infection at the surgical site, the mesh screen can be

preserved, as long as it is integrated to the fascia, thanks to its broad pores, and must only be drained and the infection treated. In open inguinal hernia repair, the use of a monofilament polypropylene mesh is advised to reduce the chance of incurable chronic sinus formation or fistula which can occur in patients with a deep infection (Simons et al., 2009).
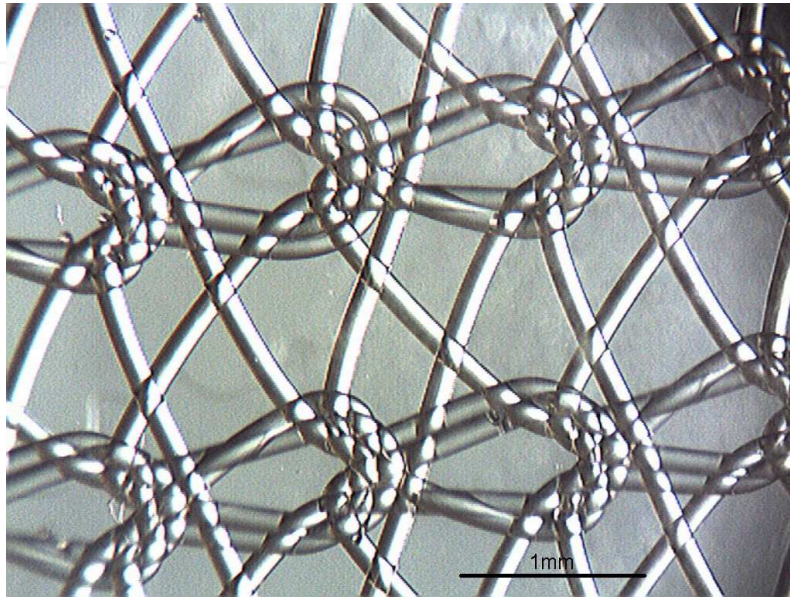

Fig. 7. Augmentation picture of polypropylene prosthesis

Considering the abdominal cavity as a cylinder, and according to Pascal's hydrostatic principle, the maximum load for its rupture is between 11 and 27N/cm. Abdominal pressures vary from 8 to 150mmHg. Klinge et al demonstrated that the prostheses that were being used until that time can bear up to 10 times these rupture tensions, much higher than the resistance of the abdominal wall itself. Thus, there is a reduction of the natural elasticity in the aponeurosis after it is implanted, since the incorporation of tissue to the prosthesis gives rise to an incongruence of resistance between the receiving tissue and the biomaterial, and can cause patient more discomfort. Therefore, it would be more reasonable to implant materials with a lower resistance and greater elasticity (Bellón, 2009). Low weight density (LW) prostheses were then developed (fig.8), characterized by a lower concentration of synthetic material and larger pores (>1,000 µm). The first experimental tests were performed with a hybrid prosthesis of LW PP and polyglactine (Klinge et al., 1998), which was later sold under the name **Vypro II**® (Ethicon, Johnson&Johnson, Somerville, USA). Then pure LW PP prostheses were developed and disseminated, such as **Parietene**® (Tyco, Healthcare, Mansfield, MA), with a 38g/m² density and 1.15 +- 0.05 mm² pores and **Optilene elastic**® (Braun, Spangerwerg, Germany), with 48g/m² and 7.64 +- 0.32mm² pores (Bellón, 2009).

Hence, as to density, the prostheses can be classified as: Heavyweight (HW), when they are above 80g/m²; Mediumweight (MW), between 50 and 80 g/m²; Lightweight (LW), between 35 and 50 g/m²; and Ultra-lightweight, below 35 g/m². Comparing them, it would be helpful to classify density (weight) and pore size uniformly in a standard fashion. Earle & Mark proposed a standard based on currently available data: Very large pore: >2,000 µm; Large pore: 1,000–2,000 µm; Medium pore: 600–1,000 µm; Small pore: 100–600 µm; Microporous (solid): <100 µm (Earle & Mark, 2008).
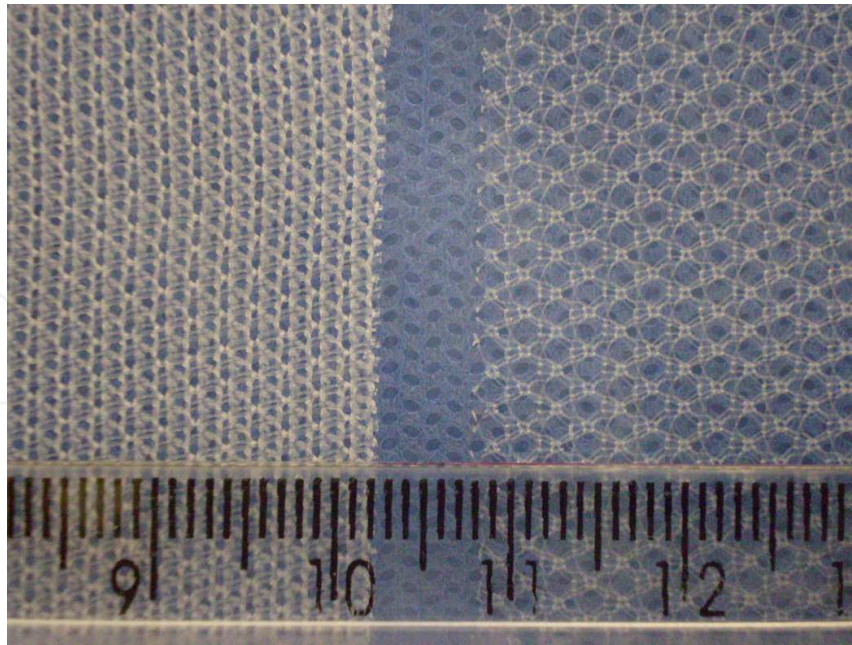
Fig. 8. Comparison between a HW (Marlex®), on the left, and a LW mesh (Parietene®), on the right.

Material-reduced (Weight-reduced mesh materials/ lightweight/oligofilament structures/largepore/macroporous>1,000 μm) meshes have some advantages with respect to long-term discomfort and foreign-body sensation in open hernia repair (when only chronic pain is considered), but are possibly associated with an increased risk for hernia recurrence in high-risk conditions (large direct hernia), perhaps due to inadequate fixation and/or overlap. They seem to shrink less, cause less inflammatory reaction and induce less extensive scar-tissue formation (Hollinsky et al., 2008; Simons et al., 2009).

5.1.2 Type II: Totally microporous prosthesis

The pores are smaller than 10μm in at least one of the three sizes. The main example is **expanded politetraflouroethylene (e-PTFE)**. It was discovered at a DuPont laboratory serendipitously by Roy Plunkett in 1938. While researching tetraflouroethylene gas as a refrigerant, he discovered that the gas spontaneously polymerized into a slippery, white, powdery wax. After some time on the shelf, it was eventually used as a coating for cables. While still working at DuPont, William Gore subsequently saw the potential for medical applications, and ultimately started his own company, W.L. Gore and Associates, in 1958. That company developed and manufactured e-PTFE under the brand name **Gore-Tex®** (W.L. Gore and Associates, Flagstaff, Arizona) for hernia repair products, among other things. There are other manufacturers of PTFE hernia prosthetics, each with a different manufacturing process, and hence a slightly different architecture (Earle & Mark, 2008). PTFE is not a mesh, but a flexible, impervious sheet. It is transformed into its expanded form (e-PTFE) after being submitted to an industrial process. It is a soft, flexible, slightly elastic material, and its smooth surface is not very adherent (Mathews et al., 2003). Therefore it must be carefully fixed with sutures, since its integration is very slow, taking about 30 to 40 days (Speranzini & Deutsch, 2001b). Its minuscule pores are actually complex fine canals,

through which fibroblasts penetrate and synthetize collagen. The e-PTFE is composed of columns of compact nodules, interconnected by fine fibers of the same material (Mathews et al., 2003). The intermodal distance is from 17 to 41μm, with a multidirectional fibrillar arrangement that provides equal strength on every plane (Amid, 2001). Bacteria, approximately 1μm in size, easily penetrate the micropores of the prosthesis and are thus protected from the macrophages or neutrophils, which are too voluminous to enter the site, perpetuating the infectious process. It is a mechanism similar to that of a foreign body which occurs with plaited threads or any materials with interstices (Amid, 1997). Therefore, when there is an infection, the mesh screen should always be removed, on the contrary of the macroporous screens. The main advantage of this material is the diminished risk of adhesions, even in direct contact with the viscerae. It is the prosthesis with the smallest tissue reaction (Speranzini & Deutsch, 2001b). Because of this, its use in laparoscopic hernia repair allows the surgeon to leave the peritoneum open once the prosthetic is in place (Earle & Mark, 2008).

5.1.3 Type III: Macroporous prosthesis with multifilament or microporous components

They are characterized as containing plaited multifilamentary threads in their composition, and the space between threads is less than 10 μm; but also because their pores are larger than 75 μm. They include plaited polyester mesh - **Mersilene**® (Ethicon, Johnson&Johnson, Somerville, USA) and **Parietex**® (Covidien, Mansfield, USA); plaited polypropylene - **SurgiPro**® (Covidien, Mansfield, USA); perforated PTFE - **Mycromesh**® and **MotifMESH**® (Amid, 1997; Eriksen et al., 2007).

The main disadvantage is during an infection, because the chance of complete wound healing after adequate drainage is difficult. When a multifilament mesh is used, bacteria (<1 μm) can hide from the leucocytes (>10 μm), because the mesh has a closer weave structure with a smaller pore diameter (<10 μm) (Simons et al., 2009).

Polyester (PE), the common textile term for polyethylene terephthalate (PET), is a combination of ethylene glycol and terephthalic acid, and it was patented by the English chemists J.R. Whinfield and J.T. Dickson in 1941 at the Calico Printers Association Ltd. in Lancashire, the United Kingdom. PET is hydrophilic and thus has the propensity to swell. PET is the same polymer used for plastic beverage bottles (Earle & Mark, 2008). It is a light, soft, flexible, elastic material, in a single direction. Its wide meshes encourage fibroblastic migration making it easier for tissue to incorporate – its pores are even greater than those of the PP, which is believed to allow faster cell migration and greater intensity of adherence to the underlying fascia (Gonzalez et al., 2005). It has good resistance to infection, although its threads are multifilament. It does not have the plastic memory of PP, which allows it to adapt to the structures on which it is placed. Another advantage is the cost, because it has a lower cost (Speranzini & Deutsch, 2001b). It is the mesh screen most used by European surgeons, especially the French (Stoppa & Rives, 1984).

In 1993 the MycroMesh® with pores all way through the mesh was introduced to allow better tissue ingrowth. MotifMESH® is a new macroporous non-woven mesh of condensed PTFE (cPTFE) for intraperitoneal application. Although the mesh is macroporous (fenestrated) it has a theoretically anti-adhesion barrier because of the PTFE content. The thickness of the MotifMESH® is reduced by 90% compared with older ePTFE meshes (Eriksen et al., 2007).

Prostheses	Definition	Examples
Type I	Pore diameter > 75 μm	Polypropyleno (PP)
Type II	Pore diameter < 10 μm	Expanded Polytetrafluorethylene (e-PTFE)
Type III	Pore diameter >75 μm Space between threads < 10 μm	Polyester (PE)
Type V	Submicromic pores	Pericardium, dura mater

Table 2. Classification of the biomaterials according to Amid (Amid, 1997)

5.2 Mixed prostheses

Also known as "second generation" screens, they are characterized by combining more than one type of material in the same prosthesis (Bachman & Ramchaw, 2008).

5.2.1 Partially absorbable prosthesis

One of the disadvantages of LW prostheses is the excessive malleability of the screen). The lack of memory, or lack of rigidity, makes them difficult to handle during surgery, especially laparoscopic surgery. To reduce the polymer density (and subsequent inflammatory response), yet maintain the intraoperative handling characteristics and long-term wound strength, prosthetics have been developed that mix nonabsorbable polymers (eg, PP) with absorbable polymers. Thus, screens composed by a LW PP structure are associated with biodegradable elements, such as **polyglactine – Vypro II**® mesh or **polyglecaprone-25 - Ultrapro**® mesh (Ethicon, Johnson&Johnson, Somerville, USA). This confers on the screen an appropriate malleability for better surgical handling, without, however, leaving a high weight of unabsorbed tissue in the organism (Earle & Romanelli, 2007; Earle & Mark, 2008; Hollinsky et al., 2008; Bellón, 2009).

5.2.2 Coated nonabsorbable prosthesis

In order to avoid visceral adhesions, erosion and even fistula formation which are possible complications of macroporous screens when inserted on the peritoneal side, screens covered with low tissue reaction material were developed to remain in direct contact with the viscerae. The two-sided **DualMesh**® was introduced in 1994, made in e-PTFE, and it was later modified with large interstices and an irregular "corduroy-like" surface on the parietal side to increase tissue ingrowth. Other available brands are: **Intramesh T1**®; **Dulex**®; and **Composix**®. The DualMesh® is also available with incorporated antimicrobial agents (silver–chlorhexidine film, type "Plus"). **TiMesh**® (GfE Medizintechnik GmbH, Nürnberg, Germany) is a titanium-coated lightweight (macroporous) PP mesh. Titanium is known for its good biocompatibility and should theoretically reduce adhesions. It is manufactured for intraperitoneal use although it has no "real" solid anti-adhesion barrier or micro-pore/no-pore site against the bowel loops. **Parietene Composite**® (Covidien, Mansfield, USA) is a woven PP mesh with a protective collagen-oxidized film (collagen-coating) on the visceral side. **Sepramesh**® is a PP mesh coated on the visceral side with an absorbable barrier of sodium hyaluronate and carboxymethylcellulose. **Proceed**® (Ethicon, Johnson&Johnson, Somerville, USA) is a Prolene® soft mesh encapsulated in a polydioxanone polymer film (PDS®) covered by a layer of absorbable oxidised regenerated cellulose (ORC); **Glucamesh**® (Brennen Medical, St. Paul, Minnesota) is a midweight PP mesh (50 g/m²) coated with the absorbable complex carbohydrate, oat beta glucan; **Dynamesh**® (FEG Textiltechnik, Aachen, Germany) is a PP mesh with polyvinylidene fluoride (PVDF) monofilament; **C-QUR**®

(Atrium Medical) is a mediumweight PP mesh (50 or 85 g/m²) coated with an absorbable omega-3 fatty acid preparation derived from fish oil, because omega-3 fatty acids have anti-inflammatory properties. The coating is about 70% absorbed in 120 days and has had all protein removed to avoid an immune response. The same mesh without the coating has been analyzed in the laboratory and found to be acceptable in terms of inflammatory response compared with more heavyweight polypropylene prosthetics (Mathews et al., 2003; Abaza et al., 2005; Eriksen et al., 2007; Earle & Mark, 2008; Schreinemacher et al., 2009). The **Parietex Composite**® mesh is composed of multifilament PE with a resorbable collagen-oxidized film made of oxidized atelocollagen type I, polyethylene glycol and glycerol, against the viscera. **Intramesh W3**® is a PE mesh with silicone layer (Eriksen et al., 2007; Schreinemacher et al., 2009).

In the mixed prostheses in general, weight is usually smaller and porosity greater. For instance, a conventional PP prosthesis PP (HW) such as Surgipro®, weighs 84g/m² and has small pores (0.26 +- 0.03mm²). Conversely, Ultrapro®, weighs 28g/m² with 3.45 +- 0.19mm²; pores; and VyproII® weighs 35g/m² with 4.04 +- 0,54mm² pores(Bellón, 2009).

5.3 Biologic prosthesis

Biologic mesh materials are based on collagen scaffolds derived from a donor source and they represent so-called ''third-generation'' mesh. According to Amid's classification they are included in the **type IV** prostheses, **biomaterials with submicronic pore size.** Dermis from human, porcine, and fetal bovine sources are decellularized to leave only the highly organized collagen architecture with the surrounding extracellular ground tissue. Other natural collagen sources in addition to the dermal products include porcine small intestine submucosa (which is layered for strength) and bovine pericardium. The collagen in these materials can be left in its natural state or chemically crosslinked to be more resistant to the collagenase produced in wounds. By increasing crosslinking, the persistence of the mesh is also increased. Uncrosslinked mesh can be totally incorporated and reabsorbed within 3 months, whereas a highly crosslinked mesh can persist for years (Amid, 1997; Bachman & Ramshaw, 2008).

Most of the human studies published on biologic materials are from difficult clinical situations. Because angiogenesis is a part of the remodeling of the mesh, these materials can potentially resist infection (Blatnik et al., 2008; Deprest et al., 2009), and they have a moderately good success rate for salvaging contaminated and infected fields, especially when placed with wide overlap. Other findings demonstrate some resistance to adhesion formation (Bachman & Ramchaw, 2008).

The basic concept behind these types of prosthetics is that they provide a matrix for native cells to populate and generate connective tissue that will replace the tissue in the hernia defect. Given that newly formed connective tissue is only 70% to 80% as strong as native connective tissue, and that hernia patients may have an inherent defect in their native connective tissue, biologic (or absorbable synthetic) prosthetics would theoretically have a higher risk of recurrence than would permanent prosthetics. With a theoretically increased risk of long-term recurrence, relatively high cost, and no clear benefit, the use of these products for elective inguinal hernia repair should be considered investigational, and are not routinely indicated (Earle & Mark, 2008; Simons et al., 2009).

5.3.1 Heterografts

These are biomaterials produced from animal tissue. Porcine heterografts, whose main and most studied example is **Surgisis**® (Cook Biomedical, Bloomington, IN, USA), derived from

porcine small bowel submucosa was one of the initial biologic grafts used and was FDA approved in 1999. Surgisis is an acellular xenograft consisting primarily of type I porcine collagen. It is harvested from slaughterhouse pigs, processed with paracetic acid, and terminally sterilized with ethylene oxide. It does not undergo crosslinking during processing. The graft is available in different thickness including four ply, for hiatal hernias and groin hernias; and eight ply, for ventral hernias. This material seems to be biodegradable and manufacturers claim it is completely replaced with native tissue at 6 months. Surgisis has been extensively studied in animal models. Agresta & Bedin say that, besides diminishing the chances of adhesions on the peritoneal side, another advantage to using a biological mesh is that the persistence of a synthetic mesh in the preperitoneal inguinal area, where scar formation can result in the possible complications of infertility and difficulties in future vascular and urological surgical procedures, is that the biological mesh does not lead to a persistent foreign body in this region and these complications may, therefore, be avoided. This is especially important in the young patient or in athletes. The theoretical benefits of its use include: resistance to infection in contaminated surgical fields; avoidance of a permanent foreign body in the inguinal region; and a reconstruction that results in the formation of natural tissue. These characteristics, together with the results of several human clinical studies which have demonstrated its safety, let us suggest its possible use in young patients without any fear of possible future complications (Agresta & Bedin, 2008).

Several porcine dermal products are also available using different processing techniques: **Permacol**® (Covidien, Norwalk, CT) was initially approved for pelvic floor reconstruction in 2000. It is manufactured by Tissue Sciences Laboratory (Aldershot, UK) and was acquired by Covidien in 2008. It is processed with Diisocynate to achieve collagen cross-linking, and is terminally sterilized with gamma irradiation. It is not freeze dried and requires no rehydration before use. There are several peer reviewed publication evaluating Permacol in gynecologic, urological, plastic surgical, and ventral hernia repairs. **Collamend**®, distributed by Davol Inc, (Warwick, RI), was approved for use in 2006. It is freeze dried, requires 3 minutes of rehydration before use, and is heavily crosslinked. LifeCell Inc, (Branchburg, NJ) introduced **Strattice**® in 2007; it is, noncrosslinked, terminally sterilized, and requires a 2 minute soak before usage. **XenMatrix**® is another porcine dermal product that received approval in 2003, and is manufactured by Brennen Medical (St, Paul, MN). It is noncrosslinked and terminally sterilized with E-beam radiation. It is stored at room temperature and does not require rehydration before usage (Rosen, 2010).

Bovine donors constitute the remainder of the heterografts and sources include pericardium or fetal dermis. **Tutopatch**® is a bovine pericardial product, is manufactured by Tutogen (Alachua, FL), and received FDA approval in 2000. Tutogen processing is a proprietary technique that involves osmotic contrast bathing, hydrogen peroxide, sodium oxide, and gamma irradiation for terminal sterilization. It is stored at room temperature and requires rehydration before use. Two other bovine pericardial products are manufactured by Synovis Surgical Innovations (St, Paul, MN): **Veritas**® received approval in 2003, and is a noncrosslinked bovine pericardium that is harvested from an isolated Midwestern slaughterhouse from cows younger than 30 months. It is processed with sodium hydroxide, propylene oxide, and ethanol. It does not require rehydration and is ready to use out of the package. **Peri-guard**® is treated with gluteraldehyde to initiate collagen crosslinking. It requires a 2 min soak before usage (Rosen, 2010).

5.3.2 Allografts

Several cadaveric allografts are presently available. Because these grafts have been minimally altered from the initial starting material, they are classified as "minimally processed human tissue" by the FDA. This is an important distinction from the heterografts, which are classified as medical devices and are under closer scrutiny by the FDA. Tissue banks typically regulate these allografts. **AlloDerm**® (LifeCell Corporation, Branchburg, NJ) is created from cadaveric skin using proprietary processing techniques that reportedly maintain the biochemical and structural components of the extracellular matrix promoting tissue regeneration. Cells are then removed by deoxycholate, and the residue is washed and lyophilized. The remnant material is an insoluble matrix composed mainly of collagen, elastin and laminin and closely resembles the composition of normal skin connective tissue (Penttinen & Grönroos, 2008). The graft is noncrosslinked, and is freeze dried, and requires a 20 to 30 minutes soak before use. The ability of AlloDerm to withstand hostile environments has been well documented. However, the graft's durability and the prevention of hernia recurrence have been less clear. **AlloMax**® (Tutogen Medical Inc., Alachua, FL) is another acellular human dermal product that is marketed through Davol Inc. It is noncrosslinked and undergoes a proprietary processing developed by Tutoplast similar to the Tutopatch previously described. **Flex HD**® is manufactured by Musculoskeletal Tissue Foundation (Edison, NJ) and is distributed by Ethicon Inc. (Somerville, NJ). It is stored in a 70% ethanol solution and remains in a hydrated form and therefore does not require rehydration before use. It does not require refrigeration (Rosen, 2010).

Implantation of a **fibroblast growth factor (bFGF)**-releasing polygalactone polymer rod into the fascial wound of rats has been carried out. This approach reduced the development of primary incisional hernias from 60 to 30%, and recurrent incisional hernias from 86 to 23%. This study also reported that type I collagen staining was significantly increased around the bFGF treated fascia, which was thought to contribute to the results (Dubay et al., 2004).

The use of the patient's hernial sac as biomaterial to correct the hernia and reinforce the surgery has also been described, since it also induces fibroplasia (Silva et al., 2004).

6. Complications from the use of mesh screens

The overall risk of complications reported after inguinal hernia operations varies from 15 to 28% in systematic reviews. The most frequent early complications were hematomas and seromas (8–22%), urinary retention and early pain, and late complications were mainly persistent pain and recurrences. Those are the two most important outcome measures. Chronic pain is an issue that primarily affects patient quality of life, and is the most common complication of otherwise successful inguinal hernia surgery (Perenttinen & Grönroos, 2008). A truly successful hernia repair requires effective bridging or augmentation that will prevent recurrence. If reoperation is required in the event of a recurrence, the incidence of chronic pain increases. Other complications described are foreign body reactions, infection, discomfort, dislocation, migration, erosion and shrinkage of the prosthesis (Junge et al., 2006; Zogbi et al., 2010). The risk of infertility has been considered significant in inguinal mesh operations (Penttinen & Grönroos, 2008). Chronic pain, stiff abdomen, and foreign body sensation are least often observed with the use of a lightweight mesh and a laparoscopic approach (Klosterhalfen et al., 2005). Besides these specific complications caused by the prosthesis, complications common to any surgical procedure, such as

respiratory or urinary infection, vomiting, constipation, urine retention, venous thrombosis, hemorrhage, anesthetic complications and even death should not be underestimated. Fortunately, lifethreatening complications were rarely reported (Simons et al., 2009).

7. Measures to avoid complications

First it should be recalled that surgical techniques using mesh result in fewer recurrences than techniques which do not use mesh (Simons et al., 2009). Besides, mesh repair appears to reduce the chance of chronic pain rather than increase it (Collaboration, 2002).

During any surgery, a meticulous, anatomical, precise and aseptic surgical technique should be used. The mesh should be positioned adequately when it is fixed, and it should go 2 cm or more beyond the limits of the margins of existing defects, so that a possible retraction or displacement will not compromise the entire coverage of the hernial defect (Amid, 2001). After all recurrences in humans invariably occurred at the mesh margin, where the mesh interfaced with tissue (Bachman & Ramchaw, 2008). Contact with bowel loops should be avoided, because the adhesions resulting from this contact may cause irreversible damage such as necrosis, digestive fistula and elimination of the material (Mathews et al, 2003). Contact with subcutaneous cell tissue should be avoided to reduce the risk of seroma and infection. It should be placed between two myoaponeurotic layers, not only to avoid contact with the viscerae, or with the subcutaneous, as described above, but also so that the mesh will not fold over and will be directly integrated to these tissues, strengthening them (Falci 1997, 2003).

After surgery, the patient should return gradually to his activities, without intense, abrupt efforts. Risk factors described at the beginning of the chapter should be controlled.

8. The ideal mesh for hernia repair: defining characteristics

Classically the first desirable qualities in the biomaterials described were resistance, durability, good tissue tolerance, flexibility, easy manipulation, non-migration, stability, pervious pores, sterilizability and economic feasibility, besides not producing cysts or malignant changes. All this is still accepted (Cumberland, 1952; Scales, 1953). Other needs were found over time, namely, they should not restrict postimplantation function or future access, they should perform well in the presence of infection and block transmission of infectious diseases, resist shrinkage or degradation over time and be easy to manufacture. (Earle & Mark, 2008). Saberski et al added another characteristic called anisotropy, and they found striking differences between elastic properties of perpendicular axes for most commonly used synthetic meshes (Saberski et al., 2011). From the surgeons' and patients' point of view, the optimal mesh should have minimal adhesion formation, excellent tissue ingrowth with minimal shrinkage, no fistula formation and promote minimal pain and seroma formation. Furthermore, it is important that the mesh causes no change in abdominal wall compliance (Eriksen et al., 2007). The mesh should be flexible but also have a good memory, and it should have elasticity in more than one dimension, allowing it to stretch in more than one direction and then return to its original shape. In this way, the mesh should match the abdominal wall dynamics as closely as possible. Flexibility and memory, which make a mesh more adaptable, are also important to optimize the surgical handling of the mesh. The mesh should have an adequate adhesive quality that requires minimal or no additional fixation, even for large defects. An ideal mesh would be a

monofilament mesh that would prevent adhesions yet still enable growth of the adjacent tissue for optimal augmentation (Bringman et al., 2010).

In healthy volunteers, documented measured intra-abdominal pressure via intravesicular measurements was up to 252 mmHg in a variety of maneuvers, including lifting, coughing, and jumping. This correlates to forces of up to 27 N/cm (Cobb et al, 2006). A tensile strength of 16 N was probably more than sufficient to augment the abdominal wall; for bridging of large defects, an increased tensile strength of 32 N may be necessary (Bringman et al., 2010). With these numbers in mind, compare a maximum force on the abdominal wall of 27 N/cm with the measured burst force of some of the more common synthetic mesh materials: Marlex® has a tensile strength of 59 N/cm, Atrium® 56 N/cm, and VyproII® 16 N/cm. Marlex® and Prolene® were both over five times stronger than the calculated abdominal wall strength, and Mersilene® was at least twice as strong (Kinge et al, 1998). A similar trend was noted in an animal study conducted by Cobb. Mesh was implanted into swine for 5 months and then tested for burst strength. Native tissue ruptured at 232 N, LW PP mesh burst at 576 N, MW at 590 N, and HW mesh at 1218 N (Cobb et al, 2006). These data have lent scientific support to the theory that synthetic mesh materials, especially traditional HW PP mesh, are overengineered for their purpose. This excess prosthetic can lead to more complications, including decreased mesh flexibility, loss of abdominal wall compliance, inflammation, and scarring of surrounding tissues, potentially leading to pain, a sensation of feeling the mesh in the abdominal wall, and mesh contraction and wadding, which in turn may result in a recurrent hernia (Bachman & Ramchaw, 2008). Actually, all commercially available synthetic prosthetics today have long-term foreign-body reactions. Given the existing products and body of evidence, the overall density should probably be somewhere between 28 g/m² and 90 g/m² to minimize recurrence and adverse effects of the host foreign-body response. Methods to decrease the density of the prosthetic include reduction in fiber diameter (ie, strength) and number of fibers (ie, increase in pore size). Studies have also shown that a PP mesh with a pore size greater than 600 to 800 mm should result in more of a scar ''net'' rather than a scar ''plate''. The ''net'', compared to the ''plate'', is less prone to contracture and stiffness of the abdominal wall. Not all small-pore prosthetics are stiff. Consider what is seen clinically with microporous PTFE, and the maintenance of pliability even with encapsulation. It may then be that the architecture (woven versus solid) of the prosthetic is a more significant contributor to performance than the polymer itself. The upper limits of pore size for adequate fixation to prevent recurrence have not been appropriately investigated. Very large pore size (4,000 mm) combined with a partially absorbable component doesn't appear to have any clinical benefits in terms of pain, and may not be sufficient to prevent higher recurrence rates when used with a Lichtenstein technique (Earle & Mark, 2008). An ideal portfolio of meshes would have the benefits of both HW and LW meshes, such as the strength of an HW mesh and the flexibility of an LW mesh with none of the adverse events. The HW microporous meshes have a lower risk of tissue-to-mesh adhesion but carry a risk of encapsulation and foreign body reaction, resulting in decreased integration. LW macroporous mesh results in better tissue ingrowth and lower (ou less) foreign body reaction but may lead to a higher risk of adhesions (Eriksen et al., 2007). A larger pore size also provides optimal flexibility for improved physical properties, allowing a better activity profile post-surgery, but relinquishes memory, which is important for handling during the procedure. A monofilament mesh with a pore size of > 2.5 mm seems ideal. In all hernia repair techniques, a strong mesh is important for augmentation of the abdominal wall and to prevent recurrences (Bringman et al., 2010).

9. Charity campaigns involving biomaterials for low income patients.

Publications on campaigns performed in Africa show encouraging results with the use of sterilized mosquito net mesh. Clarke et al. report their results, implanting sterilized polyester mosquito net mesh in 95 poor patients in Ghana, with 2% infection and no recurrences. They concluded that PE mosquito net mesh is a cost-effective alternative to commercial mesh for use in inguinal hernia repair in developing countries (Clarke et al., 2009). Optimistic results were also described in a study performed before this one, in Burkina Faso, using Nylon (100% Polyamide 6-6) mosquito net mesh, this time describing the complete absence of infection (Freudenberg et al., 2006).

10. Establishing animal models for the development of biomaterials

Animal models resembling the human hernia are a useful tool for researchers to investigate hernia treatment options. The current animal models used to study hernia repair are not perfect. Artificially created hernias in animals are poor hernia models as they do not truly recreate the biological defects that cause hernias, such as collagen defects. Furthermore, the defects that are created to test mesh products are not real-life defects that surgeons would encounter. In order to serve as a useful model, the pathology in the animal must be similar to the human hernia equivalent. One factor when considering an animal model is similarities in the elasticity of the abdominal wall. Although there is no consensus for the most appropriate test or animal model, animal models are useful when comparing different meshes in the same species either in vivo or ex vivo. Studies in humans and large animals are the only way that most issues, such as elasticity, chronic pain, foreign body reaction, and adhesion, will be observed. What problems animal models can solve and which animals are the most appropriate for use will differ depending on the purpose of the study. Small animals or even cell cultures are instructive for studying the inflammatory reaction and biocompatibility, but for abdominal wall function and elasticity, larger animals are more suitable. Although ineffective for other comparisons, pigs are useful to simulate mesh implantation within the human body as pigs have a similar body size to humans. Sheep and rabbits are reasonable models to mimic vaginal operating conditions; potentially, they are also useful models for pelvic floor damage due to pregnancy and birth (Penttinen & Grönroos, 2008; Bringman et al., 2010).

11. Conclusion

Operation techniques using mesh result in fewer recurrences than techniques which do not use mesh.

12. Acknowledgment

13. References

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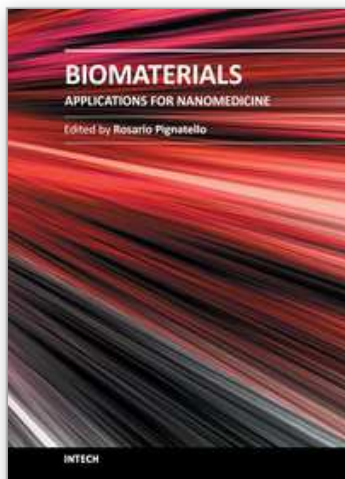
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