A 150-Year History of Autologous Treatments in Western Medicine

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Autologous therapies, whereby the patients own body samples, be that individual cells, blood, tissues or organs are removed from the patient and transplanted (replaced) at a later date have been used throughout medicine for over 150 years. Modern western medicine has long sought autologous treatments because they have been shown to be among the safest, most effective, and profoundly natural method of surgical and minimally invasive treatment methodologies.

There has never been a more powerful method of healing than using the body's own natural biology to repair itself. Many researchers and companies have identified methods of looking within the human body to repair, replace, and improve the health of patients. Several examples of using these both very old and medically new procedures are discussed below:

Skin Grafts

Skin grafting is a surgical procedure whereby skin, or a skin substitute, is placed over a burn, or non-healing wound to provide temporary or permanent cover to the area, without which the wound would take much longer to heal (if at all). Skin grafting can be used to reduce the risk of infection within the wound, accelerate healing and reduce fluid loss from the wound site, reduce scar contraction, and enhance cosmetic appearance.

The first references to the concept of skin grafting dates back as far as 800BC. One of the earliest types of attempted transplant recorded was in India where reports suggest that the surgeon Susrata grafted new noses created from skin flaps. In around 200AD, in China, the surgeon Hua-To first described the idea that you could replace diseased organs with healthy ones. However, until the 19th century only a few trials involving transplantation were reported. The first successful autologous skin graft (transplantation of skin from one location on a patient's body to another location on their own body) was performed by Berger in 1822. Its biology has come to light only within the last 50 years, and research continues into its basic mechanisms.

It can therefore be seen that skin grafting is a modern addition to surgery but with ancient roots.

There are two types of skin grafts, partial (or split) thickness grafts and full-thickness grafts. Partial-thickness skin grafts involve taking the epidermis and only a little of the dermis layers (See Figure 1), and are used to restore the functional integrity of the skin. The advantage is that they can be rapidly harvested and usually heal within several days. The wound however, must not be too deep if a partial-thickness graft is going to be successful. This is because the blood vessels that will nourish the grafted tissue must still be intact and are from the wound itself. If the wound is much deeper, a full-thickness skin graft is an option. Full-thickness skin grafts contain both the epidermis and the whole of the dermis (See Figure 1) and are often used to improve appearance. They provide better contour and a more natural colour, and less contraction is seen. This is due to the whole thickness of the skin being used, therefore more of the characteristics of normal skin will be maintained. However, full-thickness skin grafts are limited to relatively small, uncontaminated, well-vascularized wounds and thus do not have as wide a range of applications as split-thickness grafts

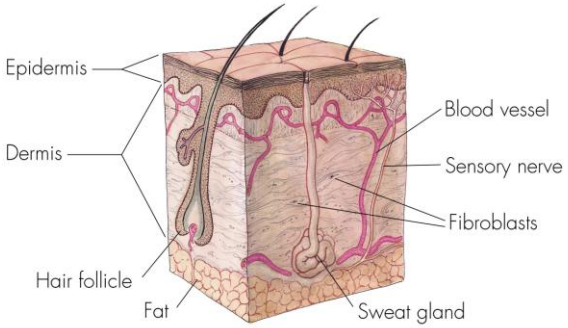

Figure 1. Cross section of components of the skin

The skin used for grafting can be taken from another area of the patient's body, (called an autograft) - if there is enough undamaged skin available and also depending whether the patient is healthy enough to undergo the additional surgery required. Skin harvested for grafting can be stored for later use as needed. The graft is wrapped in gauze and placed in a sterile, sealed container. The skin can survive within the temperature range 0-37°C, but the lower the temperature, the longer the survival time, 4°C is routinely used (McGregor and McGregor, 1995).

Alternatively, skin can be obtained from another person (called an allograft), or from an animal - usually a pig (called a xenograft). Allografts and xenografts provide only temporary covering as they are rejected by the patient's immune system within 7-10 days and are then replaced with an autograft (Kirsner et al., 1998).

In recent years, the development of synthetic, or bio-engineered skin substitutes has led to significant improvements in wound care (Bell et al., 1981; Hutmacher, 2001; Kirsner et al., 1998; Minuth et al., 1998; Wisser and Steffes, 2003). A number of these products are commercially available, or undergoing current clinical trials (Sabolinski and Bilbo, 2001). There are a number of different approaches that have been used to develop skin replacement products. The four different approaches are using: (i) cultured epidermal grafts; (ii) dermal substitutes; (iii) dermal and synthetic epidermal substitutes; and (iv) bilayered living skin constructs. Their description, available commercial products and applications can be seen in the following table, taken from (Sabolinski and Bilbo, 2001).

Heart Bypass

Coronary arteries are small vessels that supply the heart with oxygen-rich blood. These blood vessels can become blocked, due to a build up of a substance called plaque (a combination of fats and cholesterol), known as atherosclerosis. When one or more of the coronary arteries become partially, or totally blocked, the heart does not get an adequate blood supply which can cause heart pain and/or coronary heart disease. Heart bypass surgery reroutes the blood supply around the blocked part of the artery, restoring normal blood flow to the heart (Mullany, 2003).

The most common vessels to be used during bypass surgery are: (i) the saphenous vein, which is located on the inside of the leg running from the ankle to the groin, and is removed from one of the patients legs during surgery; (ii) the internal mammary artery, which is located on the inside of the chest wall, behind the breastbone; and (iii) the radial artery, which is located in the forearm. During surgery, the selected vein or artery is removed and one end is attached to the aorta (the main artery leaving the heart) and the other to the coronary artery below the blockage.

A few physicians experimented with operating on the heart as far back as the 1920's, although it wasn't until after World War II (mid 1940's) when the benefits of heart surgery were recognised worldwide. Military surgeons, faced with vast numbers of wounded soldiers with shrapnel lodged in their hearts, pioneered the earliest heart surgery techniques. Their success was limited, however, as they were only able to stop the heart for four minutes before oxygen loss led to brain damage.

In the years following, physicians experimented with many techniques to increase this time frame, even learning to freeze their patients temporarily in hopes of mimicking the slower heartbeat of hibernating animals. Heart surgery finally became possible in 1953, when Gibbon, a physician from the USA developed the first heart-lung machine, a machine which keeps the blood oxygenated and circulating the body whilst the procedure is carried out on the heart. The first coronary heart bypass took place in the USA in 1963. Today, the heart bypass operation is the most commonly performed heart operation in the world

Cancer Treatments

Since the 1970's, bone marrow and stem cell transplants have been increasingly used in the treatment of cancers such as leukaemia and lymphomas. More recently it has been used in the treatment of other cancers, such as breast cancer and some rare forms of anaemia.

The many different types of blood cells are all produced in the bone marrow (a spongy substance inside bones), stem cells are found within the bone marrow and mature to produce these blood cells. Treatment of diseases such as cancers with high dose chemotherapy drugs kills off the bone marrow, thereby rendering the patient unable to produce any new blood cells. Therefore, removal of bone marrow, or stem cells, prior to chemotherapy, if necessary removing any cancerous cells that may be present, and reintroducing it back into the patient has shown to be a more effective way of curing disease. This is because a higher doses of chemotherapy can be used (Lin et al., 2002; Lin and Copelan, 2003; Philip et al., 1995).

There are two types of bone marrow transplant, autologous transplantation, whereby the patients own bone marrow or stem cells are used, or allogenic transplantation, whereby the bone marrow or stem cells come from a donor. Advantages of the autologous therapy include timeliness as the need to wait for a suitable donor is eliminated. In addition, the risk of contracting Graft versus Host disease is all but erased, as the cells are recognised by the body as its own, and not foreign, therefore there is no risk of rejection. The harvested bone marrow is processed to remove blood and bone fragments. Harvested bone marrow can be combined with a preservative and placed in a liquid nitrogen freezer to keep the stem cells alive until they are needed. This technique is known as cryopreservation.

Chondrocyte Transplantation

Autologous chondrocyte (cartilage cell) transplantation is a relatively new procedure with the first references seen in the mid 1980's (Peterson et al., 1984). Since clinical application began in 1994 (Brittberg et al., 1994), more than 5000 cases have been documented and the results reported (Erggelet et al., 2003). Autologous chondrocyte transplantation is used to treat articular cartilage injuries (cartilage injuries to the joints), which are a common and frequent cause of pain in joints such as the knees. If such cartilage injuries are full-thickness and left untreated, potential long term problems include early osteoarthritis. When osteoarthritis becomes severe, the usual treatment is the replacement of the arthritic articular surface with an artificial prosthesis. This total knee replacement is commonly performed in patients who are over 60 years old. Problems occur when the patient is a lot younger, due to the limited lifespan of the prosthesis. Autologous transplants have been studied as an alternative therapy and the aim is to restore normal cartilage to the end of the bone, thereby restoring normal joint function.

Healthy chondrocytes obtained from an uninvolved area of the injured knee are obtained surgically, isolated and cultured. These cultured chondrocytes are then injected back into the area of the defect, and the defect covered with a piece of periosteum (the dense fibro-vascular membrane which envelops the bones). Post-operative rehabilitation is based on the patients health status and size of the transplanted lesion. However, as a general rule, the patient can begin weight bearing within the first week and start light resistance exercise by the second week, although running is not advised until around 9-10 months after grafting (Brittberg et al., 2003). In a recent report (Peterson et al., 2003) it was described that of 58 patients treated (age range 14-52 years) whose initial clinical ratings (according to the Brittberg clinical rating score) were poor (56/58) or fair (2/58), two years post operative, these ratings had improved to excellent (31/58) or good (22/58). The degree of improvement was maintained beyond the two years (currently up to 10 years) in 98% of the patients.

Predeposit Autologous Donation and Transfusion

Predeposit autologous donation and transfusion (PAD) is a process where blood is collected from a patient prior to elective surgery, stored and retransfused back to the patient during or immediately post-operatively. Interest in PAD first soared in to 1980's when there were concerns over the safety of allogenic (collected from a donor) blood transfusions with regards to the transmission of the HIV virus (www.blood.co.uk/hospitals/library/bm/issue11/BM1103.htm). The benefits of PAD are that: (i) the blood the patient receives will be a definite match; (ii) the risk of an allergic reaction will be low; and (iii) the risk of catching infectious diseases such as hepatitis and HIV is avoided.

The body can regenerate one unit of blood (which is 475ml) within 4-9 hours, and can be stored for up to a month. Therefore, donations can be made at weekly intervals up to one month before surgery. The only real disadvantage is not knowing how much blood to donate. Rarely can surgeons predict how many units of blood a patient will require, if there is not enough autologous blood, then allogenic donated blood will be called upon to make up the difference. If there are excess units of autologous blood, then they are discarded.

Fibroblast Transplantation in Scarring and Other Therapies

A scar is a mark left by a healed wound, burn or surgical incision. They are the consequence of an injury, which causes an enhanced wound healing response, resulting in collagen deposition below the skin. At first scars can appear red, or dark and raised, but they will become more pale and flatter over time. Scars can be classified according to their appearance into the following four categories: *normotrophic* scars are the same height as the surrounding skin, *hypertrophic* scars are raised above the level of the surrounding normal skin, *keloid* scars are similar to

hyoertrophic scars but spread to tissue beyond the boundaries of the original wound and *atrophic* scars are depressed and a lower level than the surrounding tissue (Clark, 1996; Bayat et al., 2003; Ferguson, 2002). As well as the skin, scarring has many implications in other organs of the body, for instance in the eye, ocular scarring can lead to cloudy vision and/or blindness (Khaw et al., 2001). Excessive scarring can lead to fibrosis of the kidney (Lewis and Norman, 1998), lung (Sheppard, 2001) and liver (Kato et al., 2001). The development of scar preventing therapies has massive therapeutic values, with widespread medical and surgical usage. For example, following burn injury, major trauma, elective surgery, cosmetic surgery, scar revision surgery, also as a possible therapy in improving the outcome for diseases such as hypertrophic scarring & Dupuytren's contracture (Neely et al., 1999), organ fibrosis, scleroderma lesions (Denton and Abraham, 2001), bleomycin-injured lung (Munger et al., breast (Sieuwerts et al., 1998), colon and ovary (Tomasek et al., 2002).1999), and neoplasias of the prostate (Tuxhorn et al., 2001),

Treatment of fine lines and wrinkles and facial atrophic scars, caused by acne, by using collagen injections has been seen since the 1970's (Knapp et al., 1977). Since 1995, rather than using bovine (cow) collagen based fillers, autologous dermal fibroblasts, which are the main cells in the body that secrete the extracellular matrix protein collagen, have begun to be used in the repair of such fine defects in a process developed originally by Isolagen Technologies Inc. (Keller et al., 2000; Watson et al., 1999). A biopsy is taken from the patient, the cells grown in culture and implanted into the affected area. This completely natural therapy has proven successful for over 8 years now and serves to treat the underlying cause of collagen deposition by replacing the cells that produce the protein rather than just the protein itself.

These new technologies have had, and continue to have, a vast impact on the treatment of slow and non-healing wounds. The goal of tissue restoration rather than tissue repair is just as evident today as it was hundreds of years ago.

Summary

Treatment of medical conditions using autologous cells, blood, organs or tissues, have been used in many different clinical situations for a great number of years. Using such therapies has become of particular interest in the past century. Autologous treatments eliminate any risk of rejection or allergic reactions. It can be seen that treatments such as those offered by Genzyme, Isolagen and others using the techniques of a patients' autologous cells to improve the appearance of lines, wrinkles, scar elimination, gingival restoration and cartilage regeneration is yet another example in the new generation of such therapies.

Table 1. Summary of the types of bioengineered skin products

Type of bioengineered cells or skin	Description	Commercial products	Applications
Cultured epidermal grafts	♦ Autologous or allogenic keratincyte sheet grafts	Genzyme: Soft Tissue Repair	In use for the treatment of life-threatening burns
	♦ Autologous fibroblast cell expansion	Isolagen: Soft tissue repair using autologous cultured fibroblasts.	In use for the treatment of lines, wrinkles and acne scar s
	♦ Autologous fibroblast cell expansion	Isolagen: Soft tissue repair using autologous cultured fibroblasts.	In use for gingival restoration
	♦ Autologous fibroblast cell expansion	Epidex: Tissue Repair using cultured fibroblasts and a patch.	In use for the treatment of non-healing diabetic ulcers
	♦ Autologous Chrondocye expansion	Genzyme: Cartiledge Restoration	In use for the regeneration of cartiledge.
Dermal substitutes	♦ Acellular or cellular dermal replacement consisting of biosynthetic or processed cadaver matrix	Alloderm: (LifeCell)	In use for the treatment of burns
		Dermagraft: (Advanced Tissue Sciences/Smith & Nephew)	In clinical trials for diabetic foot ulcers
Dermal and synthetic epidermal substitutes	♦ Biosynthetic dermal replacement with a temporary synthetic epidermal analog	Integra Artificial Skin: (Integra Life Sciences)	Approved for the treatment of life-threatening partial- or full-thickness burns
		TransCyte: (Advanced Tissue Sciences/Smith & Nephew)	In use for the treatment of partial- or full-thickness burns
Bilayered living skin constructs	♦ Skin replacement consisting of an epidermis with allogeneic keratinocytes and a collagen dermal matrix with allogenic fibroblasts	Apligraf: (Organogenesis/Novartis)	In use for the treatment of leg ulcers. In clinical trials for diabetic ulcers, excisional wounds and epidermolysis bullosa
		Composite Cultured Skin: (Ortec Internationsl)	In clinical trials for epidermolysis bullosa, donor site wounds and venous leg ulcers

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