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Stem Cell And Regenerative Therapies For Degenerative Disc Disease And Discogenic Low Back Pain

By Michael N. Brown, DC, MD, DABPMR-PAIN. Reprinted with permission.

INTRODUCTION:
Low back pain affects 1 in 3 individuals at some time in their life. Back and neck pain is the second leading cause of disability globally with a prevalence of 60-80% amongst individuals between 20 and 50 years old.[1] The cost of care for low back pain in the US alone has been estimated to be over $150 billion annually and indirect costs are staggering. A standard method of treatment for lumbar disc disease still is lumbar fusion corresponding to the therapy “no disc no pain”. Unfortunately anyone in the spine specialty disciplines of medicine can attest to how untrue that really is. I have described our approach to the back pain patient in numerous articles on this website. Our focus is a regenerative medicine approach. That did not happen overnight but over a period of 30 years of doing everything else first. Since we specialize in advanced spine diagnostics and intervention almost 100% of our patients has been everywhere else first. We will rarely see individuals for back, neck, and orthopedic extremity complaints early on in the course of injury or disease.

These patients have sought consultation of countless physicians and allied healthcare practitioners and either have been provided transient relief from some therapeutic intervention or have completely failed to respond. Most of them have already undergone multiple procedures including corticosteroid injections and epidural injections. They often have undergone years of manual therapy and physical therapy services and many continue to seek this care because it is the only thing that provides transient symptomatic improvement. This unfortunately gets expensive over time. I have stated in numerous articles on this website that low back pain and neck pain is complex and can occur from multiple sources including facet joints, ligaments, muscles, tendons, connective tissue attachments and fascia, nerves and the intervertebral disc.

The intervertebral disc especially in the lumbar spine is one of the more common sources of chronic pain. It is more common than not that a patient seeking care for chronic back pain has a combination of sources. It is our approach and opinion that the multiple pain sources need to be identified and addressed. We find many times even though we may have patient’s with a component of the chronic pain coming from the disc if we address all the rest of the connective tissue and mechanical sources of pain we often are able to forego intervention with the intervertebral disc itself.

Our foundational approach for the last 25 years has been a “regenerative medicine approach”. The foundational principles have been heavily rooted in the disciplines of orthopedic medicine which includes prolotherapy. As a physician trained in multiple disciplines including a residency in physical medicine & rehabilitation and having completed to spine and pain medicine fellowship program at the University of Washington I can say with some authority that pain and spine physician’ s predominant methods of treatment is the utilization of ablative technology. For example it is commonplace for pain physicians to use radiofrequency and thermal energy ablation nerve ablation procedures to destroy the nerves that innervate the facet joints, the sacroiliac joints, etc. The same thermal and radiofrequency ablative therapies also have been used for countless intradiscal procedures that results in thermal coagulates the annulus of the disc amongst other effects.

In the 1990s I worked for several institutions where our predominant focus of therapeutic intervention was the use of ablative procedures and radiofrequency procedures for the treatment of both joint and disc pain and low back pain patients. Having had first-hand experience of the short-term benefit rather than long-term gains with this method of treatment we eventually abandoned this practice and adopted a “regenerative medicine approach”. We have been advancing this technology ever since.

Having had 27 years of experience utilizing basic regenerative injection procedures directed to connective tissues, ligaments, and tendons it was a natural progression to begin focusing on other ortho- biologic, and cellular medicine approaches to enhance connective tissue regeneration and repair. Our next focus was the use of platelets

and platelet derived growth factors which we started working with in 1993. A number of years ago we began using cellular preparations derived from bone marrow blood prepared in a similar fashion to the platelets we were using prior. Over time we then began to adipose tissue progenitor and regenerative cells as another source of stem cells which we used for regeneration and repair.

After obtaining significant experience using both bone marrow and adipose tissue derived stem cell preparations in orthopedic cases involving the peripheral joints we later turned out attention to treating the lumbar disc. I did not take the lead in this area and continued to follow my research Associates and colleagues monitoring their clinical outcomes and techniques before I personally began to use this method myself. I traveled in multiple countries and monitored the results of my colleges work for several years before I began to utilize these methods. That does not mean that is perfect now there is still much work and research that is needed.

My initial interest however in intradiscal injection procedures dates back to 1993 when we began research on animals specifically goats looking at fibrin, thrombin and fibrin glue in conjunction with platelet concentrates with a focus on healing degenerative disc disease and annular tears this project was placed on permanent hold secondary to problems we had with our medical pathologist working with our institution. We were to find out decades later that the methods that we were doing in our animal research turned out later to be validated and noted to be effective in the treatment of degenerative disc disease.

This discussion is an attempt to review a complex topic for our patient seeking our care were facing choices for therapeutic intervention for discogenic low back pain and symptomatic annular tears. There are no easy answers for this complex problem and despite significant progress that we have made in this field stem cell therapies and regenerative injection therapies only provide some of the answers that we have been searching for and certainly are not a panacea for the treatment of discogenic back pain.

THE TISSUE ENGINEERING APPROACH:

A tissue engineering approach has become the most attractive approach in regards to treatment of various intervertebral disc disorders and degenerative disc disease. Tissue engineering involves replacing damaged tissues by biomaterials and appropriate cells.[2] Since disc degeneration is a cell mediated response to progressive structural failure treatment in the future will in fact be directed through tissue engineering with a focus on normalizing homeostasis and restoring disc function. The tissue engineering approach offers strategies and potential advantages in the treatment of degenerative disc disease. The strategies involve the use of stem cells, chondrocyte (cartilage cells) and disc cells which may include growth factors as cellular matrix connective tissue scaffolding and proteins. We are going to be referencing the term “matrix” and “matrix proteins” in this article. The term matrix references the extracelluar substances and proteins in a particular tissue. The environment outside the cell which are various biochemicals, substances, proteins, etc. all make up the “matrix”. What is

interesting is that sometimes these substances contain biochemicals, cytokines and materials that can stimulate cells to divide and repair ! The matrix substances may also contain protein infrastructure that may provide structural support for a tissue or organ.

The topic of tissue engineering is a very complex topic and one that we cannot cover completely in this document. Using principles of tissue engineering will remain our primary focus of care and research in dealing with discogenic back pain. Stem cells for example could be in part one strategy of using a tissue

engineering approach. But the principles of tissue engineering not only address what cells can be placed into a specific tissue to help replace cells or repair tissue but also what other substances must be used to restore structural integrity. We may want these cells attached or embedded into a protein structure that is injected with the cells to encourage the cells to remain in the location they were injected and populate a scaffold made of proteins! The question of the ideal carrier to which cells are attached before injected into a disc would be a tissue engineering issue. There is billions of dollars in research funds being directed to this type of research and we will see this trend continue for years to come. Some individuals are injecting stem cell and other cellular mixtures into the disc alone and others are doing this in combination with other substances such as hyaluronic acid and complex cellular matrix proteins. The field of regenerative medicine and tissue engineering is growing rapidly. We are using tissue engineering principles to grow new organs and tissues. An example is the mouse in the picture to the right growing a new era for a transplant recipient.

UNDERSTANDING THE ANATOMY AND PATHOPHYSIOLOGY OF DEGENERATIVE DISC DISEASE:
As usual I am going to try to lay down some basic principles before we can intelligently discuss why it is we utilize a tissue engineering approach and stem cell therapy for discogenic back pain. This will also include reasons why these very approaches may not be appropriate in some individuals.

DISC ANATOMY: As I have discussed in previous articles there are 2 primary regions of the intervertebral disc and multiple subcategories. The 2 primary areas involve the nucleus pulposus which is described as the softer more pliable region within the center of the disc and the annulus fibrosis which is a series of laminated protein rings on the outside of the disc as depicted in the picture to the right. As I have stated previously in a younger adult the nucleus has the consistency of a fatty-like substance. The annulus fibrosis is a series of laminated rings of proteins that are often compared to the plies of a radial tire. As we age the nucleus pulposus polyposis and annulus fibrosis is difficult to distinguish from each other but there are distinct structural, cellular, molecular and biochemical differences.[3-5]

The Annulus fibrosus:
The annulus consists chiefly of a highly structured network of collagen fibers that wraps around the nucleus and confines the nucleus. The annulus is well innervated with free unmyelinated nerve endings that make the annulus very pain sensitive. This nerve innervation in a normal disc is typically along the outer 1/3rd of the disc. Over time and with structural breakdown of the annulus the annulus can become disrupted and torn as shown in the picture to the right. This can lead to nerve fibers extending deeper into the disc and therefore we can see innervation of pain fibers all the way into the inner aspects of the disc in certain types of degenerative conditions.

While the cells of the annulus are typically fibrinous made of collagen the cells of the nucleus are more like cartilage cells (chondrocyte).[6] We are not going to go into embryological development of the spine and disc but there is a special type of structural called the notochord that is important for embryologic development of the spinal discs. It used to be thought that the notochordal cells are lost after 16 years of age.[7] Current studies show they may exist much longer than that and may be involved in intervertebral disc aging and degeneration. The cells exhibit “plasticity” with similar properties as mesenchymal stem cells.[8] Why are talking about these cells in the

nucleus? Because if you are reading about stem cell therapies you are going to come across a great deal of research being done utilizing notochordal stem cells which is derived from the disc itself. These cartilages like cells and notochordal cells have been adapted to the lack of blood supply to the disc. The cells are 8 mm away from the closest small capillaries and therefore can only gain nutrition via diffusion which I have talked about in other articles on this website. It is also widely known that the poor blood supply is one of the reason the intervertebral disc has such "poor healing potential". The pH within the disc is 6.9-7.2 which also is important for specialized cells living within the disc.

THE IMMUNE SYSTEM & DEGENERATIVE DISC DISEASE:
We are about to embark on a rather complicated subject. However, it is unfortunately necessary to discuss this rather complicated subject since part of the reason we utilize specific types of stem cell interventions in the disc is to affect immune system. First of all it is important to understand the concept of a "sequestered antigen". Look at the drawing on the right. You see the red dot in the middle.

Imagine that it is possible that from the time you were born your immune cells have never encountered cells from the red zone like in the picture. There are actually several areas in your body like this. We call these areas "sequestered antigens". Let's imagine that the small spiked looking shapes drawn to the right are immune cells and the red dot are cells that lie deep within a structure that does not have any significant blood supply to the region of the red dot.

It is therefore possible that since the time of your birth, and before your immune system was fully functional, that the immune cells circulating in your blood have never encountered the proteins that would be contained in the red dot. Therefore, if your immune cells in your bloodstream or in your tissues were to ever encounter the proteins in the red dot region your body would act as if it was a "foreign antigen". Let's take for example the lens protein in your eye. Before your immune system was fully functional the proteins that make up your lens of the eye were long since sequestered within the lens. Today as an adult if you have the unfortunate experience of having a penetrating injury injury left eye it may be possible we have to give you immune-suppressing drugs to protect your right eye since the proteins in the lens are now considered "foreign !!". Your immune cells have never seen these proteins so you will get an auto-immune reaction to your own lens proteins. Another region of your body where you have proteins that have been "hidden away" from your immune system like this is the nuclear proteins of the center of your disc.

You have complex proteins in the nucleus of your disc that have important functions. If you tear the annulus and expose the proteins of the nucleus to your circulating immune cells an auto-immune reaction can occur and inflammation takes place. It is in fact this inflammatory reaction that causes most of the pain in a herniated disc!

Here is where it gets more complicated. One of the functions of the proteins in the nucleus of the disc is nutrition. The disc has a very poor blood supply. There are small capillaries as seen in the picture to the right at the endplates of the vertebral body below and above the disc.
These "plates" are very thin and cartilage like in the center and have small capillary loops of blood vessels that serve to bring nutrition to the disc.[9] These capillaries bring nutritional substances near the endplate then are "pulled into" the center of the disc by the osmotic pressure set up by the coplex proteins inside the nucleus. When you lay down at night these proteins in the disc pull fluids and nutrition into the disc by diffusion as shown above. So long as these plates above and below the disc are intact your immune cells in the bone marrow never are exposed to the nuclear proteins inside your disc. By the time you reach adulthood the endplate consists of a avascular layer of hyaine cartilage that is partially calcified at the top and bottom of the vertebral body.[10]

When you injury your back there are times when you may "crack" the enplate cartilage and by doing so expose the nuclear proteins in the disc to the bone marrow blood cells inside the vertebra.

This sets off an immune reaction against these proteins and the body begins to attack these "foreign proteins". The only problem with that is that these are not really "foreign" proteins but are your nuclear proteins in your disc. The immune cells in the bone marrow of the vertebra now set off an autoimmune attack on your disc and begin to secrete metalloproteinases which are enzymes the begin to digest the disc!!! This immune attack also sets off an inflammatory reaction in the bone marrow which causes edema and fibrovascular reaction which can be seen as the "white or light colored signal region on the MRI noted by the RED arrows in the picture to the right.

Notice the bone above and below the disc (red arrows). Now notice the disc between these 2 vertebra. Do you notice the difference in the disc in this region compared to the other normal disks as shown by the GREEN arrows? Michael Modic, MD was the first to classify these changes.11 These changes in the vertebral endplate (red arrows) are called "Modic changes." You may see this term on your MRI report although the radiologist may simply state "endplate changes."

There are several stages or types of Modic changes described as type I, II, and III but that is not important to our conversation.[11] It is important to note that these "Modic changes" are seen adjacent to degenerated or herniated disks.[11-16] I found this to be very interesting in my early career and this point is important to our discussion and plays a role in the decisions that I make as to what type of intervention I use for specific disc disease states. You should also know that Modic changes are in fact uncommon in asymptomatic individuals.[17-19] There are many theories and pathoanatomical models describing what these changes may represent.[20-27] Vital et al for example noted that the early phases of Modic change represents edema in the endplate bone corresponding to microfractures or cracks in the endplate followed by proinflammatory chemical mediators setting off the vascular and inflammatory changes.[26] One can spend years reading about this but my "take on this" is that at sometime during your life you have a back injury where you crack the endplate of the vertebrae. This may occur with an initiating event such as a fall, or lifting injury, etc. This may represent an episode of back pain that

resolves and you do not realize that this has set off a cascade of cellular and biological events by cracking the endplate and exposing the nucleus to the immune cells in the vertebral body. You will be completely unaware that these slow biochemical, immune reactions have set off a chronic inflammatory reaction that will begin to digest the disc and set off a cascade of degenerative changes over years. These changes begin to create structural failure and disruption within the disc that can lead to a whole host of mechanical changes and instability that can later lead to chronic pain. The proinflammatory and immune response caused by these changes are an important point and relate to the choices that we make when implementing certain stem cell therapies. There are certain types of degenerative disc disease states where we choose one type of disc injection over another. This decision will be based on what both mechanical, biological and autoimmune factors are involved. As the disc is autodigested large transverse tears can form within the disc destabilizing the spinal segment which can lead to instability. Modic changes can destroy the structure of the intervertebral disc, inhibit the self recovery of the disc, and increases abnormal loading on the disc and facet joints.[28]

Vertebra can become unstable enough to slip forward or backwards exemplified in the MRI noted on the left. Sometimes the degenerative changes lead to more pain in the facet joints and posterior elements.

Sometimes the degenerative changes can lead to more pain rising from the disc. Typically however, it is a combination of factors with multiple pain generators as I have addressed in previous articles and discussions.

Although there is a finite number of disks and vertebra there is an independent number of combinations of clinical presentations and

degenerative changes which makes dealing with spinal pathology a challenging and complicated process.

DEGENERATIVE DISC DISEASE & THE MRI:
One of the first things that I look for on an MRI is what type of degenerative disc disease is present. Is the degenerative disc disease associated with Modic changes or without Modic changes? We previously reviewed Modic changes in the discussion above. Now look at an MRI to the left. Notice the disc between the vertebra at the tip of the blue arrow. Notice it is dark compared to the other disks. This is caused by dehydration or loss of water from within the disc. This disc also has a small annular tear in the back of the disc. Notice however that the vertebral endplates over the top and bottom of the vertebra do not demonstrate the "white stuff" or inflammatory changes within the vertebral body (bone) above and below the disc. This disc has no Modic changes.

This type of degenerative disc disease is pathologically completely different than the degenerative disc disease associated with Modic changes. There are many physicians that may disagree with this but it is our particular practice to take the type of degenerative disc disease seriously when trying to plan for the type of care we provide. We have protocols established based on the type of degenerative disc disease that is present. In one type of degenerative disc disease we are looking to possibly hydrate a disc and heel and annular tear or disruption within the annulus. In a disc with Modic changes we may need to consider altering the immune attack or creating an alteration of the autoimmune response. This requires 2 different approaches which may or may not utilize stem cell injection techniques based on the pathology.

IMMUNE MEDIATED RESPONSE IN HERNIATED DISC:
Now that we have made a case for the fact that exposure of the nucleus pulposus of the disc to the external environment causes and immune inflammatory reaction it should not surprise you that is similar phenomenon takes place when you herniate a disc. A similar autoimmune response occurs which involves tissue macrophages and activated T cells which are specialized cells that are involved in the immune response.[29-31] Part of the problem that causes so much pain when a herniated disc occurs is the strong autoimmune reaction and the significant inflammatory response that ensues. Unfortunately the autoimmune response sometimes is quite significant and on occasion we will place epidural cortical steroids around the nerve and behind the disc in order to quiet the strong immune response down. Steroids are not the only innervention we use as epiduralinjections. We use a whole host of different injection techniques which include growth factors from platelets, anticyokine medicastions, etc. One of the limitations to most pain physicians in regards to using epidural injections is all they use if steroids! There are times in certain pathological states where it is better to use something else besides a steroid to effect the inflammatory state in and around nerves.

We also utilize a number of different techniques in minimal invasive spine practice besides ortho-biologic and stem cell injections to treat herniated disks. Some disc herniations can be treated with the injection of oxygen-ozone within the disc. This causes an oxygenation to the nucleus pulposus pulposis and can cause am oxidative denaturing of the proteins of the nucleus which then shrink the pull herniation back off the nerve root. Following this other types of injections can then be performed as necessary to try to heal the disc or induce other changes depending on the parthology. Not all individuals with herniated disks fit the criteria for this procedure and it takes careful patient selection to know exactly which patients have a good chance of response and those were more appropriately managed by surgery.

STEM CELL THERAPY FOR DEGENERATIVE DISC DISEASE:
Typically degenerative changes of the disc occur consistently with advancing age however, it can be apparent by the second decade of life. The tempo of progression varies considerably across individuals.[32] There are many factors that influence degenerative disc disease which includes age, mechanical loading (lifestyle, work, recreation), genetics, infections and many other factors.[33] These multiple factors ultimately lead to changes on a biochemical, molecular, cellular, and

structural level which makes the process of disc degeneration extremely complex. When degenerative changes begin to effect the annulus fibrosis of the disc degenerative process becomes irreversible.[34] The loss of cells within the nucleus (a complicated subject) largely explains the limited capacity of the disc for self-healing. This is part of why stem cell therapy is so attractive to research in degenerative disc disease !!!

Lumbar fusion surgery may offer possible relief by elimination of motion between spinal segments and therefore may in certain cases alleviate discogenic pain associated with degenerative changes however this only addresses the symptoms and not the cause of degenerative disc disease.[35-38] Furthermore there is significant concerns regarding the effect that a lumbar spine fusion has on adjacent segments above and below the fusion which can lead to adjacent segment degeneration.[39,40] This can in some circumstances make the problem worse.

One of the strategies of orthopedic regenerative and tissue engineering approach to degenerative disc disease is to restore the function of the nucleus pulposus pulposis by possibly introducing shock absorption hydrogel's, matrix producing cells and molecules which can stimulate replenishing endogenous cells of the nucleus back and help replenish the matrix of the nucleus itself.[41]

THE USE OF LUMBAR DISC SCAFOLDING & MATRIX PROTEINS:
There is tremendous attention in research and development activity by countless institutions working on various types of tissue scaffolding for organs, cartilage, and yes the intervertebral disc.[42-46] Our institute will be working in close association with an institution that has a new scaffolding technology. We will be using some of our new stem cell technology in conjuction with this new intradiscal scaffolding

technology later in 2015. But that is getting way ahead of this discussion. There are a few techniques currently available that can be used in the disc. Some of these tissue preparations involve the use of placental matrix protein preparations that can be used with and without additional stem cell injections. There are occasions with appropriately selected patients were injection of commercially available matrix proteins and scaffolding preparation may be appropriate. This in our practice can be used both with and without stem cell preparations. There are also hydrogels that can be used to enhance the formation of cartilage formation from certain adult stem cells that can be isolated from an individual patient.[47] This is a far too complex of a discussion for this educational document and we will reserve that to personal communication on a patient to patient basis.

Types of stem cells used for the intervetebral disc:
In research settings there a several types of cells currently being used in animal models. These are cells that are taken from the nucleus of the disc and cultured and expanded which include condrocytes and mesenchymal stem cells.[48] FDA regulation does not allow the use of cultured and expanded cells in the US but this work shows great promise for the future. There are two sources of mesenchymal stem cells that we do use in current clinical practice. We use two sources for these cells. The first in bone marrow cells obtained from bone marrow blood. The second source is adipose tissue derived stem cells. These two sources of stem cells have been extensively studied.[49] These tissue sources and their associated stem cells are currently generating significant interest in orthopedic and spine use.[50] Mesenchymal stem cells have the capacity to differentiate into various cell types [50] including chondrocytes (cartilage cells).[49,51] and most importantly nucleus pulposis cells.[52] One of the interesting things that have come about in stem cell research is the effect of hypoxia on these cells. Hypoxia means a low oxygen environment for the cells. I was initially concerned about putting MSC stem cells into the disc because of concerns about the low oxygen environment we would be placing the cells into. It turns out that hypoxia may help promote mesenchymal stem cell (MSC) differentiation.[53] We still need more research in this area.

We have learned a lot from animal research on the effect of adipose–derived stem cells in the treatment of degenerated lumbar discs. For example adipose derived MSC plus the growth factors from platelet rich plasma (PRP) was shown development of new cartilage cells and were shown to promote nucleus pulposis cell regeneration and matrix accumulation.[54] This was done initially in rabbits and later was repeated in pigs.[54] Not only did regeneration of the nucleus and associated matrix proteins and substances get replenished but the disc height was also increased.[54] Stem cells from adipose tissue can differentiate with production of proteoglycan and collagen. These "proteoglycans" are important in providing the hydrostatic support against stress imposed on the annulus of the disc.[54]

Other research has shown similar findings. Chun and his colleges [54] created a disc injury in rabbits with a 19g needle. This resulted in of course degeneration of the disc. Next they implanted by injection adipose derived stem cells and monitored these rabbits with MRI and later careful dissection and microscopic exam of the discs treated.

Their findings following stem cell injection was rather interesting. In the pictures above the picture labeled (C) is the injured and untreated disc and the picture labeled (A) is the injured and discs treated with adipose derived stem cells. It does not take a histopathologist to realize there is a significant difference. One of the most fascinating things about the study for me was the restoration of the lamination layers of the annulus fibrosis which I did not ever think was possible even with stem cell injection.

Another issue that has been brought up in clinical research of stem cell injection therapies for disc is the problem of leakage of the stem cell injected into the disc. These cells can leak out of the disc following the injection. Some authors have suggested that this is the reason why implantation in the future should be done with scaffolding. We have addressed this problem in a unique way and since this technique is proprietary we will not discuss the method that we use in this article but we do share the specific methods if we are going to utilize them with our patients prior to the procedure.

Mesenchymal stem cells derived from bone marrow blood is becoming more popular as an intradiscal injection therapy. Many of the studies being published are being done with mesenchymal stem cells that are cultured and expanded before injected. We still cannot use these methods in the US but their work provides important information for those working in this area. Orozco et al. for example determined that patient exhibited rapid improvement of pain and disability (85% of maximum in 3 months) that approach 71% optimal efficacy which compared favorably to other procedures such as spinal fusion or disc replacement.[55] They concluded that this form of treatment was a "valid alternative treatment" for chronic back pain caused by degenerative disc disease with obvious advantages over the current goal standard such as surgery.[55]

All of this sounds encouraging but this form of treatment is technically in its infancy. Interventional spine physicians for moving into pioneering this technology may be gaining experience and some preliminary promising results but there are still many questions to be answered. Some methods used in laboratory research are unable to use in clinical practice because a regulatory burdens and additional research will be necessary before safety and efficacy can be assured. But the findings in laboratory research continue to influence our approach to this problem. For example I stated previously that leakage of the stem cell injectate can occur after disc injection. This leakage of cells has been shown in one study to induce osteophyte formation.[56] Authors of this study noted that the cells injected in rabbits did not stay in the nucleus but rather leaked out of the disc and were part of the osteophyte forming cells.[57] Osteophyte is a term for bone spurs. Our team of physicians who work and our research Consortium have collectively created techniques to prevent the cell leakage phenomenon.

The other issue is how to improve survival of a stem cell once implanted into the harsh environment of the disc. Some researchers suggest a "matrix-assisted" cell transfer utilizing

nutrient enriched fibrin matrix. They also noted at least preliminarily partial removal of the nucleus increases survival of implanted stem cell. These authors suggested that in the future we may be using a soluble augmented polymer with some type of biomatrix seeded with cells and implanted into the disc in the future.[57]

ADIPOSE TISSUE DERIVED STEM CELL EFFECT ON THE IMMUNNE SYSTEM: THE EFFECT ON INFLAMMATION.

One of the reasons we strategically use adipose derived stem cells in certain types of disc disease is the profound effect these cells have on immune function and inflammation.[58-60] The effect on immune function and inflammation is also why we use these cells in arthritic conditions and chronic inflammatory conditions like rheumatoid arthritis and autoimmune conditions.[61,62]

Remember we discussed previously a certain disc disease state where an autoimmune attack on the disc has occurred with chronic inflammation. These cells have been used to not only treat the disc and associated inflammation but is now being investigated for the same autoimmune changes and inflammation in the vertebral body as well.

Stem cells and the many supportive cells that are found with them maintain a homeostatic environment which promotes growth and regeneration. For those interested in the biochemistry of the autoimmune effects of stem cell therapy I briefly discussed some of the autoimmune effects of stem cells below which include its properties and ability to suppress inflammation through the secretion of mediators including IL-10 [63], IL-17 [64], TGF-B superfamily [65], LIF [66], soluble HLA-G67, and IL-1 receptor antagonist.[68] In addition the expression of immune regulatory enzymes such as cyclooxygenase [69], and, indolamine 2,3 deoxygenase [70] are seen which help cells "take" to the area and promote regeneration. The cells induce generation of "T regulatory cells" which have a profound effect on the local inflammatory environment. T Regulatory cells (Treg).[71]
Stem cells are capable of directly suppressing the immune systems inflammatory response by depleting certain inflammatory cells (T cells).[72] Because stem cells expressed CD34 receptors they may play a "Immunosurveillance" role for circulating CD34+ cells in circulation via activation and differentiation of these cells into dendritic cells (DC) via of toll-like receptors (TLR) agonists.[73]

Although this is a complex subject and part of this article is written for those who have a science background or who are interested in the biochemistry the important concept here is that there is a profound effect on a inflammation in a local environment such as a joint or soft tissue.

WHAT KIND OF STEM CELL THERAPY DO WE PROVIDE IN THE US?

There are actually many types of stem cell therapies that have become available worldwide. There are many stem cell procedures that are completely unavailable in the United States because of FDA regulations. We have organized a national organization of an elite team of stem cell physicians and researchers to create a laboratory and technology that will allow us to work more closely with the FDA and to develop investigational new drug licensing for our future research and development. This will hopefully someday allow us to begin to explore some of the technologies that are not available to us in the US and procedures that are often done outside the US borders. However at present time we are limited to some basic surgical transplantation technology that has been discussed in the context of this article. When you extract tissues such as adipose tissue and bone marrow and centrifuge these tissues to isolate specific cells you actually obtain a tissue "complex" which is a mixture mesenchymal stem cells and a host of regulatory cells. It is this complex mixture of the cells that is responsible for the therapeutic effect in orthopedic application.

There is rapidly emerging technology that involves taking your own stem cells and culturing and expanding specific cells in the mixture. These are methods that take mesenchymal stem cells and place them in culture and expand them in a laboratory. There are emerging methods to manipulate cells with various growth factors while they are in tissue culture to cause them to

express a specific lineage such as cartilage, muscle, etc. Imagine being able to have one cell harvesting procedure and placing your cells in a “cell banking” institution where your cells can be cultured, expanded, and you can come in periodically to have “an infusion” of stem cells that have been cultured, expanded and designed for specific use for your particular specific disease process. This technology exists but this does not occur in the US again because of FDA regulations such as the “minimal manipulation rule”. Because of these various regulations we are unable to utilize this technology unless it is authorized and used typically in clinical research.

Currently, the procedures being done today are more simple procedures that involves cell harvesting and condensation of cells by using a centrifuge techniques and transplanting these cells shortly after harvesting by transplanting the cells via injection for therapeutic application. I have been working for years on methods to provide the cell viability counts, sterility and safety necessary for this type of treatment. An example of this would be a process were bone marrow blood is aspirated and the cells are centrifuge to concentrate a specific set of cells with a specific weight. The cells have potential regenerative capabilities and they are simply placed in a syringe and injected at a target site. My personal opinion is that the US is falling behind rapidly in stem cell therapy. Although I do understand the importance of the regulations to protect the public and to eliminate unsafe practices for certain physicians

it does limit our ability to treat specific types of diseases and conditions at present time with current technology. Because we specialize in orthopedic conditions these limitations are not quite as important to us as it would be for other disease states since we have access to MSC stem cells from bone marrow and adipose tissues.

WHAT OTHER TYPES OF INTRADISCAL INJECTION THERAPIES ARE BEING USED IN OUR INSTITUTE?

In addition to stem cell injection therapy for the disc there are several cellular and regenerative injection procedures that can be directed to the joints, ligaments and supportive connective tissues to help with associated instability that occurs with degenerative disc disease. In addition both bone marrow derived stem cell preparations as well as adipose derived stem cell preparations can be used for the joints of the spine and pelvis (SI joints) as well. We typically do not need to use stem cell injections for these types of problems but on occasion we do and have found stem cell injection to be quite helpful. We refer you to our other articles on regenerative injection therapies for further discussion on spinal facet joint and sacroiliac pain syndromes.

This last few months we have been working on a long awaited stem cell technology that we think may be the specialized cell type that we have been looking for in orthopedic and spine conditions. Unfortunately I cannot discuss this technology at the present time because it is proprietary to our institute and stem cell company. We are still working on numerous patents and research in this regard. Only our private patients that we feel meets selection criteria to participate in clinical trials will have access to further information on some of our new technologies.

THE FUTURE OF STEM CELL & INJECTION THERAPY FOR THE SPINE & SPINE DISC DISEASE:

Stem cell therapies for degenerative disc disease and discogenic pain represents one of the most important technologies to emerge for this condition in the last 20 years. Stem cell injection will only play a partial role in treating disc disease however.

We believe there are many biological therapies that will also have an important role in treating disc disease which will involve scaffolding, cellular matrix proteins, growth factors, hyaluonic acid gels and methods utilizing cellular proteins obtained from your blood to assist in treating the annular disruptions seen in disc disease. Our attention and work in this area is focused on all of these methods and does not remain limited to stem cell therapies alone.

We need additional funding and resources for our continued work in this area. We appreciate you recommending our research to those who you think may be interested in helping.

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