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The architecture and spatial organization of the living human body as revealed by intratissular endoscopy – An osteopathic perspective

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ABSTRACT

This article presents an overview of research conducted by Dr Jean-Claude Guimberteau into the architecture and spatial organization of living matter and the relationship between the cells and the extracellular matrix. His research is discussed in the context of previous and current research into fascial anatomy. Andrew Taylor Still, the founder of Osteopathy, did not have access to modern research and yet his observations are proving to be surprisingly accurate in the light of recent findings. This article sets out to highlight the relevance of his insights from a purely anatomical perspective, and to draw parallels with a new way of thinking about the architecture of the living human body that is slowly emerging. Dr Guimberteau's research shows that a force applied to the surface of the skin is transmitted deep into living tissue via a continuous bodywide multifibrillar network. It also confirms the concept of the body as a dynamic functional unit, as proposed by A.T. Still. Still also proposed that structure and function are interrelated at all levels within the living human body. There is a growing body of research to support this. Intratissular endoscopy has highlighted the importance of the quality of the mobility and adaptability of the network of collagen and elastin fibers that structures the ECM in healthy living tissue. Factors such as abnormal stiffness of collagen fibers in the ECM are thought to have adverse effects on local tissue health.

1. Introduction

This paper presents an overview of past and recent research into the structural anatomy and spatial organization of the human body. It also presents an overview of the research carried out by Jean Claude Guimberteau in an attempt to shed light on the organization of the living matter that makes up the human body, and to understand the relationship between cells and the Extracellular Matrix (ECM) in the living body. His research is discussed in the context of previous and current research into fascial anatomy.

To those with an osteopathic training, the anatomical insights of A.T. Still are proving to be surprisingly accurate, and seem to be borne out in the light of recent research. This paper sets out to highlight the relevance of these insights and observations and to draw parallels with a new way of thinking about the architecture of the living human body that appears to be slowly emerging. It is intended to be a translational exploration, and aims to point out that the world of research remains highly compartmentalised and that researchers from completely different backgrounds and working in different fields have reached similar conclusions about the anatomy of fascia that tend to point in the same direction.

Two interrelated, recurrent themes running through this paper are the interconnectedness, interdependence and interplay of the structural elements in the living body; the quality of the micro-environment surrounding cells, and how it may affect mechanical signalling between the ECM and cells in specific areas. Intratissular endoscopy reveals that a force applied to the surface of the skin is transmitted deep into living tissue via a bodywide, predominantly collagenous multifibrillar network. Information provided by Intratissular endoscopy appears to lend support to the concept of the body as a dynamic functional unit, one of the underlying principles of Osteopathy. Osteopathic principles hold that structure and function are interrelated at all levels of the human body. There is a growing body of research that appears to support this (Findley and Shalwala, 2013).

Intratissular endoscopy is an investigative surgical technique that involves the introduction of an endoscope with a cold light source and a high definition digital camera with a flexible fiber-optic cable into living tissue. This provides real time magnified colour images of living, moving tissue (Guimberteau and Armstrong, 2015). This technique has provided visual evidence that reveals the importance of the quality of the mobility and adaptability of the network of collagen and elastin fibers in the ECM

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in healthy living tissue. Current research has revealed that factors such as abnormal stiffness of collagen fibers in specific areas of the ECM may have adverse effects on cellular and tissue health.

2. Background

The evolution of classical osteopathy over the course of the last century, and the ever-increasing body of scientific research designed to investigate and validate osteopathic techniques, have led many modern osteopaths and other bodywork professionals to consider the founding philosophical principles and philosophies of A.T. Still a historical curiosity rooted in an anachronistic and dated model of health and disease (McGrath, 2013; Evans, 2013; Tyreman, 2013). To an extent, the epistemology of modern research methodology supports this, and recoursing to Still's thought given the availability of modern material on the subject frequently engenders deep controversy within the osteopathic profession (Kasiri-Martino and Bright, 2016). This notwithstanding, the evolution of science and clinical practice does not occur in a vacuum, and it is important to note that compartmentalization between different fields of learning can often work to the detriment, rather than the progression of the manual therapy professions and the understanding of the human body. Therefore, translational explorations that take stock of the influences on these professions in relation to modern findings, can act as a springboard and pause for reflection on the principles that govern clinical practice, education, and research.

In this context, this paper aims to do just this, by exploring specific anatomical insights from A.T. Still in comparison with modern research that has led to discoveries appearing to confirm some of those insights. These are not intended to be taken in the context of the broader aspects of his teaching, but from a purely anatomical perspective. For those to whom Still remains an important source of osteopathic principles, it is hoped that this exploration will provide a deeper perception into relevant modern research. For those who feel he should best be retired to the annals of history, perhaps this discussion will nonetheless provide some interesting context.

However, it is to be stressed that this approach does not represent an attempt to revive anachronistic views of health and disease, nor to validate ongoing attempts in some circles for a biomechanical “meta system” that governs all health and disease, given that perspectives such as these have been largely debunked (Evans, 2013; McGrath, 2013; Tyreman, 2013). It is acknowledged that best practices regarding differential diagnosis and referral for medical treatment of patients for whom osteopathic treatment is contraindicated should be adhered to at all times; never avoided on the basis of a philosophical principle.

This perspective paper is intended solely as a translational study aiming to point out that the world of research (both in the world of modern medicine and that of manual therapy) remains highly compartmentalised, despite attempts by some authors to overcome this (Blostein, 2016; Chaitow, 2009). Even so, taking stock of this reveals that researchers from completely different backgrounds and working in different fields and at different periods appear to have reached similar conclusions about the anatomy of fascia that tend to point in the same direction, and these investigations would be of greater value if understood within a continuum, rather than in isolation. On the need for interdisciplinary collaboration, Ingber (2006) wrote that "…we need to consider work from researchers in a wide range of fields — biophysics, physiology, anatomy, developmental biology, engineering, computer science — that are often unaware of each other's findings, even though they may be highly pertinent".

Far from what could be construed as selective reading, therefore, this paper attempts to highlight modern findings in relation to early principles, in the interests of facilitating communication between different fields of learning, furthering the development of a common language between professions, and developing perspectives on the potential clinical applications of these findings.

3. Fascial nomenclature

The past 20 years have seen a renewed interest in fascia, and a revision of its role in the human body (Schleip et al., 2012; Liem et al., 2017). The term “fascia” has in the past been employed to refer to various types of connective tissue but there was no universally adopted terminology. In an attempt to address this confusing situation the Fascia Nomenclature Committee, appointed by the Fascia Research Society, has recently proposed a new definition (Stecco and Schleip, 2016; Adstrum et al., 2017; Stecco et al., 2018). This recognises the existence of a “*fascial system*”, described as a “three-dimensional continuum of connective tissues that endows the body with a functional structure and enables all body systems to operate in an integrated manner”. It is now clear that the role of this fascial network extends far beyond simply connecting things.

Guimberteau and Delage (2012), Huijing and Baan (2001), and van der Waal (2009), Levin (2018) believe that tissues in the body are not simply contiguous structures with shared borders, but are *continuous*, and transmute into one another. They describe the current model of contiguous tissue boundaries in the body as artificial and arbitrary, and mere descriptive conveniences. Levin (2018) observes that anatomists are moving away from thinking in terms of independent structures and are instead starting to think in terms of functional anatomy and integrated systems. The “loose and dense fibrous connective tissues that permeate the body” described by Adstrum et al. (2017) and Stecco et al. (2018) are much more pervasive than previously acknowledged. For many anatomists, the new definition by the Fascia Nomenclature Committee is therefore a welcome step forward in providing a global, all-encompassing definition of fascia.

3.1. *The importance given to fascia by Still*

The World Health Organization document “Benchmarks for Training in Osteopathy” describes the human being as a *dynamic functional unit*, and states that *structure and function are interrelated at all levels of the human body* (World Health Organization, 2010).

This introduces the concept that the living body exists in its entirety as an integrated whole, and that each ingredient contains something of the whole (Lever, 2013).

A.T. Still was reportedly influenced by the writings of English philosopher and biologist, Herbert Spencer (Tricot, 2004). Spencer described the unity of all living systems in which “each part lives for and by the whole” (Spencer, 1864). Recent research and theoretical models presented in this paper lend support to Still's theories of the living body as a functional unit, and confirm the interconnectedness, interdependence and dynamic reciprocity of all anatomical structures in the living body, at all scales, across all scales, and at all levels of organization. British Osteopath Robert Lever considers that the interplay and interdependence of the structural elements in the body “gives us much to consider in the light of cutting-edge science, and also serves to confirm the huge importance given to fascia by Still over 100 years ago” (Lever, 2013, 2016).

This perspective of the unifying elements of the body as a complete biological unit further reflects one of Still's fundamental principles regarding the unity of the body, the intimate structure-function relationships within it, and the importance of fascia in health. He appears to have implicitly understood the all-pervasive nature of fascia at all levels of organization in the human body: Fascia “sheathes, permeates, divides and sub-divides every portion of all animal bodies; surrounding and penetrating every muscle and all its fibers — every artery, and every fiber" (Still, 1899) and called for further understanding of this: “a knowledge of the universal extent of the fascia is imperative” (Still, 1902).

However, the study of the complex structural and functional anatomical relationships in the living body necessitates the fragmentation of the subject for the purpose of this article, as we look at things from different perspectives.

3.2. Intratissular endoscopy

French orthopedic surgeon Dr Jean-Claude Guimberteau is the first person to have filmed living human tissue through an endoscope (during surgery with permission) in an attempt to understand the organization of the living matter that constitutes the human body. Intratissular endoscopy provides access to the largely unexplored world of living human anatomy. This original research has provided much new information about the structure and spatial organization of living matter inside the human body at different levels of magnification, from the macroscopic to the microscopic. It has revealed that the architecture and micro-anatomy of the body is completely different from the “compartmentalised” view of anatomy that has been taught for centuries; i.e. an assemblage of separate parts with an inert packing tissue in between, the role of connective tissue simply being to connect and hold the separate anatomical structures together (Guimberteau, 2004; Schleip et al., 2012; Guimberteau and Armstrong, 2015). Guimberteau's films (Guimberteau, 2005a,b, 2009, 2010, 2012, 2017,2018) and video sequences (Guimberteau and Armstrong, 2015) highlight the interconnectedness, but also the interdependence and interplay of the various structural elements in the living body - a central theme running through the practice of osteopathy, and this paper.

These films have revealed the existence of a continuous, tensional fibrillar network that appears to extend throughout the body, at all levels of organization and at all scales, from macroscopic to microscopic, from the surface of the skin to the periosteum. This fibrillar network is mobile and adaptable, and its organization is fractal and irregular. The fibers in the network are prestressed, like the tensed cables in a closed tensegrity system. Guimberteau (2015) postulates that it is *“the framework in which all components of the body develop”* (Guimberteau and Armstrong, 2015). The originality of Guimberteau's hypothesis is that the body appears to be structured by a continuous body-wide fibrillar system in which specialized cells carry out specific functions depending on where they are situated, and that the fundamental architecture of this fibrillar framework never varies, regardless of tissue type, location, or the type of cells it contains.

Guimberteau's research lends support to the hypothesis of the body as a functional unit, something that was implicitly recognised by the founders of Osteopathy over a century ago. This hypothesis will be elaborated in the following section that describes the nature and extent of the multifibrillar network, and its relationship with cells.

4. Discussion

4.1. The multifibrillar network

Intratissular Endoscopy reveals that the entire body appears to be structured by a vast continuous tensional network, composed of billions of interconnected, multidirectional fibers and fibrils of different diameters. The fibers interweave and interconnect to create three-dimensional microvolumes that Guimberteau has named *microvacuoles* — simple but irregular, polygonal structures (Guimberteau and Armstrong, 2015). These are either filled with pressurised fluids or cells, depending on where they are situated.

The fibers in the multifibrillar network are composed primarily of collagen 80% and elastin 20% (Guimberteau and Armstrong, 2015). Elastin is not uniformly distributed within the network. For example, some collagen fibers are able to lengthen due to the presence of circular bands of elastin at specific points in their structure (Guimberteau and Armstrong, 2015).

Guimberteau has put forward the hypothesis that the multifibrillar network interpenetrates, surrounds, and provides the architectural scaffolding of all anatomical structures in the body, including the skin, internal organs, muscles, bone and the nervous and circulatory systems, and that the multifibrillar, multimicrovacuolar network enables the various systems within the body to function in an integrated manner (Guimberteau and Armstrong, 2015). It is interesting to note here that collagen fibers are known to constitute the most prevalent protein structure in the body (Dittmore et al., 2016).

This research has also revealed a hitherto unknown world of fibrillar chaos and unpredictable behaviour inside the living body. Although the architecture of the multifibrillar network may appear to be completely irregular and chaotic, further exploration reveals what appears to be a highly efficient system that plays a major role in movement, both macroscopic and microscopic. The irregular arrangement and unpredictable, non-linear behaviour of the multifibrillar system is described as chaos in the mathematical sense, which means that there is an underlying order within the apparent disorder. All the components of the multifibrillar system, with its chaotic configuration, form a network of interacting components, but no one component directly influences the others. The multifibrillar network mediates the multiple interactions of a complex, yet efficient living system, in constant search of equilibrium, and always in a state somewhere between stability and change. “The search for equilibrium is constant and ever changing. Equilibrium is not a fixed point in the system, but a constantly shifting set of parameters” (Guimberteau and Armstrong, 2015). The non-linear and fractal nature of the multifibrillar network is a surprising, disturbing, and yet fundamental discovery, and further research is necessary to shed more light on these findings. It is important to mention this here, but the discussion of non-linearity, fractals, and the behaviour of complex systems are beyond the scope of this paper.

This multifibrillar system is thought to enable the optimal gliding of tendons in the “sliding areas” (Guimberteau and Bakhach, 2006; Guimberteau and Delage, 2012; Guimberteau and Armstrong, 2015). An example of this can be observed during finger flexion where the movement of the flexor tendons is barely discernible in the palm. Tendon excursion can be considerable and rapid, without provoking movement in neighbouring tissue. The multifibrillar system ensures the functional interdependence of adjacent anatomical structures by absorbing and dispersing any mechanical constraint and allowing the tissues to return to their original spatial organization once the constraint is removed. This explains the absence of any dynamic repercussion of the movement at the surface of the skin (Guimberteau, 2001; Guimberteau et al., 2010). It is thought that the adaptability and responsiveness of this system is adversely affected by factors associated with inappropriate loading and trauma, such as inflammation, oedema and the formation of scar tissue (Guimberteau and Armstrong, 2015).

Guimberteau has developed his own concept of the architectural organization of the body in which the microvacuole is the basic functional unit. His films provide evidence that support the hypothesis that microvacuoles act as structuring elements within living tissue (Guimberteau, 2005a,b, 2009, 2010; 2012, 2017; 2018; Guimberteau and Armstrong, 2015). They self-assemble and gather together and appear to play an important role in the creation of the shape and form of the entire body by providing a supporting framework, or scaffolding, for cells. The relevance of this intimate relationship between the multifibrillar network and cells and how they are embedded in this three dimensional fibrillar architecture will be developed in the following sections of the paper.

4.2. *Piecing together the puzzle*

At this point, and in order to move away from a compartmentalised view of the body, it is necessary to first consider the cell in its natural environment and to discuss some of the misconceptions about the cell that have been challenged by recent research. This will be followed by a discussion of recent research that confirms the existence of a mechanical continuity throughout the body from the skin to the innermost parts of each cell, and the implications of mechanical signalling between cells and the ECM.

The cell has been studied in great detail over the past century, but this research has mostly been carried out *in vitro* on isolated cells in laboratories. Surprisingly, little is known about how the cell behaves in its natural environment inside the living body. Compared with the vast amount of research into the cell, very little has been carried out on the connective tissue between the cells. Alfred Pisinger was one of the first scientists to recognise that the cell cannot be fully understood without taking its environment into account. He went so far as to say that the cell is “strictly speaking, only a morphological abstraction”, and that from a purely biological perspective, “a cell cannot be considered without taking its environment into account” (Pisinger, 2007).

A major step in our understanding of the cell was the discovery that the cells are not hermetic “bags” filled with freely floating organelles in a cytoplasmic “soup” (Oschman, 1984; Ingber, 1993). Pollack (2001) has exposed the inaccuracy of several widely held misconceptions about the cell, including the assumption that cell function depends on the integrity of the cell membrane. He has revealed that the cell membrane is discontinuous, and that membrane integrity “may be less consequential than presumed”. This challenges the current wisdom of cellular function. Moreover, the organelles inside the cell are contained within and attached to the cytoskeleton - a mobile network of microscopic protein filaments and microtubules within the cytoplasm (Oschman, 1984; Ingber, 1993; Chen and Ingber, 1999; Pollack, 2001). The cytoskeleton is thought to provide structure, shape and coherence to cells, and to play a role in intracellular organization (Wickstead and Gull, 2011; Alberts et al., 2008). Furthermore, it has recently been discovered that cytoskeletal elements interact extensively and intimately with the cell membrane (Doherty and Mcmahon, 2008).

The cellular matrix is connected to the ECM across the cell membrane by Integrins (Chen and Ingber, 1999; Ingber 2003, 2007, 2010). Integrins are trans-membrane receptors that provide attachment of the cell to the ECM and are involved in mechanical signalling from the ECM to the cell. They span the cell membrane and connect the fibers in the extracellular matrix with the cytoskeleton. Forces acting on the multifibrillar network are transferred to the cell membranes via the integrins, which can be described as “link proteins” (Schleip et al., 2012). Oschman (2009) describes this connection as mechanical, functional and energetic, and explains that it provides a pathway for communication between the ECM and the cell. Mechanical forces acting on integrin receptors at the surface of the cell have been shown to immediately alter the organization and composition of molecules in the cytoplasm and the nucleus inside cells (Chen and Ingber, 1999; Ingber 2003, 2007, 2010). The ECM and cells are in a continuous dialogue and are dependent on each other (Schleip et al., 2012).

A long postulated physical link between cytofilaments in the cytoskeleton and the cell nucleus has recently been revealed by 3D images that show a direct connection between the cytoskeleton and the nucleus. These images were obtained by a team of scientists at the Lawrence Berkley National Laboratory in California. They provide the final missing link in a chain of connections from the skin to the nucleus of the cell (Jorgens et al., 2017; Lawrence Berkley National Laboratory 2017), and lend support to Guimberteau's hypothesis regarding the extent of the multifibrillar network (Guimberteau and Armstrong, 2015).

Oschman's definition of “the living matrix” includes the cytoskeletal framework and its relationship to the nucleus and its DNA. Every cell is thus connected to every other cell within what he calls the living matrix – “a nuclear matrix within a cellular matrix within a connective tissue matrix; a continuous and dynamic supramolecular network” (Oschman, 2015). Once thought to be an inert, amorphous substance between cells, the ECM is now widely recognised as “a bodywide communication and support system, essential to all living functions” (Oschman 2015). This forms “a totally pervasive system, a major organ that reaches into every part. It is the only system that has direct contact with all of the parts of the body" (Oschman, 2009). Langevin (2006) postulates that the connective tissue continuum serves as a body-wide, mechanosensitive signalling network. Lever (2013) states that the connective tissue matrix in its entirety is, in a sense, “architectural” as well as “energetic and informational".

Myers observes that"the real excitement here is the mechanical continuity from cell to organism, that requires a total re-think in terms of these new findings of mechanical continuity from the molecular level on up through cells, tissues and the entire human being” (Liem et al., 2017).

These discoveries are exciting because they lend support to the hypothesis that the connective tissues form a mechanical continuum that extends throughout the body, to the innermost parts of each cell. They provide information about the pathways and mechanisms of bodywide force transmission and mechanical signalling between the ECM and the innermost parts of the cell, including the nucleus. To better understand this, we must first consider the information provided by intratissular endoscopy about the architecture of the ECM, and its behaviour both at rest and during movement.

4.3. *Relationships between the extracellular matrix and cells*

Intratissular endoscopy has enabled Dr Guimberteau to study the behaviour of cells in their natural environment, inside the living body. His research shows that, far from being an inert, amorphous ground substance, the Extracellular Matrix is actually highly organised, and possesses its own complex and highly efficient three-dimensional architecture. The ECM appears to be structured by the multifibrillar network. This research suggests that the ECM is as important as the cell itself (Guimberteau, 2005a,b, 2009, 2010,2012, 2017,2018; Guimberteau and Armstrong, 2015).

Diagrams of the ECM showing a few collagen fibers loosely arranged in an amorphous ‘ground substance’ are inaccurate. Collagen fibers do not ‘float’ in the ‘ground substance’, nor are they embedded in it. The fibrils in the multifibrillar network are in fact highly mobile and are permanently hydrated (Guimberteau, 2005a,b, 2009, 2010; 2012, 2017; 2018; Guimberteau and Armstrong, 2015). As described earlier, they interconnect to create three-dimensional microvolumes, the *microvacuoles*. These microvacuoles contain either a gel like substance composed primarily of proteoglycans, or cells, depending on where they are situated. They display the phenomenon of self-assembly, as in tensegrity systems (Guimberteau, 2005a,b, 2009, 2010; 2012, 2017; 2018; Guimberteau and Armstrong, 2015).

Levin states that "the fibrillar network and the cells within it coalesce to form a structural continuum of continuous tension and discontinuous compression that defines tensegrity" (Guimberteau and Armstrong, 2015). He goes on to state that the biotensegrity model defines "the structural and mechanical relationship within cells and between cells, organs, regions and, ultimately, the structural and mechanical integrity of the organism and how it responds to external forces … this occurs at every level of organization, at all scales, and across scales". Levin also points out that it is difficult, and may even be impossible "to ascertain the true structural organization at any one scale", because we cannot visualize several scales at the same time using current technology (Guimberteau and Armstrong, 2015). He further explains that the tensegrity icosahedrons in biotensegrity are "force diagrams, and not actual physical structures that can be seen in the body". They represent forces "within an instant of time and in a constantly changing milieu, so that what applies at one instant does not exist in the next" (Guimberteau and Armstrong, 2015).

A detailed discussion of tensegrity is beyond the scope of this paper. The complexity of the balance of tension and compression within the living body is so great that further research is needed to build on this concept, but it remains the only model able to explain our capacity to resist the force of gravity (Armstrong and Guimberteau, 2016).

4.4. Structuring role of the multifibrillar network

Another important finding from Guimberteau's research is that cells are not responsible for tissue continuity. Cells are not present everywhere in the body. They tend to group together, and are completely absent in many areas of the body. It is the body-wide fibrillar network that provides continuity. Guimberteau (2015) postulates that this chaotic, fractal system of intertwined fibers and fibrils plays an *architectural* and *structuring* role within living tissue, and an important role in movement at all levels of organization. "It appears to be the framework in which all the components of the body develop" (Guimberteau and Armstrong, 2015).

All the organs of the body appear to share the same basic fibrillar architecture, which is part of, and continuous with, the body wide multifibrillar, microvacuolar network that constitutes the basic structural architecture of the body. It is important to reiterate this here, because the role of the fibrillar network seems to be more important than simply "connecting things". Guimberteau postulates that it is the *constitutive* tissue that gives form to the body. This represents a significant paradigm shift (Guimberteau and Armstrong, 2015).

Cells require a supporting framework or scaffolding, which is provided by the multifibrillar network. They are not lined up neatly next to each other, nor do they "float" in the ground substance of the ECM. They are embedded in the fibrillar network, which extends into every area of the body. There are no empty, redundant spaces in living tissue, and all available space is occupied. Guimberteau's films (Guimberteau, 2005a,b, 2009, 2010, 2012, 2017, 2018; Guimberteau and Ducoux) and video sequences (Guimberteau and Armstrong, 2015) reveal the intimate, interdependent relationships between the cells and this fibrillar network, demonstrating how the shape and form of cells alters in response to changes in tension within the network, and how their spatial relationships change – moving closer together or further apart - in response to externally applied constraint. The films also show that a force applied at the surface of the skin – even a very light touch - is transmitted deep into the tissues via the interconnected fibers of the multifibrillar network (Guimberteau and Ducoux, 2012; Guimberteau and Armstrong, 2015).

It could be argued that the visual evidence of the intimate mechanical relationship between cells and the fibers in the extracellular multifibrillar network represents the simplest, most fundamental expression of structure/function relationships in the living body.

4.5. Structure/function relationships within the body

Still's observation that "There is no real difference between structure and function; they are two sides of the same coin. If structure does not tell us something about function, it means we have not looked at it correctly" (Still, 1899) appears to be borne out by recent discoveries that variations in tension of the collagen fibers in the ECM regulate metabolic processes in the cytoplasm. This is called Mechanotransduction, and is mediated by the integrins (Ingber, 2006). When cells change their shape and spatial relationships in response to variations in extracellular mechanical constraint, these changes are mirrored by modification of biological function (Ingber, 2008). Chaitow draws a parallel between osteopathic concepts and the emerging awareness of mechanotransduction in the following statement: "One of the main tenets that guide osteopathic practice is an appreciation that the human body possesses, and depends on, self-regulatory mechanisms that in turn involve intimate inter-relationships between structure and function. He goes on to state that "the emerging awareness of the remarkable characteristics of mechanotransduction supports osteopathic concepts and practices by offering insights into some of the mechanisms involved" (Guimberteau and Armstrong, 2015).

Ingber was one of the first researchers to appreciate the "key role which mechanical forces play in biological control at the molecular and cellular levels" (Ingber, 2008). He proposed that "the mechanical properties, behaviour and movement of our bodies are as important for human health as chemicals and genes." He recognised however that "it remains unclear how the whole cell processes this molecular scale information and orchestrates a physiologically relevant response in the context of the multiscale architecture of our whole bodies" (Ingber, 2006). Ho (2008) describes the role of the extracellular matrix in "mechanically coupling cells to coordinate and control their structure and function".

As mentioned earlier, new 3D images from research carried out by a team of microbiologists at the Lawrence Berkley National Laboratory provide the first visual evidence of thread-like cytofilaments reaching into and traversing a human breast cell's nucleus, and connecting to cytoskeletal filaments (Lawrence Berkley National Laboratory, 2017).

According to Dr Mina Bissell, a microbiologist involved in this study:

> "This study establishes for the first time the long postulated mechanical link between the cell's nucleus to adhesion complexes that allow communication with the surrounding extracellular matrix and other cells. The reason we're excited is that it explains a whole lot of literature of how force and tension could be playing a role together with biochemical signals to bring about huge changes in a cell.
>
> We knew that the extracellular Matrix was affecting gene expression, but it wasn't understood until now that the cytoskeleton was actually able to connect inside the nucleus. Now we know there's a direct connection to the nucleus. That's what we're showing here for the first time. When the shape changes, biology changes"

(Lawrence Berkeley National Laboratory, 2017; Jorgens et al., 2017).

These findings appear to bear out a 2012 statement from Bissell: "Cells do different things depending on context. Form and function therefore interact dynamically and reciprocally" (Bissell, 2012).

Research carried out at the University of Illinois has demonstrated that external mechanical force can directly regulate gene expression. The study also identified the pathway that conveys the force from the outside of the cell to the nucleus. The authors state that "mechanical signalling is as important as chemical signalling, and this study shows it's a direct pathway" (Tajik et al., 2016).

Bissell (2012) and Lever (2013) specify that mechanical signalling takes place *in both directions*. Bissell (2004) describes this as "dynamic reciprocity", between the ECM on the one hand and the cytoskeleton and the nuclear matrix on the other hand. The genetic material in the cell nucleus would therefore appear to be influenced by the information carried by the matrix in both directions. This would suggest that "the cellular DNA does not have primacy in the regulatory function of tissues but is itself modulated by connective tissue matrix function" (Lipton, 2016).

Humphrey et al. (2014) explain that "resident cells continually read environmental cues and respond to them to promote homeostasis, including maintenance of the mechanical properties of the extracellular matrix that are fundamental to cellular and tissue health". The authors have discovered that "mechanical cues from the ECM trigger signalling cascades that alter gene expression and affect various processes, including cell motility and fate". Understanding the feedback mechanisms between the cells and the ECM is one of several key questions for future research in this field.

4.6. The quality of the ECM

Another insight to emerge from Intratissular Endoscopy is the importance of the *quality* of the Extracellular Matrix in healthy living tissue. The multifibrillar network interpenetrates, surrounds, and provides the basic architectural framework of the circulatory, nervous and lymphatic systems. They are therefore totally integrated into the multifibrillar network, both microscopically and macroscopically, and depend on it for support and protection during movement (Guimberteau and Armstrong, 2015). If the mobility, flexibility and adaptability of the multifibrillar system is compromised in any way, this could adversely affect the free flow of nutrients to the area and the drainage of waste products.

4.7. Blood supply and drainage

Another early observation from Still: "The rule of the artery is absolute, universal, and must be unobstructed or disease will result" (Still, 1908) may be relevant here, and has been returned to by other writers in this field. Magoun (1976) states that Osteopathic treatment "gets its results mainly through circulatory changes". Osteopathic principles and practice place great importance on the quality of local circulation and the maintenance or restoration of optimal blood supply and drainage to any given area in the body, and the optimal mobility of all parts of the body. According to Magoun, improved venous drainage "makes way for fresh arterial blood laden with oxygen and nutrients. The chemistry of the tissues changes for the better, and so does the homeostasis" (Magoun, 1976). Lever (2013) observes that it is a self-evident fact that "health, healthy tissue and normal function are dependent on a relatively efficient blood supply". What is important here is that unimpeded arterial blood flow is potentially affected by "structural malfunction". Gross structural change or abnormality, deformity and trauma are obviously likely to have "deleterious" effects on circulation. However, osteopathic theory takes this one step further by postulating that relatively subtle changes in the mobility and motion of tissue may have a negative impact on fluid dynamics and pressure gradients that can in turn alter the local physiology of tissues. This could affect tissue repair and healing, or the blood supply to a vital organ. "The point here is not that blood matters, but the assertion that structural function affects the delivery, transport, availability and even its quality" (Lever, 2013). The images recorded during Intratissular Endoscopy provide visual evidence of the adverse effects of scar tissue and adhesions on local circulation.

4.8. ECM stiffness

There are also wider implications of the importance of the quality of the collagen fibers that structure the extracellular environment. The earlier discussion focused on importance of the ability of collagen fibers in healthy tissue to return to their original spatial configuration once an applied constraint is removed; this allows us to consider the fibers in specific areas of the multifibrillar network in the ECM in terms of flexibility/stiffness, and optimum/reduced mobility and adaptability.

Recent research indicates that ECM stiffness may in some way influence the development of, or "pave the way for tumor cells". Research carried out by Valerie Weaver et al. has shown that "the structure, orientation and physical properties of ECM collagen play a key part in regulating aggressive biology of breast cancers" (Seewaldt, 2014*)*. ECM collagen remodelling and 'scarring' of ECM collagen appears to convert normal flexible fibers into "stiff aligned collagen". The article goes on to say that "Investigators have shown in mice that cancer cells preferentially invade along stiff collagen fibers", and that "stiff aligned collagen identifies focal sites of breast cancer micro-invasion. ECM collagen has a dynamic role in breast microenvironment and is an active participant that promotes tumor progression". Conklin and Keely (2012) found that increased local stiffness and "perpendicular collagen alignment" at the periphery of malignant tumors is associated with increased invasiveness.

These findings indicate that matrix stiffness can induce physical changes in the tissue that can influence the behaviour of tumor cells. This is not to suggest in any way that osteopaths or any other manual therapists should claim to prevent or treat tumors. This research simply indicates one of the possible effects of loss of flexibility of the collagen fibers in the ECM, and further research is obviously necessary in this field.

Oncology researchers are showing more interest in the mechanical environment surrounding tumors, especially the hypothesis that stiffer environments may contribute towards metastatic growth.

Langevin et al. (2016) state that inflammation and fibrosis are well-recognised contributors to cancer, and that "connective tissue stiffness is emerging as a driving factor in tumor growth". They propose that "physical based therapies may have direct beneficial effects on cancer spreading and metastasis" because these therapies have been shown to reduce connective tissue inflammation and fibrosis (Langevin et al., 2016). However, the authors point out that the question of whether ECM stiffness can promote cancer growth in the absence of other factors has not been fully answered.

Nevertheless, there is growing interest in the hypothesis that non-pharmalogical treatments could reinforce natural defences against cancer, thus contributing to primary and secondary cancer prevention. Berrueta et al. (2018) have shown that gentle daily stretching reduces local connective tissue inflammation and fibrosis. It is thought that mechanical factors within the stroma can influence the microenvironment of tumors (Langevin et al., 2016), and the authors of this paper hypothesize that stretching could reduce the growth of tumors. They believe that “stretching could become an important component of cancer treatment and prevention".

Elements of these multivalent research findings once again reflect Still's early observation: “The processes of life must be kept in motion” (Still, 1899) and the significance of movement to a multiplicity of layers of optimal functioning.

5. Memory of form

Another area to be highlighted by the *in vivo* observations of Intratissular Endoscopy are the mechanisms involved in the “memory of form” of living tissue. Self - adjusting and self regulating mechanisms within the body can be seen at work in films obtained by intratissular endoscopy (Guimberteau, 2005a,b, 2009, 2010; 2012, 2017; 2018; Guimberteau and Armstrong, 2015). The discovery of a bodywide multifibrillar network and healthy tissues returning to their original spatial configuration following movement, lend support to the idea of “normal” spatial relationships between cells and the extracellular matrix in healthy tissue in any given area, and of healthy connective tissue exhibiting a “memory of form” (Guimberteau and Armstrong, 2015).

This in turn echoes Still's statement that “the body itself may recover from displacements, disorganizations and derangements, and regain its normal equilibrium of form and function” (Lewis, 2012). Chaitow (2013) describes the instantaneous changes in force distribution throughout the entire structure of the body that follow injury. This in turn is followed by a global adaptive response to local injury that occurs over a slower time scale. He suggested that the application of treatment and/or rehabilitation methods “chosen to match the ability of the individual's self-regulating, homeostatic functions to respond positively” could “aid homeostatic mechanisms in the process of recovering from injury".

These mechanisms appear to be disturbed when tissues are injured or subjected to trauma. *In vitro* research carried out by American osteopaths Dodd et al. has shown that injured tissues exhibit altered cell shape and alignment. However, they suggest that tissues that have been injured seem nevertheless to retain a “memory” from the pre-injury state of the relationship between the cells and the extracellular matrix. Dodd and his co-authors believe that “appropriately applied counterstrain manouvers could help the injured tissues to return to their pre-injury state” (Dodd et al., 2006).

The preceding research again appears to bear out Still's early thoughts: “the body is self-creative, self-developing, self-sustaining, self-repairing, self-recuperating, self-propelling, self-adjusting, and does all these things on its own power” (Still, 1899).

To delve more deeply into the detail of what is occurring here, Dittmore et al. (2016) suggest that collagen self-repair is tension - dependent. Chaitow (2016) suggests therefore that the unloading of excessively tense tissues as performed in osteopathic functional or counterstrain techniques, some forms of kinetic taping, or the relaxation of tense tissues via massage, could influence tension related self-repair processes. It is logical to assume that these processes would be compromised by excessive fibrosis, scarring and adhesion formation.

It is also interesting to note here that Upledger and Vredevoogd (1985) observed during dissection of human cadavers that under “normal” circumstances, the “elasto-collagenous fibers of the dural membrane are interlaced and appear disorganized”. They also noticed that when the dural membrane is subjected to abnormal tension in a specific direction over a considerable period of time, the fibers within the membrane appear to react to this constraint by organizing and aligning themselves in the direction of tension (Upledger and Vredevoogd, 1985). This is an interesting observation, as it concurs with Guimberteau's previously mentioned observations of the irregular, chaotic organization of the fibers in the fibrillar network in “normal healthy” tissue, and the previously mentioned observations of stiff, aligned collagen fibers by researchers in unrelated fields of research as a possible indication of tissue that does not appear to be functioning correctly (Seewaldt, 2014; Conklin and Keely, 2012).

These insights point to the need for further research to find out what happens when the fibers in the multifibrillar network lose their flexibility, mobility and adaptability, and the quality of the ECM is compromised, and to consider how this translates into the clinical and practical setting.

6. Defining fascia

Fascia is now widely accepted as the tissue that connects and unites all parts of the body. It is increasingly recognised as “the unifying structural element of the body, and a key to understanding the reciprocal interrelation between structure and function” (Tozzi, 2015).

A simple definition of fascia could be “that which is not parenchyma (the functional tissue of an organ as distinguished from the connective and supportive tissue)" (Levin, 2018).

The fascial research community is gradually working towards a widely accepted definition of fascia. Precise fascial nomenclature is necessary to help anatomists and therapists identify specific anatomical structures within the fascial system, such as ligaments, aponeuroses, superficial and deep fascia, muscular septa and tendons. Dr Guimberteau's research has revealed that all these different anatomical structures share the same basic fibrillar architecture. They are all part of the same multifibrillar network, the only difference being that the density of the weave and the diameter of the fibers differs depending on where the structure is, and the role it is designed to perform in the body. All sub-divisions of fascia within the continuum of the fascial network are interconnected “but have their own specific roles to play, each subsystem of fascia both independent and interdependent with the entire fascia system” (Levin, 2018). For example, the epimysium, perimysium and endomysium can be considered as separate anatomical structures for practical purposes, but in reality they together form one continuous, coherent, functional structure — an integral part of the body-wide multifibrillar network - rather than separate histological entities. The muscle cells are embedded within this fibrillar architecture. However, in contrast to the longitudinal and parallel orientation of the muscle cells, the fibrillar architecture is neither parallel nor regular.

The fibers in the periosteum are densely woven, and the transition between the periosteum and cortical bone is progressive, with gradual mineralization of the fibers. Fibers from the periosteum can be clearly seen to penetrate cortical bone. There is no distinct demarcation line or visible rupture in fibrillar continuity between the periosteum and cortical bone at the microscopic level (Guimberteau, J.C. & Delage, J.P. 2012).

Guimberteau considers the collagen fibers in bone to be an integral part of the fibrillar network (Guimberteau and Armstrong, 2015). Levin (2018), and Sharkey (2019) consider bone to be part of the fascial system. The Fascia Nomenclature Committee has responded to this in the negative (Schleip et al., 2019), and it remains a subject of debate.

Beverly Johnson, a participant in the Human Fascial Net Plastination Project stated recently that attempts to separate superficial fascia from the deep fascia in the abdomen by slowly pulling it away using only blunt dissection (no tools to divide the tissues other than hands) revealed that “Our layers are not “layers”. What I saw, I would describe as a continuous fabric with different textures” (Clauson et al., 2018).

Fascia does not 'form' beneath the skin but develops concurrently throughout the body. It is much more pervasive than previously realized, and could be described as the *constitutive* tissue of the body (Guimberteau and Armstrong, 2015). The tissue between the cells shares the same basic architecture and is also part of the same bodywide multifibrillar, multimicrovacuolar network. Tozzi refers to a "distinct fascial differentiation of a bodywide structural 'net' extending from the macroscopic to the cellular depth and sharing a common embryological origin. Therefore, despite local differences in structure and form, including fiber arrangement, direction and density, the fascia shows a hierarchical continuity at different levels of complexity that truly makes it a system between and within the body systems" (Liem et al., 2017).

Guimberteau and Armstrong proposed the following definition of fascia in 2015:

"Fascia is the tensional, continuous fibrillar network within the body, extending from the surface of the skin to the nucleus of the cell. This global network is mobile, adaptable, fractal, and irregular; it constitutes the basic structural architecture of the human body" (Guimberteau and Armstrong, 2015).

This definition rests on the ongoing research to explore the exact nature and complex behaviour of this all-pervasive fluid-filled three-dimensional network of fibers, fibrils and microfibrils, the specific roles it is called on to perform in living tissue, and how it deals with the stresses it is subjected to.

7. Conclusion

On the basis of these empirical observations it appears that we can no longer consider the body as an assemblage of separate parts with an inert packing tissue in between. On the contrary, the body appears to be structured by a continuous body-wide fibrillar system in which specialized cells carry out specific functions depending on where they are situated. All the organs in the body appear to share the same constitutive fibrillar framework with architectural specificities that differ from one organ to another. However, films obtained by intratissular endoscopy from all over the body lend support to the hypothesis that the basic underlying architecture of the fibrillar network is always the same, regardless of tissue type, location, or the type of cells it contains. We cannot ignore this continuous, irregular, mobile, adaptive, fractal, chaotic and nonlinear "interior architecture" that extends from the surface of the skin to the smallest elements of our bodies, or the complexity of the relationships between these elements. Intratissular endoscopy provides a new way of contemplating form, structure and function from an entirely different perspective.

The research and theoretical models presented in this paper lend support to Still's theories of the living body as a functional unit, and confirm the interconnectedness, interdependence and dynamic reciprocity of all anatomical structures in the living body at all scales.

The scientific and anatomical communities are in the midst of a major change in the perception of how the body is structured, how it moves, and how it maintains its form. There is a need to re-define the architecture and spatial organization of the living human body. We are gradually learning more about where and how movement occurs, and what facilitates or hinders movement in healthy living tissue. This has opened up new avenues of research that can only lead to the development of more refined injury prevention and treatment strategies for future generations of manual therapists and movement teachers.

Declaration of competing interest

There is a potential conflict of interest in writing this article about Dr Guimberteau's research because I am the co-author of the book "Architecture of Human Living Fascia". However, the aim of this article is not to reproduce or promote the material presented in the book, but rather to discuss the wider implications of his research, particularly in the context of the underlying principles of Osteopathy and alongside previous and current research into fascial anatomy.

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