Of cells, fibers and living human beings

The research we have carried out in recent years has essentially aimed to reestablish the importance of the extracellular environment. In the film "Interior Architectures", we concluded that the fibrillar structures that can be observed everywhere in the body are in fact our internal structuring architecture, and are not simply connective tissue, but are actually the *constitutive* tissue of the body. This film will once again take us on a journey into a world full of surprises that appear to question certain accepted "truths". In the light of obervations made possible by this new technology, these will need to be revised. Our exploration of human living matter has highlighted the importance of our internal architecture which consists primarily of prestressed fibrillar structures rich in collagen and elastin that intertwine in 3 dimensions. Their organization is irregular and fractal, they are capable of mobility, and are prestressed. This fibrillar network extends from the surface of the skin and is in contact with the cells.

This newly defined constitutive role of connective tissue and of the extracellular world does not in any way diminish the importance of the cells or relegate them to a secondary role. The cells that inhabit this fibrillar edifice are responsible for the manufacture and production of the collagen matrix that ensures their ability to function.
The first time I saw cells in the late 1990s through a microscope during an operation, I did not think that these small polyhedrons could be cells. At first, I thought that they were air bubbles, artefacts, or microvacuoles. However, having filmed many similair sequences, and wonderful images of vascular rings encircling them, I had to admit that these polyhedral forms were indeed cells. An encounter with a living human cell is neither banal nor trivial, and one cannot fail to be moved by the experience.

INTERVIEW 1
On several occasions I have had the opportunity to show these images to specialists in cell research and I have witnessed reactions of complete disbelief. I hope that these images will persuade scientists to consider the cell in its natural environment, the human body, and to consider also that cells can behave in ways that until now remained unnoticed because they were studied « *in vitro* » under the microscope or in a test tube in a laboratory.
It is therefore time to show cells where they live, inside a living human being, *in vivo*.

Let us first see how and where cells are located in the tangle of fibers in the different tissues that we have observed in previous films. Endoscopic filmography is performed during surgery. The extremity of a contact endoscope is introduced very gently and carefully into the tissues, which allows the operator to visualize the structures at high magnification, at least 50 times. Light is provided by a source of cold light through a fibre optic cable. A high definition camera is used, with the simultaneous recording of images. Focusing is tricky because the depth of field is very small. The technique requires regular cleaning of the lens because a thin film of grease, and especially droplets of water vapor, form on it. This prevents the acquisition of clear images, and so regular cleaning of the lens is necessary.

We will follow our usual procedure of methodic exploration based on the classical anatomical distribution of tissues. The first step is to incise the skin. The surgeon then introduces the endoscope and brings the images into focus. And now all we need to do is open our eyes.

As soon as the skin has been cut, the first cells to appear are the adipocytes. There is no need to look for them because internal pressure causes fatty lobules to emerge like icebergs. 34 '37
Due to the limitations of our current technology, we are unable to show the arrangement of the cells in the dermis and the epidermis. Only the fractal aspect of the epidermal surface that reveals small polyhedrons of about 50 microns in diameter suggests a relationship with the cells. On rare occasions we can see melanocytes in the basal membrane. It must be noted in passing, and this is very important,

that there is no free plane between the dermis and the hypodermis, contrary to what is often taught. Everything is in continuity physically and histologically.

The fatty lobules vary in size from half a centimeter to sometimes 2 or more centimeters in diameter. Fat is not present in layers like sticks of butter, but in lobules which have rather rounded shapes. One might wonder why?
These lobules are filled with adipocytes and penetrated by thousands of fibers. There appears to be complete entanglement between the cells and the fibers, and we will see later that separation or dissociation of the cells and fibers is impossible. The adipocytes function as a group. The cells are linked to each other and they move together simultaneously. Their movements resemble those of a shoal of fish.

Adipocytes are usually yellow-colored cells but there are variations. Sometimes we find lobules with the same basic morphological pattern but white in color, or sometimes light brown. Within the lobules, the size of the cells is variable, usually about 70 microns in diameter. Their shapes are also variable. They can be square, round or oval, or they may resemble simple polyhedrons with four or five faces. The cells are all different and each has its own particular identity.
The cellular world that we observe is not neatly arranged. Cells are not lined up in an orderly manner like soldiers on parade.
The vascularization within the lobules is visible but not constant. Sometimes vessels are sparsely distributed. Sometimes the vascularisation is very rich as can be seen in this lobule filmed in an arm. We can see that the cells are surrounded by a small blood vessel that adapts to the morphological changes of the cells that occur during movement, thus demonstrating total cohesion between the cells and the vessels. The potential for mobility of the whole area is surprising and reveals the intimate relationships between the vessels and the cells, as well as their plasticity.
Finally, there is one last visible observation: As patients approach a state of obesity, cell density increases progressively until the cells invade all the inter-fibrillar spaces.

Deep in the the hypodermis we encounter an area of significantly greater mobility that allows sliding movements. This area is situated above the premuscular aponeurosis. Two observations capture our attention. Firstly, the existence of groups of cells that are distinct from the hypodermis, well individualized and more vascularized than the adipocytes, which we will call clusters of cells and which are a constant observation in microanatomy. We will come back to this later.
Next, at this level we see that there are areas where cells are rare. Here, one sees only what appear to be sparkling mirrors reflecting the light of the endoscope. This effect can be enhanced by applying slight traction upwards. Fibrils occupy almost the entire area. It therefore appears that cells do not fill all the space in the body and it would seem that cells are not responsible for the final shape of the body. This is a big surprise.
The aponeurosis, as you can see, is in total fibrillar continuity with the hypodermis. This almost exclusively fibrillar area ensures the physical continuity between the aponeurosis and the hypodermis. The area above the aponeurosis is a sliding zone of increased elasticity that manual therapists use to mobilize the skin. Within this almost completely fibrillar and irregular zone, we can see a few scattered clusters of yellow colored cells. And here in the irregular fibrillar weave of the aponeurosis, we find another cluster of cells, but smaller and elongated. However, cells are really very rare in this predominantly fibrillar world.

Beneath the aponeurosis we find the epimysium, perimysium and the paratendon. These are also sliding zones but for the motor or mobile structures. Cells are located on the surface of either muscles or tendons, often found in dense columns of longitudinal cells in the direction of the traction. Here, at the level of the paratendon, seen from a distance, they resemble brilliant golden or amber ribbon-like motifs gathered along the blood vessels giving the impression of intense activity. To use a simple metaphor, they resemble the houses in a village crossed by a single road. This is a totally subjective impression which I find difficult to ignore, because it is clear that these cells are close to their source of energy and information. In any event, they are different from the adipocytes.

However, this density of cells and their rich vascularisaton is not seen along the entire pathway of the tendon. They can be seen to be more sparsely distributed as soon as the camera reaches the region of the digital friction sheaths near the A1 pulley.
Here, the vessels turn inwards, deep into the tendon, and the cells, most probably sparse fibroblasts or fibrocytes, seem to be incorporated within the epitendon as if to avoid the strong constraint they would be subjected to in this area during flexion. The relationship between the lower cell density and the perceived constraint could be a factor in their distribution along the tendon. **Cells do not seem to like to suffer**.

In the the epimysium and perimysium, cells are also found in clusters nestled within the mesh of the fibrillar system. But this is not as immutable as one might think. Look at the layout of the cells in this cluster. On the sides, the cells look as if they are leaving the cluster in single file, like processional caterpillars, before passing between the fascicles to enter the body of the muscle along the vessels. This is because the fibrillar network extends into the muscle, and the cells inhabit it, as you can see in these sequences which show the cells balanced on the scaffolding formed by the fibrils. So muscle cells are not the only cells in the muscle. 8'50 As for muscle cells, I was only able to film a few on one occasion due to the difficulty of penetrating a muscle with an endoscope. Here they are, long and narrow with what seems to me to be a view of a division of the sarcomeres.
What is certain is that these cells appear as soon as the mechanical stress requires it, as in this annular ligament in a manual worker. We can see that the muscular differenciation has increased even though the annular ligament is a predominantly fibrous structure.
Cells can respond to a mechanical requirement by increasing their numbers and by becoming more functionally adapted to the requested mechanical constraint.
But sometimes we see exactly the opposite, such as muscle cells at a musculotendinous junction, as if they are located outside the dynamic contractile system.

INTERVIEW 2

These previous observations are disturbing because, even if the concept is difficult to understand, we get the impression of cellular mobility, an attraction of cells to the blood vessels and, finally, a strange impression of life within life.

When you observe the vessels, it is surprising to see arteries and veins almost completely coated by layers of cells which gather together along the vascular pathways. The cells are piled up on each other, and apparently do not have a pericellular blood supply. One gets the impression that they obtain their blood supply directly from the source. Moreover, I tried to film the inside of a cubital artery and I was surprised to find that the cells of the intima are arranged in a pseudo-parallel, longitudinal fashion, in the direction of the blood flow. That is, in the direction of constraint.
Once again, we see the disposition of structures in the direction of constraint.

The observation of nerves is very delicate because the risk of damaging a nerve by dissecting it into fascicles for the purposes of a film is too great.
Only the epineurium can be examined, and this also reveals the presence of cells. These are adipocytes, sometimes sparsely scattered but at other times in great abundance. I have often observed a "brown spot", which is a reactive phenomenon on the surface of a nerve, as in this case when there is compression on a nerve caused by some sort of obstacle. I did not know how to explain this until

endoscopic exploration provided evidence of an abnormal concentration of cells in the area of these brown spots. **Could cells gather in a specific place and for a specific purpose?**

Observation of the periosteum is disappointing. Endoscopic research is not very fruitful here and I have never been able to locate any cells. However, it seems likely that the thicker fibers, packed with minerals, almost certainly hide the presence of cells.
On the other hand, observation of bone reveals that the organization of the longitudinal cortex is clearly discernible along the lines of force. Parallel vessels are found here. Within the scaffolding we find the Haversian canals, the canaliculi, and the lacunae which contain the osteocytes. It is also possible to observe cancellous bone, and the presence of hematopoietic cells or adipocytes within the trabecular network of intersecting fibrillar struts of hydroxyapatite, as in all other tissues.

INTERVIEW 3
After exploration of the distribution of cells within different types of tissue, one would expect the findings to be predictable, and consistent with traditional anatomical teaching. However, some peculiarities have emerged, such as the relationship with constraint, the proximity of cells with the fibers and blood vessels, the absence of cells in certain areas, and a strange impression of cell displacement that weakens our certitudes. A more thorough analysis of the images reveals further details and situations that are difficult to understand or explain, especially the arrangement of the cells.
How are the cells arranged, organized and oriented? Medical teaching would have us believe that cells are everywhere, filling all spaces, and distributed in an orderly manner. We will see that a more nuanced picture emerges.

We will now look at the most anticipated organization: sheets of cells that cover the surface of these structures, much like wild flowers growing in a spring meadow. There are tens of millions of them and they are everywhere, like gold nuggets on the surface of the muscles, tendons, nerves and veins. I have not been able to discern any apparent logic in their arrangement. They are not arranged in any obvious order. The disposition of these fields of cells is astonishing. The outer limits of the groups of cells are sometimes regular, but sometimes not at all, and often seem to spread to infinity. Sometimes the cells crowd together. Sometimes they are less crowded with surprisingly empty areas.
What is the explanation for the cells clustering together in one place, in a specific area? Why are the groups well delineated in some places but not in others? However, cells are not randomly disposed. The impression of lifting a veil on some sort of subterranean life disturbs me somewhat. 13'30

Sometimes cells seem to concentrate around the vascular axes as if in search of some indispensable need, leaving unoccupied spaces elsewhere. The presence of vessels is quite variable and is not homogeneous but two things are certain. The cells move with the vessels during movement. Another constant observation is the tropism of the cells towards the vessels.
During exploration, the endoscope sometimes reveals a small group of cells that seem to appear from nowhere. They appear to be alone, or nomadic. In other cases small groups of up to ten cells appear to be isolated at a distance from the main group of cells. What are they doing there? Have they been in this location since embryogenesis, with a fixed permanent base at a distance from the other cells, or are they engaged in a temporary migration process? **Do cells migrate**? We know that, in vitro, the answer is yes. But how do they actually behave in the living body?

There are many examples of this phenomenon. For example, here we can see a small group of cells, then an area with no cells and then, at a distance, two other cells appear.

What could explain this sequence where we see a small group of cells that seems to be taking some sort of obligatory or required passage, one by one, with cells at the front almost seeming to fight over the

passage and the others dispersed at the tail of the pack. There is a strange impression of general collective movement, but composed of more selective or individual movements within the general flow of movement.
The grouping together of cells in this way is a captivating discovery, and yet it has never been mentioned. It is, however, a frequent and evident anatomical observation.
Clusters of cells can be easily identified in this sliding area situated beneath the hypodermis and above the aponeurosis. Their forms are varied and they resemble bunches of grapes, or rows of fish-eggs due to their greyish color. They are often oblong in shape, and they tend to be quite long and not very wide. They are generally very well vascularized by a central arterial branch and its ramifications but this is not a constant observation. Some groups appear to be poorly vascularized.
There is a large variety of shapes and sizes, ranging from about 500 to 1500 microns. The number of cells in each cluster depends on the its length. A cluster of 2 mm contains at least 5 million cells. In the following sequence you will see what seems to me to be an essential observation: the mesoscopic continuity between a cell cluster and the fibrillar architecture that appears to provide a supporting scaffolding) for it.

We can clearly see that these groups of cells branch off and form extensions which themselves extend into the fibers. One even has the impression that the fibers originate in these clusters, or emerge from them. However, it is impossible to discern even the slightest presence of fibrils within the clusters. The fibrils just seem to disappear.

Another surprising observation is often made at the junction between clusters and cells, where dense bulges of cells are frequently observed, as if the cells here are packed together very tightly. What is the reason for this?
This relationship between fibers and cells does not appear to be a simple contiguous relationship. The cells do not simply sit on the fibers. Their relationship seems to be much more complex.
So let us try to visualize more closely this relationship between the fibrillar extracellular world and the cell. It is easy to demonstrate that these groups of cells are completely integrated into the fibrillar framework and even when we attempt to break apart this mesh of fibers and cells, the groups of cells remain attached to the fibers.

In these images we see very clearly that the cells are included in the fibrillar framework. They are an integral part of it, as are the vessels. The cells are as wrapped within this network. But the term wrapped or swathed, implies a physical separation whereas in fact there is total continuity. Here we see a mesh of interlacing fibrils penetrate a group of cells. The fibrils extend into the intercellular membranes. There is a real and total histological fusion between these two elements. These microfibrils are barely 5 microns in diameter.
These two elements, the cell and the fibrillar architecture are inseparable.
This has two essential consequences. The first effect is on the behavior of the cells whose shape and position depend on the mechanical behavior of the fibrils. In this sequence we see the cells change shape and retract following the section of a fibril. Then they are flattened as the overlying fiber descends.

In the next 4 sequences we see that the cells move, change their appearance, dilate, or sag a little in reaction to the slightest mechanical impulse. These are only very slight movements but let us not forget that these images were filmed at a scale of 10 microns. They are, however, distinct and clearly visible.

The fibers are responsible for and play an essential role in the mechanical behavior of the cells.
The slightest stretching along a fiber causes a change in the orientation and position of the cells, and may even cause a change in shape. Oval cells become round or narrower. The mobility and flexibility of these groups of cells are surprising, considering the complexity of their arrangement. This phenomenon

is obvious and could be an example of mechanostimulation triggering mechanotransduction. The interconnections between the extracellular matrix and the cytoskeleton, via the integrins, and to the nucleus has already been amply demonstrated in vitro by others. Nevertheless, we can draw the irrefutable conclusion that any movement imposed on the surface of the skin induces morphological changes of the cells due to the fibrillar continuity. However, it is not possible to draw therapeutic implications from this.

The second consequence is summarized in this sequence in which we see an alignment of cells on a fiber. We get the feeling that the role of the fibrillar network is not limited to that of our internal architecture but that it also serves as a network of pathways, passages and side roads.

Here the endoscope passes at random along a fiber. Suddenly two cells appear. They are isolated from the rest of the group like ladybirds on a blade of grass. As the endoscope moves further along the fiber two more arise, closer together. This gives rise to the following questions: why are they alone? What are they doing here? Have they moved into this position? If so, how and why? Is this the result of cell division?

Sometimes we see several cells together, or small groups like a tribe which, one is tempted to say, are moving up along this fiber. In other instances we see what resembles a real invasion of cells that form columns that can be fairly dense at times. In these images we can see that they are indeed fibers. If you look closely at the lower part of the picture, you can see the mobility of the fiber as it enters the aponeurosis.
But notice also the other end which is crowded with cells rather like cars in a traffic jam. This is often the case. However, not all fibers are colonized by cells. Some fibers do not harbor any cells. But these columns of cells, which remain mobile, can either be overcrowded as they are here, or they can be be highly vascularized. This raises the question of the relationship between cells, fibers and vessels. Look at the vascular richness and the density of cells in this column. You will also notice that there are cells almost everywhere, often packed closely together, but that in some areas there are no cells. Why is this? Some cells are densely packed, others more scattered, and some are alone. The cells that are on their own are spherical in shape.

The relationship between fibers, cells and vessels is undeniable and can be perceived as fusional and global. Separating them introduces means that the results are subject to omitted variable bias. Any scientific conclusions are therefore debatable.

Cells appear to be surrounded by microvessels which are an integral part of the fibrillar network. Sometimes these pericellular micro-vessels are evident and this provides us with superb images, almost reassuring in their classic anatomical conformity. Nevertheless, we observe only one vessel, rubicon red and doubtless arterial, whereas we can see veins, which are bigger, in the immediate surroundings.

However, sometimes things are less obvious and pericellular circles are not found everywhere. Instead, we see one or several branches of a microvessel. On the other hand in some tissues such as fat lobules one gets the impression that the vascularization is much more modest, but this can be misleading. Look at this sequence. It seems that these cells are not surrounded by vessels. But if you film the same area a few seconds later, pericellular vessels become visible.
It is also important to indicate the curious phenomenon of the presence of small bubbles measuring around 5 to 15 microns within the groups of cells. The bubbles are well distributed, in contact with the cells, and are found along the entire length of the fiber supporting the cells. This is another constant and regular observation for which there is currently no explanation.

In conclusion, these cells seem to move, migrate and change shape. What can we learn about the morphology of cells that are living in their original environment, the human body? Cells in the skin, bone, tendons or muscles are difficult to observe in vivo because they are very compact. The cells in the fat lobules are more easily observed. They are golden yellow, polyhedral, angular, closely packed and poorly differentiated.
On the other hand, the cells in the sliding zones, particularly those in clusters, are very interesting and lend themselves to observation. It cannot be said that the cells in these clusters are fundamentally different from the adipocytes. However, to the trained eye they are brighter and less compact, but the nucleus of the cells remains invisible. Light peripheral pressure causes the cells to bump into each other but they stick together and do not dissassociate. The adhesion and cohesion between the cells appears to be strong.

But this adhesion between cells is not the same everywhere. Sometimes they are grouped together with strong intercellular cohesion, and their shapes are more angular or polyhedral. In other cases, the intercellular cohesion is weaker and the shape of the cells more spherical. Sometimes cells are isolated and round. The relationship between the shape of the cells and peripheral tension is obvious.
Even in a homogeneous group of cells, one might see a cell next to a neighbor that is twice as small. Some are olive shaped, some pointed, some appear to be stuffed, others stunted.
On the other hand, there are no visible morphological differences with regard to the location of the cells. The shape of an adipocyte in the forearm is comparable to that of an adipocyte in the back or the abdomen.
Here too there is an infinite variety of shapes and sizes. All cells are different. Each cell seems to be morphologically unique.

We lent out some some samples of cells in the sliding zones for study using both classical and electronic microscopes. The results showed the existence of both mature and immature adipocytes. There were also fibroblasts producing collagen. They appeared to be immature, with several nuclei, and very rich in mitochondria. However, progress will also be made in this area of scientific research in the future.

INTERVIEW 4
All of these sequences aim to show the reality of cellular life in the living body, and to reveal behavioural characteristics that will add to the already abundant existing body of knowledge. However, the observation of cells in a living person encourages greater reflection than observation of the fibers. I do not use the term anthromorphism lightly, because there is a powerful feeling of a distinct behavior, an attitude, and a "way of being" that is displayed by cells.

Every time I explore cells in their natural environment, I cannot help but think of them as living beings, and even if I do not see them moving spontaneously, when I witness the migratory flow of cells going to programmed destinations, I get the impression of life within life, taking place without our knowledge, and beyond our control and consciousness.

This leads to the question of their mode of operation.

And to come back to more concrete considerations, how does this fibrillar architectural entity made up of a 220 billion cell meta-society manage to function in a combined, coordinated and well - balanced way? Where does information come from? How, for example is the daily loss of 20 billion cells replaced at the rate of 20 million cells produced every second? These figures are mind-boggling! And yet this is the reality, it's our reality!
There are still so many things we do not know about living matter, and this encourages us to continue the endoscopic exploration of living anatomy which throws new light on the life that unfolds within us and without us.