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Evolution of a Theory: Connective Tissue and Silicon. Past, Present and Future of a Possible Connection

Evolución de una teoría: el tejido conectivo y el silicio. Pasado, presente y futuro de una asociación posible

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Abstract

The history of science serves to understand the evolution of a currently solid theory, which presented difficulties, leaving unresolved questions for future studies that could expand the connection between that initial theory in relation to its general and current implications. Examples of how a science progresses from ambiguous knowledge to multidisciplinary work are: the analysis of connective tissue, its importance for the original cell theory and how timely the chemical composition of the extracellular matrix remained to be explored in future research, as well as the rediscovery of silicon in its trajectory from being a toxic substance to becoming a potentially beneficial element for human health.

Keywords: cell theory, connective tissue, extracellular matrix, silicon, health

Resumen

La historia de la ciencia sirve para comprender la evolución de una teoría que, aunque sólida en la actualidad, ha presentado dificultades en el pasado e incógnitas aún sin resolver, las cuales han abierto la puerta a estudios posteriores que amplían el vínculo entre esa teoría inicial en relación a aspectos generales y actuales. El análisis del tejido conectivo, su importancia para la teoría celular original y como en su momento la composición química de la matriz extracelular quedó pendiente de investigación, junto con el redescubrimiento del silicio que pasó de ser tóxico a considerarse un elemento potencialmente beneficioso para la salud humana, son ejemplos de cómo una ciencia progresa desde saberes ambiguos hasta el trabajo multidisciplinar.

Palabras clave: teoría celular, tejido conectivo, matriz extracelular, silicio, salud

Introduction

From the philosophy of science, T. Kuhn highlighted the differences between ancient practices and theories regarding the ways in which a science is currently represented in teaching, a situation he referred to as incommensurability. He also considered the role of the scientific community in their creation and continuity, understanding the potential applications of those theories. Considering the incorporation of new premises into cell theory, this work demonstrates its solidity, serving as an example of theoretical evolution that is consistent with Kuhn's concept of normal science.

In its transition to becoming a rationally based knowledge, 19th-century medicine was empirical and occasionally considered speculative. The cell theory that emerged from the laboratories of T. Schwann (1810-1882), R. Virchow (1821-1902), and R. Kölliker (1817-1905), among others, required the entire medical community to review previous concepts, however showing certain excessively conjectural aspects.

This theory emerged as a result of a constant search to understand the changing and dynamic phenomena of life from its origin to full human development, with adulthood considered to be the peak of organic maturity. There was a concurrent desire to understand the mechanisms that would replace the ambiguous concept of vital force, as researchers began to accept the existence of molecular forces at work within the organism.

The ancient concept of fiber was associated with the relatively rigid components of the human body, such as ligaments and bones. In the early 19th century, through empirical evidence, X. Bichat (1771-1802) characterized it as fibrous tissue, and defined it as a structure for future studies. It was not until 1830 that J. Müller (1801-1858) referred to it as connective tissue (Gabbiani, 2022, p. 4) when the principles of cell theory had not yet been established.

Kölliker (1854, pp. 189 and 205-206) observed how this fibrous tissue, featuring spindle-shaped or star-shaped cells, also served as a relatively flexible support for vessels, nerves, and glands. Virchow focused his microscopic explorations on this tissue, which led to disagreements and questions about the emerging theory he supported.

He suggested the principle of “omnis cellula e cellula,” definitively incorporated into cell theory to silence criticisms, and highlighted the importance of the extracellular matrix (ECM), where the connective tissue contained both adjacent and scattered cells, in addition to the set of nerves, vessels, and blood as specific third element for each species (Virchow, 1858, p. 27-29).

S. Ramón y Cajal (1852-1934) wrote about the formation process of connective tissue, which was the subject of heated debates. Some of his hypotheses suggested a blood origin, also arising from fixed cells (fibrocytes), a possible endothelial origin, or an origin from residual germ cells, which Cajal referred to as cyanophilic cells. Furthermore, he suggested that, along with the action of certain stimulants, these cells would undergo division and transition into fibroblasts and eventually develop into mature connective cells (fibrocytes) (Cajal, 1896, pp. 93-100).

Microscopic observations were conducted through tissue dissection with acids until in 1889, I. Van Gieson (1866-1913) published a method that is still valid: the trichrome stain for connective tissue fibers, which generally involved dilutions of fuchsin, picric acid, and hematoxylin for the nuclei.

Previously, in 1876, E. Ziegler (1849-1905) had investigated "colorless blood cells that migrated from vessels in cases of inflammation", with the unusual characteristic that by using the suffix -blastem, he indicated the morphological capacity that those undifferentiated cells had to gradually develop a spindle-shaped elongation (Ziegler, 1887, p. 153). Although normal histology was of interest, it was necessary to study the pathological tissues, and the new theory undoubtedly provided a valuable guide for understanding diseases by stating that all abnormalities originated in cells and tissues.

Keloids are diseases characterized by an excess of fibrous material. They were first recognized in 1790. In the late 19th century, M..Kaposi (1837-1902) could microscopically describe how the fibers compressed the blood vessels and identify other diseases where the skin appeared dry and limiting motion, a condition that was considered to be caused by a reduction in connective tissue. These lesions were designated as sclerodermas in 1837, a term that later extended to all diseases involving the connective tissue or corium that supported the epithelial cells of the skin (Gabbiani, 2022, p. 27 and 48).

Other diseases, which were suspected to originate from blood vessel contraction that included connective tissue in their composition and how these alterations also affected the patient's nerves, were added

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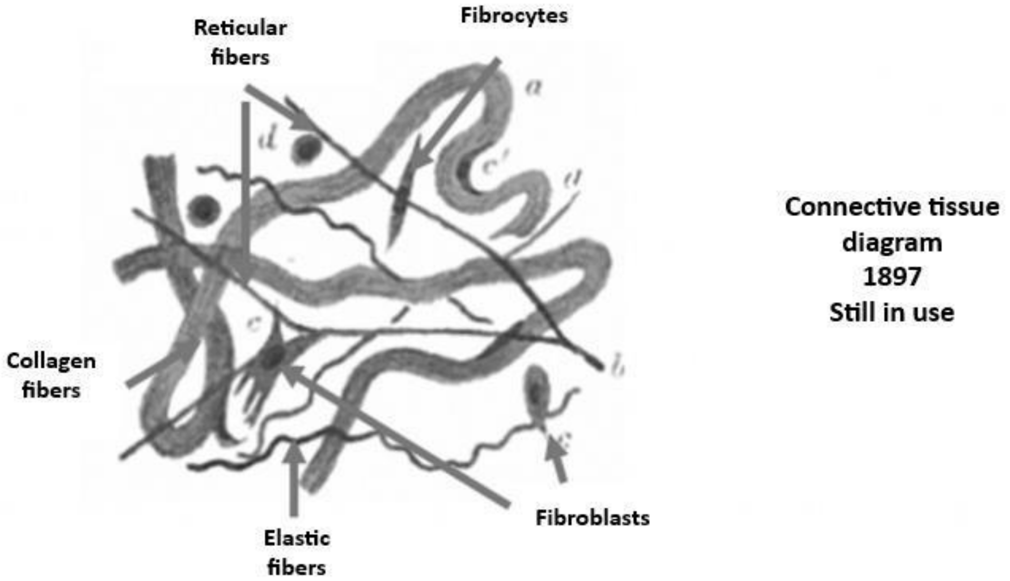

to the classification. Consequently, all diseases that presented similar patterns were designated as *collagenopathies*, although currently, this term only applies to diseases that exhibit changes in the collagen molecule (Gabriani, 2022, pp. 49–51).

Nevertheless, the connective tissue contained different cells, particularly those occasionally referred to as fusiform fibrous cells, which were difficult to see and remained in the ECM (Virchow; 1858, p. 45). Based on generally agreed descriptions, these cells can be considered fibrocytes, a term that some researchers now prefer to call fibroblasts when referring to the range of active cellular morphologies of connective tissue, including fibrocytes as the mature or inactive (quiescent) version of fibroblasts. Fibrocytes have recently regained attention in research, when their capacity to activate as fibroblasts in response to normal or pathological external stimuli requiring increased connective tissue was rediscovered using alternative methods. This process may be explained by two possible mechanisms: either from residual fibrocytes in the ECM or through the migration of blood cells, lymphocytes, or Maximov's polyblasts, which were recognized in 1994 as circulating fibrocytes dependent on the hematopoietic system (Gabbiani, 2022, p. 13).

While Ziegler argued that fibroblasts, in a general sense, produced substances to form connective tissue, Virchow (1858, p. 137) had coined the name of one of these substances: *collagen*.

As Kuhn wrote, the changes in concepts within a science are not individual but rather collective involving a group of scientists, and the process through which a theory is accepted is not the same for all communities, as was the case with connective tissue. This tissue represents new challenges for 21st-century histology and pathological anatomy with regard to the need for quality of life, the environment, and therefore, multidisciplinary collaboration.

Collagen and its importance

In the bibliography mentioned, there is a noticeable interest in studying the different cells that make up the ECM and their role in tissue repair, as well as the substances that could be involved due to the variety of known pathologies in which fibrous tissue was present.

In 1940, biochemistry successfully identified the bands of collagen or *gelatin* fibers synthesized by fibroblasts, which had been previously mentioned and precisely localized using histological techniques. In 1974, its production process was described. This process began with the synthesis within the cell of a collagen molecule known as pro-collagen, which was 25% larger than extracellular collagen.

When this molecule was secreted by the cell into the ECM, it underwent modifications through interactions with other elements until it became true collagen. By the mid-century, three types of fibers were differentiated according to their staining properties: collagen fibers (trichromatic), elastic fibers (various colorations), and reticular fibers (affinity for silver salts). It was believed that these fibers were composed of different proteins: collagen, elastin, and reticulin. Nevertheless, in 1950, it was suggested that reticular fibers were actually very small collagen fibers and that the difference in size explained their distinct staining properties. At the same time, L. Pauling (1901-1994) and R. Corey (1897-1971) deemed it appropriate to study collagen as a macromolecule, thus being possible to differentiate type I collagen (skin, bone, and tendon), type II collagen (cartilage), type III collagen (fetal tissues, blood vessels), and type IV collagen (basement membrane), each with its respective subunits (Bentley, 1976, pp. 119-120 and 122).

Currently, 21 types of collagens have been identified. Type XVII is found in cell junctions, while type XXI is found in the gums as well as in cardiac and skeletal muscle tissue (Osorio Bastidas, 2008, pp. 108-109).

It was also discovered that smooth muscle fibers had the same capacity as fibroblasts to generate collagen, a process that required specific enzymes, thus initiating the study of cofactors (Bentley, 1976, p. 121). These cofactors included other substances present in the extracellular matrix (ECM), known as coenzymes when organic, and also the inorganic ones, such as ions, which are generally metallic.

This is how it was established that zinc is a key element in the extracellular matrix (ECM), and the enzymes that are zinc-dependent were called metalloproteinases or MMPs. Nowadays, 28 enzymes are known to be centrally involved in the remodeling of normal tissues and in pathological processes due to their ability to activate growth factors, surface receptors, and adhesion molecules. They are subclassified into five groups: collagenases, gelatinases, stromelysins, minimal MMPs, and membrane-type MMPs, which exhibit different shapes but generally produce denatured collagen or gelatin when degrading interstitial type I, II, and III collagen. These enzymes are regulated by tissue inhibitors of MMP or TIMPs (Pereira Prado, 2016, pp. 21-22).

The study of MMPs and other enzymes has intensified the use of technologies to recognize and understand cellular responses to the presence or absence of those stimuli and their multiple transformations in the process of generating normal or pathological connective tissues.

Additionally, these investigations include the analysis of the inorganic cofactors that enable cells to synthesize collagen, as a key component of the widely distributed connective tissue in the body. Furthermore, the direct application of collagen, a fractionated molecule in its natural process, results in an assimilation that compensates for the deficiency but requires repeated applications. However, no results have been reported regarding any residual incorporation or activation of new collagen in the recipient tissue (Nitecka-Buchta, 2014, p. 8).

Epidemiology and nanotechnology

Although recently the presence of microparticles in the oceans has led to the study of Si in water, it was R. Zsigmondy (1865-1929), in 1916, who began research on particles smaller than microns in colloidal substances (Scott, 2006, p. 141). However, it was only in the middle of the century that it became necessary to optimize the methods of measurement for particles of combustion materials considered to be the cause of environmental pollution (Buzea, 2007, p. 44-45).

While the prefix micro- refers to something small, the prefix nano- highlights phenomena fluctuating between the atomic level and the range of 1 nm to 1000 nm (or 1 µm), this is why particles of this size are called nanoparticles (NPs) and microparticles (MPs) when they are > 1 µm. However, there is no consensus among authors, some limit the term NPs to those particles from the atomic or molecular level to 50 nm or 100 nm. Examples of such magnitudes are the diameters of the DNA double helix of approximately 2 nm, that of a bacterium of approx.1000 nm, whereas the HIV virus has a diameter of 100 nm (Buzea, 2007, pp.21 and 24) and the collagen molecule has a diameter of 1.4 nm and a length of 300 nm (Osorio Bastidas, 2008, p. 103).

The field of NPs has diversified. At present, it includes epidemiology, a science that studies the different factors of incidence, distribution and possible intervention in the diseases affecting the population. This gave rise to nanotoxicology, which studies all NPs <100 nm known as ultrafine particulate matter, and environmental science, which analyzes the collective behavior of particles or particulate matter, i.e. the set of NPs ranging from 0.1 nm to > 0.1nm. As an example, the NPs produced by combustion measure 20 nm and pollen 10 µm. To cover this new knowledge, nanotechnology emerged as the science of design, synthesis and application of materials at nanometric level, which includes nanoengineering

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applied to the reproduction or repair of damaged tissues through the use of scaffolds built with nanomaterials that allow artificially stimulated cell proliferation for organ transplants or artificial implant therapies, speculating that it may be the science that prolongs life (Buzea, 2007, p. 23).

As the pharmaceutical and food industries frequently use NPs and expose humans to direct or indirect consumption, they promoted the study of NPs to measure their possible toxicity, including the discussion on the reliability of the in vitro models used for the assessment of toxic effects (Lebre, 2022, p. 7).

In connection with silicon (Si), it was A. Uhlir (1926-2016) who began to study it in 1956 and discovered its porosity. However, it became of interest four decades later when its photoluminescent capacity was noticed. From then on, silicon NPs have been used for numerous purposes, including optical chemistry, bioimaging, as a biomolecular detector, in tissue engineering and for drug administration (Maniya, 2016, p. 257).

Some studies have identified differences in potential toxicity between artificially produced NPs and MPs, due to their lower capacity for absorption or dissolution in an organic medium as they do not increase the levels of the carrier substances in blood or urine (Lee, 2016, p. 14). Therefore, including both scales is suggested. For example, NPs with a size between 15-30 nm caused toxicity, while 70, 300 and 1000 nm NPs of the same material did not show hematological, histological or biochemical alterations in different organs (Petrache Voicu, 2015, p. 2).

Furthermore, Si NPs have shown to be biocompatible because they tend to degrade. As research has increased in association with other elements such as Mg and Zn, it was concluded that they locally enhanced collagen growth (Tong, 2020, p. 416). Therefore, their use as carriers or vehicles, incorporating other elements, would ensure their slow absorption, which may be beneficial due to the various forms that Si NPs may adopt, from fiber fleece for wound healing (Grotheer, 201, p. 22-23) to dressings or bandages with antimicrobial silica compounds (Pielesz, 2021, p. 61-62). Recently, innovative experiences have also been reported in optics with encouraging results.

Measurement methodology

Nowadays there are direct biochemical tests using radioactive isotopes that have determined that humans fully excrete degraded Si as orthosilicic acid after 24hs. (Pruksa, 2014, p. 7). Another recent method, though limited due to its high cost, is the inductively coupled plasma optical emission spectroscopy (ICP-OES) by light excitation (Boqué, 2021, p. 3).

Other indirect markers analyzed for the relationship between Si, collagen and ossification, are:

> in blood for bone formation, total alkaline phosphatase (ALP), bone alkaline phosphatase (BAP); osteocalcin (OCT); Type I procollagen C-terminal extension peptide (PICP) and procollagen I N-terminal extension peptide (PINP). And for resorption: tartrate-resistant acid phosphatase (TRAP); C-terminal telopeptide of type I collagen (ICTP); β-CrossLaps (β-CTX) and N-terminal telopeptide of type I collagen (NTX)
>
> in urine resorption markers; urine calcium excretion; hydroxyproline; pyridinoline (PYD); deoxypyridinoline (deoxyPYD); C-terminal telopeptide of type I collagen (ICTP); α-CrossLaps (α-CTX) and N-terminal telopeptide of type I collagen (NTX) (Romero Barco, 2012, p.150).

Samples of saliva were collected from laboratory animals, to determine, using the ELISA method (enzyme-linked inmunoassay), the bone alkaline phosphatase (BAP) present in collagen, a marker of bone formation, as well as the C-terminal telopeptide of type I collagen (ICTP) for resorption (Pellegrini, 2006, p. 247), a marker used in humans that follows the same process too (Mishra, 2015, p. 50). Additionally, the noninvasive sampling of saliva was equally used in humans to measure MMP-8, which in excess degrades type I and III collagen (Memon, 2022, p. 5).

Microscopy

The histological procedures made it possible to obtain flat or 2 D images, which were necessary for optical microscopy (OM). However, the first microscopists recognized that cells belong to a threedimensional system, and that understanding what was observed presented cognitive challenges that had to be addressed in addition to the external consensus on what was valid to observe, as shown in the discussions on the cell elements of connective tissue.

Moreover, while OM enabled researchers to observe structures measuring up to 0,2 µm due to its resolution that is dependent on its energy source—, the light or visible light waves of the electromagnetic spectrum—, the Transmission Electron Microscope (TEM) in the 20th century achieved a resolution of 2 nm using electron beans. This was a completely different method limited to small and rigorously processed samples that were very finely sectioned, yet allowing for the observation and discovery of various cell ultrastructures, bacteria and viruses.

By 1960, computational engineering began to work on geometric relationships and programming language (Birmingham, 2018, p. 146). Meanwhile, in 1975, in the field of Natural Sciences, the gene transcription technique or Southern Blot emerged. This technique provided a better understanding of the cell composition by dissociating cells using methods currently known as sequencing that, once transported onto a membrane, can be examined as bands of various concentrations depending on their atomic weight.

This method would later give rise to other techniques such as the Northern Blot technique for the analysis of RNA and the Western Blot technique for proteins (Peña-Castro, 2013, p. 242).

Furthermore, when dissociative techniques seemed to discredit the trichrome-stained micrometric sections obtained from the histological method for OM, the fluorescence in situ hybridization (FISH) technique emerged. In this technique, RNA is labeled with specific antibodies directly on histological sections instead of dissociating cells, as is done in sequencing methods (Marx, 2021, p. 9). These sections can be observed using a fluorescence microscope within the same tissue. Moreover, Long Cai improved the FISH technique with super-resolution microscopy (SRM) arguing that, essentially, every 2D image involves a 3D structure, in line with computational engineers who claimed that the notion of a 2D or a 3D image involves different cognitive skills, because while the first requires topological relations of less effort, the second requires to establish relative or projective spatial relations (Birmingham, 2018, p. 147).

SRM in pathological tissue fixed in formalin radically increased the optical resolution of the OM up to ~10 nm, close to the resolution limits of transmission electron microscopy (TEM). Nevertheless, the sample preparation protocols optimized for one technique may not be fully compatible with each other, and the results from the two modalities require an interpretive effort (Hauser, 2017, p. 15). This group includes correlative light and electron microscopy (CLEM), which uses fluorescent dyes on specific luminescent particles that can support TEM (Van Hest , 2019, p. 13) and is in constant improvement.

These technological advances also led researchers to turn their attention to optical microscopy techniques, which are well developed in histology and histopathology, from the primitive tissue dissociation to their determination using specific staining techniques. In addition to the various trichomes proposed by Van Gieson, Cajal, Gomori and Masson, and their variants, progress was also made in the differentiation of elastic fibers: Unna and Verhoeff as well as orcein and resorcinol fuchsin being the best known. The Gomori technique stands out for reticulin (reticulum) because it consists of type III collagen fibers that have affinity for silver salts that stain them black, whereas collagen generally remains yellow.

When using TEM, fibroblasts appear elongated, with branching, basophilic cytoplasm, fine chromatin (euchromatin) and visible nucleolus, while fibrocytes are also spindle-shaped but exhibiting contiguous tight junctions, acidophilic (or eosinophilic) cytoplasm and dense chromatin (heterochromatin) (Osorio Bastidas, 2008, p. 113).

Immunohistochemistry (IHC) also contributed through the use of specific antibodies, demonstrating a wide range of applications to differentiate connective tissue and certain proteins with different functions depending on whether they are in normal or malignant neoplastic states. There are numerous antibodies and studies exploring their potential capabilities; some of them are mentioned here because they are useful for characterizing specific cell types, such as:

> Vimentin and desmin, both intracellular cytoskeleton proteins, belong to the intermediate filaments (IFs) group. Vimentin is found in mesenchymal cells, in some epithelial cells, Schwann cells or glial cells, while desmin is found in the smooth muscle but has

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> no relation with contraction, but rather with structure and interconnection (Martínez Pérez, 2010, p. 5).
>
> Moreover, fibronectin characterizes fibrocytes (Bucala, 1994, p. 75), whereas *S100A4* (or FSP1) is a fibroblast-specific protein that is indicative of transitions from other cell lines (Lendahl, 2022, p. 2). On the other hand, α-SMA acts as a differentiating marker of myofibroblasts (Gabbiani, 2022, p. 60-61).
>
> Additionally, MMPs and TIMPs have specific antibodies. For example, *MMP-1* is synthesized by macrophages, fibroblasts and dendritic cells, promoting cell survival. *MMP-8, is* synthesized by neutrophils, has anti-invasive properties, while *MMP-13* is exclusively synthesized by fibroblasts (Pereira Prado, 2016, p. 22).

Overview of silicon and its significance for health

Since the study of cofactors began, the importance of vitamins D and K related to osteocalcin, a protein involved in bone calcification has been highlighted. In 1970, E. M. Carlisle (1922-1987) published his results obtained in vivo on the value of silicon in ossification. Although his research was validated, it was not until 2002 that interest in this mineral, its utilization by the body, its toxicity and methods of administration began to grow (Price, 2013, p. 1).

Additionally, although organic silicon supplements already exist and monomethylsilanetriol (MMST) is known to have better absorption than choline-stabilized orthosilicic acid (Price, 2013, p. 4), it is necessary to know that silicon, as a metalloid, sometimes behaves as a metal. It is the second most common element in nature after oxygen, especially in the oceans, and it is also the third most abundant trace element in the human body (Jurkić, 2013, p. 1-2).

As previously mentioned by Cajal (1889, p.139), among the inorganic substances present in the human organism through silicic acid taken in through food or beverages, silica was concentrated in the hair and certain fluids, and it is now known to be present in the skin and arteries (Price, 2013, p. 2).

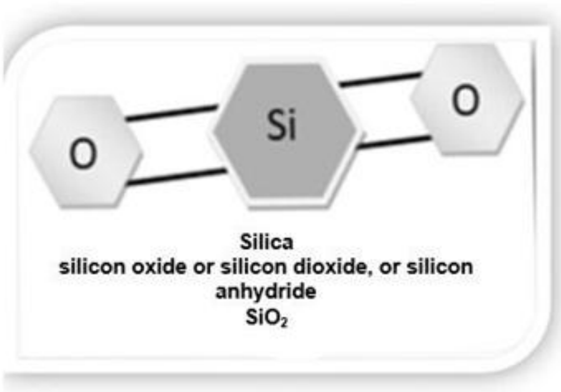
As part of the chemical family of silicic acids, the monomeric orthosilicic acid variant (H4SiO4) is soluble in water and stable in highly diluted aqueous solutions. Upon further dilution, through storage or heat exposure, it concentrates and forms colloidal silicic acid or hydrated silica gel (Jurkić, 2013, p. 1-2), leading to a diversity of applications as an additive in processed foods, a clarifying agent in beverages, an anticaking agent, and is also found in bandages, medicines, and vitamins (Natarajan, 2017, p. 1575).

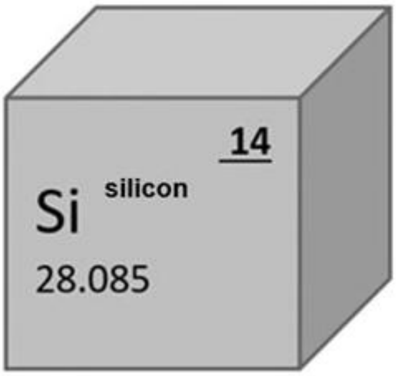
In addition to its positive involvement in ossification, especially with the glycosaminoglycans present in the joints, Si has been found in other tissues such as the aortic wall and the skin. It was further suggested that, while it interacts positively with vitamin D, Si can promote ossification independently of this vitamin, which requires sunlight to develop. Other epidemiologically significant interactions that are currently under study include those with Alzheimer's neurodegenerative disease and heart diseases due to its relationship with connective tissue (Jurkić, 2013, p. 4 and 6).

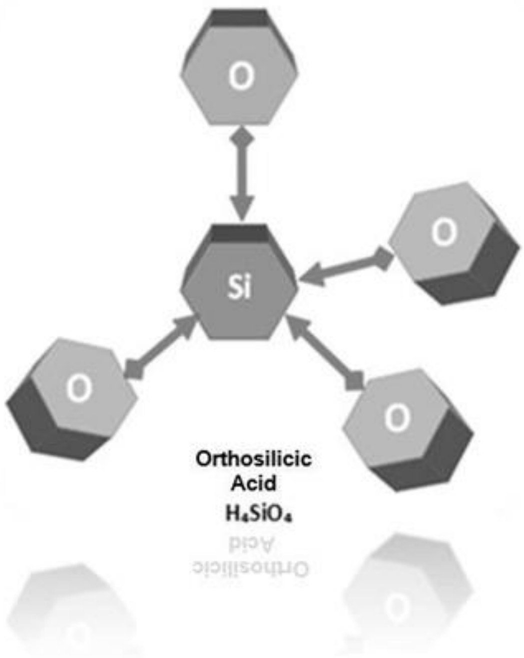
Moreover, as diet becomes more important, particularly the intake of apples, oranges, different vegetables, fish, whole grains, and some dried fruits (Natarajan, 2017, p. 1575), the digestive tract serves as its absorption route, and its bioavailability occurs when it transforms into orthosilicic acid as a result of the acidic pH of the stomach. It is also speculated that a possible cause of its decline in the body is stomach alkalinization as a consequence of aging (González, 2003, para. 14).

Additionally, from the extrapolation of data obtained in mammals, an optimal intake of between 10 to 31 g/dL daily of Si is suggested, which is compared with excretion. Therefore, low levels in urine would indicate a low intake level associated with bone loss (Nielsen, 2014, p. 3). In men, the Si present in the blood has levels similar to other elements such as iron, copper, and zinc, and in the urine, it is found in similar magnitudes to calcium (Jurkić, 2013, p. 4). Due to this correlation between dietary Si and excreted urinary Si, controversies arose when elevated levels of Si in renal patients were associated with negative health outcomes. Although it was shown that those elevated levels may be due to water and dietary intake, high concentrations of Si lead to skepticism and distrust, undervaluing the positive properties that this element offers (Natarajan, 2017, p. 1577); as when it comes to toxic aluminum in renal patients, some studies have demonstrated that with the administration of Si, hydroxyaluminosilicate complexes are formed, which can be secreted, thus reducing Al deposit in the patients' tissues (Reffitt, 1999, p. 141).

In all cases the investigations on this matter are recent and there is no consensus on how to administer Si due to insufficient research on dosage and timing to address its benefits, the body's tolerance and identify its potential interactions with other elements. However, although its study began due to the presence of microparticles in ocean water, the supply of this essential nutrient for life is not consistently guaranteed due to tap water potabilization.







This is the case in countries such as Argentina, where 25% of the population consumes well water (Sánchez, 2019, p. 7), and chemical studies of tap water do not indicate the presence of toxic levels of Al, but neither do they report the presence of Si (AySA, 2016, p. 129). Paradoxically, it is argued that hard water is indicative of better Si absorption (Schoppen, 2006, p. 534), providing a valuable opportunity to conduct epidemiological studies on these issues.

Final Comments

According to Kuhn, the exercise of making scientific thinking more flexible cannot be found in university textbooks because the response to Kuhn's incommensurability is that there is no adequate measure that can be used to evaluate the effect still generated by old theories, such as the cell theory, proposed over a century ago, and the controversies and mysteries they engender and that continue to exist. However, without acknowledging them, it would also be impossible to explain the meaning of current applications and connections, as in the case of silicon.

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This element also underwent a theoretical transition; from being considered toxic to promoting beneficial research due to its porosity, which makes it useful as an internal drug carrier, especially when it converts to orthosilicic acid, linking it to bone tissue, connective tissue in general, and collagen. In addition to being present in the environment, humans are continuously exposed to this element through food and beverages, and especially water. Although epidemiological research and economically accessible quantitative and qualitative methods are still insufficient, classical histotechnology techniques along with recent technologies sparked renewed interest in what is regarded as normal science.

Additionally, and as Kuhn posits, because (normal) science must specify which entities are deemed certain in the universe and which are not at a specific moment, it is the role of the history of science and epistemology to demonstrate how the identity of the cell theory was prioritized and consolidated, while leaving room for subsequent theoretical and technological contributions, thus expanding and extending the initial incomplete theoretical network, which allows for an understanding of new and current applications in a more open world than that of the pioneering laboratories that gave rise to it.

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