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RESEARCH ARTICLE

Scientific Achievements and legacy of Professor Eduardo Couve Montané: A narrative review.

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ABSTRACT
Reviewing the history and achievements of professors can teach and inspire the next generation to pursue their research and legacy. For this reason, the present paper reviews the scientific achievements and legacy of Professor Eduardo Couve.

Professor Eduardo Couve developed an outstanding academic career in the University of Valparaíso. In his research he merged his knowledge in cell and oral biology with his accurate management of microscopy, especially electron and confocal microscopes. This allowed him to develop interesting and diverse papers.

Through all his research it is possible to observe a logical and consistent cycle of evidence production influenced by advances in microscopy and collaborations. The conceptualization of the pulp as a sensory organ and a multicellular barrier from an evolutionary perspective, shows a thorough analysis and reflective process of the available evidence and the influence of the different areas of knowledge for a better understanding of dental pulp and tooth.

The real impact of his influence on the countless generations he taught and on all the colleagues he worked with and enjoyed collaborations with, may never be measured, but surely the influence of his career and research will be present for a long time in the development of dental research both in Chile and abroad.

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INTRODUCTION

Research leaders/mentors and professors are essential in the development of science and future generations of researchers. Institutions support the progress of research in frameworks of dissemination, measuring impact, obtaining funding, and provide the environment for research teams and laboratories, allowing the continuous growth of different areas of knowledge[1–3].

Reviewing the history and achievements of professors can teach and inspire the next generation to pursue their research and legacy, and in this way be part of the science construct which is in continuous evolution. For this reason, the present paper reviews the scientific achievements and legacy of Professor Eduardo Couve.

Professor Eduardo Couve developed an outstanding academic career in the Institute of Biology of the Faculty of Sciences of the University of Valparaíso, alongside his responsibilities at the Faculty of Sciences, he held classes in the Master's program in Neurosciences, and also taught undergraduate and graduate students at the Faculty of Dentistry.

His research in cell biology and dental pulp allowed him to develop important papers, some of them earned him to be the cover of the year of the prestigious scientific journal, Journal of Dental Research (JDR), and being keynote speaker in national and international meetings, including the International Association for Dental Research-General Session.

This study summarizes his research in these main areas: Cell Biology and Neuroscience, and Dental Pulp Biology.

Brief Academic History of Professor Eduardo Couve

Professor Eduardo Couve Montané received his degree as Dental Surgeon at the University of Chile, Valparaíso in 1976. He completed a postgraduate scholarship at McGill University under the supervision of Charles Leblond (1984), working in cell biology, morphometry and electron microscopy. In addition to internships in Germany, Canada and the United States.

He was Professor of the Institute of Biology, Faculty of Sciences, University of Valparaíso and taught courses in Oral Biology at the Faculties of Sciences and Dentistry, undergraduate and graduate.

He participated as an academic in the Master's program in Biological Sciences-Neuroscience and a visiting researcher at the Interdisciplinary Neuroscience Center of Valparaíso (CINV). His research was focused mainly on the biology of odontoblasts, innervation, glial cells and vascular components in the dental pulp of human teeth. He published more than 30 articles in journals such as the Journal Dental Research, Anatomical Record, Archives Oral Biology, and PNAS. His research was financed through competitive funds as DIUV and Conicyt-Fondecyt. He was President of IADR-Chile in 1992 and a member of the Editorial Committee of the Journal of Dental Research from 2014 to 2019.

Cell Biology and Neuroscience

Professor Eduardo Couve was fundamental in the development of microscopy in the Faculty of Sciences of the University of Valparaíso. He developed his research with special emphasis on microscopy techniques, merging his knowledge in cell and oral biology with his accurate management of microscopy, especially electron and confocal microscopes. This allowed him to establish numerous collaborations and as a result of them, the development of interesting and diverse papers.

The electron microscopy is a major research tool in cell biology, for this reason the use of this technique for the analysis of the components and organization of different cells, with special reference in the characterization of the organization of organelles, is important to clarify the alteration of the internal polarity of the cells with the possible participation in process like cell migration and secretion events[4–6].

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Furthermore, the electron microscopic applications can be very broad, from the demonstration of the isolation of a novel gram-positive aerobic bacterium species (Corynebacterium alimapuense sp. nov.) to the analysis of organic pollutants, to give some examples[7, 8].

In neuroscience field, the electron microscope can show morphological cell changes during neurodegeneration and neurotoxic processes[9], as the role of aminochrome in the formation and stabilization of neurotoxic oligomers, protein degradation by inhibiting autophagy/lysosomal system[10,11] as a consequence of disruption of actin and tubulin normal morphology[12]. Also the oxidative stress when aminochrome is one electron reduced[13], that can be prevent with the neuroprotective role of glutathione transferase mu 2 (GSTM2) and DT-diaphorase[10, 14]. Similarly, through the study of hippocampal cells lines from normal and trisomy 16 fetal mice (which is a model of human trisomy 21) it had been observed the neuronal characteristics and the different response to specific neurotransmitter stimuli that can be related to neuronal physiology in Down syndrome[15].

In the same way, electron microscopy can be used for analyze, for example the distribution of glutamate and GABA in tentacles of the sea anemone, P. papillosa, supporting a function of these neurotransmitters as signaling molecules in the nervous system of sea anemones [16], and also the capacity of secretory organelles of delivering sodium channels to the plasma membrane in isolated peripheral nerve, demonstrating an autonomous capacity of the axonal biosynthetic system[17]. Moreover, electron microscopy technique can provide images for quantitative morphometric analysis of exocytotic events by neuroendocrine cells[18]. In these cases the use of electron microscope in conjunction with other techniques such as immunohistochemistry allow a better understanding of the signaling, quantal release, and relevant processes during adaptation or recovery of the nervous system.

Regarding this, the immunohistochemistry and confocal microscope play an important role in determining the activity of cells. Fluorescence microscopy, using a variety of fluorescent indicators for specific targets, has been a big step in monitoring cell physiology[19]. In central nervous system, by fluorescence, it had been possible to establish that specific bipolar cell (BCs) types in the inner retina can be nitric oxide (NO) sources, supporting the involvement of NO signaling in physiological and pathological processes in the retina[20].

As it was mentioned before Professor Couve developed his research joining his knowledge in cell biology with his remarkable skills in the management of microscopy. In addition to these collaborations, two special areas of research were of interest to Professor Couve, autophagy and myelin.

It is critical to try to define standards for the definition of autophagy between the different researchers. Concerning this Professor Couve was part of the guidelines for the use and interpretation of assays for monitoring autophagy. Even though there are no absolute criteria for determining autophagic status applicable in every biological or experimental context, it is crucial for the field emphasizing the key issues that need to be addressed for monitoring and demonstrating autophagy[21].

On the other hand, the possibility to perform research with the taiep rats (acronym for trembling, ataxia, immobility episodes, epilepsy, and paralysis) myelin mutant, allowed the proposal model of an early microtubular defect observed in oligodendrocytes with a permanent bound of microtubules to transitional elements that form the intermediate compartment between endoplasmic reticulum (ER) and cis Golgi apparatus. This microtubular-ER complex in taiep rats progress in a spatial and temporal relation with the gene expression, intracellular localization and synthesis of important proteins as proteolipid protein (PLP) and myelin basic protein (MBP), and constitutes an accumulative alteration with blockage in the normal intracellular transport of myelin triggering a

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dysmyelination followed by a demyelination observed in taiep rats[22–24]. This model also allowed to observe a slow and delayed maturational changes of its electrophysiological properties with a remarkable deterioration in the responses and excitability of central nervous system tracts[25].

Dental pulp Biology

The dentin-pulp interface works as a multicellular barrier to insure functionality, defense and longevity of human teeth. Several cell types are located at the dentin-pulp interface with sensory and repair functions as odontoblasts, nerve fibers, immunocompetent cells, schwann cells, blood vessels and stem cells. The understanding of the crosstalk between odontoblasts, nerve fibers and immune components throughout the life cycle of a tooth can provide important insights from a biological and clinical perspective.

As it was demonstrated in the previous section, microscopy is an important tool in biological sciences. In dental pulp biology, Professor Couve did an impressive advance in the understanding of odontoblasts biology, innervation, schwann cell biology and the interplay between the different elements within dental pulp (Fig. 1).

Odontoblasts are essentially dentin-secreting cells, and through the use of electron microscopy it has been possible to comprehend the temporal dynamic of the dentinogenesis process. In primary molar teeth it had been describe that the dentinogenesis process shows a sequential evolution in its globular mineralization pattern in relation with the morphology and the biosynthetic activity of odontoblasts[26].

In permanent teeth, developing premolars are a valuable model for the study of functional and morphological changes during dentinogenesis. It has been shown that the thickness of pre-dentin changes in relation to the dentinogenic state of human premolars[27]. During dentinogenic activity, the morphology of odontoblasts varies, and the analysis of different functional stages during the life cycle of human odontoblasts can provide a comparative morphology of cells that are differentiating or participating in dentinogenesis (secretory odontoblasts) with those related to the fully formed primary dentine (aged odontoblasts)[28]. It has been establish different phenotypes in the life cycle of human odontoblasts: pre-odontoblasts, short cylindrical cells which are developing the intracellular machinery needed for active synthesis and secretion; secretory odontoblasts, organized into a single layer of elongated columnar cells highly

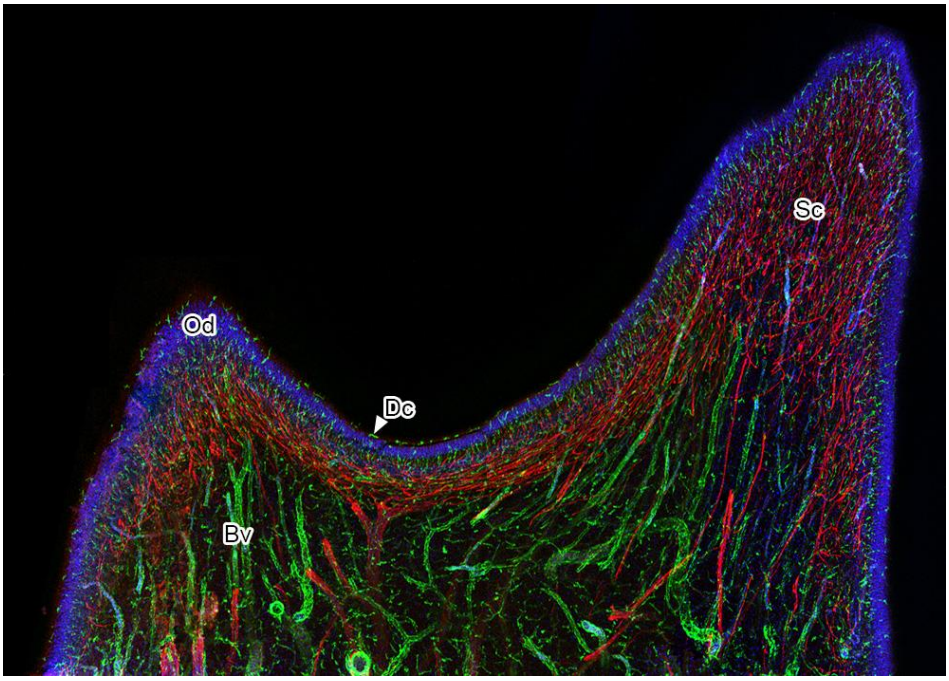

Figure 1: Immunofluorescence of Odontoblast, Schwann Cells, Dendritic cells, and Blood Vessels within Dental Pulp.

Od: Odontoblast layer; Bv: Blood Vessels; Dc: Dendritic cells; Sc: Schwann cells. Image of Professor Eduardo Couve in his Oral Presentation in Danish Endodontic Society, January 2018.

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polarized, these differentiated cells show an increased size and produce primary dentine; transitional odontoblasts, narrow cells with organelles reduced in number and less polarized, which mark the involution of secretory activity; and aged odontoblasts, shorter cells more crowded than secretory ones giving the odontoblastic layer a pseudostratified appearance with the presence of large vacuoles, these cells show a marked reduction and relocation of the secretory machinery[29,30].

Odontoblasts are long-lived postmitotic cells within dental pulp, for this reason the mechanisms that constitute their longevity are essential. Regarding this, the characterization of the autophagic-lysosomal system of human odontoblasts, which is a fundamental mechanism to ensure the turnover (with degradation of cellular components), cell viability and dentinogenic secretory activity allows to comprehend the autophagy as a strategy for normal organization and functionality of odontoblasts enable their survival for several decades[31]. It has been described, a specific autophagic pathway for the elimination of damaged mitochondria. This process is termed mitophagy and prepares the physiological clearance of mitochondrial components during cellular differentiation or stress. Changes in this autophagy activity and the progressive accumulation of lipofuscin granules determine an old odontoblast condition, reducing the capacity of response after injury, during aging. In this way mitochondrial autophagy is mandatory for survival and might explain the functional decay of odontoblasts with age[32].

Although odontoblasts are predominantly dentin-secreting cells, they are also critically involved in the transmission of sensory stimuli and in the cellular defense against pathogens, performing secretory, sensory and defensive functions[30]. They are connected by junctional complexes forming a densely packed palisade at the dentin-pulp interface, and together with an impressive network of trigeminal nerve fibers, form a complex sensory organ detecting and transmitting changes in temperature, mechanical stimuli and pain[30, 33]. This organized network can response after pathogen invasion in dental caries, where the relationship between reactionary dentinogenesis, the neurogenic changes of innervation and dendritic cell recruitment demonstrated a coordinated neuroimmune response required to contain caries pathogen invasion and to promote dentin-pulp healing[33]. However in some cases after important pulpal pathogenesis with chronic inflammatory response, the innate immune mechanism for containment and killing bacteria may contribute to cytotoxic and proinflammatory effects with the consequent progression of disease[34].

The relationship between remodeling of the odontoblast layer and neuroimmune changes has been described in different events during the life cycle of teeth. In caries, the process reactionary dentin formation is related to remodeling within the odontoblast layer with changes in the junctional complexes and a decline in the intercellular interconnectivity. These remodeling events are associated with an overexpression of growth-associated protein 43, which is a modulator of neural plasticity. The neuroplasticity during caries progression is evident through the observation of nerve fibers branching and sprouting, forming a complex terminal network at dentin-pulp interface, correlated with immune cell infiltrate into the reactionary collagen matrix, which act as sentinels against pathogen invasion[33].

During physiological events in the life cycle of teeth as physiological root resorption (PRR) in human primary tooth it has been also observed this interplay between odontoblast layer and neuroimmune responses. PRR is an odontoclastic resorption process which finally allows the replacement of primary teeth by permanent teeth[35]. In the early stages of PRR a well-developed peripheral nerve network related with an early segmental degradation of myelin can be observed, toward the middle stage the nerve fibers become slightly reduced with fragmentation of neurofilaments. Advanced stages show a large reduction of neurofilament, the fragmentation was the hallmark of axonal

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degeneration with a progressive demyelination during the PRR process. The role of schwann cells in the genesis of a microenvironment that supports the nerve repair and myelin removing is associated with a putative immunocompetent function of schwann cells and the recruitment of inflammatory cells observed during advanced PRR. This multicellular orchestrated response suggest that dental pulp in primary teeth maintains its capacity for defense and regeneration, being fundamental the appropriate pain management and the election of conservative procedures, which achieve the preservation of the primary tooth[36].

This crosstalk between the different multicellular components within dental pulp is important to consider for its regenerative potential. Currently, tissue engineering and regenerative medicine fields have been developed as a promising approach in response to the necessity to restore structural and functional properties of damaged tissues or whole organs. In regenerative dentistry is essential the determination of the histological gold standards for the definition of regenerate dental pulp. Concerning this, through the observation of the presence of blood vessels, innervation, lymphatic vessels, immune cells, and dentin formation it had been possible to establish the characteristics of a true regeneration of dental pulp[37].

The regenerative potential of dental pulp mainly relies on the adaptive capacity of injured peripheral nerves and the reprogramming of schwann cells (SCs). SCs display phenotypic plasticity with a large-scale change in gene expression during development, differentiation and regeneration[38]. As it was mentioned before, sensory nerves within dental pulp develop a dynamic response to dentin caries progression and after injury during physiological root resorption, these events support the crucial role of SCs during the life cycle of teeth and its preservation under pathologic conditions[33, 36].

Within the dental pulp of young teeth, SCs form a prominent network which is slightly disorganized in adult teeth. This network is constituted by the 2 mature SCs phenotypes: nonmyelinating SCs (nmSCs) and myelinating SCs (mSCs), providing trophic support, and participating in nerve regeneration to preserve sensory function[39]. Age-related changes of SCs have been related to a myelin decrease and diminished responses during regeneration of injured nerves[40].

Schwann cells secrete neurotrophic factors or express receptors for these factors in response to axonal damage. In this sense, the expression of nerve growth factor receptors (NGFR) such as p75NTR is upregulated in damaged nerves, having a correlation with the remyelination of the compromised axon[41]. In human dental pulp p75NTR is expressed in nerve fibers and SCs in response to injury during peripheral nerve sprouting and regeneration[42]. The significant reduction of p75NTR expression in old adult dental pulp suggests an attenuated plasticity and regenerative capacity of aging dental pulp[39].

Moreover, it has been observed a close spatial and functional relationship between nmSCs and dendritic cells, indicating a complementary role in surveillance and defense of dentin-pulp interface[39]. The neuroinflammatory activation of SCs had been reported during axonal degeneration of PRR in primary teeth[36].

Therefore the neuronal, glial and immune components orchestrate a complex scenario to sense and respond to external stimuli and changes at the dentin-pulp interface[43]. The comprehension of the dental pulp as a sensory organ with capacity to repair and regenerate, reveals from an evolutionary perspective, the increasingly complex multicellular network within dental pulp to ensure and protect the long lasting teeth and contribute to our understanding of the elaborate responses within dental pulp in different clinical scenarios.

CONCLUSION

This narrative review had the aim to describe and analyze the diverse papers of Professor Eduardo Couve in order to examine his scientific

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achievements and his legacy.

The extensive and rigorous study of cell biology as well as the collaboration and continuous interaction with colleagues from physiology and neuroscience fields, influenced -and he in them- in his deep vision and understanding of teeth. Considering this interrelation between different disciplines is currently important, when the entire ecosystem of health evidence points to a constant and expeditious flow from basic science and primary studies to evidence synthesis and clinical guidelines, which will allow better decisions in health, and where all fields are essential for the growing and evolution of science.

Moreover, the research of Professor Eduardo Couve shows a logical and consistent cycle of evidence production influenced by advances in microscopy and collaborations. After reviewing his publications it is evident that the conceptualization and demonstration of the pulp as a sensory organ and a multicellular barrier from an evolutionary perspective, is the result of a thorough analysis and reflective process of the available evidence and the influence of the different areas of knowledge for a better understanding of dental pulp and tooth.

Although the professor's research is complete and has provided fundamental concepts in pulp biology, there are still many key questions that were of his interest for example: what is the evolutionary advantage of having a dental pulp with more sensitive endings than any other tissue in the body? Is the complexity of pulp biology a requirement in relation to a limited replacement and an increase in the longevity of the dentition? Or how should the clinical perspective of treatments change, based on this new understanding of the pulp neuroimmune response? Among others.

The impact of his academic and research career can be observed through his many publications and also through the tributes realized after his passing, as the international association of dental research-Chile, which dedicated a special award with his name for the best oral biology presentation in its annual session; and the faculty of science of University of Valparaíso, where the microscopy laboratory was renamed in his honor. Certainly, the real impact of his influence on the countless generations he taught and on all the colleagues he worked with and enjoyed collaborations with, may never be measured. Surely his career and his vocation will be present for a long time in the development of dental research both in Chile and abroad.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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