



A TRIBUTE TO
Professor
Christian de Duve

on his 90th birthday

As its name implies, the ***Journal of Cellular and Molecular Medicine*** is an appropriate stage for a tribute to Professor C. de Duve on his 90th birthday. Indeed, the work of Christian de Duve led to an explosion in cell biology, with the discovery of lysosomes and peroxisomes and of their function. From the deciphering of the physiopathology of lysosomes followed the first molecular explanation of an intracellular genetic disorder, Pompe's glycogenosis, the prototype of lysosomal storage diseases. In turn, this basic knowledge paved the way to rational molecular medicine, with the first effective cure of another inborn lysosomal disorder, Gaucher's disease, by replacement therapy with recombinant glucocerebrosidase, now a current practice. How did this story develop and what does the example of de Duve tell us?

Christian de Duve was born in 1917 in the South of England, where his family had found refuge from the first invasion of Belgium by German troops in 1914. He grew up in the French-speaking upper-class atmosphere of Antwerp, an affluent city open to the world, while benefiting from a solid classical greco-latin education. No doubt this familial, cultural and educational background took a great part in fostering a rich blend of intellectual qualities: open-mindedness with unlimited curiosity, dedication to hard work yet leaving due place for culture (de Duve is a talented pianist and a music lover), thorough quantitative analysis with uncompromising intellectual rigor, enterprising spirit with social responsibility, not to mention a unique style! Fascinated by experimental medicine and the example of Claude

Bernard, Christian de Duve obtained his MD at the catholic University of Louvain in 1941 and immediately moved to research on insulin action in the laboratory of physiology, awarded with a Masters degree in chemical sciences (thus anticipating the future MD PhD programme). This integrated biomedical education was strengthened by two additional years of training abroad, first in biophysics at the Medical Nobel Institute in Stockholm with Prof. Hugo Theorell, then in biological chemistry at Washington University with Profs. Carl and Gerty Cori (and by the same token, enjoying mentorship by three Nobel Prize winners).

With this unusually broad expertise, Christian de Duve was ready to return to his alma mater and to create, in 1947, his own laboratory dedicated to physiological chemistry, primarily aimed at deciphering the mechanism of insulin action...yet led to the serendipitous discovery of lysosomes, then peroxisomes! The quality of this laboratory rapidly attracted a large team of brilliant young minds: to name a few, Jacques Berthet and Henri Beaufay, with whom the theory and practice of analytical sub-cellular fractionation was developed; Gery Hers, who mainly continued on the regulation of carbohydrate metabolism and identified the first lysosomal disease by elucidating a familial glycogen-storage disorder (Pompe's disease); Robert Wattiaux and Pierre Baudhuin, associated with the story of lysosomes and peroxisomes, and many others. Their lasting collaboration and the establishment of several new ones was a key to success.

Pasteur once wrote 'chance favours prepared minds'. Let us take the discovery of lysosomes as an example of how de Duve's mind helped him to be favoured by chance. It needed curiosity, freedom, consistency, integration and vision. Let also this example continue to inspire scientific committees and maintain the same freedom for truly original scientists, driven by curiosity and long-term challenges, despite inevitable fierce competition for limited resources (but also avoidable pollution by evaluation on short-term results and blind 'scientometry'). To address the mechanism of insulin action on the liver by a biochemical approach, de Duve and his team measured in liver extracts a series of phosphatase activities, such as glucose 6-phosphatase, and attempted to identify where these activities were localized based on sub-cellular fractionation, an

approach that had been recently developed by another Belgian scientist, Albert Claude. 'Tissue fractionation studies' was the beginning title of not less than 18 classical papers contributed by C. de Duve and his team, a story summarized in the Nobel lecture review 'Exploring cells with a centrifuge', still enjoyable to read [1]. In these investigations, acid phosphatase, whose function was unknown, served as a control. Quite unexpectedly, instead of vanishing with time due to proteolysis or denaturation, the activity of acid phosphatase paradoxically increased when sub-cellular fractions were ageing. Rather than discounting this incidental observation as a mere anecdote distracting from the main project, de Duve and his colleagues went on to show that the effect of ageing was mimicked by mechanical disruption, freezing-thawing and detergents, indicating that enzymatic latency was due to sequestration by a membrane impermeable to the substrate. Moreover, this property was shared by other hydrolases, all with an optimal activity at acidic pH. Combined with the integrated and rigorous analysis of the differential sedimentation profiles of more than 40 enzymes in rodent liver contributed by several laboratories worldwide, these three lines of evidence led to a new concept of cytoplasmic compartmentation, that is gathering of all acid hydrolases in acidified vesicles, accessible to substrates only by membrane fusion and serving as the cell's stomach [2].

To prove the existence of the putative lytic body, named 'lysosome', required its isolation in pure fractions. This was first a puzzle, as 'lysosomal' enzymes co-sedimented with mitochondria. However, naked-eye inspection of the conventional rat liver 'mitochondrial' fraction revealed a stratification, with a yellow (lipofuchsin-rich) layer over the red (cytochrome-rich) mitochondrial pellet. The separate collection of the two populations was sufficient to resolve lysosomes from mitochondria [1]. Further purification by density centrifugation after loading with an undigestible low-density compound allowed large-scale isolation for functional studies. Nevertheless, for many scientists, 'seeing is believing'. Although a biochemist, de Duve managed to acquire the first electron microscope for the Belgian scientific community and, in collaboration with Alex Novikoff, formally established lysosomes as the well known, yet so far obscure pericanalicular bodies [3]. Final evidence was provided with the cytochemical demonstration of acid phosphatase by

electron microscopy, in collaboration with Marilyn Farquhar [4].

The significance of lysosomes was systematically explored in other tissues and contexts. A comprehensive review [5] paved the way to the integration of lysosomes with (i) pinocytosis, that blossomed with the discovery of receptor-mediated endocytosis and the elucidation of low-density lipoprotein processing and cholesterol homeostasis by Goldstein and Brown [6]; (ii) phagocytosis, anticipated a century ago by Metchnikoff; (iii) autophagy, a still elusive process; (iv) genetic lysosomal diseases, with the elucidation by Gery Hers of the origin of Pompe's glycogenosis [7]; (v) acquired lysosomal diseases, such as foam cells in atherosclerosis [6] and (vi) pharmacology, illustrated by the anti-malaria agent, chloroquine [8].

A similar approach, based on the identification of another group of enzymes catalyzing oxidation reactions and sharing a distinct distribution, unravelled the existence of peroxisomes and ignited active research with Paul Lazarow and others on their still intriguing biogenesis. Thus, the development and application of the same rigorous methodology led to the unexpected discovery (almost a pleonasm) of two major, totally unrelated sub-cellular compartments.

International recognition was soon to come, with joint tenure at the catholic University of Louvain and the Rockefeller Institute in New York since 1962, and culminating with the Nobel Prize of Medicine in 1974, shared by Christian de Duve, Albert Claude and George Palade for their discoveries on the structural and functional organization of the cell (see [9]). In response to this highest of scientific honours (and the challenge it conveys), de Duve took on a second direction in his professional life. He harnessed his fame to create the International Research Institute of Cellular and Molecular Pathology in Brussels, originally called the ICP (and renamed this year 'de Duve Institute'). From its origin, the ambitious goal set to the Institute was to exploit multidisciplinary approaches in order to better understand diseases and to derive rational therapies, with a motto «Mieux comprendre pour mieux guérir», and a logo intertwining the DNA double helix with the staff of Aesculapius (Fig. 2). Under de Duve's strong vision and leadership, a core Institute was generated by merging the four leading laboratories (Biochemistry, Experimental medicine, Endocrinology and Micro-

biology) from the Faculty of Medicine at the University of Louvain, which provided strong support ever since while allowing independent direction. The Institute was reinforced by autonomous fund raising, the creation of new laboratories (such as a Tropical diseases unit) and a special training program for foreign post-docs (long before the Curie fellowships). The Institute further attracted Thierry Boon and his team to create the Brussels branch of the Ludwig Institute for Cancer Research, an association of tremendous mutual benefit. In this branch, the first human tumoural antigen was cloned and several important discoveries on tumour immunity continue to be made.

Having completed these two outstanding success stories, de Duve did not limit his ambitions to a well-deserved retirement. Instead, he enjoys writing textbooks of remarkable clarity on cell biology, both on structures [10] and biochemical machineries [11], and took on his extraordinary abilities as an indefatigable speaker of infectious enthusiasm, to spread scientific knowledge and combat the 'intelligent design' theory. Indeed, his favourite activity has focused on the origin of life, pursuing on scientific grounds his previous debate challenging the view of the late Jacques Monod, that life is too complex ever to occur elsewhere in the universe [12]. Over the last decade, de Duve has been extensively assembling and integrating lessons from pre-biotic chemistry, evidence on early forms of life on earth and astronomical data on the conditions compatible with the emergence of life in the cosmos. He convincingly argues that life is far from a most improbable, single chance event. To the contrary, because it obeys the laws of chemistry, life should by necessity emerge whenever adequate conditions are provided, which are inevitably to be repeated given the immense time duration and multiplicity of galaxies of our universe: 'life is a cosmic imperative' [13, 14].

Whatever aspect one may speculate on in an exceptional destiny, it is clear to those who have had the privilege of closely interacting with Professor Christian de Duve, that an admirable blend of intellectual freedom, self-confidence, leadership and immense scientific culture likely explains how he could encompass in one professional career three distinct, yet equally successful scientific lives: first, as primary investigator and head of one, then two laboratories at the forefront of biochemistry and cell

biology on both sides of the Atlantic ocean; second, as founder and first director of a multidisciplinary international research institute in Brussels; and third, as a free-thinking mind actively pursuing bold studies on the origin of life and committed to fight dogmatic theories, dangerous for the choices of mankind.

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