In memoriam:

André Goffeau: from proteins to genes to genomes: the Goffeaumic approach to life sciences

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André Goffeau, professor emeritus at the Université catholique de Louvain (UCLouvain), passed away at his home in Overijse, April 2, 2018, at the age of 83.

His training[1]

Agronomist in tropical sciences (1957) and graduate in botanical sciences (1958) from UCLouvain, André Goffeau took his first steps in research at the Plant Physiology Station of Yangambi in the Belgian Congo. He was accompanied by his wife Jacqueline Depraet. His first publication was a review article (in French) on the effect of gibberellins and other growth regulators on tropical plants[2]. When Congo became independent (1960), the Goffeau family returned to Europe, to Versailles (France) where, at the Plant Physiology Laboratory (INRA), he developed a research project on chloroplasts isolated from algae. More particularly, he studied the effect of γ–ray irradiation on chloroplast photophosphorylation[3]. His supervisor was Josy Bové, not to be confused with the environmental activist José Bové, actually the son of Josy. This period ended with a PhD thesis in botanical sciences, presented at UCLouvain in 1964.

His postdoctoral experience

André then moved to the Free University of Brussels in the laboratory of Professor Jean Brachet, a prominent researcher in molecular embryology. There, he demonstrated that the chloroplasts isolated from the unicellular algae, *Acetabularia mediterranea*, have an endogenous protein synthesis machinery, independent of the known cytosolic machinery[4].

In 1965, André crossed the Atlantic Ocean to join Albert Lehninger's laboratory in Baltimore, in the Department of Physiological Chemistry, at the Johns Hopkins School of Medicine. This name must be familiar to many “old” students since Lehninger was the author of the popular book "Biochemistry" which, for nearly 20 years, fed the dreams, or maybe the nightmares, of biology students. It was undoubtedly a hard experience for André who was entrusted with the

[1] Foreword : This short biography does not claim to be exhaustive. Reference to publications will only be made for Goffeau’s early work not covered by companion papers. For a more detailed analysis of Goffeau’s scientific input, see companion papers as well as Goffeau’s autobiography: Goffeau A (2004) Yeast transport-ATPases and the genome-sequencing project. Comprehensive Biochemistry 43:493-536.

[2] Goffeau A (1961) Action des régulateurs de croissance chez quelques espèces cultivées au Congo. Agricultura 9 : 215-237

[3] Goffeau A and Bové JM (1965) Action of γ-ray irradiation on photophosphorylation reactions. Biochim Biophys Acta 102: 103-115

[4] Goffeau A and Brachet J (1965) Deoxyribonucleic acid-dependent incorporation of amino acids into the proteins of chloroplasts isolated from anucleate *Acetabularia* fragments. Biochim Biophys Acta 95 : 302-313

task of looking for a rat mitochondrial protein which, much later, proved not to exist. Nevertheless, this research led him to purify and characterize a new mitochondrial enzyme, nucleoside diphosphokinase, of the bovine liver[5]. The year 1966 saw the return of André to Europe, to the Institut National Agronomique in Paris, in the laboratory of Genetics of Professor Heslot. After plants, algae and rat liver, he shifted to the fission yeast *Schizosaccharomyces pombe* as a model for the genetic and biochemical approaches he was developing.

In 1968, a student revolution spread in the streets of Paris. Another one, albeit quiet, emerged in André's laboratory. Indeed, studying the activity of mitochondrial ATP synthase as a function of pH, André noticed the unusual shape of the curve, which in addition to the peak expected at pH 9, presented a shoulder at pH 6. Experimental abnormalities as such are commonly found by researchers. A vast majority of them result from manipulation errors, a laps in concentration, of whatever else might be the cause of the considered artifact. However, in very rare cases, these abnormalities could be signs of an unknown phenomenon. The talent and luck of a researcher are to detect these rare cases that can lead to a discovery. Unfortunately in this case, the discovery was not exploited on the spot because after ten years abroad, the now five members of the Goffeau family (Philippe, Thierry and Catherine were welcomed as siblings) returned back home to Belgium in 1969. André was appointed Professor at the Faculty of Agronomical Sciences of UCLouvain.

The teacher

André was endowed with the task of teaching biochemistry to future bioengineers in chemistry. With his unmissed lab coat even during his classes, he considerably impressed his students. Goffeau was very critical of himself and was dissatisfied with his teaching, despite the time and effort he devoted to it (he used to get up at 4 AM to prepare for his lecture of the day). Thus he chose to pass on his teachings to one of his colleagues. André's talent was rather revealed in teaching young fellows how to do research. He trained PhD students and postdoc fellows from all continents, coming from countries such as France, Italy, Czech Republic, Slovakia, Poland, China, Brazil and more. After their stay at UCLouvain, many of them kept contact with André and his ultimate satisfaction was to periodically meet them and help them make progress in their scientific life.

The plasma membrane H^+-ATPase

André's first project of this new era focused on the genetics and bioenergetics of yeast mitochondria. Noticeably, and with the help of collaborators and a couple of PhD students, he managed to obtain nuclear mutants of the yeast *S. pombe*, which were altered in mitochondrial functions. The major interest of these mutants was that, unlike the budding yeast *Saccharomyces cerevisiae*, *S. pombe* mutants affected in mitochondrial functions are stable and do not give rise to secondary pleiotropic mutants also known as "petites" and characterized by large deletions within their mitochondrial genome.

[5] Goffeau A, Pedersen PL and Lehninger AL (1967) The kinetics and inhibition of the adenosine diphosphate-adenosine triphosphate exchange catalyzed by a purified mitochondrial nucleoside diphosphokinase. J Biol Chem 242: 1845-1853

However, the primary interest of ATPase activity versus pH was still in André's mind, and in 1971 he revived this topic with the help of some of his students. It took a few years from the initially intriguing observation of a shoulder of ATPase activity at pH 6 to demonstrate unambiguously that this was due to a plasma membrane ATPase that was contaminating the mitochondria preparation. Several more years were needed still to isolate and characterize this enzyme from *S. pombe,* then elucidate its physiological role in membrane transport activation. Indeed, thanks to the energy released by the hydrolysis of ATP into ADP, this H^+-ATPase enzyme generates a proton flow from the inside to the outside of the cell and thus, creates a difference of proton concentration and electrical charge which activates secondary transporters that move nutrients and other molecules across the plasma membrane. The same enzyme was concomitantly found in other fungi by other labs.

There were, of course, as for any scientist, difficult periods. Many collaborators at André's laboratory remember February 20, 1986, the "black day", when a competing team published, with a few months in advance, the nucleotide sequence of the gene encoding the yeast proton ATPase. Although this particular scientific battle was not won, many others were, luckily nourished by perseverance and talent. In particular, biochemical approaches led to several seminal results such as the *in vivo* and *in vitro* demonstration of a H^+ electrochemical gradient; the identification of an aspartyl phosphate as a catalytic intermediate; the isolation of mutations that confer resistance to vanadate (a common inhibitor of P-type ATPases); the identification of several residues critical for proton translocation; the characterization of a second proton pump; the identification of proteolipids within the plasma membrane. André also extended this project to other pumps such as Ca^{2+}-ATPase from yeast or from *Schistosoma mansoni,* as well as to proton ATPases from Archae.

The pleiotropic drug resistance chapter

While working on H^+-ATPases, André had its attention brought to a gene, *PDR1*, on *S. cerevisiae* chromosome VII. Several *PDR1* mutants resulted in increased yeast resistance to various drugs with unrelated structures. It turned out that *PDR1* was a regulatory gene and the mutations resulted in increased expression of several target genes. One of them, *PDR5*, encodes an ATP-binding cassette (ABC) transporter and has been the main target of André's research in the nineties. Its sequence indicated homology with the human enzyme involved in cystic fibrosis (CFTR) or the enzyme that is responsible for the resistance of certain cancer cells to chemotherapy (P-glycoprotein). PDR5 was the first yeast ABC transporter to be purified and was thus used as a paradigm. Overexpression of PDR5 in yeast led to several advances: the identification of more than 300 amphiphilic compounds of different structures that are transported by PDR5, the purification and enzymatic characterization of PDR5. This project was later expanded to other members of the ABC transporter family.

During his last years in the lab, André became interested in the phylogenetic classification of transporters from Hemiascomycete yeast species. His last project concerned the anti-cancer agent, 3-bromopyruvate. With colleagues from abroad, he used yeast as a model to understand how this compound is transported and interferes with metabolism.

Sequencing the *Saccharomyces cerevisiae* genome: a dream come true

We cannot hide the double life of André. Indeed, he maintained an affair, somehow unfaithful, with the Commission of the European Union. Actually, he had been hired back in the sixties, at a time when EURATOM, an early version of the EU Commission, used to hire researchers to develop European research. Fortunately for André, then the Commission wanted his officers to continue being active in research and host a lab, therefore maintaining contact with practical science. In the Research Division, André became responsible for developing research programs. For instance, with other pioneers like Dreux de Nettencourt and Fernand Van Hoeck, he launched the first programs in Biotechnology. With Ati Vassarotti, he expanded the exchanges of young researchers within Europe, a programme currently known as the Marie Skłodowska-Curie Actions.

André's latest initiative at the EU Commission is worth telling. The dream of biologists is to explain life in all its facets. The advent of molecular biology has made access to DNA, the repository of the genetic inheritance that directs the development of every living being. In the eighties, sequencing techniques were still laborious and usually confined to short sequences, typically in the range of a gene. There were dreams to go for more complex projects, such as sequencing a whole genome, ultimately the human one. However, with the technical means of the time, it required hundreds of researchers and several decades of work. Hence, André developed the idea of characterizing an organism whose genetic message is shorter: the yeast *S. cerevisiae* with a genome of fifteen million characters, two hundred times less than the human genome. The choice of this organism made sense. Because it lends itself well to biochemical and genetic studies, *S. cerevisiae* has become a model species for eukaryotes, including plants and animals. André had to convince many skeptical researchers and science officers, not so much about the interest of obtaining the sequence of this particular genome, but about whether the task was achievable. Indeed, it required coordinating tens of labs, each one sequencing a fraction of the genome. This European Commission funded project started in January 1989 and brought together not fewer than 30 European laboratories that shared the work. The chromosome III sequence was published in 1992. The most unexpected discovery was that, although *S. cerevisae* had been used for decades as a simple and convenient model for eukaryotes, more than half of the genes were still unknown. The European consortium then tackled other chromosomes and this initiative was joined by Japanese, Canadian, and US teams, which sequenced some of the chromosomes. The whole genome was deciphered in 1996. A special issue of Nature was published putting together all the data of this unprecedented enterprise.

Epilog

André was a great advocate of basic research. He had posted on the wall of his lab this quotation delivered in 1927 by Albert I, King of the Belgians, who had been a strong advocate of scientific research: "The public does not sufficiently understand that pure science is the indispensable condition of applied science and that the fate of nations which neglect science and scientists is marked for decadence".

In his acceptance speech for the quinquennial prize of the Belgian National Fund for Scientific Research, awarded in 1986, he had these words: "Thus, a fundamental research can be lead by unpredictable sequence of events, from a curiosity to another to results of medical interest that no interventionist program of applied research could have brought."

With the yeast genome project, André was also a great visionary. However, without his strong determination and great input, this project would never have been launched and completed. Indeed, before launching the *S. cerevisiae* genome sequencing program, André had written to scientific celebrities to ask for advice concerning this project. Many answers were highly skeptical, doubting about the feasibility and the interest of sequencing a genome. These negative opinions did not affect Goffeau's determination. His considerable contribution earned him to be named Doctor Honoris Causa of four universities: University Louis Pasteur in Strasbourg, University of Wroclaw, University Pierre et Marie Curie in Paris, and Comenius University in Bratislava. He had also been elected member of the Academy of Sciences in Belgium and in France. However, André was not so much interested in honors. His strongest motivation was that of a researcher whose dream was to discover and share with the scientific community. To some friends who asked him to coordinate a new EU project, he wrote: "*Money, power and fame …vanish quickly. The only reward is finally the joy to interact with people you trust, to learn from them and eventually to stimulate your own research"*

André is survived by his wife Jacqueline, and their three children Philippe, Thierry and Catherine.