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Big Science Is Rescuing Us

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Natale G. De Santo

During the endless days of the pandemic we have learned that the medical dimension of Covid-19 is neither unique nor the best focal point to look into what, how and why it happened. What happened was the result of the interactions of virus and health systems, between testing and treatment strategies, between people's behaviour and political

decisions. This is something very complex that requires more complex methods of analysis and more complex strategies of intervention.

When historians of medicine of future generations analyse the data of the Covid-19 pandemic they will certainly focus on the huge number of clinical works related to the effects of the virus - so many that no single scientist could attempt to analyse them all, to find a rationale in a suitable time without the assistance of algorithms and artificial intelligence. However the huge number underscores the needs and the importance of clinical scientists, the need to support clinical science and to finance bedcare studies that are very pivotal in discovering the drugs the patient needs and the findings of fundamental science confined to the bookcases of libraries. Basic science data, collecting dust in those libraries, represent the undiscovered treasure that has been already financed by our communities, and is waiting for translation into cures. Clinical science has been, for a long time, a kind of "Cinderella" in the hands of badly financed scientists who have entered into unappealing and less remunerative careers (1).

Modern vaccines have shown that, without fundamental research, there is no research for humans. However it can't be separated from applied research. The former generates the application where the latter, in association with technology, fertilises fundamental research (2).

Vaccines have demonstrated the value of interdisciplinarity and exchanges that go beyond national borders (as demonstrated by Patrick Berche in this issue).

Vaccines are a testimony that a bench-bedside balance (3) has been achieved by translational medicine and this will be an incentive for careers in clinical medicine. With production of vaccines 'Big Pharma' has shown that probably the two cultures of Snow were - as says Rita Levi - Montalcini - a wrong approach (4), and has given strength to Dietrich von Engelhardt's vision of «Culture as a Therapy - Therapy as Culture» (5).

The historians of the forthcoming centuries will also discover that 'Big Science' came to the rescue of humankind. It did so with the velocity that characterises every aspect of life in our days. Big Pharma made available new vaccines by making full use of fundamental discoveries already available from various disciplines.

On December 31 2020 the *New England Journal of Medicine* published a report on safety-efficacy of the Pfizer-BIONTech Vaccine that 4 days before had been injected into humans (6). Wounded humankind saw light at the end of the tunnel of the Covid-19 pandemic. Probably the hope generated has been not less fulfilling from that nurtured in the hearts of the internees in the concentration camp of Görlitz by the notes of the *Quartet for the End of the Time* of Oliver Messiaen coming out from Barack 27b in the night of January 15, 1941. Messiaen left us a message: "I am convinced that joy exists, convinced that the invisible exists more than the visible, joy is beyond sorrow, beauty is beyond horror".



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4. Levi-Montalcini R. L'asso nella manica a brandelli. Milano, Bandini & Castoldi, 1998.

5. von Engelhardt D. Culture as Therapy - Therapy as culture. In. Human Clinical research, op. cit pp.19-34.

6. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020; 383(27):2603-2615.

Raymond Ardaillou: A Doctor's Story

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Nicole Lelièvre-Ardaillou

Nicole Ardaillou is a medical doctor. She worked in biological research as a research director at the National Institute of Health and Medical Research initially in haematology and blood thrombosis and then in nephrology with her husband. Since her retirement she has been working at "La Chaîne de l'Espoir" (Chain of hope)

a non-governmental organisation whose aim is to treat, in developing countries, children whose state of health requires surgery. She has carried out missions in Cambodia and Burkina-Fasso (see photo below)



Nicole Ardaillou in Burkina-Fasso (2010), squatting first on the right

His life before his schooling in medicine

Raymond Ardaillou (RA) was born in 1930 in Villeneuve sur Lot, a small town of 11,000 inhabitants at that time, situated on both banks of the Lot, a tributary of the Garonne, halfway between Bordeaux and Toulouse. His father ran a wholesale grocery shop and his mother stayed at home. He was an only child. His childhood was marked by the war from the age of 9. When the French army was defeated by the Germans, his family took in many refugees in the summer of 1940. They were still upset when they remembered the Luftwaffe bombings that had targeted them.

One of his memories is the presence of American ambulances with volunteer doctors, often from Louisiana, who accompanied the Allied armies and stayed in the courtyard of the shop of his father before going back to USA which, at that time, was not yet at war. They told him how they had treated the wounded soldiers and this gave him his first inclination to become a doctor. An armistice was signed; Villeneuve was in the free zone, which led Jewish refugees to stay there.

In October 1940, Raymond began his schooling at the High School which was filled with local and refugee children. The conversation at home was mainly about the war. His parents listened to the news on the French-speaking Swiss radio, and the BBC, which had a programme produced by the French government-in-exile that De Gaulle had set up. The Germans invaded the free zone in November 1942. They were the object of numerous attacks leading to reprisals on the population with the burning of houses and churches, hangings and shootings. Raymond lived in a milieu of opponents of the Vichy collaborationist regime.

He was deeply influenced by an Alsatian priest and the headmaster of his college who organised, with the help of nuns from a convent, the protection of Jewish children and was awarded the title of "Righteous among the nations" by the Israel government. The Jewish families, if they had not fled to Switzerland or Portugal, hid in farms in the countryside. During this period Raymond worked at school. He was good in all subjects and first in his class. Finally, Allied troops landed, first in Normandy, then in Provence, and France was again governed by French people concerned about the interests of the country.

This period was difficult because a hunt for real, or supposed, collaborators was organised. His father, as a member of the Resistance, was appointed as a juror in the courts before which these collaborators appeared. He clashed with the communists who demanded the death penalty for all the accused. In fact, those who were judged were subordinates and remained in France, while the leaders fled abroad. He managed to save several of the detainees. But the war was not over. The French army was reconstituted and charged with driving the Germans out of their pockets of resistance at several points along the Atlantic coast. The army also participated in the liberation of Alsace.

Raymond had a death in the family, one of his uncle's brothers. Peace came at last. Raymond was sent to England in the summer of 1946 to improve his English and then received his English correspondent at home. He finally had to decide what career he was going to pursue. His father discouraged him from working with him because he foresaw the end of wholesale grocers who were being replaced by supermarkets. He decided to go into medicine and his parents sent him to Paris in September 1947, where he stayed with a friendly family.

Learning medicine in Paris

It was a new life in post-war Paris where ration tickets were still being used. The first year was preparatory with courses in physics, chemistry, animal and plant biology. No more classroom lessons, but in amphitheatres, and practical work (chemical reactions and animal dissections). Raymond passed the final exam without difficulty and actually began studying medicine in 1948. At that time, medical education was double, one compulsory at the Faculty, one optional, inherited from Napoleonic days, purely in hospitals with two successive competitions: "externat" and "internat", the last corresponding to getting a resident position. He was admitted to "externat" at his first exam and did his first training course in a surgery department where he learned how to assist the resident and how to learn some basic procedures required by a doctor, including putting on casts. He was admitted to "internat" two years later and left Paris in July 1953 to do his military service as a doctor at an Algiers military hospital.

Military doctor in Algiers, resident in Paris and getting married

In Algiers, he was given the responsibility of caring for sick soldiers of the French expeditionary force returning from Indochina where they had fought the Viet Minh. The soldiers were affected by various parasitoses. Some of them were from French West Africa and Raymond accompanied them by train to Casablanca where they embarked to Dakar or Conakry. He returned to Paris in October 1954, just before the outbreak of the Algerian war, and began his work as a resident in successive Parisian hospitals. In May 1956, he was again called up for service in Algeria, as the army needed more doctors and he ended up once more in the military hospital in Algiers. The atmosphere was different compared with two years earlier and, although the French did not have to fight a real war, they had to face ambushes

and attacks. He returned to Paris six months later and found himself in Jean Hamburger's nephrology department at Necker hospital, where Gabriel Richet was assistant.

He was immediately enthusiastic about an innovative service with the first artificial kidneys, the treatment of fluid and electrolyte imbalances, the first kidney biopsies, and the first renal transplant, which was only half successful as the transplanted patient survived only for 3 weeks. This hospital service had a worldwide reputation and he remembers being called in the middle of the night by the Soviet embassy to arrange for the emergency hospitalisation of a member of the Politburo. He woke up his boss who stood by to receive the Russian personality. He worked mainly with Richet who proposed a thesis subject for him and who, at the end of his time as a resident (1959), offered him the opportunity to be his assistant in a medical department at Tenon Hospital, of which Richet became the boss and which he wanted to turn into the second nephrology department in Paris. Two years earlier, he had met me at Necker Hospital where I was a medical trainee and we decided to get married.



Raymond Ardaillou, 1995

Assistant in Tenon and becoming Professor of Physiology

Gabriel Richet had several ambitions: to develop research programs based on clinical investigation, to have a modern nephrology department built with a dialysis unit, intensive care beds, a laboratory for biological examinations specific to renal diseases and a research laboratory. As soon as the building of the new nephrology department was finished, Richet immediately wanted to extend this building by persuading Inserm (National Institute of Health and Medical Research) to create a research unit close to the clinical unit. With the help of Raymond and, then, of Claude Amiel, who died prematurely, he succeeded in his entire project.

The first research programs were to demonstrate the role of hypercalcemia in metabolic alkalosis and to study the functioning of the acid-base equilibrium by measuring the H⁺ ions coming from food (metabolism of aminoacids containing sulfur and of phospholipids, dissociation of aminoacids in plasma) and those excreted in urine (ammonium and titratable acidity). In 1966, Raymond became Professor of Physiology. He would have preferred to have been Professor of Nephrology, but this was not possible for lack of a vacancy. He had at this time a triple function: teacher, head of a functional investigation department, and deputy director of the research unit

headed by Richet. This period was very rich in research studies of which I enumerate the main ones: the effects of calcitonin on renal function and its role as a marker of severe infectious diseases, the tubular reabsorption of bicarbonates in subjects with renal insufficiency, the role of the kidneys in the catabolism of polypeptide hormones and the first work on glomerular physiology; these studies continued for several years.

Raymond and his team demonstrated that the glomerulus was not a simple filter, but a complex organ carrying hormone receptors, essentially angiotensin II, and synthesizing chemical mediators. He used two innovative techniques, the isolation of glomeruli and the in vitro culture of fresh or immortalised mesangial and epithelial glomerular cells, both murine and human. He showed that angiotensin II acts on mesangial cells to induce a vasoconstriction of the glomerular capillaries and that the glomerular synthesis of prostaglandin E2 and leukotrienes increases in different models of glomerulonephritis. I joined him in the early 1980s to work with him and carry out my own research using the new techniques of molecular biology. I had worked previously in a laboratory of haematology and blood coagulation.

Head of the research unit

In 1985, Gabriel Richet retired and Raymond succeeded him as head of the research unit for the next 13 years, where 3 teams, one of which he headed, continued their own work. This period was rich in discoveries in animal models and humans. He was one of the first to use transgenic mice in the study of experimental renal fibrosis and demonstrated the major role of angiotensin II receptor antagonists in the prevention and treatment of fibrosis. He also studied natriuretic peptides and demonstrated their role in maintaining sodium balance in renal failure, the effect of nitric oxide on renin secretion, the role of active forms of oxygen and that of several cytokines including TNF. In addition to these in vitro and animal studies, he carried out numerous studies in humans concerning natriuretic peptides, the renin-angiotensin-aldosterone system including the genetic variants of its components.

Several American textbook publishers asked him to write the chapters devoted to his favorite fields. In France, he assumed many responsibilities in the administration of research and education. He succeeded before his retirement to have a new modern building for research constructed at

Tenon hospital with an aseptic animal ward. He received an award from the Academy of Sciences for his discoveries in the physiology of the glomerulus. Abroad, he was awarded numerous distinctions. He was elected member of the Royal Academy of Medicine of Belgium, of the Medical Academies of Serbia and Romania, of the Academia Europaea in the medical section. He was appointed Professor Honoris Causa of the Polish University of Pomerania, and honorary member of the Medical Association of Santiago of Chile.



Raymond Ardaillou, Athens

His retirement and the French Academy of Medicine

Raymond was elected to the Academy of Medicine in 1996, the year in which he gave up his duties as head of department at the hospital. For three more years he retained his functions of responsibility of the Physiology Department at the Faculty and of head of the research unit. In fact, he continued to go to Tenon hospital regularly where he kept an office and participated in teaching and research projects. His last scientific publication was in 2008. In parallel, he worked at the Academy, where successive responsibilities were

entrusted to him: deputy secretary from 2003 to 2010, then "perpetual" secretary from 2011 to 2015. He participated in the writing of many reports and in the reorganisation of the Academy whose statutes had not changed since 1820 (A new article of law voted by the National Assembly and decrees of application by the Council of State detailing the status). Finally, as you know he became a member of the European Association of Professors Emeriti.

I have tried to summarise the life of my husband. I hope he will be able to continue to work. This is always the case since he is regularly solicited by the Academy authorities to write or for proofreading, which he does with great pleasure.

Main Scientific publications

Selection of 16 publications among about 300

Ardaillou R, Sizonenko P, Meyrier A, Vallee G, Beaugas C. Metabolic clearance rate of radio-iodinated human calcitonin in man. *J Clin Invest* 49 : 2345-52, 1974.

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Chansel D, Pham P, Nivez MP, Ardailou R. Characterization of atrial natriuretic factor receptors in human glomerular epithelial and mesangial cells. *Am J Physiol (Renal Fluid Electrolyte Physiology)* 259: F619-27, 1990.

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Chatziantoniou C, Pauti MD, Pinet F, Promeneur D, Dussaule JC, Ardailou R. Regulation of renin release is impaired after nitric oxide inhibition. *Kidney International* 49: 626-33, 1996.

Chatziantoniou C, Boffa JJ, Ardailou R, Dussaule JC. Nitric oxide inhibition induces early activation of type I collagen gene in renal resistance vessels and glomeruli in transgenic mice: role of endothelin. *J Clin Invest* 101: 2780-9, 1998.

Boffa JJ, Tharaux PL, Placier S, Ardailou R, Dussaule JC, Chatziantoniou C. Angiotensin II activates collagen type I Gene in the renal vasculature of transgenic mice during inhibition of nitric oxide synthesis: Evidence for an endothelin-mediated mechanism. *Circulation* 100: 1901-8, 1999.

Tharaux PL, Chatziantoniou C, Casellas D, Fouassier L, Ardailou R, Dussaule JC. Vascular endothelin-1 gene expression, synthesis and effect

on renal type I collagen synthesis and nephroangiosclerosis during nitric oxide synthase inhibition in rats. *Circulation* 16: 2185-91, 1999.

Paillard F, Chansel D, Brand E, Benetos A, Thomas F, Czekalski S, Ardailou R, Soubrier F. Genotype-phenotype relationships for the renin-angiotensin-aldosterone system in a normal population. *Hypertension* 1999, 34 : 423-9.

Participation in textbooks of nephrology

Sraer JD, Sraer J, Ardailou R, Richet G. Le glomérule : organe cible et lieu de synthèse d'hormones et de médiateurs chimiques. In *Actualités néphrologiques de l'Hôpital Necker* 1980, Grünfeld JP, ed. Flammarion, Paris, 1980, p 277-96.

Ardailou R, Paillard F. Metabolism of polypeptide hormones by the kidney. In *Advances in Nephrology*, vol. 9, Maxwell MH, ed. Year Book Medical Publishers, 1980, p 247-69.

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The Race to Vaccines Against Covid-19

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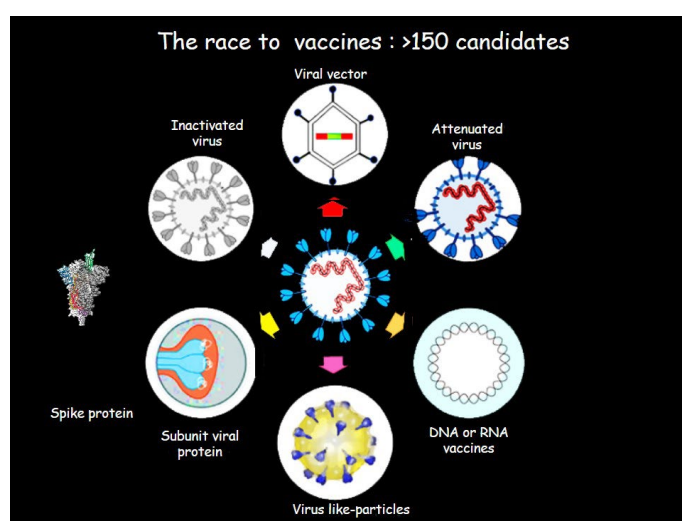


Dr. Patrick Berche

A deadly pandemic spread rapidly around the world within a few months, resulting in 1.7 million deaths by December 2020. This health crisis has induced an economic collapse, putting down the world economy. Covid-19 convalescents develop a good protection against reinfection, which remain exceptional. Patients develop T-cell and humoral

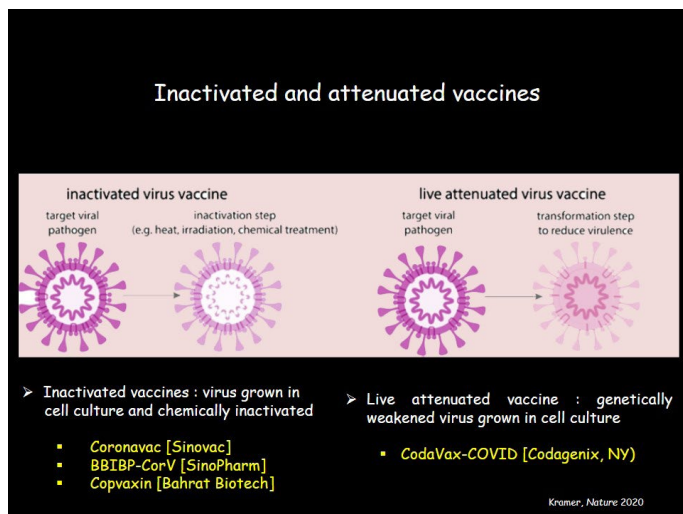
protective immunity with production of neutralizing antibodies blocking viral infection (1).

1. Grifoni A, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals *Cell*, 2020;181: 1489-1501.

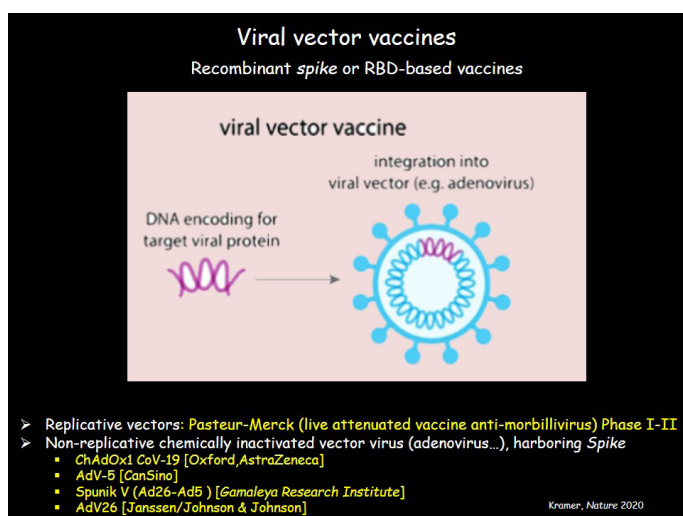


How can we get out of this health crisis, unprecedented since the Spanish flu? In the absence of effective antiviral drugs, the only effective ways against SARS-CoV-2 remain

barrier measures and lockdown of the population. The only way to stop the circulation of virus is to reach what is known as *herd immunity*, that is, protection against contagion of about 60-70% of the population (2). This can take years, with a very significant human cost.



The purpose of vaccination is to accelerate this process and to protect vulnerable people against severe infections. Consequently, the stakes for the development of vaccines appear to be an emergency. This is the reason why many pharmaceutical companies have entered the race to produce vaccines using various, and sometimes revolutionary, technologies, with the hope of ending the pandemic. Researchers all over the world started working on anti-Covid-19 vaccines. More than 150 vaccine candidates are currently in preparation. Vaccination strategies have followed conventional methodologies using either inactivated (as for the flu vaccine), live attenuated viruses, or purified proteins administered with adjuvants. Most vaccines use the Spike protein as a target, which allows the virus to attach to its specific receptor to enter the cytoplasm of cells. Innovative methodologies, such as



heterologous viral vectors carrying the gene encoding the Spike protein, the major viral virulence factor, have been or are being tested. Other trials have used vaccines carrying nucleotide sequences of the virus spike gene, DNA or RNA, a methodology never before used in humans on a large scale. To-day, there are nine vaccines in phase III of the process for being licensed for widespread use (Table 1): (i) three are inactivated whole vaccine, prepared by cell culture, as for the flu vaccine; (ii) four are non-replicating viral vector vaccines using benign virus (adenoviruses...) harbouring the spike gene (DNA) in their genomes (the AstraZeneca-Oxford is the prototype approved for large scale use); (iii) two are RNA vaccines (Moderna, BioNTech) are currently used in the population in Europe and USA, twelve months after the discovery of the SARS-CoV-2 in January 2020.

Vaccines	Names	Protection	Side effects
Inactivated	Coronavac [Sinovac]	>70%	Mild
	BBIBP-CorV [SinoPharm]		
	Copvaxin [Bahrat Biotech]		
Unreplicating vector viral	AdV-5 [CanSino]	>80%	Mild
	Sputnik V (Ad26-Ad5) [Gamaleya]		
	AdV26-COV-2 [Janssen/Johnson & J.]		
	ChAdOx1 [Oxford/AstraZeneca]		
mRNA	MRNA-1273 45 [Moderna]	>95%	Mild
	BNT162b1 [BioNTech Pfizer]		

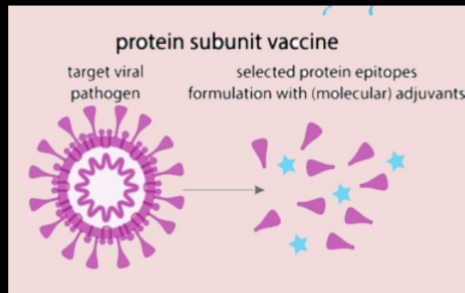
TABLE 1: anti-Covid-19 Vaccines phase III (Dec. 2020).

The most promising are RNA vaccines that have benefited from ten years of intense and innovative research. Injected into tissues, very fragile RNA is quickly destroyed by cellular enzymes. The innovations consist in developing synthetic viral messenger RNA resistant to degradation, and packaged in protective lipidic nanoparticles allowing access by fusion to cell cytoplasm (3,4). One uses synthesized, modified RNA (5) of *spike* viral gene (or its internal fragment encoding the *Receptor-Binding-Domain*). The Spike protein is translated and presented by dendritic cells to T and B lymphocytes. The results of the Phase III clinical trials of the SARS-CoV-2 vaccine candidates are very encouraging. Overall, they provide very good protection and are well tolerated (6). Comparisons between the different vaccines under development remain difficult because of

- Evers MJ, et al., State-of-the-art design and rapid-mixing production techniques of lipid nanoparticles for nucleic acid delivery. *Small Methods* 2018; 2: 1700375
- Kowalski PS, et al., Delivering the messenger: advances in technologies for therapeutic mRNA delivery. *Mol Ther* 2019; 27: 710-28.
- Karikó K, et al., Generating the optimal mRNA for therapy: HPLC purification eliminates immune activation and improves translation of nucleoside-modified, protein-encoding mRNA. *Nucleic Acids Res* 2011; 39: e142.
- Kramer F. SARS-CoV-2 vaccines in development. *Nature* 2020; 586: 516-27.

2. Omer SA, et al, Herd Immunity and Implications for SARS-CoV-2 Control, *JAMA*. 2020; 324(20):2095-96.

Protein subunit vaccines

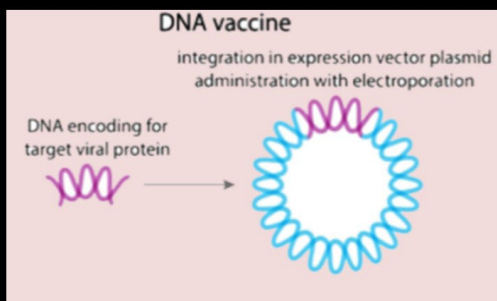


- Protein Spike produced in Baculovirus used with adjuvant or incorporated in Virus-like particles (VLP) without genome and displaying spike protein on the surface
- NVX-CoV2573 [Novavax, Gaithersburg, MD] S in nanoparticles of phospholipidiques (Matrix-M)
- Vaccine Sanofi-GSK: S + adjuvant

Kramer, Nature 2020

the wide variety in age groups, methodologies and modes of administration. However, there is a gradient in the level of protection, from inactivated and non-replicating vector vaccines to mRNA and recombinant protein vaccines. All of them induce neutralising antibodies, as occurs from natural infection. The results of phase III trials show a remarkable efficacy of mRNA vaccines, which confer 95% protection and good tolerance despite minor side effects, as with other vaccines. Notwithstanding uncertainties on the duration of protection and the putative contagiousness of those vaccinated, mRNA vaccines will protect the most

DNA Vaccines

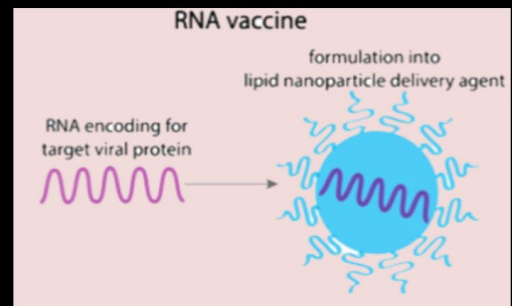


- DNA vaccines plasmid DNA encoding the Spike protein under a mammalian promoter (+ nanoparticles): 4 vaccines Phase I.

Kramer, Nature 2020

vulnerable persons and might reduce the circulation of virus. Easy to prepare, they could open a new era in the history of vaccinology (7), with potential applications in many non-infectious diseases, such as cancer.

RNA vaccines



- RNA vaccines RNA encoding the Spike gene packaged in lipid nanoparticles (LNP).

- Pfizer BioNtec (US + Germany)
- Moderna (US). Phase III

Kramer, Nature 2020

Finally, the main challenge of vaccination against Covid-19 remains to convince the population of health benefit and safety of vaccines by restoring confidence. Transparent communication is essential, as well as the fight against misleading, fake news. The other challenge is logistical: how to vaccinate hundreds of millions of people with vaccines requiring two injections and stored at low temperature? In any case, the rapid implementation of vaccination will help save lives, reduce hospitalisations, including admissions to intensive care units, and thus reduce the strain upon healthcare systems, which is often to the detriment of other serious medical conditions. The rapid deployment of vaccines is the key factor to get rid of the Covid-19 pandemic.



7. À Pardi N, et al, mRNA, a new era in vaccinology. *Nat Rev Drug Discov* 2018; 17: 261-79



Nature Protection: Strategies, Interventions and Critical Issues A European Perspective

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The definition of “nature protection” refers to various environmental problems such as the disappearance of species, destruction of forests, soil erosion and pollution. The International Union for Protection of Nature, founded in Fontainebleau in 1948, was the first large world-level organisation to

deal with the natural environment. In 1956 it took on the more comprehensive name of the International Union for Conservation of Nature and Natural Resources.

The words “protection” and “conservation” have different and complementary shades of meaning. “Nature protection” indicates the set of laws approved by governments for the safeguarding of species, the environment, the landscape, the soil, and for the establishment of protected areas such as parks and reserves, etc. and thus expresses a juridical and administrative concept (1).

“Nature conservation,” on the other hand, means the preservation of ecosystems and their biodiversity in perpetual function, including the preservation of representative samples of them through national parks and nature reserves (2), and thus expresses a technical-scientific concept. In some cases, where humans have caused greater or lesser damage to the environment, it is possible to intervene with works of restoration. “Restoration,” also called biological reconstruction (3), is a measure aimed at restoring the ecological equilibrium that has deteriorated. Nature protection is a preventative measure to avoid damage, while biological reconstruction is a measure to repair the damage done. It is a particular form of management which Bioret et al (4), call active restoration.

There is also another aspect, that of the “ethics of conservation,” which is a moral problem regarding future generations. This idealistic position began with some 20th century thinkers such as Paul Sarasin (Switzerland), Jean Massart (Belgium), John Muir (USA), Oscar de Beaux (Italy), Pieter van Tienhoven (Holland), Aldo Leopold (USA), Fairfield Osborne (USA), and Roger Heim (France), and continues with contemporary thinkers such as Jean-Marie Pelt (France), author of the 1977 book “L’Homme re-naturé”.

Today it is certainly positive that we have technicians and professionals in nature protection, but this is not enough to save nature. For nature protection to be concrete and effective, the cultural movement dedicated to it must be able to protest and say no; it must be able to rebel against the bad decisions of administrators. Unfortunately, few in the movement today have the same idealistic motivation of their predecessors or their strength to act.

Even after more than 5,000 years of history, notwithstanding the great environmental changes brought by the extension of agricultural areas, deforestation and urbanisation over such a long period of time, one can talk today about a “Wild Europe” because a number of European nations still feature some areas of very great naturalistic, ecological and landscape value, three of which are described below.

The great primordial forest of Białowieża in Poland is the last great flatland forest in Europe. Part of it is virgin forest prevalently of hornbeam and English oak and inhabited by the European bison. In 2016 deforestation began in various zones of the forest, which the European Commission declared illegal.

This was confirmed in the 2018 judgement of the European Union Court of Justice, which ordered the immediate repeal of illegal logging permits.

In northern Germany is the Lüneburgerheide Nature Park, of great landscape value, with its extensive Calluna vulgaris heathlands. At the centre of the Park are Undeloh and Wilsede, two rural villages with ancient Teutonic houses, which, until the 1950s (when I visited Lüneburgerheide), had kept their architecture and urbanistic structure intact. Unfortunately, today the village of Undeloh has been reduced to a banal touristic site, the same as those found

1. Géhu J.-M. 2006, Dictionnaire de sociologie et synécologie végétales. Berlin-Stuttgart, J. Cramer.

2. Miller K.R. 1980, Planificación de parques nacionales para el ecodesarrollo en Latinoamérica. Madrid, Fundación para la ecología y la protección del medio ambiente.

3. Bănărescu P. 1987, Problema reconstrucției ecologice a faunei de apă dulce în România. Ocrotirea naturii mediului înconjurător 31(1): 9-13.

4. Bioret F, Estève R. Sturbois A. 2009 Dictionnaire de la protection de la nature. Rennes, Presses universitaires.

all over the world. It is very difficult to understand how a nation like Germany could have allowed such a mockery.

Camargue, in France, is a vast marshland area on the Rhône delta, with the Vaccarès salt water lagoon at its centre. One of the first protected areas established in France and in Europe, today it is threatened by grave environmental problems caused by three main issues: a) ecological problems due to the increase of fresh water resulting from rice cultivation in adjacent areas, b) touristic problems intensified by the construction of a modern vacation village near Saintes-Maries-de-la-Mer, which has ruined the ancient landscape of the Camargue, c) urbanistic problems caused by the construction of major roads on the dunes between Grau du Roi and Palavas les Flots, with grave damage to the dune environment, which, when I saw it in 1960, was still intact.

These three areas are protected by government laws, but each of them has its critical points. The Bialowieza forest will probably be threatened by drainage, which in part has already happened in the northern part of the forest in the area of Siemianowka, and in all that part of the forest which belongs to Ukraine. The Lüneburgerheide Nature Park is protected but not sufficiently conserved. The Camargue is well conserved in its central area, but not so well in the contiguous areas, which should have been better protected.

In addition to national parks and nature reserves, Europe has natural environments worthy of conservation in areas that, in some cases, are quite vast, among them mountains, lagoons, dunes, lakes, peat bogs, and waterways. For their conservation, the EU approved the Habitat Directive 92/43 EEC "Conservation of natural habitats and habitats of species" of May 21, 1992, with the goal of safeguarding biodiversity through the conservation of some natural and semi natural habitats of Europe's wild flora and fauna. The directive called for the establishment of an ecological

network of special areas of conservation, called Natura 2000, to guarantee the maintenance and, where necessary, the restoration of a sufficient state of conservation of the natural habitats and of the species of community interest. In order to apply this directive, European nations created lists of species and habitats, accompanied by regulations for their management and conservation. In order for the conservation to be effective, it is indispensable to ensure that habitats are not damaged by humans. In June 2020, the European Environment Agency published "State and Outlook of the Environment Report" – SOER 2020. The judgement was sharp: "A situation that is anything but edifying, almost thirty years from the Habitat Directive and even longer from the Birds Directive. The visionary policy of Natura 2000 is certainly ambitious, but clashes with a formula of a Union of Nations each of which keeps close to home the responsibility for, and political directions regarding environmental issues." The Report indicates that only a small part of the habitats and species is in a good state of conservation. The habitats exposed to the greatest pressures are those in grassy lands, wet zones and coasts.

The results of this work indicate that the conservation of natural environments and species is critical in Europe. What has been said about the national parks and nature reserves also holds for the habitats of the EU: the habitats are certainly protected on the European level and that of the individual nations, but they are not conserved in a concrete and effective form.

The challenge of the 2000s for the salvation of the last natural environments of Europe, and also of its national parks, is still open!



Fish-ing for New Models in Aging Research

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Aging represents the primary risk factor for many human pathologies, including cardiovascular, and neurodegenerative diseases, cancer and diabetes. An exciting approach for treating or postponing the onset of these pathologies, and thus extending human health-span, is to slow down the aging processes.

Great contributions to aging research have arisen from invertebrate model organisms, particularly yeast (*C. cerevisiae*), worm (*C. elegans*), and fly (*D. melanogaster*), which are naturally short-lived and are optimal genetic models. In these organisms evolutionary conserved aging-related pathways, such as the Insulin/Insulin-like Growth Factor and Target of Rapamycin (Insulin/IGF and TOR) pathways have been identified. However, as non-vertebrates, these models lack vertebrate-specific organs and systems (e.g., blood, bones, and an adaptive immune system), as well as many key genes which are involved in human aging and age-related pathologies. Common vertebrate model organisms used in biomedical research are mice and zebrafish, both characterised by long median lifespans of over three years, making it difficult to experimentally follow the entire course of aging as a continuous longitudinal process.

The African turquoise killifish (*Nothobranchius furzeri*) is gaining popularity as a candidate model to bridge the gap between short-lived invertebrates and long-lived vertebrates, and also to explore more of the rich diversity of aging phenotypes observed in nature. The turquoise killifish (usually <7cm long and sexually dimorphic in size and colouration) has an invertebrate-like lifespan and yet maintains conserved features of vertebrate aging. These peculiarities represent an evolutionary adaptation to the natural habitat. Turquoise killifish are distributed throughout Central and Eastern Africa in freshwater environments characterised by pronounced seasonal differences in water availability resulting from alternating dry and rainy seasons. Killifish inhabit seasonal water pools that fill during the short rainy season and dry up

completely during the subsequent, and longer, dry season. To survive and reproduce in this transient environment, killifish produce desiccation-resistant embryos that have entered a developmental arrest stage called diapause, which suspends all developmental processes and provides higher tolerance to various stresses, including the long drought. The diapause embryos remain in this suspended state until the next rainy season, where the ponds refill. Diapause, consisting of three stages, is obligatory and can last different lengths of time, depending on external stimuli.

Laboratory lifespan in turquoise killifish is consistent with natural aging observed in the natural habitat, where adult populations have been observed to decline in size and individual fitness, and eventually disappear before pools have dried out, indicating that their rapid aging is not an experimental artefact due to laboratory conditions. Thus, this fish ages at an accelerated pace, more so than other vertebrates, however, all life stages are comparable to humans (Fig. 2).

What are the features of aging of the turquoise killifish? At a morpho-physiological level, killifish display loss of pigmentation, spinal kyphosis, sarcopenia, a decline in fecundity, and vision deterioration (Fig. 1). As killifish age, they spend less time actively swimming and swim more slowly, exploring new environments less vigorously. Furthermore, aged killifish perform worse on a test of active avoidance, indicating that a global decline in overall health occurs during aging (1).



Figure 1: Age-dependent appearance of the African turquoise killifish (*Nothobranchius furzeri*) along the whole life. The image is taken from Platzer and Englert, Trends in Genetics (2016).

At molecular level, a decrease in mitochondrial copy number and function, an increase in senescence-associated β -galactosidase staining, shortened telomeres, loss of regenerative capacity in the fin, as well as an increased risk of cancer, especially in the liver, have all been abundantly demonstrated.

1. Singh PP, Demmitt BA, Nath RD, Brunet A. The Genetics of Aging: A Vertebrate Perspective. Cell. 177(1):200-220 (2019).

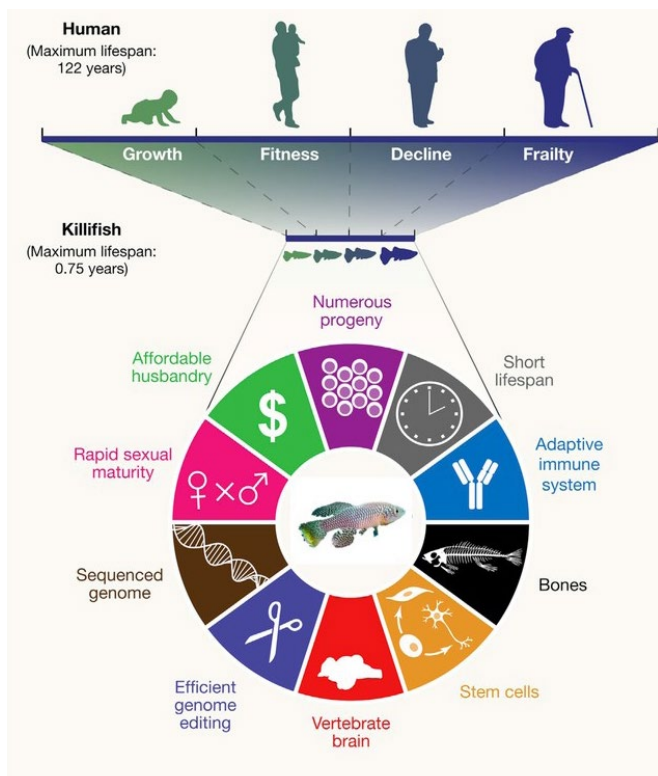


Figure 2: Comparative age-stages between humans and killifish and the key morphological and molecular aspects of killifish for aging research studies. The image is modified from reference 1.

During aging, in the turquoise killifish there is a decay of neurogenesis, which persists throughout the entire life in all fish, paralleled by increased age-dependent gliosis and global changes in brain transcriptional regulation which are conserved between killifish and humans (2,3), and remarkably display hallmarks of Parkinson's disease, including deterioration of dopaminergic and noradrenergic neurons and an accumulation of α -synuclein-containing

2. D'Angelo L, De Girolamo P, Lucini C, Terzibasi ET, Baumgart M, Castaldo L, Cellerino A. Brain-derived neurotrophic factor: mRNA expression and protein distribution in the brain of the teleost *Nothobranchius furzeri*. *J Comp Neurol*. 522(5):1004-30 (2014).
3. Baumgart M, Groth M, Priebe S, Savino A, Testa G, Dix A, Ripa R, Spallotta F, Gaetano C, Ori M, Terzibasi Tozzini E, Guthke R, Platzer M, Cellerino A. RNA-seq of the aging brain in the short-lived fish *N. furzeri* - conserved pathways and novel genes associated with neurogenesis. *Aging Cell*. 13(6):965-74 (2014).

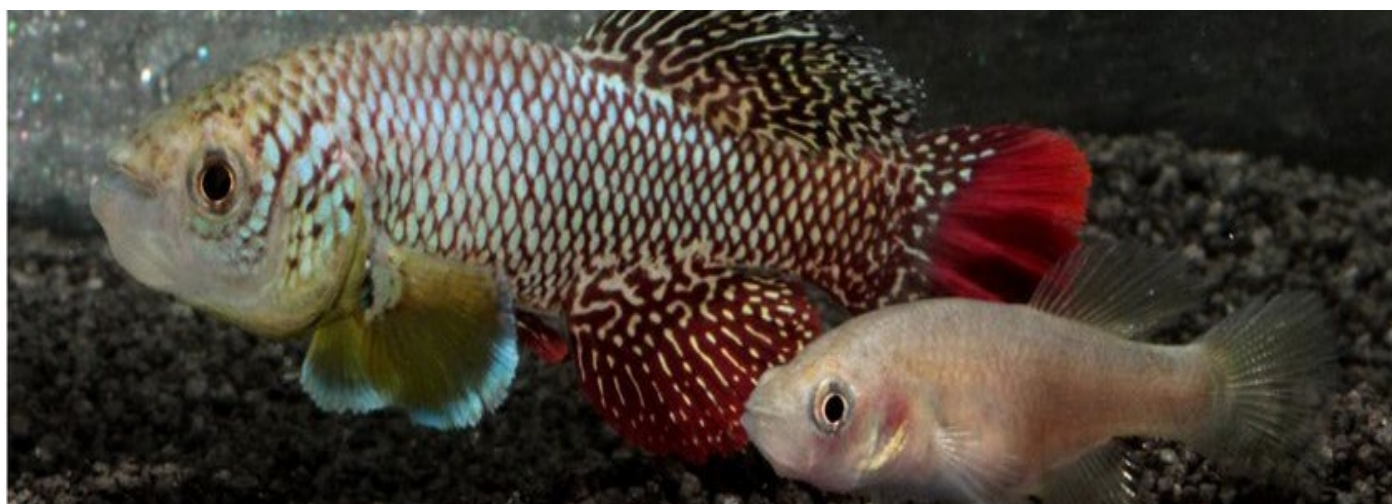
inclusion bodies (4).

Notably, the lifespan of turquoise killifish can be manipulated by conserved interventions such as dietary restriction, temperature, and drug treatments, as well as by the gut microbiota. Interventions such as dietary restriction and **supplementation of resveratrol to feed** have prolonged lifespan and improved cognitive health in laboratory-raised killifish, indicating that the underlying aging processes are similar to those in other species.

In addition to exploring aging, the turquoise killifish possesses many experimental advantages including an XY-based sexual determination system, embryonic diapause, and several developmental processes. Recent advances in genomics and genome engineering approaches have provided efficient and reliable ways to generate precise edits to the genome of turquoise killifish (5). Engineering approaches rely either on transgenesis, which allows for random integration and expression of exogenous genes in a temporal and tissue-specific manner, and by high-throughput genome editing approaches (6).

In conclusion, aging studies should greatly benefit from studies on the African turquoise killifish, the shortest-lived vertebrate known to science and characterised by an accelerated pace of aging (Fig. 2). Thanks to the ease of laboratory husbandry and amenability to genetic manipulation, this species is emerging as a new model organism for aging and biomedical research.

4. Matsui H, Kenmochi N, Namikawa K. Age- and α -Synuclein-Dependent Degeneration of Dopamine and Noradrenaline Neurons in the Annual Killifish *Nothobranchius furzeri*. *Cell Rep*. 26(7):1727-1733.e6 (2019).
5. Reichwald K, Petzold A, Koch P, Downie BR, Hartmann N, Pietsch S, Baumgart M, Chalopin D, Felder M, Bens M, Sahm A, Szafranski K, Taudien S, Groth M, Arisi I, Weise A, Bhatt SS, Sharma V, Kraus JM, Schmid F, Priebe S, Liehr T, Görlach M, Than ME, Hiller M, Kestler HA, Völff JN, Scharf M, Cellerino A, Englert C, Platzer M. Insights into Sex Chromosome Evolution and Aging from the Genome of a Short-Lived Fish. *Cell*. 163(6):1527-38 (2015).
6. Harel I, Valenzano DR, Brunet A. Efficient genome engineering approaches for the short-lived African turquoise killifish. *Nat Protoc*. 11(10):2010-2028 (2016).



Go! Borderless!

Nova Gorica and Gorizia, the European Capital of Culture 2025

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Prof. Emer. Lucija Čok

For centuries the cities of Gorizia and Trieste, under whatever statehood they were, were regarded by the inhabitants of the wider regions as their homeland. The Treaty of Rapallo (1920) marked the Slovenian borders within the former Kingdom of Yugoslavia and cut Gorizia off from Vipava

and Isonzo Valley and Trieste from Istria, thus alienating the inhabitants of the two regions from their economic and cultural centres. It has been shown over time that there are no righteous borders. Strategic shifts in European governance have shown that the civilizational momentum of an enlightened world that wants peace, respect and understanding between nations, cannot be suppressed by borders. The decision of the expert jury considering candidates for the European Capital of Culture 2025, nominated Nova Gorica and Gorizia as a unified, symbolic, cultural capital, and this has shown that there is always a way to find new solutions.

Under the title "Go! Borderless", the project proposes to create a symbolic, common cultural and urban space between the two cities Nova Gorica in Slovenia and Gorizia in Italy, which in the past were a single city. The programme that led the EU expert jury to choose these cities for the European Capital of Culture in 2025 - at a time when the world is plagued by more disasters than ever from climate change to the Covid-19 pandemic - offers the right answers and hope for the future. The program's creators, a group of cultural operators from both sides of the border, led by Neda Rusjan Bric, Vesna Humar and Lorenzo De Sabbata, have proposed, in their project, new, unconventional solutions to enrich coexistence at the border, starting from the current reality to new paths. The new paths will not be the same as previous ones; they will be more noble and direct, because they were born as a lesson on how to know better one's surroundings as well as the external world in times of crisis. Where, in the First World War the emerald River

Isonzo (Italian) or Soča (Slovene) flowed bloodily, where, in the Second War barriers were erected and iron wire put up, new generations found solutions to problematic borders in cooperation and joint efforts for a better quality of life.

Mutual respect and trust between the inhabitants of the two Gorizias have grown with this project. Since the easing of borders with the Osimo Treaty (1975, ratified 1977), numerous INTERREG projects, economic integrations, cultural and educational cooperation have been carried out. When Slovenia joined the EU in 2004, the two cities founded The Square of Europe next to the former railway station on the border. This initiative has grown after firm integration steps. In the last 15 years, however, the goals of the square of friendship to be a harmonious neighbourhood have been increasingly lost; evidence of this is, for example, the fact that the two municipalities could not even agree on a common name for the square. The Italian part of the square is called Piazza Transalpina, the Slovenian part is called the Square of Europe. The new mayors, Klemen Miklavic and Rodolfo Ziberna, have clearly overcome these old prejudices and, together with mayors from other provinces on both sides of the border, supported the Go! Borderless project, which moved from words to deeds and put the idea of a successful neighbourhood into practice. Already the candidacy itself is a realisation of the borderless principle, for it has been financed by both municipalities and the Friuli Venezia Giulia region.



Mayors Rodolfo Ziberna and Klemen Miklavic (displaying the flag) with the team after the jury announcement.

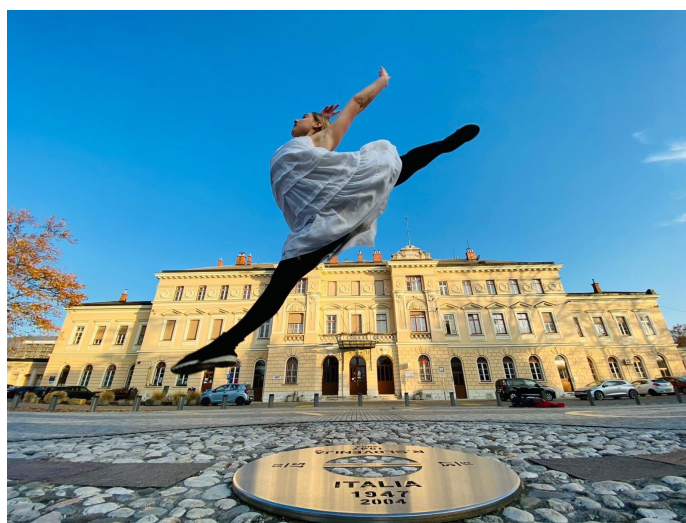
The program includes several intriguing projects - from the urban development plan to transform a now abandoned

square into a new centre for the united city (EPICenter), to the European platform for the interpretation of the history of the XXth century, offering historical interpretations from both perspectives (GO! Share), to a project on communication and passive bilingualism, increasing the international visibility and orientation of the area by creating new contacts and the flow of knowledge (GO! Europe), and sustainable development and a green future for the inhabitants of a pleasant city (GO! Green).



The GO! borderless bid-book

the content has been created by a cross-border team, composed of the representatives of the population on both sides of the border. It has grown from the needs of this space, where many challenges have to be faced. The topic of "border" is conceptualised not only concerning the particular geography of the two cities, but also horizontally – as division lines in societies, e.g. between minorities and majorities. Concrete changes from passive bilingualism to the functional one had already started with the dynamic action in the educational and cultural sectors.



Borderless artist Noemi Capuano

The successful communication between societies in interpreting the common historical events is hard to achieve. The tasks of this project will take place in an objective and collaborative discussion of historians, not guided by daily politics, and will start with the painful events of past history, for example the 12th Battle of The First World War, which is found in Italian historical sources called "Disastro di Caporetto" (2) and by Slovenian historians as Miracle of Kobarid ("Čudež pri Kobaridu").

Go! Borderless is definitely a powerful project, whose symbolism can be found in its name as well as in its content. The plan to use the European Grouping of Territorial Cooperation (EGTC), GO, as the delivery structure, has a strong potential to form a new set of good practices in combining different EU legal and financial mechanisms to achieve complex goals. The participation of the population and the professional public and political management, from both sides of the border in shaping the content of each area, the awareness of the general population about the importance of achieving the goals they have set themselves, and the conviction that such a project is precisely the approach to working on the coexistence of people along the border is an indicator that there are solutions to difficult borders, as the President of the Republic Italy, Sergio Mattarella, said in his New Year's Eve address to the nation. By obtaining the title European Capital of Culture 2025 for the cities of Nova Gorica and Gorizia, his prediction is also achievable.



Sergio Mattarella e Boris Pahor in Trieste at the restitution of Narodni dom to the Slovene minority



1. Application book reachable at <https://issuu.com/go2025/docs/go2025eng?fr=sOWZmNTI1MTI3OTM>

2. Belviso, F., De Paulis, M.P.; Giaccone, A. 2018. Il Trauma di Caporetto. Turin, Academia University Press. Series Biblioteca Historia Magistra.

On the Armenian Genocide

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Below is the testimony of Yeghis Keheyán, for over forty years a researcher in Italy, and the daughter of survivors who escaped the Armenian genocide of 1915. Here are the incredible sufferings, the mourning and the massacres, which annihilated three thousand years of history, civilisation and thought, which flourished in one of the happiest countries in the Mediterranean.



Yeghis Keheyán

I was born into a family where every day after dinner, my grandmother, who survived, told us about the genocide. As children first, then as teenagers and, until her death, we listened to her telling her story, always the same sad story.

My grandparents lived on a plain, not far from Adana and near the railway that ran to Mersin, in the village of Kars-Bazar, where my grandmother's father-in-law (my great-grandfather) was a prominent figure among the local Armenians.

Adana (formerly Antioch of Cilicia), founded by Alexander the Great and capital of the homonymous province, is the fifth largest city in Turkey in terms of population and is located not far from the East Sea, near the Seyhan River. It became Armenian in 1132 and was part of the Armenian Kingdom of Cilicia until 1360. The Armenians continued to settle in that area over the centuries, forming a creative and prosperous population. At the end of the 19th century, Sultan Abdul Hamid II, enlivened by pan-Islamism, promoted a systematic extermination campaign against the Armenians, a campaign that, in 1896, caused the death of over 200,000 people, as documented by Jacques Morgan, Constant Vautravers and Edmond Khayadjian in their work "Histoire du peuple arménien: depuis les temps les plus reculés des annales jusqu'à nos jours".

I stress the fact that my grandmother did not know her exact date of birth and told us that she was born during the Adana massacres. She married at a young age and when the carnage began in 1915, she already had two children.

They lived very well and were well integrated into Turkish society. My great-grandfather had a close friendship with the *kâimmakâm* (in Ottoman times, a *kâimmakâm* was a state official, considered a representative of the Sultan

or the Grand Vizier at the local level). My grandfather's family was large, consisting of five brothers who lived in great harmony with their children and grandchildren. One evening, suddenly, the Turks entered the houses of the Armenians, taking all the adult males. My grandfather was the youngest. They were all taken from home and slaughtered and then their bodies were cut to pieces. My grandfather witnessed the atrocities against his relatives but he managed to escape. He began a long march towards the Deirel-zor desert, the so-called "Death March", which saw thousands of people fall on the arid ground. My grandmother and her two little children, one of whom was my father, walked for months and during the walk, the Turks, seeing her exhausted by fatigue, advised her to throw one of her children into the river.

On the road to salvation

They walked without looking back. During the trip, my grandmother also lost her sister and other family members. They walked for months, sometimes stopping for weeks under the scorching desert sun. Eventually they arrived in Aleppo where they stayed until 1919. My grandfather, being very enterprising, immediately began to work: he made candles, worked the grain and sold it. When the situation seemed to have returned to normal, they decided to return to their old homes. They stayed there until 1922 when the Turkish government expelled the Greek inhabitants of Izmir and other cities. Three thousand years of history, art, thought, power and glory had flourished in one of the happiest countries in the Mediterranean and all this ended with the massacre and forced expulsion of the Greek Christians and of course, with them, the Armenians. My parents arrived at the port of Mersin where they boarded a Greek ship bound for Athens. The ship of salvation...



BOOK REVIEWS

Alain Touwaide (ed): “Greek Medical Manuscripts – Diels’ Catalogue”

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Dana Baran

A landmark book.

Dr. Alain Touwaide's five volume set, meticulously dealing with "Greek Medical Manuscripts - Diels' Catalogue", was edited by De Gruyter Publishing House (1). Michael Friedrich, Jost Gippert, Marilena Maniaci, Paolo Odorico, Steve M. Oberhelman, and Dominik Wujastyk composed the Scientific Committee of this edition. Such a difficult, yet extremely useful, scholarly endeavour was meant to continue, correct, complete and "newly revise and update" the work of the famed German classicist Hermann A. Diels, who, with his group of highly trained philologists, in 1905, 1906 and 1908 had published a comprehensive catalogue of Greek medical authors, texts and their medieval translations. The database of these manuscripts was critically re-dimensioned by Dr. Touwaide, a proficient scholar and founding scientific director of the Institute for the Preservation of Medical Traditions (Washington, USA), already a significant international academic society.

All the codices mentioned in Diels' catalogue – an acknowledged reference point – were exactly, even though not "photographically", reproduced and comparisons were ceaselessly operated. For rendering information easily accessible, a *Finding Aid*, followed by *Notes for consultation*, accompanied each volume, specifying Indices of Manuscripts in Diels' Location and Shelfmark, City and Library names - 1. Names according to Diels; 2.

Standard English names; Manuscripts Current Location and Shelfmark; City and Library names, where manuscripts of this surprisingly "dynamic" and rich *Corpus Medicorum Graecorum* can be found.

The suggestive cover image conceived for the books, a "collage of illustrations in medical treatises from the 1st to the 16th century CE, from Greece and Rome, to the Arabic World and China", hints at the extent of Greek medicine and reciprocal influences exerted within these multicultural spaces.

Tomes and contents

Tome 1 consisted of "Diels' Catalogue with Indices"-Part I: Hippocrates and Galen; 1. Hippocrates; 2. Galen; Addenda to Part I; Part II: The Other Physicians; Addenda to Part I and Part II, along with the Supplement I referring to Hippocrates, Galen and The Other Physicians. An Index of Authors and Works was integrated inserting: 1. Greek titles; 2. Latin titles; Index of Manuscripts and Table of Concordance; City and Library names - 1. Names according to Diels; 2. Standard English names; Manuscripts and Diels' Bibliography with: 1. Catalogues of Manuscripts - 1. Short-reference List, and 2. Full-reference List; 2. Editions of Anonymous Greek Medical Texts - 1. Texts from manuscripts; 2. Texts from papyri, and 3. Reference Works. **Tome 2** focused on "Manuscripts of the Corpus Hippocraticum", containing texts by, or attributed to, Hippocrates, whereas **Tome 3** examined the "Manuscripts of the Corpus Galenicum", with texts by, or attributed to, Galen. **Tome 4** reconsidered "Manuscripts of the *Ceteri Medici*", reviewing texts by, or attributed to, the "remaining authors", while **Tome 5** analysed all "The Manuscripts and their Texts", incorporating descriptive annotations from the Diels' three volume catalogue. If, in Tomes 2 through 4, information expressed the type of Contents, Tome 5 reflected the type of Manuscripts.

1. Touwaide A.(ed): "Greek Medical Manuscripts - Diels' Catalogue". Berlin/Boston: De Gruyter Publisher (Medical Traditions Series) December 7/16, 2020 (ISBN 978-3-11-060064-3 e-ISBN (PDF) 978-3-11-059996-1 ISSN 2567-6938) (\$91.99)

Final scope and beyond

Yielding reliable details on the History of Medicine, its multifaceted concepts, the progress of medical “Ideas”, terminology and methods, discovering more and more precise, appropriate and handy documentary sources, were the immediate purposes of this complex and almost exhaustive approach. On the other hand, as intended, this impressive work would certainly facilitate the passage from classical printed versions to online open access publications, concerning Greek medical antiquity classifications and interpretation. Surprisingly, present-day societies incessantly get news from the Past enabling reformulation of the Present, its cultural patterns, received ideas and general understanding, modulating the Future. Diachronic and synchronic variations intermingle in the attempt of finding and implementing the right common denominators, as things happened with this updated catalogue. Another step forward to a standardised, cross-referencing system was made, so helpful for the contemporary, globalised world where the naturally controlled chaos of heteroglossia should be, little by little, transformed into an intelligently differentiated homoglossia. This fascinating “archaeology of medical knowledge” encompasses epistemological coordinates, stimulating “from bench to bedside” translation in medical bibliography, too.

“Towards a New Diels”

The effort, Dr. Alain Touwaide and his team invested in achieving this masterpiece of medical catalography and library science, aimed at pursuing prior investigations in this domain. Dr. Touwaide’s writings on “Greek Medical Manuscripts, such as “A Bibliography” (1991), “Manuscripts, histoire du texte et édition de traités médicaux et pharmaceutiques grecs et byzantins (1990-1992)” (1994), “Byzantine Medical Manuscripts: Toward a New Catalogue” (2008) and “A Census of Greek Medical Manuscripts; From Byzantium to the Renaissance” (2016), displayed checklists of Greek medical manuscripts identified in worldwide collections, constituting a consistent addendum to the Diels catalogue and a prerequisite of these five tomes. As planned, Alain Touwaide’s lifelong project will doubtless culminate in a readily available “New Diels” Catalogue within many people’s mental grasp, covering missing data and authors, clarifying doctrines and authorships, improving practical aspects connected with current research practice, building up professional teams, strengthening interdisciplinary and transdisciplinary cooperation, while stimulating a vivid interest among niche scientists, sometimes including medical doctors, as well. Enclosing linguistics, extensive cultural competencies in medicine will assuredly improve, the roots of deeply intricate human civilization networks being better defined functionally.

Alain Touwaide, an experienced researcher (Fig.1)

The author, a distinguished researcher in interrelated fields, proved once again to master not exclusively the norms of modern paleography, codicology, catalography and bibliographology. But he obviously demonstrated his expertise in medical doxography and, implicitly, in medical and pharmaceutical historiography. Apart from philological skills, Dr. Touwaide’s teaching abilities are remarkable. By no coincidence he is a prominent member and Councillor of the centennial International Society for the History of Medicine (ISHM).

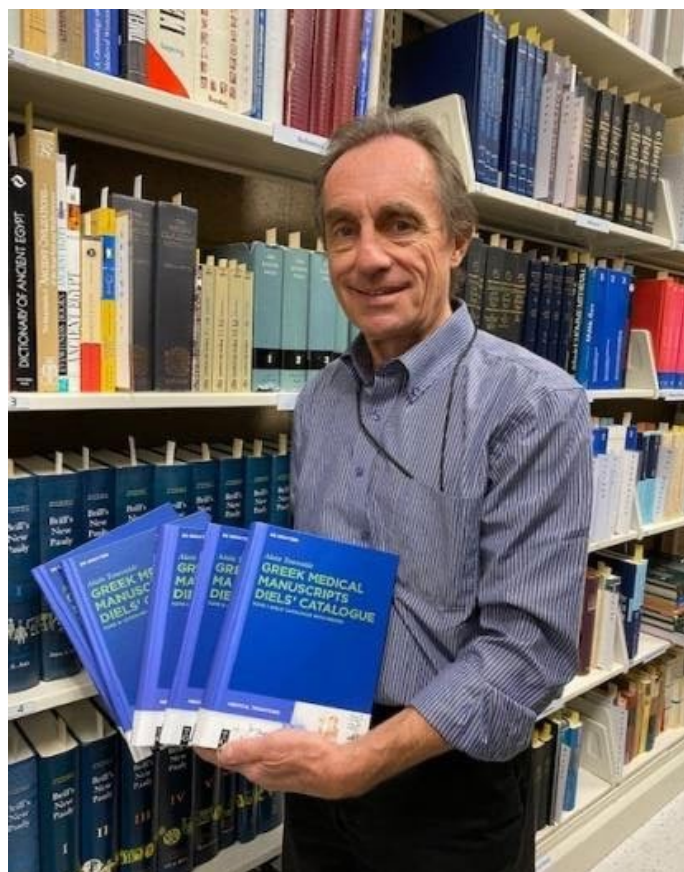
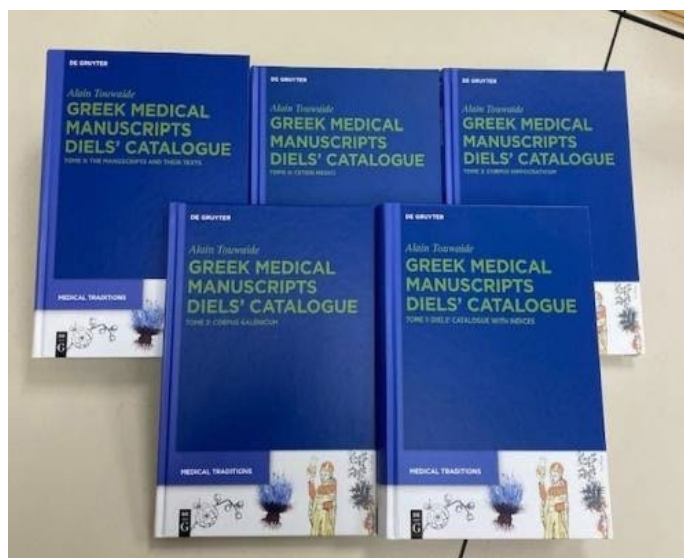


Figure 1: Alain Touwaide, an experienced researcher.





The Situation of Retired University Professors in Parma

Alberto Girlando

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In the 4th issue of EAPE Bulletin, Natale G. De Santo reviewed the rules to become Emeritus in Italy, and he explained why, due to university autonomy, the rules are different from university to university (1). Before describing the situation at my university (or ex-university), it is probably worthwhile to give a little of history of the Emeritus title in Italy, trying to understand why it is, in general, rather rare, while for instance in the United States the title is given, as far as I know, to any retiring Professor who prefers to remain active in the university.

The Italian universities ruling for the nomination of Emeritus is based on a national law, issued in 1933, that was almost 90 years ago and during the fascist regime. Just two year before, the fascist regime required that all the university professors made an oath of allegiance not only to the State and the King-as it was at the time of the constitutional realm-but also to the fascist regime. Professors who were not willing to comply were fired; only 12 out of a total of about 1000 professors refused (2). Thus, universities were totally under the control of the regime and everything was strongly centralised. In the same 1933 law, the retirement age for professors was confirmed as 75 years. Therefore, the title of Emeritus given to retired professors was rather rare, just because of the simple matter of age, and essentially it was an honorary title given by the Ministry following a proposal by the faculty, in recognition of 20 years (or 15 in which case the title was "Onorario") of service for the university. In fact, the 1933 law did not require any reason for the conferment of the title other than years of service, and also stated that "Emeriti professors do not have any particular academic prerogative." Since after the Second World War, and the fall of fascism, this part of the law has not been modified and is still valid today. On the other hand, professors regained their full autonomy and freedom of thinking and teaching.

The number of students and, subsequently, of university professors, increased significantly after the war, and, in particular, in the seventies and eighties. There were about 15,000 ordinary professors by the year 2000, and an even greater number of Associate Professors, a new position in the academic career formalised in 1980. At this point the number of candidates for the emeritus title increased, and universities started to introduce restrictions. At the same time, the government decided that there were too many professors and consequently advancement of career for younger people became difficult. The average age to become ordinary professors increased from 40 to 50 years or more whereas the retirement age moved from 75 to 72 and finally to 70 years following the last law passed in 2010. Politically, the move was to "make space" for younger academics. Actually, what happened was that retired professors were not replaced, and in 10 years the number of ordinary professors decreased from about 15,000 to less than 10,000. But younger colleagues looked on them as blocks on their careers and on their requirement for space. Therefore, universities started to make it more and more difficult to achieve Emeritus status, even when there was a small number of candidates, because most had become professors around 50 years of age, and with retirement at 70 they may not have held the position for 20 years, as required by the 1933 law – at most they could become "Onorario". On the other hand, at 70 a university professor has accumulated years of experience and may still be willing to continue to work in the university, even if not entitled to become Emeritus. Some universities decided to create a new title called "Senior Professor" or a different title, which can be granted, upon request of the professor concerned, employing a procedure far simpler from that of Emeritus, but still allowing him/her to continue to work within the university (for instance, publishing papers) for at least a limited time – whilst, in contrast, the Emeritus title is permanent.

1. De Santo N G. EAPE Bulletin 1 (4), 60-62 (2000)

2. Boatti G. "Preferirei di no", ET Saggi, Einaudi (2017)

At Parma University the situation of Emeriti is somewhat unusual. The regulations have been modified several times in the last few years. The last "Regulation" (2015) has become somewhat less restrictive than before. The procedure has to be initialised by the Director of the Department, upon solicitation of former colleagues of the candidate and within one year of his retirement – or the Rector can independently initiate it. The candidate must have been "correct" (whatever this means) with regards the interlocutors within and outside the University, and he/she must not have violated the laws or the ethical code of the University and so on. The adherence to these conditions is ascertained by the Rector. Apart from these pre-requisites, it is sufficient that the candidate satisfy just one of the following conditions to be eligible: 1) to have a high scientific profile, as testified by publications, and have been appointed in some important role in scientific or academic societies; 2) to have a high scientific profile, as testified by publications, and to have received national or international awards and recognition for scientific activity; 3) to have a high scientific profile and to have served the University in some high ranking appointments (e.g., Department Director, Rector Delegate...); 4) to have a high scientific profile and have brought important innovations in teaching methods, as appreciated by the students. The candidacy has to be supported by at least three letters of recommendation from Emeriti or full professors from other universities. The application must be approved by the majority of the Full Professors of the Department and of the Senate, upon request also with secret scrutiny. Thus, the requirements are not too high, but the procedures are under the full control of the academic authorities (Department Directors and the Rector).

The Emeriti in Parma now have right to space in the Department, can continue to participate in research, and can even be responsible for projects. They retain their official e-mail address, and access to bibliographic resources. What is curious, in my opinion, is that people who have almost the same rights as the professors in service, are not listed among the personnel of the Departments, nor have their names in the University phone book. The Parma University website simply lists all the Emeriti and Onorari who have been appointed over the years, without distinguishing between deceased or active. At present, the list has 36 Emeriti and 3 Onorari. About two thirds of these have been nominated in the last 20 years or so, and only one is a woman.

On the other hand, Parma University has decided to disregard completely all professors who, for one reason or another, did not become Emeriti, but who wish and feel themselves to be part of the University community. Retired professors disappear from the University website

the same day of retirement, and also the institutional e-mail should be withdrawn after one year, as for technical and administrative personnel – this is written in the last Regulation about e-mail addresses, although it seems that this rule has not been implemented, at least not for all personnel. There are no Associations of Professors, as in other universities, nor Senior Professors or the like. Parma University decided instead to nominate "Professors ad Honorem" - famous people at local or international level, such as the founder of a local car industry or a celebrated singer-songwriter. They bring visibility to the University, and this is regarded as more important than the cultural prestige brought about by the former professors.

To conclude I will add some personal thoughts, based on my life experience and reading. Since their foundation, there always has been a struggle between universities and governments, the former advocating freedom of thinking, the latter aiming to have control of it. After fascism, university professors were given complete freedom of thinking and teaching. But since the seventies, all over the world, universities and professors have changed their role in society. In a world now dominated by efficiency and economic return of every action, from fund raising to students' education, quality of research is measured by the value of money it brings to the university, and students are clients that pay and have to be satisfied, i.e., they have to pass exams and get their degrees. As a consequence, universities are run like companies, with a lot of centralisation and bureaucracy. Governments have created agencies to evaluate universities and professors, establishing numerical rankings that distort the very aim of the universities (3), and essentially force the professors to follow the "mainstream" and to seek visibility at the expense of rigor and integrity, to the point that "...many research findings published in the recent literature may indeed be false" (4). So, again, freedom is indirectly endangered. Young people are the most affected by this deleterious state of affairs, at least until this is the only world that is presented to them. Scholarship by Emeriti, who no longer have pressures arising from the whims of "politics" and "fashion", should be encouraged by universities, because scholarship is important for the integrity of science, and is also the essence of a good university education (4).



3. Gadd E. "University rankings need a rethink", *Nature* 587, 523 (2020)

4. Leng G. and. Leng R I. "The Matter of Facts. Skepticism, Persuasion and Evidence in Science", MIT Press (2020), Chapters 23-25



2021 Missive

Garabed Eknayan

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Dear friends,

2020 has been a year that is best forgotten. It certainly was not what I had anticipated in my last New Year missive when I reported my retirement on January 1, 2020. It started getting complicated in January with reports from Wuhan, followed by an illness of my older sister in February, and then through no fault of hers things have been getting worse by the week. Rather than lament the varied troubles we all have endured during the pandemic or whine over what could have been, I want to share with you some apolitical lessons I learned over the past year:

1. I am delighted that 2020 is over. Covid vaccines are finally available. I got my first dose on December 29. At least the Covid calamity is likely to be over by this time in 2021.

2. The difficulties we've all had to cope with notwithstanding, I am grateful that most of us were lucky to get through the year without serious trouble or major indisposition.

3. I feel blessed that everyone I hold dear is still around and aging gracefully. I have dearly missed their hugs, kisses and shared celebrations due to the social isolation imposed by that horrible predator termed Covid-19.

4. I still believe that wine and scotch are divine gifts, but now realize that they were created to be shared. They just do not taste the same and certainly are not nearly as enjoyable when consumed in isolation.

5. I have learned a new way to keep busy with all the free time that retirement and the lockdown provide: It is just as easy, or may be just as difficult, to take 3 hours to do what can be done in 30 minutes. Actually, when you take longer doing something you get a greater sense of accomplishment once you are done with it. An age old wisdom is that people who become good at this, usually end up claiming that there is not enough time to do everything! My wiser mother used to call it plain old 'laziness'.

6. Speaking of the apathy of laziness, the monotony of life that comes with the lockdown presented a major challenge halfway through the year. The easy downhill path of letting things slip by from then on was increasingly tempting. I had to make a concerted effort to put a stop to it by restoring some order to the otherwise daily dulling routine of 'eat, s**t, sleep, repeat'. I have since resumed my rituals of waking up early, exercising, shaving, showering and getting dressed every day as if I am going to work, and

then finding something to do. By the end of the day though, I sometimes still question its futility but refuse to let it get me off track again.

7. As for waking up early, I continue heading to my computer and do my best at maintaining some level of intellectual productivity. But, finishing a manuscript is taking longer and longer, the number of times I end up revising a paragraph greater and greater, and the time I spent just staring at the computer screen more and more drawn-out. But I continue to forge ahead and plan to do so as long as I can.

8. I am increasingly aware of becoming forgetful. Never having been one of good memory that does not really bother me now. Hence, my New Year resolution: Apply this expanded skill of mine to forgetting the horrible year that 2020 has been.

And now, with 2020 behind me in a few months I will be 86 years old. The oldest I have ever been but also the youngest I will ever be again. I still don't understand why people complain about getting old, it does come with inconveniences but sure beats the alternative. Bravura and bragging aside, the realities of old age are increasingly in my thoughts. As I dwell on them, I find solace in the wisdom of Khalil Gibran, with whose poem on Fear I would like to conclude my missive:

*It is said that before entering the sea
a river trembles with fear*

*She looks back at the path she has travelled,
from the peaks of the mountains,
the long winding road crossing forests and villages.*

*And in front of her,
she sees an ocean so vast,
that to enter
there seems nothing more than to disappear forever.*

*But there is no other way.
The river can not go back.*

*Nobody can go back.
To go back is impossible in existence.*

*The river needs to take the risk
of entering the ocean
because only then will fear disappear,
because that's where the river will know
it's not about disappearing into the ocean,
but of becoming the ocean.*

And now without any more maudlin and looking forward for more villages and forests to cross in years to come, I wish you a Happy New Year full of wonderous surprises. Thank you for being my friend and dear companion on various segments of my journey in the river of life. I love you and miss you. And finally, to sum 2020 up:



January 1, 2021

Campanella

NEWS



Minutes of EAPE Council Meetings

Luigi Campanella

Senior Group Italian Society of Chemistry, Secretary of EAPE, Rome

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November 16, 2020

Present: Natale Gaspare De Santo, Les Ebdon, Maria Oxenkuehn-Petropolou, Liv Mjilde, George Christodoulou, Nikos Markatos, Georgia Drosatou, Dennis Cokkinos, Patrick Berche, Michael Kunze.

1. At the beginning Patrick Berche delivered a presentation about vaccines against Coronavirus and their technical approaches with the necessary clinical trials on volunteers and reviewed unsolved questions.

2. The General Secretary is in contact with the Agency APRE with the aim to collect preliminary information about the new European Horizon Programme 2021-2026.

3. The President Elect agreed to recirculate the statement about 'Health and Wealth' with a view to EAPE becoming signatories.

4. The following point of discussion dealt with the disagreement between the number of registered members and the number who have paid fees. It concerns the problem of assigning the new fees to the person responsible for their payment, which is proving difficult due to lack of registration. Georgia was consequently asked to make a list of new members who have paid, along with the email addresses of those who communicated with them. Each member of the Board can help with this action as they know to whom they wrote to promote registration as an EAPE member. The new template to welcome new members during last month was discussed and finally approved.

5. About Committees, President De Santo confirmed that they should represent our voices and activities. A correspondent for each of them is needed, and there must be seven members of each committee. We have two well-structured, officially constituted committees: Enrolment and Advocacy, and Ethics. Other committees are being organised: Nature (reference Franco Pedrotti, Nature protection: a European perspective), Mental Health (reference George Christodoulou) and Culture (reference Sherban Lupu).

6. For the Assembly at least 25 persons are needed. According to Nikos's proposal it could be scheduled on 14th December at 5 p.m. Paris time. Only recognised members will be invited to take part. To change by-laws a special assembly could be scheduled in March giving more time to discuss, by email, the proposals of the President. Can we have such an additional assembly?

The President suggested changes to the Board composition:

President elect- satisfactory

10 EAPE members elected by the Council. From the elected members the Treasurer and Secretary are chosen.

Nominating Committee: do we want to have a nominating committee?

7. Cultural events: Dennis, with his committee, have decided to organise and manage a meeting, with invited speakers, in his field of research and profession. Each presentation will be of 500 words and will be reported in the Bulletin and on the EAPE website.

8. George proposed a similar arrangement (as in 7.) on the theme of the mental health effects of the Covid-19 pandemic. It was agreed to discuss this outside the meeting.

9. The next Congress will be discussed in the December Council Meeting according to the calendar already approved.

10. Concerning the Supplement on the World Day of Older Persons (which will go to print at the end of the week), the President suggested that next year EAPE should organise an event in a country where we speak about Emeriti in the context of Older Persons. Les was asked to contact the Creative Ageing Group in order to see if we can act as the voice of the Group for emeriti/retired professors. Professor Gricar may be of help.

11. It was agreed to have an additional Board meeting on November 30th at 1 pm Paris time (Les to schedule on Zoom) to prepare for the Council Meeting and deal with held over business.

December, 2020

Present: Natale De Santo, Les Ebdon, Patrick Berche, Maria Ochsenkuehn-Petropolou, Liv Mjelde, Nikos Markatos, Georgia Drosatou and Luigi Campanella.

In opening the teleconference Natale De Santo apologised for delay in the publication of EAPE Bulletin no.6. (Material submitted by November 20) due to Corona virus infection of the Publisher. Galley proofs will arrive in a few days.

Natale also explained the mail sent to all members of the Board just before the start of the teleconference concerning the inquiry into academic freedom proposed to EAPE by Jochen Ehrich, Emeritus Professor of Pediatrics at the University of Hannover and former secretary for the last 27 years of the European Academy of Pediatrics, in the name of the European Association of Pediatric Nephrology

Luigi Campanella commented that in the proposing letter three different aspects emerge: 1) academic freedom in its largest sense, freedom of research, teaching and communication; 2) freedom of organising and managing hospital activities especially in the case of pediatrics; 3) academic freedom in communicating and sharing results of research free from editorial and patenting interests. Les Ebdon substantially agreed and it was concluded that an answering letter will be prepared by Les and Luigi.

With regard to the next steps for the Association, Natale De Santo focused on the need to change by-laws, making them more suitable to the aims and the activities of EAPE. He made particular points and suggested the nomination of a committee working on variations to the actual by-laws; on this committee could be members of the Board and EAPE members. It was concluded that three members are now nominated: Les, Dennis and Luigi, and that other names can be proposed by any members of the Board.

In the last part of the teleconference it was agreed 1) the new welcoming form should be addressed to new members after their membership was finalised; 2) A New Year greetings letter would be sent from the President to all members containing a short summary about the activities of EAPE during 2020; 3) an event, on-line, during 2021 should be finalised to discuss activities aimed at increasing the visibility and member numbers of EAPE; 4) the Congress is delayed to 2022 due to the pandemic: it is considered essential for the future success of EAPE, strictly depending on human contacts.

January 14, 2021

Present: Natale De Santo, Patrick Berche, Maria Ochsenkuehn-Petropolou, Les Ebdon, Liv Mjelde, Nikos Markatos, George Christodoulou and Luigi Campanella.

Communications from the President

Two letters from General Secretary were mailed (a) to members regularly paying their fees and (b) to those who have not yet confirmed their affiliation, this letter containing information about the Bank Account.

The Financial Report was presented and explained by Maria showing that of the 295 registered members only 153 had paid their fees for 2020. This is very negative for EAPE as the fees are the only source of income for EAPE.

Les has created a very useful contact with the Association of Slovenia Professors Emeriti and EAPE can cooperate with this Association by the submission of a European proposal on areas in which the two or more Emeriti Associations are active.

Jochen Elrich has agreed to organise the Committee on Meeting the Needs of Children and Old-Old. He has already started to exchange documents and emails with the members of the list he received. Judith Hall from Canada joined the committee and has already paid the subscription fee

Bulletin Issue 6 and Supplement are almost ready to be mailed. A general index is in preparation for 2020 year. Issue 1 of 2021 is expected to be published on February 1st; only the editorial remains lacking. All members of the Board are requested to promote diffusion of the Bulletin as an important source of knowledge and as a good method of information about the Association.

Committees

The Board proposed that non-members of the Association but who are members of Committees, do not have to pay registration fees. The President opposes this decision with the support too of George and, in considering their arguments, the Board stated that to be a member of an EAPE Committee the committee member is requested to be a regular member of the Association and pay the normal membership fee.

Dennis proposed a Committee on Cardiovascular Disease but following comments that the committees should be more multidisciplinary he agreed with the modification of his proposal by George to establish a committee on Prevention and Health Promotion. George was authorised to prepare a written proposal on this basis.

Following the clarification concerning the registration fees of members of a Committee who are not members of the Association, the Committee on Mental Health was officially accepted and was authorised to move on. George would be the Chairman and Prof. Vincenzo Bonavita would be the Vice-chairman. George announced that Prof. Nancy Papalexandri had applied for membership of the Committee on Mental Health and that her application has been accepted. Franco Pedrotti is to assume the Head of the Committee on Nature Protection. He

invested his pension in buying 42 hectares of forest with the intent to dedicate the forest to scientific research. Now at late age he has gifted this forest to the Italian Nature Fund to be visited by tourists and scientists.

The Board observed that the high number of committees in the Medical Sciences is the result of the updated composition of the Association with physicians prevailing on other professions.

By laws

All members of the Board thanked Dennis for his valued work in reviewing By Law Article 5:

Add to Paragraph 2: "They can participate, elect and be elected to the various committees of EAPE."

I again want to point out that we have, probably only one paying Corresponding member, but we could get many more in various committees if they do not have to pay. Actually, as we have only two National Committees up to now (Greece and Italy), we could ask colleagues to become Councillors of their countries with the further aim to develop National Committees.

Academics or Members of EAPE of exceptional achievement and who have rendered meritorious services to EAPE can be elected by the Board as Honorary Members.

1. When the final By-laws are approved there will be a cost for a lawyer which will be not less than €3.000 even with friendly terms.

2. When the Board changes, the bank needs appropriate notice. The bank account remains inactive for a duration of about two months until the new Board of Directors is established. There must always be a member in Greece, authorised by the Board of Directors, to be responsible for the bank accounts' requirements.

This cannot be arranged through the By-laws but can be settled by the Board of Directors.

Finally concerning the platform to be adopted for the on-line meetings of the Board it is opportune to have no choice and let open all the possible Doors (Skype, Zoom, Meet, Team, Webinar).

Connection failed and General Secretary is forced to leave the meeting.



FORTHCOMING CONGRESSES

The Centenary Congress of the International Society for the History of Medicine (1921-2021)

Riga, August 2021

*The 47th Congress of the International Society for the History of Medicine (ISHM) was initially scheduled to take place in Riga (Latvia), in August 2020. This pre-centenary Congress of the ISHM has been postponed to **August 21st-23rd, 2021** due to the ongoing SARS-CoV-2 pandemic and in the hope of a classic "face to face" meeting. Nevertheless, the Congress has been formally opened virtually on August 24th, 2020. The 47th ISHM Congress will be held in August 2021 as the *Centenary ISHM Congress* either in an online version, or in a physical form, if possible. In one way or another, there will be a chance to meet each other again, analysing and better understanding the history of medicine and medical ethics, as well.*

Under these particular circumstances, *the call for papers has been renewed* and the deadline for abstract submission is now **March 8th, 2021**. The limit for one presenting author is of three abstracts (English language), as specified on the

Dana Baran

ISHM General Secretary

Email: ishmsecretariat@gmail.com

site of this scientific event (<http://ishm2020.rsu.lv/>; www.facebook.com; [twitter.com › ishm2020](https://twitter.com/ishm2020); [express.converia.de › frontend](http://express.converia.de)).

Celebrating one hundred years of uninterrupted activity – except for WWII time-lapse – is a unique moment. Globalised pathologies and fight against various life threatening conditions redimension the necessity of international cooperation in an attempt to draw useful lessons from the past intended to improve present and future history of humanity.

EAPE members are kindly invited to visit the Congress website and participate in the 47th ISHM Congress.



■ INSTRUCTIONS TO AUTHORS

The Bull Eur Assoc Profs Emer is a multidisciplinary journal fostering the idea that the vocation for research and teaching is for life and protecting full use of the human capital of professors emeriti.

The Bulletin adopts the Vancouver style. Authors are invited to visit the website of the Association and read the last issue. Manuscripts shall be in good English in Word, font 12, with good illustrations and shall be emailed to the editor in Chief, Natale Gaspare De Santo MD.

• Email: nataleg.desanto@unicampania.it

Original manuscripts (Word file) around 900-1100 words shall include affiliation(s), email and phone numbers of the authors, as well as 5 keywords from the manuscript. Preferably titles should not exceed the length of 50 characters (spaces included). A portrait of the 1st author is required. 1 Figure and 1 Table (emailed on separate sheets) and a maximum of 6 references and a minimum of 3 are allowed. References must be numbered and ordered sequentially as they appear in the text. When cited in the text, reference numbers are to be in round brackets.

Manuscripts related to news about emeriti and their associations shall be limited to a maximum of 500 words, and up to 3 references; no portrait of the author is required, but 1 Figure or 1 Table can be added.

All manuscripts undergo editing.

At the end of the article number references consecutively in the order in which they are first mentioned in the text. For articles with more than 6 authors, list the first 3 authors before using "et al."; For articles with 6 authors, or fewer, list all authors.

JOURNALS

1. *Journal article published electronically ahead of print*: Authors may add to a reference, the DOI ("digital object identifier") number unique to the publication for articles in press. It should be included immediately after the citation in the References.

Bergholdt HKM, Nordestgaard BG, Ellervik C. Milk intake is not associated with low risk of diabetes or overweight-obesity: a Mendelian randomization study in 97,811 Danish individuals. *Am J Clin Nutr* 2015 Jul 8 (Epub ahead of print; DOI: [doi:10.3945/ajcn.114.105049](https://doi.org/10.3945/ajcn.114.105049)).

2. *Standard journal article*. List all authors when 6 or fewer; when 6 or more, list only the first 3 and add "et al." Abbreviate journal titles according to *Index Medicus* style, which is used in MEDLINE citations.

De Santo NG, Altucci P, Heidland A et al. The role of emeriti and retired professors in medicine. *Q J Med* 2014;107: 407-410

3. Committee on Infectious Diseases, American Academy of Pediatrics. Measles: reassessment of the current immunization policy. *Pediatrics* 1989; 84:1110-1113.

BOOKS and other MONOGRAPHS

1. Personal authors

Antier JJ. Jean Guittou. Milan, Paoline, 2002

2. Committee report or corporate author

World Health Organisation. Good Health Adds Life to Years. Geneva, WHO, 2012.

3. Chapter in book

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