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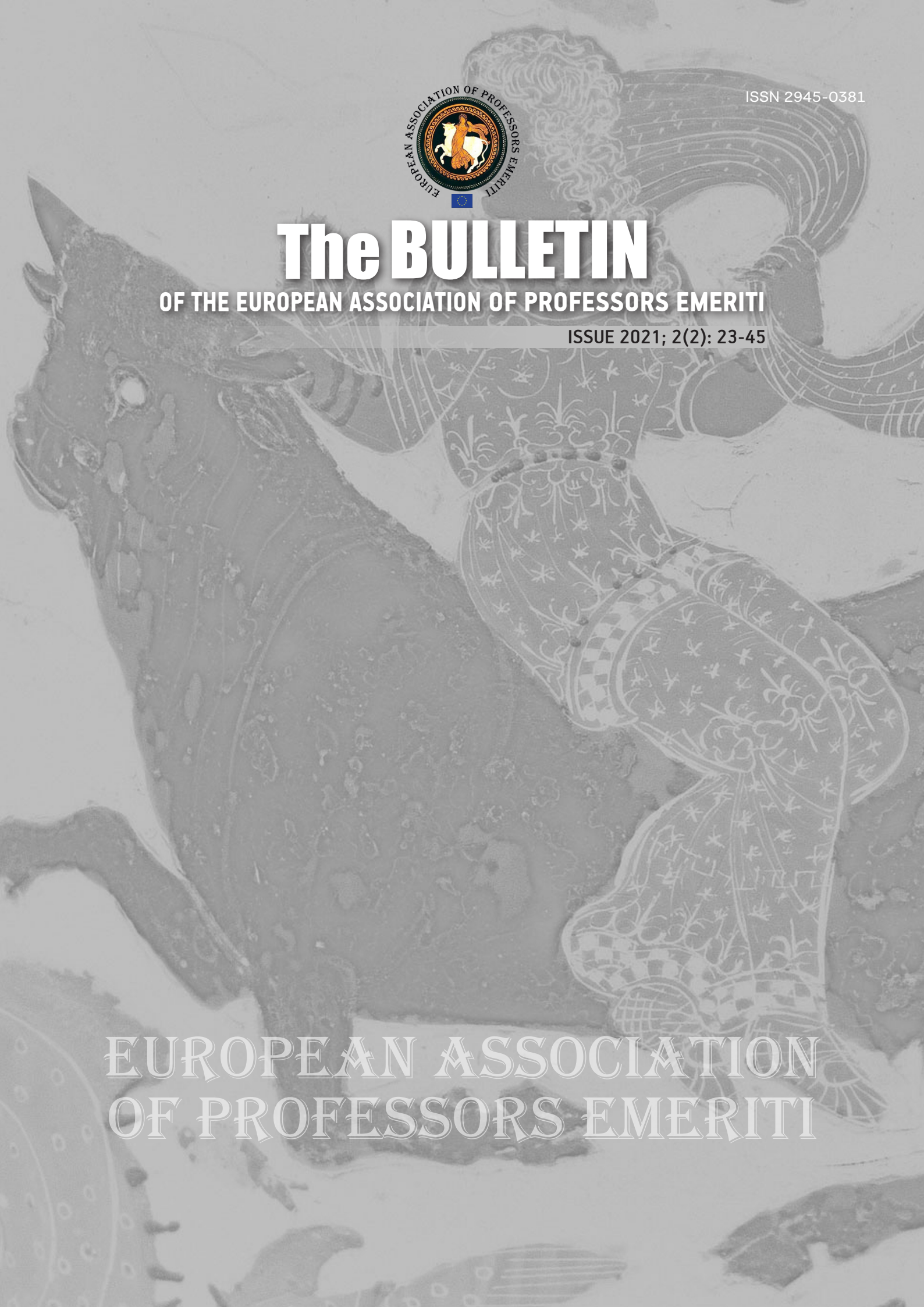

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PAGE CONTENT

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From the Needs and Wants of Children and Old-Olds to Technology

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Natale G. De Santo

I am happy to introduce the first paper of the EAPE Committee on *Linking the Wants and Needs of Children and Old-Olds*. It is authored by Jochen Ehrich Emeritus Professor of Paediatrics at the University of Hannover who, over the last 20 years, has continuously investigated European care for children. He entitles the paper *"Meeting the Wants and Needs of Children and Old-Olds: The impact of Complex System Thinking on Resilience, Prevention and Therapy"*.

I take the opportunity to remember that paediatricians in Europe care also for adolescents. This allows me to introduce a book written by Francesco Stoppa a brilliant Lacanian psychoanalyst-philosopher and captivating author of: *The ages of desire: Adolescence and Old Age in the Society of Eternal Youth* (1). The book opens with *The Three ages of man*, painted by Giorgione in 1500-1501 (Palatina Hall, Palazzo Pitti, Florence). The Leonardo-style painting consists of 3 half-length people. In the centre a young man looking into a music score. On his left an adult who teaches (?) and discusses with him. The adult represents the facts, the creative things, the achievements, the testimony of the presence of adults in the world and also, to a certain extent, their responsibilities in mentoring. On the right is an old man who does not care about the music score, who does not care about the relevance that the young and the adult contribute to teaching, learning, practicing and living with music. It is just an obligation for them. The old man looks into the eyes of the observer-into our eyes. He probably thinks the other two -discussing work and production of things- are not relevant. They discuss projects and achievements, the old man thinks that "inoperosity, or a choice to do nothing, is not absence of creativity", and that he has no obligation to show that he is performing well, he is just exempted from performing and from performances and that he is not obliged-as the young man is-to reclaim his identity, independence and creativity.

He-the old man-can even think of a world without himself, and there is no melancholy for his own withdrawal. But the young and the adult do not care for him. They do not see him and he is perfectly aware that his importance has nothing to do with memory of past things but in his presence. Probably he is thinking about a world without him, whereas he is preparing his setting. Probably he is the waiver of his own withdrawal. He has the feeling, typical of an author, who has in his hands the first copy of his last printed book. He recalls Donald Woods Winnicott and "the fight to be real" as well as the words needed "to express the loneliness one feels when deciding to change the world" (Springsteen) and "that times are changing" (Bob Dylan). "The old man is the writer that has completed a work" ... "The old man devolves to the future, the future he will not see, the benefits to get the answers to the puzzles related to his own existence. This knowledge is delegated to others".

What technology is

We can remember that Heidegger thought that technology would drive the world to a mere resource to be used. Indeed, we are still humans after the first and second wave of Covid-19 pandemic. Technology has given us distance teaching, smart work, online psychotherapies, medical and business consults, links with the world, including concert and theatre halls, and sport events We were and are humans since there is technology.

Being emeriti, we must be proud to have decided to work through technology. *Technologia ancila scientiarum*, allows us to hypothesise and establish bridges of hope. However, for Heidegger a) "technology is not an instrument, it is a way of understanding the world" b) it "is not a human activity, but develops beyond human control"; and c) technology is "the highest danger", risking us only seeing the world through technological thinking.

We are endangered, but probably the dangers may be less than the benefits. Richard Baldwin says that we

1. Francesco Stoppa. Le età del desiderio. Adolescenza e vecchiaia nella società dell'eterna Giovinezza. Milano, Feltrinelli 2021

live in a society of great changes (*Globotics Upheaval: Globalisation, Robotics and the Future of Work* (2). The changes are driven by automation and globalisation" that have to do with 800 million jobs in the human cloud and will cause job displacements. Ours is a world of telemigrants who sit in a country and work in the offices of another country, of remote work and robots that make work in presence less important and keep migrants in their countries and will reshape the world and will have effects on white collars and will probably reduce their incomes and life-styles. The author—founder and editor-in-chief of *Vox*—is Professor of International Economics at the Graduate Institute in Lausanne, visiting professor in leading universities and consultant-advisor of a long list of international institutions.

The monograph is not disruptive it is positive. It calls for the use of both brain and heart. The "happy end" can be achieved. Being "humane is an advantage not a handicap". Remote work, telemigrants and white-collar robots may be domesticated. However, we must bear in mind that "old rules will not count" and the "future does not set appointments". Luckily enough, robots lack the "humane empathy", so they are not invincible since they work only on the already known. We and our children may protect ourselves by selecting jobs done by huge groups of people, working together in well-defined places (by definition work in presence). We have the capability to determine the height and pace of transformation.

In Baldwin's pages we meet and become familiar with Amelia, working as a digital assistant at the help-desk online at the Swedish Bank (Skandinaviska Enskilda Banken-SEB). Amelia also works in London and Zurich, can read 300 pages in 30 seconds and simultaneously manage thousands of calls. Amelia is a white-collar robot!

2. Baldwin R. Rivoluzione globotica. Il Mulino, Bologna, 2021

What are the Promising Avenues for Medical Research in 2021

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Raymond Ardaillou

It is always difficult to predict the immediate future of medical research, especially since discoveries are often unexpected and result from observations in areas that funding providers have neglected. However, this paper tries to give some examples of areas that are growing and leading to new treatments. I have selected three of them: immunotherapy for leukaemia and solid tumours, genome "surgery" and new vaccines. Also, I will try to see if these recent discoveries were prepared in the past by researchers who were unable to exploit them.

1. Immunotherapy for leukaemias and solid tumours

It is an old idea. In 1969, Georges Mathé (Fig. 1), in France, developed active immunotherapy and demonstrated that the combination of BCG vaccine and irradiation plays a positive role in the evolution of leukaemia (1). However, the deficient knowledge of innate immunology at that time prevented him from going further. The anti-tumour control mechanism deployed by T lymphocytes is now well known. James P. Allison and Tasuku Honjo won the 2018 Nobel Prize for Physiology or Medicine for discovering a cancer treatment by suppressing negative immunomodulation (2). Naive T cells circulate between blood and lymph nodes. Dendritic cells are the

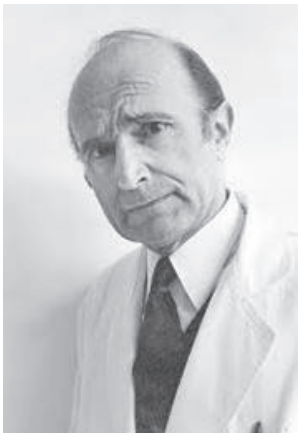

Fig. 1 - Georges Mathé

1. Mathé G., Pouillart P, Lapeyraque F. Active immunotherapy of L1210 leukaemia applied after the graft of tumour cells. Br J Cancer. 1969 ; 23: 814–824.

2. Félix d'Hérelles, the first to have studied infection and destruction of bacteria by microorganisms that he denominated bacteriophages (with permission of the French national academy of medicine).

first to face an infectious invasion in peripheral tissues, and transport pathogen fragments to draining lymph nodes where they present bacterial antigens to naive T cells which become activated and clonally expand. These effector T cells acquire new functions that are specific to the pathogen encountered and, for example, induce neutrophil activation and recruitment in response to bacterial pathogens. A similar process occurs with malignant tumours. It has been known for many years that these tumours are often invaded by lymphocytes. We know now that T lymphocytes constitute a means of defence of our body and we have learnt by which mechanism. They possess specific surface markers which bind to tumour cells and eliminate them. Among these surface proteins, one of them, CTLA4, is inhibitory. Thus, a monoclonal antibody against this protein has been proposed to inhibit this inhibitor. The tumour cells defend themselves by expressing PD1 ("Programmed cell death protein") receptors that bind to PDL-1 ("Programmed cell death protein ligand"), the latter being lymphocyte surface molecules that prevent PD1 from inhibiting T cell activation, proliferation and survival as well as cytotoxic secretion within cancer cells. Anti-PD1 or anti-PDL1 monoclonal antibodies break this axis and allow the T lymphocytes to act. These drugs are called "immune checkpoint inhibitors" (ICIs); they are more and more numerous. Used alone or in combination with conventional treatments, they are being tested extensively (3). Their name ends with "mab" for monoclonal antibody. Research is also in progress to identify predictive markers of their efficacy. Their beneficial role is confirmed in refractory or relapsing advanced solid tumours without being constant. One of the avenues explored for better treatment of these patients is to search the intestinal microbiota for help (4). Depending on its characteristics, the response to treatment is more or less effective and transplanting faeces from responders to resistant subjects improves the effect of the drugs; hence the idea of creating a bank to store beneficial faecal samples. Another treatment has been proposed in leukaemias and myelomas- CAR-T cells (for T cells carrying a chimeric receptor). T lymphocytes taken from the patient are multiplied and genetically modified in vitro so that they express an artificial receptor, known as chimeric, which will make them recognise tumour cells and destroy them (5). CAR-T cells can be engineered to target virtually any tumour-associated antigen. Other treatments are emerging, such as the administration of oncolytic viruses or antibody-chemotherapy conjugates where chemotherapy molecules are guided by the antibody to tumor surface antigens. Many problems remain to be overcome, including dose, safety, durability, and indeed efficacy without forgetting the cost of these treatments. Therefore, they are often combined with conventional chemotherapy as a last resort.

2."Surgery" of the genome

In this case, the past discovery by Félix d'Hérelles (Fig.2) in 1917 (6) that bacteria can be attacked and destroyed by microorganisms that he called bacteriophages, led to study the means of defence of bacteria. One hundred years later, Emmanuelle Charpentier and Jennifer Anne Doudna showed the role of the CRISPR system, already discovered by a Spanish researcher, Francisco Mojica, who called it *"Clustered Regularly Inter-Spaced Palindromic Repeats* (CRISPR)" (7). The merit of Emmanuelle Charpentier and Jennifer Doudna is to have understood the importance of this discovery. They demonstrated that DNA cleavage by CRISPR was possible by formation of a complex between Cas9 nuclease and two RNA, and recognition of the sequence containing the foreign infecting virus that was to be cleaved by pairing these RNA with the target DNA. This simple, robust and easily programmable system could cleave, specifically, a given DNA sequence by performing a double-stranded cut. The journal "Science" published this discovery very quickly (8) The two researchers immediately understood they had discovered a universal system which opens up fabulous prospects for "genome surgery" in humans since the already known process of creation of transgenic animals was not possible in man. They were awarded the Nobel prize in 2021. Since then, many advances have been made such as use of alternative nucleases and adjunction of a new DNA segment. The two cuts made by the nuclease are repaired by recombination in presence of the necessary donor DNA sequence. This donor DNA must contain nucleotide sequences that precede and follow the cut site. It is thus possible to modify

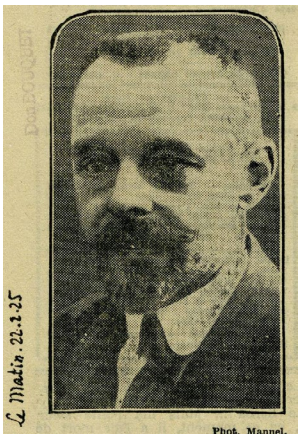

Fig. 2 - Félix d'Hérelles

3. Ma X, Zhang Y, Wang S, Wei H, Yu J Immune checkpoint inhibitor (ICI) combination therapy compared to monotherapy in advanced solid cancer: A systematic review. J Cancer. 2021; 12: 1318–1333.

4. Derosa L, Routy B, Kroeme G, Zitvogel L. The intestinal microbiota determines the clinical efficacy of immune checkpoint blockers targeting PD-1/PD-L1. Oncoimmunology. 2018; 7: e1434468.

5. Whilding LM, Maher J. CAR T-cell immunotherapy: The path from the by-road to the freeway? Mol Oncol. 2015; 9: 1994–2018.

6. D'Hérelle F. Microbiologie - Sur un microbe invisible antagoniste des bacilles dysentériques. *Comptes rendus hebdomadaires des séances de l'Académie des sciences*, 10 septembre 1917, tome 165, p. 373-375.

7. Díez-Villaseño C, Guzmán NM, Almendros C, García-Martínez J, Mojica F. CRISPR-spacer integration reporter plasmids reveal distinct genuine acquisition specificities among CRISPR-Cas I-E variants of *Escherichia coli*. RNA Biol. 2013; 10: 792–802.

8. Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual RNA-guided DNA endonuclease in adaptive bacterial immunity. Science. 2012 Aug 17; 337(6096): 816–821.

a few nucleotides of the targeted gene, to introduce one or more missing exons, or even to introduce a complete gene. All these methods offer researchers the ability to modify the genome of plants, animals and even human cells (9). The CRISPR technology can be used in biotechnology, biomedical research and therapeutic applications. It allows the specific modification of the nucleotide sequence of a gene, or of a non-coding element (such as a microRNA), to make it non-functional. It also makes it possible to eliminate or introduce from one to several thousand nucleotides in order to correct a mutation responsible for an inherited disease. The modifications made can also lead to the identification of the function of a gene, which is then rendered non-functional, and to the evaluation of the phenotypic consequences of mutations induced in cells or whole organisms. Genome surgery has also been applied in animals to male gametes, the easiest to modify, in order to remove genes responsible for hereditary diseases. In this case, not only the affected animal is treated, but also its offspring. We see the ethical questions raised, since the genome can theoretically be modified not for therapeutic purposes, but to give birth to the desired child.

3. The RNA vaccines

Presented at the beginning of 1961 in a pioneer article (10) for which they were awarded the Nobel Prize, François Jacob (Fig.3) and Jacques Monod wondered how the message carried by the genes, through DNA, was transmitted to the place where the proteins are synthesised, on structures called ribosomes. According to their hypotheses, this transmission had to be carried out by an RNA, which they described as a "messenger", a copy of the DNA sequence made of a chain of nucleotides. At that time many vaccines were utilised. They were created on the model of attenuated viruses, bacteria, or bacterial toxins. At the end of the 1980's, only DNA interested researchers who were mainly involved in gene therapy. However, Katalin Kariko was interested in messenger RNA. Imagining it would provide cells with a mechanism that would allow them to make therapeutic proteins themselves, independently of the nucleus, a solution avoiding modification of the cells' genome and thus risking the introduction of uncontrollable genetic modifications. But direct use of messenger RNA raises several problems; in particular, its administration provoked strong inflammatory reactions that could be suppressed by introducing mini modifications in the structure of the RNA, making it more acceptable to the immune system. Their discovery, published in 2005, made a lasting impression, pulling Ms. Kariko and her colleagues out of the darkness which they were in (11). Many teams in the world considered that mRNA was a promising tool for vaccine development as well as in infectious diseases or in cancers or hormone production. After entering the cell cytosol, mRNA gives birth to the targeted protein of the virus, bacteria or tumour followed by the production of antibodies or, in the case of tumours, by the activation of naïve T cells. Concerning the production of hormones, we can hope that the RNA should substitute for defective cells by producing the missing hormone. Several advantages were highlighted: mRNA does not enter the nucleus avoiding the risk of genome mutations, its immunogenicity is attenuated by wrapping it in an envelope of lipids; if a mutation of the targeted protein occurs, the structure of the mRNA can be easily modified; it does not need the adjunction of an adjuvant to boost the immune reaction. A problem is its easy degradation and short lifespan at the body temperature making its conservation at a low temperature obligatory. As observed with the pandemic of Covid-19, it has proven to be the vaccine of choice and the two preparations on the market (Pfizer and Moderna) are the most in demand. These vaccines contain RNA coding for the protein Spike of the virus capsid, gateway for the virus to enter the cell. In reaction, there is a production of specific antibodies, first IgM, then IgG leading to protection that must be boosted by a second injection one month later (12). The other therapeutic possibilities mentioned above are still in the experimental field at the animal level.

Fig. 3 - François Jacob

In conclusion, it is interesting to observe that all the recent discoveries have more or less remote precursors/scientists who paved the way by their own discoveries. Very often they were stopped by the level of current knowledge at their time or, more rarely, by the fact they did not realise the importance of their discovery and the consequences to be drawn from it.

9. Rodríguez-Rodríguez DR, Ramírez-Solís R, Garza-Elizondo MA, Garza-Rodríguez M, Barrera-Saldaña H. Genome editing: A perspective on the application of CRISPR/Cas9 to study human diseases Int J Mol Med. 2019; 43: 1559–1574.

10. Jacob F. et Monod J., Genetic Regulatory Mechanisms in the Synthesis of Proteins. J. Mol. Biol. 1961; 3: 318-356.

11. Foster JB, Choudhari N, Perazzelli J, Storm J, Hofmann TJ, Jain P, Storm PB, Pardi N, Weissman D, Waanders AJ, Grupp SA, Karikó K, Resnick AC, Barrett DM. Purification of mRNA Encoding Chimeric Antigen Receptor Is Critical for Generation of a Robust T-Cell Response. Hum Gene Ther. 2019; 30: 168–178.

12. Kis Z, Kontoravdi C, Shattock R, Shah N. Resources, Production Scales and Time Required for Producing RNA Vaccines for the Global Pandemic Demand. Vaccines. 2021; 9: 3.

Epidemics: Focus on Antique and Early Medieval Outbreaks

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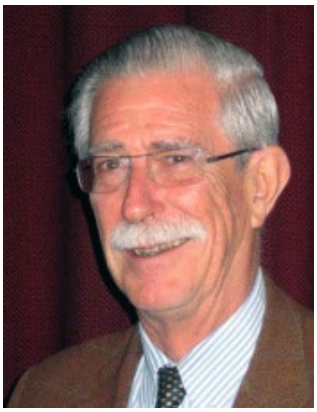

R. Van Hee

Introduction

Epidemics have existed since mankind tried to gather in communities, in order to create an agrarian way of living, and better accommodate to various types of challenges.

A delicate symbiosis got installed between pathogens and insects on the one hand, and the sedentary humans and their surrounding domestic animals on the other. Both became prey to various microorganisms, which could coexist in increasing numbers in these communities, and from time to time could infect each other, whether from animals to men or from man to man. So did cattle become the host for cowpox viruses, or pigs, birds or horses be carriers of viruses responsible for airway or pulmonary diseases, that eventually could infect humans.

For the human race, incapable of visually detecting these infective agents, the aetiology of such diseases remained obscure for thousands of years.

It is understandable that in these circumstances humans turned to equally invisible gods and devils to explain the occurrence of individual diseases or collective epidemics.

Moreover the greater such human communities grew in size and number, the more frequent became such outbreaks of infectious diseases.

With the advent of script in the river basins of Mesopotamia and Egypt around 3.000 B.C., we became more informed about symptoms, evolution and outcome of such diseases. Equally the coincidence of epidemics with long periods of drought or excessive rain fall became apparent. So was a pestilential disease in the biblical city of Ur around 2.000 B.C. paralleled by bad harvests and increasing famine, resulting in a decimation of the urban population. Around the same time an analogous outbreak was seen in pharaonic Egypt, with an analogous catastrophic outcome.

More explicit reports followed in classical Greece.

The Plague of Athens

Well known and documented is the report by the historian Thucydides (ca.460-400 B.C.) of the so-called **plague of Athens** (430-426 B.C.). His report '*On the Peloponnesian War*' has been translated into Latin and later into most vernacular languages, and contains relevant details concerning the disease (1). It started in Africa, moved around the Mediterranean and passed through Palestine,

Picture of Thucydides on a mosaic from Jerash, Jordan. Roman, 3rd century A.D. Berlin: Pergamon Museum.

to reach Greece at the dawn of the Second Peloponnesian War. The report is very clear in depicting the symptoms. There were massive deaths, not only in the military forces of the two fighting cities of Athens and Sparta together with their allies, but equally in the urban civic populations. Approximately a quarter of the inhabitants died. The disease was most probably typhus, though infections like leptospirosis have also been incriminated.

The Antonine Plague

Still more explicit is the report of another great epidemic in Antiquity, called the **Antonine plague** and occurring in the Roman Empire in the second century A.D. This time it was the great Galen who depicted the epidemic in his '*Methodus*

1. Mark, J. J. (2020, April 01). Thucydides on the Plague of Athens: Text & Commentary. *World History Encyclopedia*. Retrieved on April 1, 2020 from https://www.ancient.eu/article/1535/

Medendi' (2). Galen arrived in Rome in 164 A.D., when the epidemic was at its height. The whole city was in shock as a result of a terrible disease, characterized by fever, dry mouth, pustule formation and prostration. Thousands of citizens succumbed from the disease and the just reigning emperor Marcus Aurelius (from the Antonine family) had to address the social and economic consequences of the disaster. The hospital on the Tiber island got overcrowded as did the cemeteries. Recent investigations of the DNA of skeletons of the epidemic detected, irrefutably, smallpox as the cause of the disease. This diagnosis matched quite well with the account of Galen.

The Cyprian Plague

Less than a century later a new epidemic ravaged the Empire, now in the sub Mediterranean city of Alexandria, but soon spreading over the north African coast, and to the Italian peninsula and beyond. This **Cyprian plague** started around 250 A.D. and was well described by bishop Cyprianus of Carthago. In his '*De Mortalitate*', he cites the symptoms, in particular fever and diarrhoea, and pointed to the disastrous prognosis (3). Treatment consisted of Galenic bloodletting and diet, but couldn't prevent life threatening dehydration. So did the population of Alexandria fall from 500.000 to less than 200.000 inhabitants. Most probably the disease may have been the result of a Shigella infection, signalled by the massive gastroenteritis.

The Justinian Plague

Still more impressive was the so-called **Justinian plague** in the early 6th century A.D. To prevent progressive invasion of his territories, Emperor Justinian (ca.482-565) had been obliged to mobilize thousands of extra soldiers, and raise high taxes to provide their pay, and simultaneously sustain the needs of the common population, which experienced consecutive years of bad harvests and famine. This epidemic, probably for the first time, was a real plague, induced by the 'Pasteurella pestis' bacterium. Indeed not only did the reported manuscripts point to this diagnosis, but DNA research of human remains could unequivocally acknowledge the deadly bacteria. Brought by the Moghul invasions in the previous years, rats colonized the warlike hordes and so introduced the deadly microorganism in Europe.

Picture of Emperor Justinian (center figure) on a mosaic from 547 A.D. in the apse of the Basilica of San Vitale, Ravenna.

The catastrophe had a death toll, unseen in the Western world up till then. Most reports allow an extrapolation of the mortality, reaching half of the entire population, grossly from 200 to 100 million inhabitants of the Roman Empire. Emperor Justinian, living in the very afflicted city of Constantinople, hardly survived the epidemic, one of the 20% survivors in the city.

In the epoch making '*The Fall of the Roman Empire*', Kyle Harper stressed the role which this plague played in the progressive decline of the Roman Empire, at least in the West (4). But he also described the concomitant influence of the climate on these successive epidemics in the 2nd, 3rd and 6th centuries. Indeed a thorough investigation led him to correlate a period of ideal climate, the so-called 'Roman climate optimum' (or RCO) from ca. 250 B.C. to ca. 150 A.D., with the prosperous flourishing of the Roman Empire (that equally existed in the Han Empire in the East). On the contrary the worsening of the climate in the centuries that followed, induced bad weather, whether drought or excessive rain fall with flooding, bad harvests, famine, malnutrition, and increasing susceptibility to infection.

Harper's research therefore sets out a paradigm of effects of climate change on health and disease in worldwide history, at least for Antiquity.

Plagues from Carolingian era to XIV Century

There are less documented reports of epidemics in the Carolingian era of the Middle Ages. One of the reasons may indeed have been the better climate experienced in this period. From the 8th century onwards a better climate led to prosperous harvests, a consequent clear increase in population in East and West, and an apparent health improvement of their inhabitants.

Of course the plague did not disappear and between 541 and 767 at least eleven endemic flare-ups have disturbed our regions, but they remained local and could be controlled.

In the centuries to follow good harvests and crops of all sorts grew continuously in number in a tender climate. Various illuminated manuscripts, like the '*Books of Hours*' testify of these prosperous years.

2. Littman R.J. & Littman M.L. Galen and the Antonine Plague. *Am J Philology* 1973, 94: 243-255.

3. Scourfield J.H.D. The De Mortalitate of Cyprian: Consolation and Context. Vigiliae Christianae 1996, 50: 12-41.

4. Harper K.The fate of Rome. Climate, disease, & the end of an empire. Princeton & Oxford: Princeton University Press, 2017.

Not that infections didn't exist, on the contrary, but they were constrained to individuals or resulted in minor outbreaks, mostly in the poor urban quarters.

The rather abrupt climate change at the end of the 13th century put an end to this rather prosperous era. Indeed the winter of the year 1309-1310 inaugurated a sort of mini-glacial environment, that would subsist for several centuries, even up to the 19th century. The paintings of Peter Breughel father and son, in the mid-16th century, demonstrating frozen rivers and ponds testify to this so-called mini Ice Age (5).

It is therefore not surprising that some decades later, in 1346, a new plague epidemic would conquer Europe and devastate its population and economy.

Of the second real plague epidemic in this 14th century, there is more than abundant literature, which will not be discussed here. However, from then on a clear-cut parallel may be drawn between recurrent epidemics and the ongoing bad climate. This gives us something to think about concerning our own future, with respect to health and climate change (6).

5. Van Hee R. Infectious diseases: relationship with climate in the past and present. Vesalius. Acta Soc. Intern. Hist. Med. 2020, 26 (2): 86-99.

6. Sales R.N., Shultz J.M. & Solomon C.G. The Climate Crisis and Covid-19 . A major Threat to the Pandemic Response. N Engl J Med 2020, 383: e70.

Meeting the Wants and Needs of Children and Old-Olds: The impact of Complex System Thinking on Resilience, Prevention and Therapy

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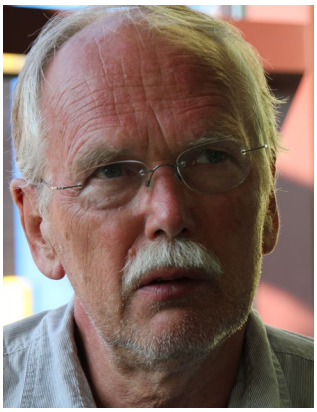

Jochen Ehrich

In 2021 medical care could be better than it currently is in many countries. Developing countries have post-hoc needs and rich countries have post-thought needs in answering the question of how medical care could be improved despite technology-related cost increases in the context of comprehensive cost-benefit analyses for their population.

Patients of young and old age belong in many aspects to the most vulnerable parts of society. Their health depends approximately 85% on *general health* care and 15% on *medical care*. The current disparities in the quality of health care are due to several factors such as the lack of application of the root-cause-effect, long-term consequences model and little consideration of the life-cycle model. In spite of undoubted great progress in medical care, in recent years an increasing distrust in the health care systems has developed in parallel among populations of European countries, thus creating a success-mistrust paradox.

Health care systems are complex networks (1) that are shaped by experts from many fields of medicine, psychology, sociology, economics and politics. The role of philosophy has been small in this network. Questions arise as to whether this lack of integration of philosophical perspectives contributes to deficits in the healthcare systems and how philosophy could lead to new ways of complex systems thinking. Health care systems of many European countries have great problems to implement the necessary changes in healthcare services from the theoretical level via the political executive to the practical level. Many healthcare systems lack forward-looking sociological-philosophical concepts for adapting to the constantly changing social conditions with regard to adequacy, accessibility, affordability and availability of healthcare.

In this article, a stronger involvement of clinical

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philosophy in health care (2) is presented with three examples: the improvement of *resilience*, *adherence* in the context of therapy and integration, and *resonance* in the treatment triangle of patient-family and treatment-provider. Practical philosophy can be helpful in conceptualisation and operationalisation in the context of translating theoretical concepts into clinical practice. Although financial benefits of the presented concept cannot yet be proven, it is obvious that patients and their families could benefit from application of *complex systems thinking and philosophy* to patient-friendly health care.

When dealing with children and old patients, clinical philosophers must seek cooperation with physicians and nurses in maternal and neonatal, community and hospital care , in highly specialized centres of excellence, socio-medical, psychiatric, geriatric, rehabilitation, palliative care centres, and in public healthcare service systems. A particularly close cooperation must be established with psychologists, social workers, teachers and church pastors, avoiding destructive competition. Cooperation with ethics committees, forensic medicine and hospital management is desirable. In the case of the latter, questions concerning the remuneration of philosophers and cost-benefit analysis of their activities should be clarified. The increasing sub-specialisation of medicine will also require continuing education in clinical philosophy. Therefore, the question arises as to how a curriculum for training with final accreditation can be created in collaboration between philosophy and medicine. Without accreditation of clinical philosophy, the integration of philosophers in hospitals will hardly be possible.

Resilience training

Resilience is a well-known phenomenon in medicine among those individuals who go their positive way despite the most adverse environmental conditions (3). *Individual resilience* is not an inherited trait and it does not apply generally to all conflict situations, but it has been selectively learned in an individual for specific constellations. Individual resilience is based on self-confidence, curiosity, and doubt. The critical question in child healthcare is: "Who can competently support children during their difficult learning processes of adapting successfully to a crisis which may lead to an acute disease or to a life with a long-term disease?" The immediate answers by all care-givers will automatically be: "But this is what we are doing everyday." However, will this be enough? The principle of sub-specialisation has taught paediatricians that one should always include the best experts during treatment of complicated cases. Child healthcare services may benefit from specially trained advisers who can teach resilience strategies to children at risk. In my opinion, this concept is also applicable to geriatric care.

It is also important to empower the individual physician to be resilient when asking: "What can I do or change myself? What should I not do?" Relying on other people in the fragmented healthcare system is a poor solution principle for crises in healthcare.

In the context of improving care systems in Europe, *collective resilience* means that countries remain capable of acting in a crisis. A prerequisite for collective resilience of all stakeholders in the health care systems of the countries is the formation of networks and the commitment of all to the network. Ultimately, this means that all people may benefit from complex systems thinking to champion unavoidable conflicts between physicians in practice and in hospitals, between generalists and organ specialists, and between physicians and non-physicians.

Understanding non-adherence

Non-adherence (Non-A) to required treatment measures such as medication adherence are more often attributed to patient behavioural disturbances than to physicians' lack of adherence to treatment guidelines, although Non-A occurs in both groups (4). In adolescent kidney transplant recipients, estimated Non-A ranges from 30% to 70% and poses a high risk for graft rejection. The causes of Non-A in adolescents are related to their understandable autonomy aspirations and desire for normalcy. However, Non-A also correlates with lack of adherence to insufficient understanding by caregivers, as well as health insurance deficits and other institutional system barriers. The purpose of philosophical counselling in Non-A is to think through the problems that inevitably arise within a complex treatment and relationship system, and to initiate debate about how to promote positive problem solving.

From my own experience with more than 1000 transplanted children and adolescents, I conclude that "non-cooperative" patients suffer from lack of communication with health care providers, feel misunderstood and not taken seriously in their inner distress and doubt. In order to accept their personal reasons for Non-A, they blame the health care providers for their "failure" and block a processing of their own conflicts by this pain avoidance behaviour. Their blaming in turn reinforces the tendency of physicians to selectively assign Non-A to patients and families. The resulting mutual blame is a symptom of unresolved

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conflicts that are highly stressful for all concerned. Caring for a transplanted organ requires significant discipline and adjustment of patients' and families' lifestyles within very tight constraints, including lifelong medical monitoring. These demands may clash with patients' desires to maintain and defend their personal autonomy. This, in turn, can reinforce tendencies to resist measures that involve discomfort and monitoring. In other words, Non-A occurs at the borderline between the rational and medical sense of treatment on the one hand and the emotional and personal sense of life of patients and families on the other. It is the goal of philosophical counselling to create a contact between all parties involved that allows closeness and mutual understanding. Although Non-A appears as meaningless behaviour from the outside, it has a special meaning from the inside view of patients. The challenge of philosophical practice is to decode and understand the relevant and individual meaning of all parties involved in order to make the essence clear to them. My experience is that patients in such conflict situations prefer to accept the help of "neutral" persons who are not part of the immediate treatment team, rather than help from the caregivers they have known for a long time and who are part of the conflict.

Any patient's psychosocial crisis involves and increases the risk for Non-A. Therefore, questions of coordination of psychological and philosophical counselling arise. Philosophy differs from psychotherapy in that it is not therapy. It is concerned with intensifying the patient's experience of life. Philosophy is therefore a reflection on existence and a contribution to the communication of existence to patients when their existence is threatened. After interpreting the particular crisis that triggered a Non-A, patients have relevant rational and emotional reasons for Non-A from their point of view. These rationales are a meaningful signal of perceived incompatibilities and communication breakdowns. These reasons must be understood by the physicians, even if they hurt them. Acceptance of the patient's perspective by the treatment team can enhance the patient's sense of autonomy and foster their trust in the care givers, which in turn contributes to the avoidance of Non-A.

Resonance in the context of clinical-philosophical counselling

Resonance is an experience created in the moment as a temporary form of meaningful communication. In this sense, resonance in everyday life lies outside the idea of creating structures in the sense of formality or mutual responsibility, obligation or even permanence. Instead, resonance is played and re-played in the present moment(5).

Resonance in the context of clinical-philosophical consultation is an experience of belonging, intimacy and mutual understanding. In this sense it is a meaningful and profound experience, which distinguishes it from the anonymous character of everyday life and a medical consultation in form and content. At the same time, resonance in philosophical counselling is not a ritual. The counselling, while planned, is not exceptional to everyday life and is an important part of everyday life. Resonance is an emotional connection based on an appeal to share human experience. Thus, the relationship between patients and philosophers is very different from the doctor-patient relationship. The extent to which patients are fundamentally more likely to reveal themselves to clinical philosophers than to physicians and psychologists is worthy of debate.

Resonance in philosophical consultation is an entity that must be distinct from the social interactions from which it emerged. It is a co-production of objectivities and subjectivities that, through processes similar to the notions of feedback or reverberation, create a therapeutic phenomenon that is greater than the sum of its individual medical parts.

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Professors Emeriti at Spanish Universities

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Dr Malcolm Phillips

There is interest in the possible role of retired high school teachers as supervisors of career paths of newly hired young professors(1,2). A recent book from the Jagellonian University in Krakow has made significant additions and broadened the discussion in Europe (3).

Miguel Ángel Negrín Medina, Juan José Marrero Galván from the University La Laguna, have analyzed for the monographs of the Jagellian University the status of professors emeriti in Spain within the framework of didactical experimentations of high school teachers in experimental science (4).

In Spain the enrollment and the duties of professors emeriti is regulated by Law 27/1994, the 29th of September, of modification of the retiring age for university teaching staff (BOE no. 234 on the 30th of September) and by Law 6/2001, 21st of December, of Universities (BOE no. 307, 24th of December).

Professors emeriti in Spain retire at 70 years of age. Only 3% of them can be nominated emeriti and for this will receive a compensation compatible with their pensions. The emeritus status can be conferred only on professors who have had a tenure of at least 10 years. Merits are ascertained through a grid made of 3 blocks: (I). Related to their investigation and teaching career path; (II). Related to the attraction and obtaining resources for research; (III). Related to administrative management exerted in university and research. Each university independently selects the blocks of merits and the extent of its application.

Concerning career path, assessment is made of inherent research, awards and quality teaching. Attraction is assessed by resources, projects, visits to international institutions, role in projects Importance is given to administrative roles as chancellor, vice-chancellor, dean, chief of department, chief of a research unit, participation in relevant committees. Emeriti can (i). Represent the institution, (ii). Help in research; (iii). Help in teaching, and (iiii). Assist with funding sources. The paperwork is very exhaustive and includes comparison of the status, duties, and achievements of emeriti in Spain with present status in USA, Europe and worldwide (5,6).

In Spain at the end of 2017 there were 694 emeriti, 57,790 professors aged fifty years or more and 17,985 professors aged sixty years or more. This allows to foresee that there will be more pressure from the ageing community to acquire the emeritus status and its benefits. Thus now lower forms of assessments are being discussed, including less honorable states not requiring a payment and also imposing less duties.

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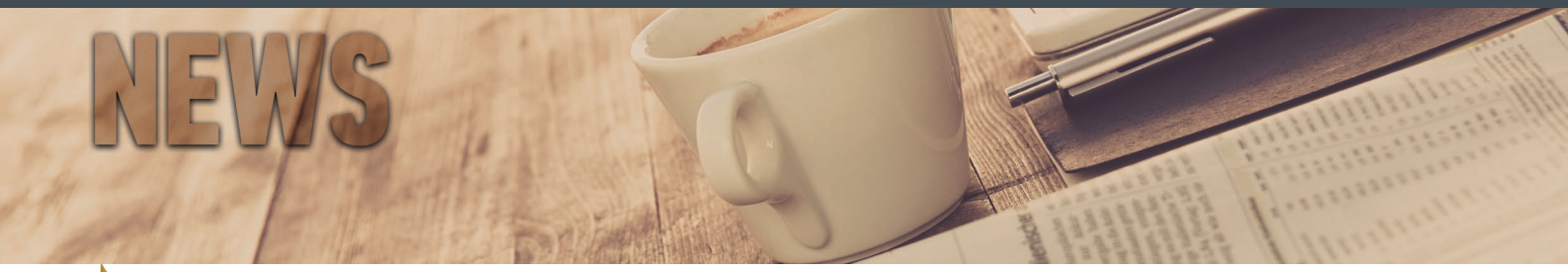

Starting the Debate on Academic Freedom in Paediatric Healthcare Service Systems in 2021 in Europe

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The project "Safeguarding Academic Freedom in Europe" (SAFE) assessed the de facto protection of academic freedom in Europe (1). The results showed that the legal protection of academic freedom in Europe leaves much to be desired. In 2021, Eric Kaufmann reported on Academic Freedom in Crisis: Punishment, Political Discrimination, and Self-Censorship (2). Academic freedom is essential to the proper functioning of universities including the departments of paediatrics. Karran wrote: "In the view of a significant majority of academic staff throughout Europe, the protection of academic freedom in practice has reached a disturbingly low level: higher education institutions rely on their institutional autonomy to infringe individual academic freedom. Academic staff do not sufficiently participate in the taking of academic, but also strategic, decisions in senates/boards or faculty/departmental councils, and job security (including tenure) is inadequately protected"(1).

This article aims to open the debate on *academic freedom in paediatrics*. Based on the number of paediatricians being trained and those retiring, in 18 of 36 European countries the numbers of general and specialised paediatricians were decreasing in 2012 (3). In 2020, 25 of 48 countries were expecting to have a shortage in paediatric nephrologists by 2025 (own unpublished data). The ongoing survey of the European Society for Paediatric Nephrology on "diversity of kidney care for European children" revealed that 38% of countries answered the question "Do you have problems with vanishing paediatrician scientists in your country?", with "YES". Forty percent of countries answered the question "Do you have enough candidates to choose successors for leading positions in paediatric nephrology?", with "NO". Fifty-six percent of leading paediatric nephrologists from 48 European countries reported that the possibilities for research ranked among the top incentives of junior paediatricians to start an academic career at university children's hospitals (preliminary unpublished data). What could be the reasons for the imbalance between the wishes of young paediatricians and the chances offered at universities? The alarm signals on the crisis of academic freedom in general justify a discussion on the future of pediatric care.

Academic freedom in paediatric departments of university children's hospitals enables paediatricians to engage in controversial research and critical inquiry concerning complex child healthcare. It creates a scientific atmosphere to advance human knowledge in health sciences and to protect the health and well-being of children. Academic freedom is the right of academic staff members to teach undergraduates and train postgraduates. Academic freedom includes the right of paediatricians to practice research and publish the obtained findings regardless of prevailing opinion, prescribed doctrine, or institutional preferences. It includes the freedom of paediatricians to express their critical opinion about workplace institutions and broad public issues. It also includes the freedom of academic paediatricians to participate in national and international academic organisations and governing bodies. Last but not least, it includes mechanisms that regulate the functions of paediatricians at their own workplaces, sustaining security of appointment and income of paediatricians.

The challenges of academic freedom in medicine including paediatrics are related to a multitude of factors listed in the table 1 and 2.

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TABLE 1

Systemic factors challenging freedom of research in paediatrics

1. Lack of political freedom (gap between power and intellect).
2. Laws that forbid therapeutic trials with children.
3. Power- seeking politicians and ministries of health, etc.
4. Primacy of the market. Are money and competition the dominant motivators of science?
5. Bureaucracy of international and national funding programs.
6. Nationalism.
7. Religious beliefs.
8. Inadequate sponsoring of pharmaceutical industry.
9. Professional congress organisers.
10. Editorial boards of Journals and reviewing processes of submitted manuscripts.
11. Poisonous competition among scientists.
12. Reductionism in research and lack of complex systems thinking.
13. Lack of support for multi-centric, national and international, randomised, prospective controlled therapeutic studies.
14. Forbidden sending of biological material to laboratories in foreign countries for further diagnostics.
15. Lack of ethical committees.
16. Inappropriate diagnostic algorithms, outdated therapeutic guidelines, inadequate legal restrictions.
17. Inadequate political or scientific leadership.
18. Fragmented child healthcare services.
19. Uncertain development that paediatrics may disappear from primary care.

TABLE 2

Individual factors challenging freedom of research in paediatrics

1. Lack of incentives for young researchers.
2. Lack of individual idealism and collective visions.
3. Lack of access to online literature.
4. Lack of support for participation at international congresses.
5. Lack of time for research after routine work.
6. Lack of infrastructure concerning laboratories, institutes of statistics, etc.
7. Lack of training in research methods.
8. Lack of adequate and motivating supervision.
9. Lack of curiosity, energy, self-confidence and self-determination.

In summary, democratic governmental systems are based on freedom and equality in which power is held by elected representatives or directly by people. They exist in politics, economics and also in science. In the sense of Aristotle, the correct middle path between the opposing pair of freedom on the one hand and necessity, responsibility and order on the other, reflects the highest value. How does this concept apply to academic freedom at universities? Also, what do we know about diversity of academic freedom in European medicine? A spontaneous answer could be that academic freedom is closely related to the degree of general political freedom. Democratic governments have freedom of speech, freedom of the press, freedom of movement, and freedom of choice of profession written into their constitutions, and non-democratic systems severely restrict these freedoms. However, in most countries, bureaucracy is probably the most frequently cited cause of restricted academic freedom. For understandable reasons, its limits set by policy makers in totalitarian regimes may be the most frequent taboo. In conclusion, this short article aims to open a discussion among members of EAPE on diversity of academic freedom in Europe.

NEWS

Academic Freedom in Communist Czechoslovakia

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Academic freedom in the former Czechoslovakia was blocked by the socialist regime until 1989. Mitigation occurred during the so-called Prague Spring in 1968, which was suppressed by the invasion of the Warsaw Pact troops on the orders of the representatives of the Kremlin and the communist traitors of our Republic. This period was followed by hard normalisation, which reinforced the power of the communist party, supported by Moscow. All important positions in the Republic and in the academic community were occupied by loyal communists. Whoever was not a member of the party had his career stopped.

Professor Miroslav Mydlik

As an example, I will mention the career story of Professor Miroslav Mydlík, MD, DSc., who never joined the Communist Party. As a young doctor he joined the Ist (now IVth) Internal Clinic of the Faculty Hospital in Košice (now the University Hospital of L. Pasteur) and the Medical Faculty of the P. J. Šafárik University (UPJŠ), at the end of 1959. After completing attestations in internal medicine and later in nephrology, he defended his dissertation thesis in clinical nephrology (1971). From the very beginning, he devoted himself to nephrology very intensively, he founded the Dialysis Centre in 1966. Already in this period, the arrogance of the communists members of the clinic became apparent, undermining his authority and enforcing their own decisions. In 1979, he submitted his habilitation thesis at the Department for Science and Research of the Medical Faculty of UPJŠ. The Scientific Council was in the hands of the communists, who said: "While we are in power, Mydlík will not be an associate professor." The thesis was stored in a safe and until 1990 was locked there. Only after the fall of the communist regime in Czechoslovakia, was Mydlík accredited Associate Professor (1991). In the meantime, he became a Doctor of Medical Sciences at Charles University in Prague (1984) with the support of Prague professors and moderate communists from Košice. When the position of head of the First Internal Clinic became vacant, he was one of two candidates, of course they chose a communist. One of the members of the Communist Party committee of the Faculty Hospital commented on Mydlík: "He is neither a party member nor anything".

Due to the conflict between two important representatives of the Faculty Hospital, heads of clinics, he was not appointed a member of the kidney transplantation group. He could not freely publish scientific papers in foreign journals, and therefore many times he sent manuscripts e.g. via Hungary. He could only attend European or world congresses with approval of the Scientific Council of the Faculty of Medicine, i.e., the Communist representatives, even though he had been invited to give a lecture. On one occasion when travelling by train to Athens, on the border with Hungary, there was a check by border police to see whether he had permission from his employer to lecture abroad. A satisfaction for all the hardships he endured during his career, was that he achieved the title of full Professor of Internal Medicine in 1992. He became head of the IVth Internal Clinic and later Nephrology Clinic and Chief expert for nephrology at the Ministry of Health of Slovakia. He became Chairman of the Medical Association in Košice and, in 2015, was admitted to the "Hall of Glory of Slovak Medicine" (1).

Not less than 15 papers have appeared relating to the achievements of Professor Miroslav Mydlik, who was a founder of EAPE in September 2016 and substitute councillor of the the first Board of Directors. Some are listed here (2-6). Many obituaries appeared on the web sites of national and international associations including Slovak, EAPE, the European Renal Association, the International Association for the History of Nephrology.

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Chemistry Faces Covid-19

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Nobel Prize winner, Joshua Lederberg, stated that the biggest danger for human kind is from viruses. This claim cannot be forgotten at this time when we are looking for a reason for hope and that hope, after ensuring adequate sanitary services and responsible behaviour of citizens, can come only from Science.

Medical sciences undoubtedly represent the queen of disciplines, but many other disciplines can play a very important role.

At this particular moment the basic core of knowledge is provided by a group of biosciences such as medicine, virology, biology, biotechnology. It is fundamental to have an intradisciplinary group that speaks the same language at the start of any research activity.

After the working group started it was absolutely necessary that it acquired interdisciplinary features because a scientific problem has to be regarded from different competences and cultures. This is the only approach to increase the likelihood of finding an acceptable and positive solution. Generally speaking, the successful team must be as heterogeneous as possible. Perhaps chemistry can guarantee a specific attitude in criticism, a forma mentis, with its epistemological characteristics that are highly dependent on conceptual, theoretical and experimental diversity. For these reasons, chemistry can support and act as a "glue" in the group of disciplines that have made up the fundamental historical group to combat Covid-19 Some may think that such a heterogeneous group would have difficulties in language and culture for the benefit of the work, but this interaction, among heterogeneous competences, clearly fits into a holistic vision of the health problems, related to hygienic, environmental, alimentary and social conditions. Speaking of the coronavirus, it is probably the best way to face such an integral approach if Chemistry is taken into consideration. In fact Chemistry can contribute by looking at aspects and problems poorly considered before and which can only be highlighted through a sensitivity that is characteristic of this discipline. This is the profound value and meaning of working in diversity. A fundamental issue is related to particulate matter (PM). A sound scientific literature describes the role of PM as an efficient carrier to transport and to diffuse a great amount of chemical and biological contaminants, including viruses.

PM plays a negative role if it shows binding capacity to retain bioparticles. The latter would remain in the air for hours or days in active and vital conditions. Waiting for better times, when different styles of life will be adopted in order to improve environmental conditions, for their physical and chemical characteristics they can be considered co-indexes and co-markers of the possible spread of viruses.

This hypothesis could be easily checked by advanced instrumental analysis by taking samples of air in certain areas and analysing them for their chemical pollutants and virus content, or better still, investigating possible chemical or physical bonds between the two components.

Other than viruses it does not seem easily understood why real regulations about PM consider only the weight and the size of the particulate without any scientific interest regarding its nature, to correlate to hygiene and safety limits.

During several international congresses chemists have presented proposals focused on the determination of PM toxicity levels together with its weight; for instance when immobilising PM particles on specific collecting filters the abiological component could be able to give information about the toxicity level of the collected PM.

Another point refers to the fact that, starting from the way in which a virus multiplies in human host cells, a question comes up as to why, in some cases, viruses cause the death of cells and therefore of organisms, while in other cases no, or modest, damage is observed? A possible answer may be a genetic or epigenetic difference between living beings as well as a difference of antinflammatory and antioxidant patrimony that varies from person to person. These patrimonia differences can be determined through many chemical or biochemical tests.

Another important aspect of chemistry concerns scientific data, their meaning, but above all how they are obtained and how they must be communicated.

Chemistry is a predominantly an inductive science, thus the scientific method is synonymous with an experimental method. For this reason, it is essential that communication and data sharing must proceed successfully, but these latter conditions presuppose easy accessibility to magazines,

journals and research results. This is why the chemical community has always defended "Open Science criteria".

Speaking of the composition of an ideal inter-disciplinary group to deal with viruses, another point is the organisation of the work. Organisation is defined as the set of processes and structures with which people interact and manage them, in a coordinated manner, through a series of rules to achieve a common and sharable goal. The organisation therefore is the best management condition for starting any project, since the organisation is independent on any activity, be it economic, scientific, technological or others. The purpose of organisation is always to guarantee a regular continuity for the full duration of the project. It is based on three main functions which are the mission, the project and the strategy; all the other functions, for example the layout of the laboratory structure and the group of researchers, closely depend on these three. A primary condition for achieving the objectives is that all the functions are strategically aligned with each other and, last but not least, every person must be able to interact with a multidisciplinary perspective. These considerations lead to the important conclusion that organisation system and project activity are related and strictly joined.

NEWS

A Poem by Philip Resnick

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Professor Emeritus Philip Resnick taught Political Science at the University of British Columbia for over four decades. He is author of numerous books, including several works of poetry.

Following a distinguished career in Political Science Professor Resnick focused on writing poetry. He will publish a collection of his pandemic poetry this spring. At the Emeritus College he leads a special interest group, "Poetic Odysseys", reading, writing and listening to poetry.

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Years ago, I received a copy of the third volume of Braudel's "Civilization and Capitalism". It has turned out to be a perfect tonic in this period of Covid-19 confinement as I have been re-reading it in recent days. It has inspired the following reflection.

La longue durée

Inspired by Fernand Braudel's extraordinary saga
on *The Mediterranean in the Age of Philip II*,
I once set out to grapple in my *imaginaire*
with a fanciful project -
The Aegean in the Age of Pericles.
A mere poem, it turned out in the end,
for to embark on such a voyage
would have involved half a life-time
and I was already into overtime.
Now on re-reading Braudel's
Civilization and Capitalism 15th-18th Century
I sit in awe at his underlying vision,
his mastery of intricate details,
bonds of commerce, currency fluctuations,
emerging city centres and nascent nation-states,
how England, separating itself from the continent,
became an island,
how industry wedded to finance and the division of labour
reshaped the modern world,
how *à la longue*
trade, colonies, slavery and transportation
have brought us to where,
despite wars, plagues, and would-be revolutions,
we find ourselves today
with capital and markets still in the ascendant.

(17.05.2020)

A Poem by Maro K. Papathanassiou

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The Family Relic, the Talisman

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High up in the icon stand
from eyes indiscreet
and sacrilegious hands
well-kept and securely
a small icon, a talisman
a precious family relic
the mother carefully kept hidden
in all her life.

Her faiths' stalwart support
a bridge, a link with holiness
it was for her a relic and a talisman
that sometime from the past
came to her family,
brought from the Holy Land.

Every Saturday
secretly from all
the mother to the small icon
piously burned incense
asking for divine help
and its protection
for all the family
and mostly for the children.

With this, she secretly crossed them
in all their illnesses
so that they would quickly get well
and that the evil would stay away.

Into her deep age the mother
kept the talisman as her helper.
When she was to leave this life
she left it secretly to her child
who would honor it
and who would piously continue
the family tradition.

High up in the icon stand
away from eyes indiscreet
and sacrilegious hands
together with the family talisman
incense also is burning for the mother's soul
gratitude and nostalgia
from her beloved child.
(22-23.4.2019)

Translated by D. Cokkinos (6.3.2021)

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

Riga, August 2021

Dana Baran
ISHM General Secretary
Email: ishmsecretariat@gmail.com

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.

Minutes of EAPE Council Meetings

Luigi Campanella
General Secretary of EAPE
Email: Luigi.campanella@Uniroma1.it

February 15, 2021

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

At the beginning of the teleconference the President gave the floor to Dr. Karvounis, the CETRI representative, in order that he could present to the Board a possible cooperation between the participation of EAPE with European Calls in Horizon Program and explain the expenses (perhaps modify after the discussion), which will arise from the preparation and submission of a proposal to E.C.M. Dr Karvounis focused on experience; top organizing capacity and ICT expertise of CETRI. He described the different steps by which cooperation will be substantiated: choice of the topic, definition of the role of EAPE, preparation of the proposal to be submitted articled in all the foreseen WPs. It is not very easy to write a good proposal, that will be accepted by EC, because these proposals are competitive and they need other partners and a lot of experience and skills to be well written. The Board of EAPE has assigned to Dennis, Nikos and Maria to look after the possibility of an E.C. project, which is within the scope of EAPE, in order to increase the budget depending at present only on the annual fees of the EAPE members. The cooperation with CETRI falls within this line of behaviour. It is observed that due to the poor finances of EAPE any cost will be recognized only in the case of approval of the proposal and that the topics to be preferred must be of an intercultural nature, so corresponding to EAPE characterization.

Georgia Drosatou informed the Board that the EAPE bank account stands at 3.001.96 Euros after payment of 1.860.00 Euros for the 6th Bulletin and the Supplement (S1). We have not yet paid for the 7th Bulletin which will cost 644.80 Euros. 36 members (old and new) have paid their registration fee for 2021. 18 of them are Greek members. Georgia will contact our members (one by one) to remind them of the payment of their subscription.

March 16, 2021

Participants: Les Ebdon, Patrick Berche, Maria Ochsenkuehn-Petropolou, Liv Mjelde, Nikos Markatos, George Christodoulou, Georgia Drosatou and Luigi Campanella.

In the absence of President De Santo, the General Secretary chaired the meeting.

The first point to be discussed concerned the financial situation of the Association with costs of nearly 12000 Euros a year as follows:

1. Bulletins. If 6 bulletins are published per year, the cost is estimated to be 3.868.80 €. Each bulletin costs 644,80€.

2. Annual expenses for the website: 254,20€.

3. Annual invoice for the Accountant's fee: 650€.

4. Annual expenses for the Secretary's salaries including insurance: 6730,52€.

5. Bank expenses for the transactions approximately 280€.

With a subscription fee of 40€ a year, we need 300 members to continue as we are. Is this realistic and how can we achieve it?

Alternatively can we find some new, regular sources of income? The answer to this question covers four possible fields:

- Participation and financial support from European Projects.
- A virtual congress with income from the fees (reduce for young) of the participants.
- Publication of an Abstract Book financially supported by a pharmaceutical medical company.
- Decrease of the number of Bulletins in the year.

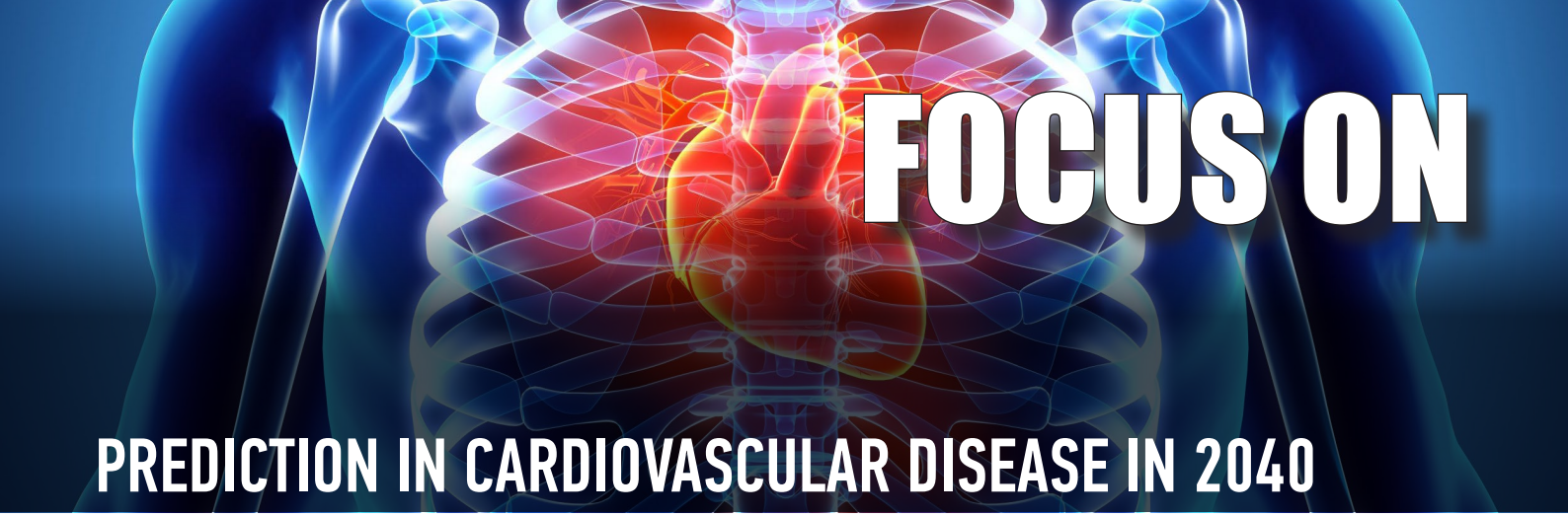
For the first point it is proposed to have careful attention to Horizon Calls. Meanwhile participation of EAPE in the European Digital Program could be a good opportunity. Dennis had originally proposed a Q and A program of 30 minutes, to discuss interaction of Professors Emeriti with younger generations. The two possible dates are June 29, or July*.

The following point of order concerns the proposal of variation of by-law. It is accepted that the proposal from Luigi to distinguish simple points, easily agreeable, from more complex ones. In this line the following variations are now approved by the Board:

- Electronic vote.
- Replacement in all the articles of the word chairman with President.
- In the absence of the President the Board Meeting is chaired by the President-elect.
- No requirement for electronic signature of minutes.
- Institution of Honorary Members but in very strict numbers. Possible institution of Honorary (or other name) Committee formed by the past presidents.
- Non-European members have to pay membership fees unless recognised as Eminent members (a new kind of member-to be considered) and invited to be a member of a Committee.

The following points are delayed to the next teleconference (now scheduled for 15th April at 1.00 pm Paris time) due to today's absence of the President:

- Admission or not as members of the Association, of associate and assistant professors.
- Advisory committee.
- Post of past president.
- Use otherwise than originally foreseen of the money collected by Natale to have a meeting aiming to change by-laws.



Predictions in Cardiovascular Disease in 2040

Dennis V. Cokkinos

Professor Emeritus (cardiology), University of Athens

Honorary President of the Association of Professors Emeriti of the University of Athens / Past President of EAPE

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Dennis V. Cokkinos

By 2020 the first quintile of the 21st century had elapsed. It is customary at such milestones to venture predictions for the future.

I can quote four predictions and statements concerning perspectives for the next 20 years.

The Patriarch of contemporary cardiology Eugene Braunwald expressed enthusiastic predictions for the next 10 years as regards coronary artery disease during the European Society of Cardiology annual Congress in 2018. He mainly focused on non-invasive coronary artery imaging and the detection of vulnerable plaques, the use of genomics to define risk with greater precision and target medical treatment. New drugs especially PCSK9 inhibitors for further lowering cholesterol with a 3 or 6 month injection, even starting at 30 years of age have been introduced.

Ortendahl (1) et al. offer a less favorable approach; they predict that advancing age and increasing obesity and type 2 diabetes prevalence will raise cardiovascular mortality by 2040, unless acute interventions and pharmaceutical therapies are upgraded.

Two more approaches from a social viewpoint must be given: Dame Ann Johnson (2) in 2016 stressed that health needs to be valued as a common good, necessitating the participation of individuals in the maintenance of their own health. The clinician scientists of tomorrow are admonished to appreciate the interplay between social, economic, genetic and biological drivers of individual and Public Health.

Many authors continuously, and in 2020 in the Lancet Non-Communicable Diseases and Injuries (NCDI) Poverty Commission argue that for Universal Health to improve a gap must be bridged in the health coverage of the poorest billion of our world's population.

We have asked four expert colleagues, Emeriti Professors to make their predictions for the next 20 years in an equal number of very important aspects of cardiovascular diseases which occupy a large space in today's efforts.

Giuseppe Mancia, (University of Milan-Bicocca), President of the Hypertension Foundation of the European Society of Hypertension will address the continuing population load of hypertension.

Dimitris Sideris (University of Ioannina) with great clinical and experimental experience, will discuss the prospects in heart failure.

John Camm, (St. George's University of London) will give his predictions on the future treatment of arrhythmias, which he has been studying over the last many years.

Ulrich Sigwart, (University of Geneva), will assess the future of invasive cardiology and the evolution of stents, in which he was pioneer.

They have produced an outstanding and far-reaching statement which will be valuable to all scientists besides physicians. I hope that more predictions as regards the future of medicine will follow.

1. Ortendahl JD, Diamant AL, Totb PP, et al. Protecting the gains. Clinical Cardiology. 2019;42:47-55.

2. Johnson Ann. Health of the public in 2040. Lancet. 2016. PIIS014-6736. (16) 002-64-6.

These considerations are profoundly affected by the Covid-19 pandemic in many ways:

Funds for research are preferentially funnelled towards combating the deadly virus. The costs for the vaccines' production and propagation must be staggering. Joseph Hill3, Editor-in-Chief of Circulation early in 2020 pointed out that our own ways of conducting cardiological research are necessarily being affected (3).

The virus also affects the myocardium. Troponin elevation is associated with higher mortality. Moreover, decrease of acute coronary units in favor of acute Covid-19 units will very probably affect acute coronary syndrome care.

However, it must not be forgotten that cardiovascular diseases still are and will remain the main cause of mortality and morbidity even after the Coronavirus pandemic has been defeated.

Our efforts should not abate.

3. Hill JA, McGuire DK, De Lemos JA. Science in a time of crisis. Circulation. 2020;141:1277-78

Predictions in Cardiovascular Disease in 2040: Arterial Hypertension

Giuseppe Mancia

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Giuseppe Mancia

Hypertension has a staggering prevalence around the world and a unanimous prediction is that unfortunately in the next 20 years the number of individuals with a blood pressure (BP) elevation will increase by 20-25%, keeping this condition as the number one cause of death worldwide. This can be opposed by fighting against the increase in the prevalence of factors and comorbidities that accompany and favour a BP increase such as excessive salt intake, a low potassium consumption, socioeconomic factors enhancing stress, type 2 diabetes and obesity. It can also be opposed by extending effective antihypertensive treatment to a larger fraction of the world population because of the evidence that lowering an elevated BP protects against virtually all hypertension-related cardiovascular and renal outcomes.

BP can be reduced, albeit to a limited degree, by appropriate lifestyle changes, which are difficult to be extensively implemented, however, because adherence to their prescription is extremely poor, as exemplified by the failure to achieve long-term reduction of an excessive body weight by low caloric diets or physical exercise, and thus to benefit of the documented BP-lowering effect of this measure(1). Fifty years of clinical research, however, have resulted into a large number of effective antihypertensive drugs and drug combinations which, in principle, can adequately reduce BP in more than 90% of hypertensive patients, achieving the BP value at which cardiovascular protection is maximized in most of them. Regretfully, however, this is far from what happens in real life, in which BP control does not exceed 15-20% of the global hypertensive population, with uncertain evidence of any substantial time-related improvement in western countries and evidence of a progressive worsening in the much larger low income hypertensive population.

It is now clear that low adherence to antihypertensive drug prescriptions is the most important factor behind this disappointing situation, which keeps hypertension as the first cause of death worldwide. This makes improvement in adherence to BP-lowering treatment a key goal to pursue in the next decades. After being overlooked for years, adherence has become a major topic for research not only in hypertension but also in the other areas of cardiovascular preventive medicine. This has shown that adherence to antihypertensive treatment (as well as to antidiabetic and lipid-lowering treatment) is extremely low and that this leads to a marked increase in hospitalization

1. Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. N Engl J Med 2013 Sep 5;369(10):954-64. doi: 10.1056/NEJMra1203528.

for cardiovascular events and mortality. Evidence from real life studies has also shown that adherence depends on psychological, socioeconomical and educational factors, that the patient-doctor relationship is primarily involved, but also that the choice of proper treatment strategies plays a key role(2). Recent studies, for example, have shown that starting antihypertensive treatment with a two-drug combination markedly improves long-term adherence to treatment compared to starting treatment with monotherapy, with a concomitant substantial long-term reduction of treatment discontinuation, a more frequent BP control and a parallel increase of cardiovascular protection(3). An important goal for the next twenty years will thus be to try to make initial drug combinations the most common treatment type for hypertension, at variance from its current use in only a small number of patients. In conjunction with an increased awareness of the protective effect of antihypertensive treatment, an improvement of the doctor-patient relationship and the use of technologies that may 1) remind patients to assume drugs and 2) allow doctors to more timely know BP values and intervene, this might result into a marked improvement of the adherence to and the extent of BP control and cardiovascular prevention.

Future research might further help by providing a more in-depth knowledge of the factors involved in low adherence to treatment at individual level, a better ability to measure adherence in medical practice and perhaps also by discovering other means to effectively reduce an elevated BP. After years of discrepant results it seems clear that device treatment of hypertension, such as renal denervation, can be a helpful adjunctive antihypertensive measure, presumably via reduction of sympathetic cardiovascular control which is high in many patients. There is also the hope that future research will provide agents capable of reducing BP with rarefied (e.g. monthly oral or even parenteral) administrations, a treatment schedule that might substantially minimize the problem of low adherence to preventive treatments and its assessment.

2. Chow CK, Teo KK, Rangarajan S, et al. PURE (Prospective Urban Rural Epidemiology) Study investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA 2013 Sep 4;310(9):959-68. doi: 10.1001/jama.2013.184182.

3. Mancia G, Rea F, Corrao G, Grassi G. Two-Drug Combinations as First-Step Antihypertensive Treatment. Circ Res 2019 Mar 29;124(7):1113-1123. doi: 10.1161/CIRCRESAHA.118.313294.

Heart Failure - What Lies Ahead

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Dimitris A. Sideris

In heart failure (HF) the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs. Its causes vary. Once established, however, the elimination of the cause does not usually result in restoration of normal function, with few exceptions. The mechanism of HF is poorly understood, so that it is not possible to apply a targeted personalized treatment to the patients. Up to now favorable results have been observed mainly in cases with reduced ejection fraction but not with preserved ejection fraction. Possible therapeutic approaches will be presented and from the existing trends an extrapolation of the possibilities will be attempted.

Treatment, apart from causative, includes medicines, electrical interventions, transplantation and mechanical assistance and replacement. Digitalis, is the oldest drug still used. Because of its narrow therapeutic window and its failure to reduce mortality it is now considered a second-line medication. Several neuro-endocrine interventions have proved promising. Beta-blockers, inhibitors of angiotensin-converting enzyme or angiotensin-receptor blockers are the contemporary standard treatment of choice. Neprilysin inhibitors retard degradation of natriuretic peptides; omecamptiv mecarbil activates a cardiac myosin; levosimendan is a calcium sensitizer that may have positive inotropic action; neuregulin-l proteins are important for the development and function of cardiac myocytes. All these factors have yielded positive

results in improving survival, symptoms or reducing hospitalizations. Relieving congestion is another important target. Torasemide and bumetanide are considered to be superior to furosemide, a loop diuretic. Acetazolamide, a carbonic-anhydrase inhibitor, and similar diuretics may enhance the distal effects of loop diuretics. Aldosterone antagonists can improve symptoms and reduce mortality. Vasopressin-receptor antagonists (e.g. conivaptan) may treat euvolemic hyponatremia. Reducing afterload may also alleviate the work of the heart. The essential factor for vasoconstriction is nitric oxide (NO), that activates soluble guanylate cyclase (sGC) causing an elevation of intacelular cyclic guanosine monophosphate (cGMP). It is reduced and its degradation is increased in HF. Nitroxyl is a second-generation donor of NO. Vesiciguat is an oral soluble sGC stimulator which increases cGMP production. Both have shown favorable effects in HF. Augmentation of natriuretic peptides (e.g. sacubitril/valsartan) may also alleviate congestion. Sodium glucose cotransporter 2 inhibitors (empagliflozin, canagliflozin) may have beneficial effects in HF even without diabetes. The electrical approaches, pacemakers, defibrillators, ablation, are primarily targeted to treat cardiac arrest rather than HF. Resynchronization treatment is useful in cases with LBBB, while, with normal QRS duration, cardiac contractility modulation using nonexcitatory electrical signals has been tried.

The results of using stem cell therapy are inconsistent. They have failed to create new myocardium and their action is considered to be obtained through paracrine mechanisms. In this context mitochondrial transplantation is being tied(1).

All the above therapeutic approaches are expected to alleviate HF, but not halt the course of the myocardial and elastic fibers being replaced by connective tissue. Cure is expected with cardiac transplantation. However, even if the problems with rejection are met, the insufficient number of donors is prohibitory. Mechanical assistance and artificial heart, progressing from the intaaortic balloon pump(2) to left ventricular assist devices which are currently used for destination therapy; they offer an exciting field of study of the recovering myocardium with views into possible regeneration pathways.

The total artificial heart(3) has had a slow but steady progression. The inexorable course of HF is finally expected to be met only by a similarly steady course of technology, as artificial kidney "cured" renal failure, alone or in combination with gene therapy which in a halting but steadfast way is treading forward.

1. Naim C, Yerevanian A, Hajjar RJ. Gene therapy for heart failure: where do we stand? Curr Cardiol Rep.2013;15:333.

2. Moulopoulos S.D, Topaz S, Kolff W.J. Diastolic balloon pumping (with carbon dioxide) in the aorta - a mechanical assistance to the failing circulation. Am Heart J 1962; 63: 669.

3. Cook JA, Shah KB, Quader MA, et al. The total artificial heart. J Thorac Dis. 2015 Dec; 7(12): 2172–2180.

The Future of the Management of Arrhythmias

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John Camm

Today we are usually surprised when an arrhythmia suddenly crops up, seemingly "out of nowhere", but then we begin to scratch our heads about the investigation, diagnosis and management. We are generally too late to do anything but offer rescue therapy, generally to alleviate symptoms and occasionally to extend life. An arrhythmia is an expression of an underlying disease or condition. Often multiple circumstances can provoke the same arrhythmia and the underlying diseases or disorders usually present long before the arrhythmia emerges. Progressively we will be able to predict the occurrence of an arrhythmia and intervene to prevent its development and the disaster it might provide. Great strides are being made in the epidemiology surrounding arrhythmias, the accurate prediction of arrhythmia occurrence using techniques

such as computer modelling and artificial intelligence, the mechanisms supporting them and the identification of the substrates that support the rhythm disorders. Of course, proving that an intervention might deter the appearance of an important arrhythmia in the long-term is fraught with difficulty. Clinical trials of long duration are expensive and difficult to sustain, but registries and trials within registries are beginning to happen and will make it possible to evaluate early therapeutic gambits. Arrhythmia mechanisms are exposed by detailed mapping of the electrical hot spots and circuits within the heart, which will soon be a non-invasive, readily available and appropriate for any and many rhythm disturbances. The substrate for an arrhythmia will be revealed using electrical, biochemical, radiographic and other imaging techniques that are approaching resolutions that will identify irritable and compliant tissues even before an arrhythmia presents.

If we miss the chance to anticipate an arrhythmia, even a clinically silent arrhythmia, it will not lie dormant for long. Modern society is infested with electronic gadgets that can sense disturbances of the heart rhythm. Pulse monitors, plethysmography devices and ECG recorders have been squeezed into vests, phones, watches, rings and other everyday gadgets and garments (1). A large proportion of the population will be watched over by these electronic angels, eager to sound the alarm and expose the danger. If arrhythmias are not detected by these inquisitive gizmos, opportunistic and systematic screening will expose them. Dynamic digital, facial, or retinal scans encountered during daily life or purposeful ECG screening of the population-at-large will reveal rhythm abnormalities or their precursors. The physician/cardiologist will initiate therapy at an early stage and prevent the arrhythmia from becoming a disease in its own right and causing death or disaster in its wake (2). What a change this will be – in the "driving seat", at last.

Not every electrophysiological aberration will support a serious or symptomatic arrhythmia. Risk assessment becomes increasingly important to target the medical resource. Which patient with ventricular premature beats and poor left ventricular function will die suddenly from ventricular fibrillation, which patient with atrial fibrillation will harbour a life-threatening thrombus? Biosensors of every kind are being interrogated to discover those which hold the answers to these secrets. Huge population studies and the big data that these populations furnish will disgorge these truths someday not too far away. The patients that we target for increasingly sophisticated therapies will change out of all recognition- it will be a new world, not brave but better.

For years we have juggled with drugs that are half therapeutic and half poisonous, trying to use them at the right dose and in the right circumstances to tip the balance in favour of success. The search for agents that are more arrhythmia specific with few, if any, off-target effects has been a mantra for antiarrhythmic drug development. Arrhythmias are caused by processes which must be amenable to medical therapy – we have not made the right discoveries yet but the Livingstone spirit to explore and discover will grow strongly in this almost forgotten arena. Many novel ideas and new progress is certain (3).

Surgeons demonstrated that it was possible to restore a heart prone to arrhythmia to a normal heart by severing an accessory AV pathway. Almost every arrhythmia can now be tackled using these sophisticated techniques, which are highly dependent on accurate imaging of the heart to identify structural and functional abnormalities, detailed electrophysiological mapping of the heart and easily controllable energy sources. A new form of energy, known as electroporation, has emerged from the field of cancer surgery and offers a method of very careful dosing of energy which may differentiate between tissue types sufficiently to destroy only pathologically disrobed tissue. This success story will continue to expand to levels far in excess of what is happening today.

The watchwords for the future of arrhythmia management are early discovery of arrhythmia and early intervention, highly focussed therapy with few off-target effects and holistic and patient-centred care.

1. Chandrasekaran R, Katthula V, Moustakas E. Patterns of Use and Key Predictors for the Use of Wearable Health Care Devices by US Adults: Insights from a National Survey. J Med Internet Res. 2020 Oct 16;22(10):e22443. doi: 10.2196/22443. PMID: 33064083; PMCID: PMC7600024.

2. Kirchhof P, Camm AJ, Goette A, et al. EAST-AFNET 4 Trial Investigators. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. N Engl J Med. 2020 Oct 1;383(14):1305-1316. doi: 10.1056/NEJMoa2019422. Epub 2020 Aug 29. PMID: 32865375

3. Heijman J, Hohnloser SH and Camm AJ. Antiarrhythmic drugs for atrial fibrillation: lessons learned from the past and opportunities for the future. Europace (2021) doi: 10.1093/europace/euaa426

Interventional Cardiology: Predictions for the Next 20 Years

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Ulrich Sigwart

Interventional cardiology is a rather young discipline; it was launched not even half a century ago (1). Since then it has replaced open heart surgery in the majority of cases. The advantages are lesser morbidity, shorter hospital stay and, in general, lesser expenses. The discipline of interventional cardiology, although employing methods previously reserved for surgeons, is still considered a daughter of internal medicine and cardiologists specializing in interventions are officially still called 'internists'.

The reasons for this separation reside in historic classifications that are no longer valid. The term 'internal medicine' is outdated and ought to be replaced by 'general medicine'. The coming 20 years will hopefully take into account that the battle between cardiovascular surgeons and interventional cardiologists is coming to an end: both disciplines employ mechanical methods to improve cardiovascular function and the patient's well-being; their approach may differ, but not to the point of creating separate disciplines. The targets of either discipline are identical; the methods are in the process of merging.- I am convinced that in the coming 20 years 'Interventional Cardiology' will have separated itself from 'Internal Medicine' and merge with 'Cardiovascular Surgery' to an entity under the same roof! Such entities do exist already and may simply be called `Cardiovascular Centre'. Hybrid units are already established.

What are the targets for improvement?

Ongoing attempts to improve imaging for interventional procedures are likely to be successful in the coming years. This should include higher spacial resolution, reduction of irradiation to patients and operators alike and cheaper production. With more and more transluminal techniques for diagnosis and treatment of all kinds of human pathology such endeavours are of the highest priority.

It appears to me that catheter procedures will develop further in the years to come and require highly sophisticated installations exploited jointly by interventionists with a background in either surgery or cardiology. Targets are new vascular support systems -commonly called stents-, which were introduced to cardio-vascular medicine in 1986 (2). Such endovascular support systems ought to be genuinely anti-thrombotic; they should be elastic with extremely thin walls and improved cover. Ideally such devices should disappear once the artery is stabilized.

For the time being bio-resorbable metals, like special magnesium alloys, are high on the agenda, but the search for even stronger products is ongoing. In the early 90's of the last century I have tried everything to persuade the industry to focus on thinner stent struts in order to improve hemodynamics and reduce turbulence. With the existing metal alloys limits were obvious, however. In my mind this area will be addressed in the coming years. Removal of atherosclerotic material without the risk of creating embolization will certainly come up with new approaches and drugs inhibiting intimal hyperplasia may hopefully find their place for local delivery as well.

In short, there is reason to believe that transluminal techniques will remain at the forefront of all kinds of therapeutic interventions for years to come.

1. Gruntzig,A Transluminal dilatation of coronary-artery stenosis, 1978 Lancet. vol. 1, no 8058, p. 263.

2. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L: Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med. 1987;316:701–706

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*).

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.

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Antier JJ. Jean Guitton. 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

De Santo NG. The priority: broadening the boundaries of paediatrics and turning basic science into cures. In Erich J, Corrard F, De Santo NG, ed. This I think should have priority in child health care services. Joachim Barke, Hannover 2018:69-71.

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2. Online journal article

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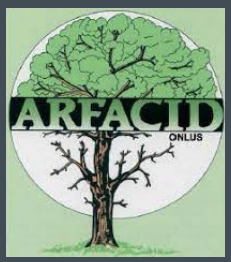

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