Editorial

Be more, do more, research more
The importance of developing local science

Thomas F. Lüscher

What brought mankind forward

There were times when our ancestors lived in a dangerous environment. Indeed, primates including *homo sapiens* and its predecessors were neither strong nor particularly fast. They were an easy prey for predators: but they were smart and became eventually the dominant species.

Why could this happen? First, they developed the concept of cause and effect, they learned to see events in causal terms, that one event followed another consistently and they used this to shape their environment – this made them the tool makers of the evolution. Then they discovered how to make fire and weapons and suddenly they were no longer a prey, but predators themselves. Finally, they learned to work together, to communicate, to talk to and inform each other about dangers and opportunities and to pursue them together. Working together was a key-success-factor of these social animals who alone would not have survived the struggle for survival. Thus, rational thinking, communicating with each other and working together made us the dominant species.

What brought humans forward? The ambition to be more and to do more.

What brought Medicine forward

Over thousand of years humans developed culture, they started to discover their body, learned how to treat wounds and injuries. Then, they tried to understand serious events such as illness and disease. They started to use herbs to treat the obvious and developed myths and beliefs for events they could not understand. Even in the 14th century when the pest hit Europe, the uncomprehensible was considered a punishment of god for the sinful. But during Renaissance a new way of understanding the unthinkable evolved: Observation and causal thinking developed what we today call science: To understand the body and its organs and with close observation as the anatomist Andreas Vesalius (1514-1564) showed with his seminal autopsies. Then William Harvey (1578-1657) concluded based on simple experiments in animals and on the veins of his forearm that the blood circulates in a pulsatile fashion in our body – the body was no longer a mystery, but an object of observation and experiments: As such modern science medicine was born.

What brought science and medicine forward? The ambition to be more and to do more.

What has been achieved

The rise of modern medicine in the 16th century was only a start, but it changed our mindset from belief to knowledge, from assumptions to proof and from discoveries to practical applications. Of course, this process took centuries and is still ongoing, but the achievements are impressive. At first, infections were the primary target: What were the causes of the pest, cholera, smallpox and tuberculosis? In a bold experiment, Edward Jenner (1749-1823), based on the observation of many that cow pox protected from small pox, inoculated in 1757 an 8 year old boy with cow pox and the boy was subsequently immune to small pox. 1 Jenner called this procedure vaccination from latin word *vacca*, the cow. Against all odds, Robert Koch (1843-1910) and Louis Pasteur (1822-1895) convincingly showed that invisible microbes and not supranatural forces were the cause of the tuberculosis and that hygiene was the remedy. But infections remained a threat until Alexander Fleming (1881-1955) discovered Penicillin and numerous antibiotics followed, among them streptomycin.
After the Second World War, an English epidemiologist with the name of Austin Bradford Hill performed a seminal experiment that changed clinical research. To prove that streptomycin was indeed superior to the then established therapy with bed rest, he recruited patients with acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved and unsuitable for collapse therapy. He then randomized them to either treatment. As he reported in the British Medical Journal in 1948, 27% died in the streptomycin and 27% in the control group. He concluded “The difference between the two series is statistically significant; the probability of it occurring by chance is less than one in a hundred" and as such evidence-based medicine was born.

Hill’s approach also stimulated cardiovascular medicine that became the major cause of morbidity and mortality after effective remedies against infectious disease became available. The first randomized cardiovascular trial was led by Edward Freis in patients with severe hypertension that showed in 1967 that blood pressure lowering with antihypertensive drugs reduced death, myocardial infarction and stroke. And it continued with numerous trials thereafter showing that streptokinase reduced mortality in acute myocardial infarction, that statins prevented major cardiovascular events, that anticoagulation prevented strokes in atrial fibrillation and eventually that percutaneous coronary intervention represents the treatment of choice in acute coronary syndromes. Today evidence-based recommendations are available in prevention, in intervention, for the prevention of sudden cardiac death, and valvular heart disease, in thromboembolism and heart failure among other conditions – a true success story.

What remains to be discovered

But it does not end here: further research remains badly required, too many patients suffer from diseases that are untreatable, too many still die of conditions that are untreatable. For instance, although the history of the management of acute myocardial infarction is impressive, mortality remains overall at around 10% for now due to our inability to manage cardiogenic shock appropriately.

Also, although neurohumoral blockade and cardiac resynchronization therapy markedly reduced mortality and hospitalizations for heart failure with reduced ejection fraction or HFrEF, we are far away from a cure of the condition. Furthermore, heart failure with preserved ejection fraction or HFpEF remains an enigma without an effective treatment.

Finally, although the genetics of many forms of non-ischemic cardiomyopathies are now understood, we lack effective means to correct the genetic mutation and its biological consequences in heart muscle – possibly genetic engineering will help. Another example is valvular heart disease: Yes, we can replace stenotic aortic valves surgically and now even with transarterial valve implantation or TAVI, but we have no

---

**Figure 1.** The development of scientific knowledge. Humans developed in evolution to the “thinking animal”, to discoverers and scientists up to today's molecular medicine.
remedy to prevent the shrinking and calcification of aortic leaflets that eventually lead to aortic stenosis. But there is more. In every country there are specific opportunities, typical unmet medical needs, unresolved scientific issues; although science is a global enterprise today, it must grow locally.

Thus, there are many unanswered questions in cardiovascular medicine that wait for young scientists and cardiologists around the world that want to be more, do more and research more.

How to publish research

Only discoveries that are published do exist: Thus, any research needs to be finished, written up and submitted to a scientific journal. Only what can be read by others, will advance science and medicine.  

Most journals, and in particular the best and most respected, work based on the peer review system, i.e. they ask expert in the field to evaluate the submitted work to make suggestions, to provide constructive criticism, in an attempt to make good papers even better and to reject those who do not make the bar. What are the criteria editors use when assessing submitted work? (Table 1) First, innovation: Research is about new findings, about expanding our knowledge base and about new treatment targets and novel remedies for disease. Second, precision: Research must be precise, performed with state-of-the-art equipment. Third, stringency: Research must provide proof, supply data that convince the sceptics and are accepted by experts. Forth, honesty: Research must provide proof, supply data that convince the sceptics and are accepted by experts. Forth, honesty: Research builds on trust of others, only correctly obtained data are reproducible; and the scientific process is build on reproducibility of findings. Fifth and last, be in time: The scientific

| Criterion | Remarks |
|-----------|---------|
| Innovation | Research is about novelty either as a true discovery or as incremental innovation or more solid evidence with a larger cohort, longer follow-up or better mechanistic insight. |
| Precision | Measurements should be made with state-of-the-art equipment. If possible, mechanistic insight and causality should be provided. |
| Stringency | Data presentation should follow a logical stream in order and regards explanation of the findings. |
| Honesty | Science relies on proper and correct data reporting; anything else is not scientifically correct research. |
| Timeliness | Science is a global endeavor and hence there is a lot of competition. Being in time, means being first. |
| Reference | Give credit in you manuscript to those who work in your field, cite those who set the basis of your work – they may be your reviewers. |
process is competitive, you are not the only one working in your field of interest; indeed, most scientists who ever worked in history work today.

**How to become successful**

If you want want to be more, do more and research more, what do you have to do? First, one needs proper training in an excellent institution with mentors devoted to education of the next generation – the better the mentor, the more you will grow. Second, you must find out what fascinates you - it will boost your professional and personal development.

**References**

1. Stokes I. An anatomical disputation concerning the movement of the heart and blood in living creatures. British Journal of Diseases of the Chest. 1977;7:1305.
2. Riedel S. Edward Jenner and the history of smallpox and vaccination. Proc (Bayl Univ Med Cent) 2005;18(1):21-5.
3. Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae. 1929. Bull World Health Organ 2001;79(8):780-90.
4. Streptomyces Treatment of Pulmonary Tuberculosis. A Medical Research Council Investigation 1948;2(4582):769-82.
5. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. Jama 1967;202(11):1028-34.
6. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. The Lancet 1998;332(8607):349-60.
7. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344(8934):1383-9.
8. Steffel J, Verhamme P, Potpara T, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39(16):1330-93.
9. Neumann F, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40(38):3143-53.
10. Mach F, Baigent C, Catapano A, et al. 2015 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111-88.
11. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41(3):407-77.
12. Priori S, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 2015;36(41):2793-867.
13. Baumgartner H, Falk V, Bax J, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38(36):2739-91.
14. Konstantinides S, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41(4):543-603.
15. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129-200.
16. Luscher T, Obeid S. From Eisenhower’s heart attack to modern management: a true success story. Eur Heart J 2017;38(41):3066-9.
17. Luscher T. Lumpers and splitters: the bumpy road to precision medicine. Eur Heart J 2019;40(40):3292-6.
18. Haas J, Frese KS, Peil B, et al. Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J 2015;36(18):1123-35a.
19. Mosqueira D, Mannhardt I, Bhagwan J, et al. CRISPR/Cas9 editing in human pluripotent stem cell-cardiomyocytes highlights arrhythmias, hypocontractility, and energy depletion as potential therapeutic targets for hypertrophic cardiomyopathy. Eur Heart J 2018;39(43):3879-92.
20. Siontis G, Overtchouk P, Cahill T, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. Eur Heart J 2019;40(38):3143-53.
21. Luscher T. Good publishing practice. Eur Heart J 2012;33(5):557-61.