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Special article

The making of a physician-scientist—the process has a pattern: lessons from the lives of Nobel laureates in medicine and physiology

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Biography

Physician-scientists are catalysts of translational research. With one foot in the practice of medicine and the other in research and discovery, they are uniquely positioned to bridge the gap between laboratory and bedside. In so doing, they enhance patient care, improve medical education, and increase the prosperity of the biomedical enterprise. Although, science has never been more accessible and directly applicable to human health, there is a paradoxical scarcity of physician-scientists. Causes of this shortage include prolonged training and the associated debt-load, the corporatization of medicine, inadequate research funding, and the complexity of a dual career. While striving to reduce these obstacles, we should inspire the next generation by celebrating the physician-scientist career track as one of Medicine's most rewarding. To this end, life lessons from five groups of Nobel laureates in medicine and physiology have been distilled, revealing the essence of the practices and philosophies that allowed these 'ordinary' people to achieve the extraordinary. The common threads in their stories guide young physician-scientists to seek out training and employment where a culture of research is embraced, to find a dedicated mentor who will help identify worthy research questions and guide their career, and to establish research partnerships which offer creative synergy and buffer the frustrations that accompany research. Further inspiration comes from those great researchers whose contributions shaped Medicine but did not lead to the Prize.

Introduction

Our ability to translate science into medicine, to move investigation between the patient's bedside and the research laboratory, has never been greater. Translational research is an overarching approach to discovery that steps over arbitrary, traditional barriers that divide medical specialties and separate basic science from medicine. Translational research utilizes complementary skills and approaches of researchers from diverse disciplines to accelerate discovery. Physician-scientists are ideal leaders of translational teams. They combine fluency in physiology, molecular biology, or proteomics with privileged access to patients and a passion for preventing and curing human disease. Without physician-scientists, our amassed genomic and proteomic repositories are as undecipherable as Egyptian hieroglyphics without the Rosetta stone. Physician-scientists, versed in medicine and physiology, if conversant in molecular biology, proteomics, or genomics, are uniquely positioned to translate the language of disease. Upon receiving the Nobel prize for their discoveries relating to atherosclerosis and cholesterol transport, gastroenterologist Michael Brown (1985), speaking for his long-time colleague and co-recipient, Joseph Goldstein said, '*Joe and I were trained as physicians and we still perform clinical duties. Yet, we realized that the understanding of a complex problem such as atherosclerosis requires the tools of basic science. We are fortunate to live at a time when the methods of basic science are so powerful that they can be applied directly to clinical problems*'. Today our 'good fortune' is even greater.

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Environmental scan

Since its inception in 1901, 101/172 laureates in medicine and physiology were MDs.[1] However, the number of physician-researchers is declining (4100–7300/year between 1968 and 1980)[2] and fewer medical students are planning research careers.[3] If both need and opportunity are great, why is the supply of physician-scientists waning? First, corporatization of medicine has co-opted the academic mission, financially rewarding high patient-throughput and procedural medicine over research and discovery. A biopsy of an academic physician's day reveals increasing hours spent on clinical practice at the expense of research.[4] Hippocrates' aphorism regarding the duration of medical training suggests a second impediment, for if '*Life is short, the art long*', the 'dual arts' of a physician-scientist are longer still, a time commitment made more onerous by mounting debt. Finally, the full-time clinician does not and should not accept suboptimal patient care from the clinician-scientist; nor does the Ph.D. scientist hold the clinician scientist to a lesser standard of excellence than that used to judge their peers. The expectation of the clinician scientist is to be competent in both domains-dilettantes are not tolerated.

Alfred Nobel

Although not a physician-scientist, Alfred Nobel's career as an inventor–entrepreneur is instructive. Between 1850 and 1852, Nobel studied with Théophile Jules Pelouze, inventor of guncotton, working beside Pelouze's prize student, Ascanio Sobero, inventor of nitroglycerin.[5] Alfred perpetuated his mentors' explosive phenotype, patenting nitroglycerin. Inspired by his brother Emil, who perished during a nitroglycerin explosion, Alfred invented dynamite, a stabilized nitroglycerin preparation. In Nobel's lifetime, physicians learned the therapeutic value of nitroglycerin for angina pectoris.[6] Paradoxically, Nobel, who suffered from angina, rejected the prescription saying, '*Isn't it the irony of fate that I have been prescribed nitroglycerin, to be taken internally! They call it Trinitrin, so as not to scare the chemist and the public*'. Nobel's career reminds physician-scientists that trainees commonly acquire their mentor's phenotype, that personal adversity frequently inspires the research question and that reticence in translating basic discoveries is common.

The following lessons from the lives of selected laureates in medicine and physiology can inform career planning for physician-scientists who are about to take up the torch.

Set a worthy goal

Impatience with the status quo and a sceptical bent starts most physician-scientists down the road of discovery. The journey starts with the belief that their hypotheses must be tested, for its intrinsic beauty and the betterment of humankind. The Nobels and their worthy goals are shown in the figure. Each followed Michael Brown's advice, and overcame the inertia that mires some in repetitive science (*Figure 1*)... they selected question's whose answers mattered.

On the shoulders of giants

The notion that discoveries spring *de novo*, fully formed, into minds of rare genius, is largely false. As the 16th century Spanish theologian Stella Didacus noted, '*Pygmies on the shoulders of giants see further than the giants themselves*'. Even great ideas are built on a foundation of precedents and are usually developed simultaneously by several groups. The hypothetical delay that would have resulted had 'your favorite laureate' not existed is usually only a few years.[7] Einthoven received the Nobel prize for improving the string galvanometer (the device used to record the EKG). He neither invented it (that was French engineer Clarence Ader, 1897), nor did he pioneer clinical electrocardiography (that was British clinician, Thomas Lewis). British physiologist, Augustus Waller, was first to record the human EKG (1887), a demonstration that Einthoven witnessed. Waller's impact was lessened by his technology (the vibration-prone capillary electrometer) and his lack of translational vision, '*I certainly had no idea that the electrical signs of the hearts action could be used for clinical investigation*'. Einthoven's refinements-incorporating advances in electromagnetism, recording technology, optics, and quartz chemistry, created a recording system that produced traces of modern quality.[8] Einthoven acknowledged that his work was built on others (*Figure 1*). He said of Thomas Lewis, the father of clinical electrocardiography who was overlooked for a Nobel, '... *the general interest in ECG would certainly not have risen so high-without his work*'. The realization that perfecting knowledge and making incremental discoveries are meritorious pursuits should encourage young physician-scientists.

Seek the best training and mentorship

Born on the remote island of Java, Einthoven's family moved to Utrecht. At the University of Utrecht, Einthoven had two mentors competing for his talents-eye-chart inventor, Hermann Snellen and Franz Donders, who was interested in 'active currents in the heart'.[9] Einthoven selected Donders' path and was pointed towards the study of cardiac electrical activity. Donders also assisted him in becoming the Professor of Physiology at the University of Leiden, illustrating the dual role of mentors: establishing the 'big question' and opening doors.

To achieve excellence it helps to have seen excellence in action. The nascent physician-scientist should seek out an environment populated by accomplished mentors where the atmosphere buzzes with discovery. It is the student's responsibility to seek out such an environment. This act often involves a move and thus frequently initiates the research journey. *Caveat emptor*: by learning your prospective mentor's pedigree and the career paths of previous trainees, one can avoid 'black-hole' laboratories (those into which many trainees stray, but from which few physician-scientist faculty emerge).

Cultivate courage

Werner Forssmann's experiences after pioneering the right heart catheterization, can be summarized as 'No good deed goes unpunished'. Forssmann, a urologist, was inspired to perform right heart catheterization to administer life-saving drugs to the heart by patients he had encountered during clinical training (*Figure 1*).[10] Ignoring a 'No' from his Chief at Eberswalde Hospital, Forssmann solicited the help of Nurse Gerda Ditzen (guardian of the X-ray room). She agreed to be Forssmann's first subject; however, once immobilized he claimed her keys, advanced a urethral catheter via the left brachial vein, walked to the X-ray machine, and confirmed its location in his heart. He subsequently repeated the procedure in a terminally ill woman, confirming the catheter's position at autopsy. He reported his experience in *Klinische Wochenschrift* (1929;45:2085). Forssmann's achievement led to his employment at Charité Hospital, Berlin (1929). Annoyed by Forssmann's cheek (publishing without his new boss, Dr Sauerbruch) he was released, only to be rehired in 1931 and fired in 1933. Following imprisonment during World War II, Forssmann was deemed 'too old' to obtain an academic post and worked as a General Practitioner, his discovery apparently forgotten. One evening, his wife summoned him home with the news that a stranger had called about a Nobel prize. Forssmann's saga reminds physician-scientists to cultivate optimism and persevere.

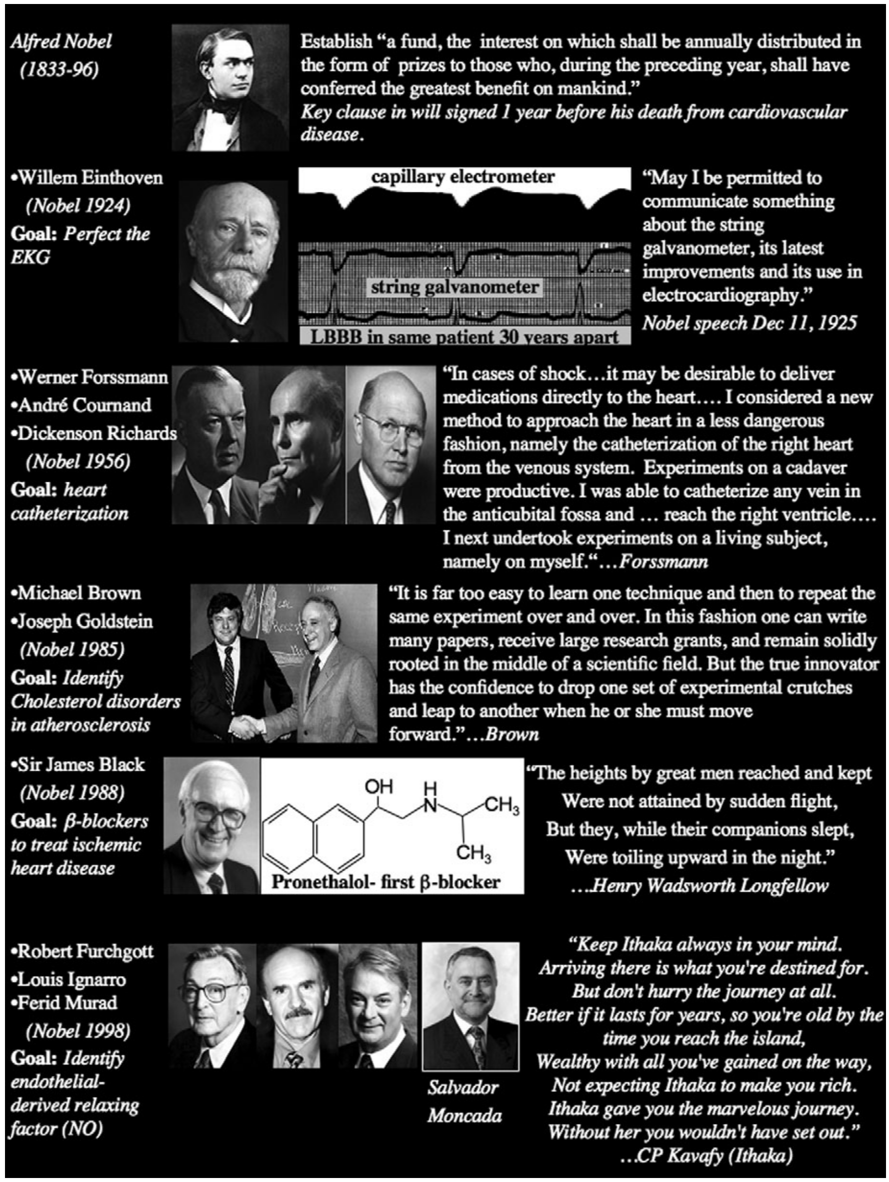

Figure 1 Images and observations relevant to individuals in the article. Images obtained with permission from http://nobelprize.org/.

Publish your findings

Many young physician-scientists struggle to write, a discipline in which they are largely untrained. Enthusiasm for writing may also be tempered by the gratuitous harshness that pervades peer review. It was Einthoven's amazing 1906 paper,[11] describing the telephonic transmission of EKGs that prompted Thomas Lewis to visit and begin his clinical EKG program. Likewise, Forssmann's Nobel was the direct result of his 'case report', written 20 years earlier. Like a message in a bottle, it drifted across the Atlantic, eventually arriving on the shores of New York where Richards and Cournand were striving to measure the *'state of the blood as it enters the right heart . . . and its rate of flow.*[12] Cournand recalled, '*In one of our early planning sessions . . . Dick Richards produced a 1929 issue of Klinische Wochenschrift*'. Publications are the sparks that kindle collaborations and blaze trails. The Laureates' careers show the necessity of timely communication of results.

Keep an open mind

Ideas that are 'ahead of the curve' usually sound implausible and excite ridicule from the conservative majority. The feasibility of Einthoven's EKG machine, a 300 kg behemoth that used buckets of saline as electrodes, appeared dubious. When considering new ideas, the physician-scientist should heed André Cournand's call for open-mindedness, *'Novelties should not be rejected precipitously . . . dissent should be tentative rather than unyielding*'. This philosophy may explain why he and Richards were open to receive the fruits of Forssmann's publication, a seed that lay dormant for 20 years.

Establish research teams/partnerships

After training, there is usually a 5-year period during which junior faculty make incremental advances toward autonomy. During this period, mentorship remains important but a role for research teams/groups emerges. While promotion committees may admire the lone wolf and prizes tend to go to individuals, most research comes from focused teams. Dr Black, the Scottish physician who left academics and joined the pharmaceutical industry to create, in quick succession, β-blockers (propranolol) and the histamine-2 antagonists (cimetidine) said, '*... the majority of significant research discoveries result from the concentrated efforts of small, well-resourced teams of talented and highly-focused scientists, who are unencumbered by the organizational distractions, decision time lags, and lack of direction frequently encountered in large public and industrial institutions*'. Young physician-scientists are well-advised to join a thematic research group, which will become their scientific support network. The group may be large or a *folie à deux*, but should be 'real', not assembled merely to acquire funding. A true group attacks problems of mutual interest, sharing ideas and resources, and co-publishing.

An excellent example of effective partnering is the collaboration of Goldstein and Brown. Having interned together, they arrived in Dallas in 1971–72, newly minted Assistant Professors. They initially had separate labs, but soon joined forces to pursue a common goal understanding cholesterol metabolism in patients with premature atherosclerosis. Their team approach to Science was as remarkable as their discovery that familial hypercholesterolaemia patients have a defect in low density lipoprotein (LDL) receptors that causes accumulation of atherogenic LDL in blood.[13] Many physician-scientists will attest the benefits of close partnerships in achieving a greater goal. Issues of independence can be dealt with by delineating areas of individual interest, having independent grants, and specifying individual contributions to publications. Science has enough discouragements without going it alone.

Intellectual agility

The best physician-scientists are agile and recognize when a chance observation, a brainstorm, a concept 'borrowed' from another discipline, or new technology offer the possibility of a quantum leap. Such leaps require the energy to leave one's comfortable orbit. Physician-scientists are beneficiaries of a scientific sea change. Simple, powerful tools allow manipulation of gene and protein expression and mining of human tissues. Simultaneously, a new physiology has turned the laboratory into a virtual rodent hospital. High fidelity catheters and miniaturized imaging platforms exploit the physician-scientist's clinical skills and offer images rivalling those used in medicine. This liberates the physician-scientist's from specialty-restricted research, freeing them to exploit overarching pathways that regulate gene transcription, apoptosis, ion channels, mitochondrial metabolism, etc. These pathways do not respect the specialty-based boundaries of a passé Medical model; nor should physician-scientists (Brown–Goldstein, *Figure 1*). Perhaps, soon agile cardiologists may cure cancer, much as gastroenterologists helped solve the riddle of atherosclerosis.

Hardwork and protected time

The achievements of Nobels better reflect persistence than prescience (Sir James Black, *Figure 1*). At St Andrews Medical School Black recalls, '*I learned ... the joys of substituting hard, disciplined study for the indulgence of day-dreaming .... a new-found love affair with knowledge*'. Since patient care expands to fill the available time, one should negotiate ≥50% protected time for research. Young physician-scientists should consider positions that offer predictable clinical rotations and limit *ad hoc* clinical work. While no 'high-impact' publication will make up for poor clinical care, the rumoured demise of the 'triple threat' is premature. Engaging in research, teaching, and clinical practice constitutes a beneficial, mutually reinforcing triad.

The relevance of a fruitfly

Relevance, a consideration in every paper or grant proposal, should be defined broadly. How often has the relevance of studying potassium channels in the lowly fruitfly (*Drosophila*) or heart formation in the transparent zebrafish been questioned? Nature performs her miracles similarly in the great and small. Zebrafish and humans have 86% gene homology and 77% of human disease-causing genes have a *Drosophila* counterpart.[14] Mutations of the *Drosophila* Ether-a-Go-go K+ channel gene, which causes Go-go dancer-like leg twitching upon ether anaesthesia, are analogous to mutations in the human homolog, (HERG), which predisposes the heart to twitching (fibrillation) and sudden death. Conversely, basic science-oriented physician-scientists should understand epidemiology and clinical trials and ask: Are my discoveries true in humans? The best physician-scientists are pluripotential and ecumenical, neither seduced by the simplicity of reductionist science nor blinded by the physician's white coat.

A complete person

L'Affair Carrell illustrates history's harsh judgment of flawed character in an otherwise great physician-scientist. Alexis Carrell, a French surgeon who developed the vascular suture, which made transplantation possible, deservedly received the 1912 Nobel prize. In the 1970s, streets in many European cities were named in his honour. However, when the French right-wing, Front National, began to trumpet Carrel's intolerant social views, Paris and other cities removed his name from their streets.[15] The pressure to publish in elite journals and secure grants has also leads some astray. Remember, patients, colleagues, and history judge the physician-scientist by more than achievement.

Remember Ithaka

The Nobel prize is not a goal for which one can/should plan. Many worthy contributions are not so honoured. This befell Thomas Lewis in the 1920s and more recently, Salvador Moncada,[16] who was overlooked for the 1998 prize for the discovery of nitric oxide. While the recipients merited their Prize (*Figure 1*), so did Salvador Moncada. He was elected to the US National Academy of Sciences (1994), because he '*discovered that mammalian vascular tissues generate nitric oxide that is biosynthesized from* L*-arginine*', and '*elucidated the relevance of this pathway*'. Perhaps, his omission reflects the arbitrary three-recipient rule. It highlights that contributions by the many lead to prizes for the few. An excerpt from *Ithaka*, by Greek poet CP Kavafy, offers perspective (*Figure 1*). The true prize of a research career is the journey.

Conclusion

The time is right to become a physician-scientist. You are needed by the Society and the tools to ply your dual arts have never been sharper.

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