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Special article

One hundred years of Nobel Prizes and 150 years of anesthesiology

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There are few individuals that are so well known to the worldwide scientific community as Alfred Nobel. He was born in 1833 in Stockholm. His father, Immanuel Nobel, was a chemist and inventor. Alfred and his three brothers, Robert, Ludvig, and Emil, grew up in Stockholm, but some of their teenage years were spent in St. Petersburg, Russia. Alfred Nobel developed into a cosmopolite. Throughout his adult life, he lived in many places.

During his last 10 years, Alfred Nobel lived in San Remo, Italy. At that time he suffered from angina pectoris and was prescribed, by his doctors in Paris, to take nitroglycerine for his chest pain. He could not envision how this substance could be taken internally!! He refused and did not follow his doctor's orders. Alfred Nobel died, in his San Remo home, from a stroke, on December 10, 1896. This is the reason why the Nobel Prize ceremony still is held on December 10 and why the decorations of the Concert Hall and the City Hall in Stockholm are made up with flowers from San Remo.

The testament

In Alfred Nobel's testament he states that the majority of his fortune (31 of 33 million Swedish kronor) should be used for five prizes to those who "have conferred the greatest benefit on mankind." The five areas that should get equal parts were:

- Physics: for the most important discovery or invention
- Chemistry: for the most important chemical discovery or improvement
- Physiology or medicine: for the most important discovery
- Literature: for the most outstanding work of an idealistic tendency
- Peace: to the person(s) or organizations who have done the most or the best work for fraternity between nations, for the reduction of standing armies, or for holding peace congresses

In addition to the five original Nobel Prizes, a prize in economics was added in 1969. This was based on a generous gift from the Swedish National Bank in the memory of Alfred Nobel.

The Nobel Foundation

In order to fulfil Alfred Nobel's will, a Foundation was established in 1900. It is the Foundation that is responsible for the organizations and structures around the Nobel Prize. The Foundation is also the visionary body embracing strategies for the future.

The Nobel Foundation has delegated the scientific working process involved with the different prizes to the Nobel Assembly/Nobel Committee at Karolinska Institute in Stockholm for the Prize in Physiology or Medicine, to the Norwegian Nobel Committee for the Peace Prize (Sweden and Norway were in union until 1905), to the Swedish Academy for the Prize in Literature, and to the Royal Swedish Academy of Sciences for the Prizes in Chemistry and Physics. It is also the Royal Swedish Academy of Sciences that appoints the Prize winners in Economics.

The selection procedure

In order to be awarded the Nobel Prize in Physiology or Medicine, the candidate must have been *nominated during the year*. The *moment of discovery* is the most

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important scientific criterion. The discovery must have resulted in a paradigm shift proven to be *good for mankind*. All these three criteria must be fulfilled. Some delay between the actual discovery and the award is often required before a discovery proves to be good for mankind.

Some Nobel Prize statistics

Over the 100 years of Nobel Prizes, there were 9 years during which Nobel Prizes were not awarded. For the Prizes in Physiology or Medicine, Chemistry, and Physics, the United States has been the dominating country during the past 50 years. Prizes awarded in Literature and Peace have, however, a different geographical distribution.

It is also of interest that 28 women have been awarded Nobel Prizes. Six of them in Physiology or Medicine, 3 in Physics, and 3 in Chemistry. In Literature and Peace, there are 9 and 7 women Laureates, respectively. The Peace Prize has also been given to 18 organizations. According to Alfred Nobel's testament it is not possible to award Prizes in Physiology or Medicine, Chemistry, Physics, or Literature to institutions.

Nobeliana Japonica

Today, there are twelve Japanese Nobel Laureates. The first Japanese Nobel Prize was awarded to the physicist Hideki Yukawa, in 1949, for "his prediction of the existence of mesons on the basis of theoretical work on nuclear forces". The second Japanese Nobel Prize was also in the field of physics. It was given to Sin-Itiro Tomonaga, in 1965, who, together with Julian Schwinger and Richard Feynman, received the award for "their fundamental work in quantum electrodynamics, with deep-ploughing consequences for the physics of elementary particles". A third Japanese Nobel Prize in Physics was given to Leo Esaki, together with Ivar Giaever, United States, and Brian Josephson, United Kingdom, in 1973. In 2002, the fourth Japanese Laureate in Physics was awarded a Novel Prize, Masatoshi Koshiba.

The first Nobel Prize in Chemistry for Japan was given to Kenichi Fukui, who, in 1981, together with Roald Hoffman from the United States, received the award for "their theories, developed independently, concerning the course of chemical reactions". In 2000, a Nobel Prize was awarded to the Japanese chemist, Hideki Shirakawa, who, in conjunction with Alan J. MacDiarmid and Alan J. Heeger, had discovered conductive polymers. In 2001 a Japanese, Ryoji Noyori, was awarded the Nobel Prize in Chemistry: and in 2002 a chemistry prize was given to Koichi Tanaka. The first Japanese Nobel Prize in Physiology or Medicine was awarded to Susumu Tonegawa in 1981. He received the Prize for "his discovery of the genetic principle for generation of antibody diversity". In 1974, Eisaku Sato shared the Nobel Peace Prize with Sean MacBride from Ireland.

It was of great importance for Western culture that Yasunari Kawabata was awarded the Nobel Prize in Literature, in 1968, for "his narrative mastery, which with great sensibility expresses the essence of the Japanese mind". The second Nobel Prize in Literature to go to Japan was given to Kenzaburo Oe, in 1994, for that he "with poetic force creates an imagined world, where life and myth condense to form a disconcerting picture of the human predicament today".

Kenzaburo Oe shares with Selma Lagerlöf, Swedish Nobel Laureate in Literature from 1909, an imaginative and mysterious world filled with fantasies. One of Kenzaburo Oe's wishes during his Nobel week in Stockholm in 1994 was to sit at the desk that Selma Lagerlöf used for her writing. When he visited the Selma Lagerlöf museum, Mårbacka, in Värmland, Sweden, a picture was taken to commemorate this event. It is with freedom and the free word that fantasy can survive, without which creativity does not exist.

A subjective selection of a few early Nobel Prizes

During the first 10-year period, from 1901 to 1911, two Nobel Prizes in Physiology or Medicine were awarded for scientific work within the field of immunology. The very first Nobel Prize in Physiology or Medicine was awarded to Emil Adolf von Behring in 1901 ". . . for his work on serum therapy, especially applications against diphtheria." In 1908, the Nobel Prize was shared between Mechnikov and Ehrlich ". . . in recognition of their work on immunity." It was Mechnikov, who, in an elegant series of experiments, identified the cellular response to foreign material, i.e., the inflammatory reaction. He used a starfish in its larval stage and put a rose thorn into it. After some time he, by using a microscope, identified that the larva was swollen and had some clustering of reactive cells around the rose thorn.

It was also in these early days, in fact in 1902, that Sir Ronald Ross was awarded the Nobel Prize ". . . for his work on malaria by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it."

In 1906, Santiago Ramón y Cajal shared the Nobel Prize with Camillo Golgi ". . . in recognition of their work on the structure of the nervous system." It was Cajal who first introduced the concept of synapses which has had an enormous influence on the understanding of the function of the central nervous system.

Early discoveries in anesthesia

In the years preceding the first Nobel Prizes, general anesthesia was discovered mainly as a result of the inhalation of diethyl ether. One still argues whether it was Crawford E. Long, in the late 1830s, or William Morton, in the mid 1840s, who discovered general anesthesia. Although there was a little over 50 years from this discovery of general anesthesia to the first Nobel Prize in 1901, the impact it had on the development of surgery was certainly already at that time proven to be good for mankind. The difficult part, from a Nobel Prize perspective, would have been the identification of the discoverer, had general anesthesia been nominated for the Prize. Among other discoveries in anesthesia in the late nineteenth century was that of cocaine, by Carl Koller, who used it for local anesthesia when performing glaucoma surgery. Certainly, this was also a major discovery that was for the good of mankind. It challenges the curious mind, what would have happened if this discovery had also been nominated for the Nobel Prize. However, already at that time, the competition was strong, and it cannot be denied that the impact of, for instance, Santiago y Cajal's concept of synapses is indeed hard to surpass.

Other discoveries in anesthesia/intensive care medicine

Later, there were several good examples of discoveries awarded the Nobel Prize in Physiology or Medicine that have had an impact on the conduct of anesthesia, such as the award given to Willem Einthoven "... for his discovery of the mechanism of the electrocardiogram." Another important prize was the one given to Karl Landsteiner in 1930 for his discovery of the human blood groups. He performed straightforward incompatibility experiments in six of his colleagues; in a systematic pattern, he mixed serum with cell elements of their blood. He discovered a pattern that guided him to the discovery of human blood groups. Certainly this was an important Nobel Prize for mankind, for surgery, for control of trauma and shock, and for intensive care medicine.

Control of metabolic regulation

Anesthesia and intensive care medicine have developed into the control of metabolic reactions. One could identify a few discoveries or breakthroughs in the fields of fluid therapy (Ringer) and parenteral nutrition (Seldinger, for the technique of how to introduce intravenous catheters and Arvid Wretlind, for total parenteral nutrition).

The discovery of insulin is an excellent example of how discoveries can lead to the control of metabolism. In the early 1920, Banting, in London, Ontario, Canada, presented an idea to his teacher in carbohydrate chemistry, Professor Macleod in Toronto. It was known that the absence of a pancreas resulted in a metabolic syndrome that could not be cured but was helped by starvation. Various extracts of pancreas had been tested, but had never worked. There was something in the extracts (proteases, as later understood) that destroyed the active part that could control blood sugar. The idea Banting had was to ligate the pancreatic ducts (from which the substance that destroys the protease is released) and then, at a later stage, make an extract of the remaining parts of the pancreas. It worked, as proven by Banting and the PhD student Best during some summer experiments in 1921. Blood sugar levels in dogs were clearly shown to be decreased by the extracts from pancreatic tissue in which ducts had been ligated. Soon all the patients in various sanatoriums, mostly children, could be treated by the extract and they immediately recovered from their grave starvation. This success story was published in a scientific article in 1922, and, in 1923, the Nobel Prize in Physiology or Medicine was awarded to Banting and Macleod. It is of great interest to note that new insulin indications are of importance even today. This is nicely illustrated by van der Berghe et al.'s recent article in the *New England Journal of Medicine*, in 2001, in which it was shown that insulin therapy in critically ill patients, targeted to result in blood sugar levels of less than 110 mg/dl, decreased intensive care unit (ICU) mortality from 8% to 4%.

Penicillin and polio

There are more excellent examples of Nobel Prizes in Physiology or Medicine that are well within the field of intensive care medicine. One is the prize awarded to Fleming, Chain, and Florey in 1945 "... for their discovery of penicillin and its curative effect in various infectious diseases." Alexander Fleming had already made his important discovery in 1930. It was, however, not until the 1940s that Chain and Florey produced a drug which was shown to have an enormous effect on infectious diseases, not least during the last years of World War II. Someone has stated that the population of the world would have been halved if penicillin had not been discovered. Indeed, it has had a great impact on human life on earth.

Another major step forward within the field of infectious diseases and intensive care medicine was the discovery, by Enders, Weller, and Robins, "... of the ability of poliomyelitis viruses to grow in cultures of various types of tissue." They were awarded the Nobel Prize in 1954, and their discovery led to the production of polio vaccines that have had a significant impact on the development of that disease worldwide.

Possible future breakthrough areas in anesthesia and intensive care medicine

The basic mechanisms of general anesthesia are still not known or understood. There may not be one single mechanism that explains this neurological effect of various pharmacological agents. If such a mechanism is found, however, there will probably be several nominations suggesting a Nobel Prize. Chances would most likely be good for such a discovery to withstand the scrutinizing process and hard tests leading to the prestigious award of a Nobel Prize.

There is also another field close to anesthesia and intensive care medicine—the cellular utilization of oxygen. Not too long ago, in 1998, the first Nobel Prize in Physiology or Medicine awarded for the discovery of a gaseous transmitter, (nitric oxide) was given to Robert Furchgott, Louis Ignarro, and Ferid Murad. It is most likely that there will be other important discoveries of how gaseous molecules penetrate cell or nuclear membranes of various types of cells. Such a breakthrough for oxygen would, no doubt, give us important tools for how to, in clinical practice, better take care of patients in severe shock and multiorgan failure. During these conditions cells are known to be incapable of using oxygen, showing so-called cytopathic hypoxia, although adequate amounts are delivered.

Concluding remarks

To a large extent, the history of 100 years of Nobel Prizes in Physiology or Medicine also describes the development of modern medicine. Although neither the discovery of general anesthesia itself, nor the discovery of local anesthetics, has been awarded a Nobel Prize, there are certainly many examples, such as those above, of Nobel Prizes that are well within the field of both anesthesia and intensive care medicine. There are, for the future, several challenges for researchers involved in mechanisms of anesthesia, as well as in oxygen biology, to carry out breakthrough investigations that might be worthy of a Nobel Prize.

An Idea lives on

The Nobel Prizes award:

- Extraordinary achievements in natural sciences
- Promotion of peace
- Idealism in literature

These achievements are publicly recognized worldwide in December each year. Most importantly, however, the Nobel Prizes stimulate freedom of thought, fantasy, and creativity in the young generation—key factors for continued development and for the making of new future discoveries of importance for humankind.