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Van den Ende Memorial Lecture

CONTRIBUTIONS BY YOUNG MEN TO MEDICINE

N. Sapeika, B.A., M.D., Ph.D., F.R.S.S.Af.
Department of Physiology and Pharmacology, University of Cape Town

It is a great compliment to have been asked to deliver the van den Ende Memorial Lecture instituted in this medical school. The name which we commemorate today conjures up in our minds a friend and colleague who had many fine attributes. Among these is the fact that he was a scientist with a deep love for his subject, who, early in his medical career, showed ability as a research worker.

In choosing a subject for this memorial lecture there came to mind certain individuals who are famous for the outstanding and far-reaching contributions they made to medical science and who made discoveries very early in life. This topic is the main theme of my address.

Outside the medical profession there are well-known examples of brilliant young men whose names will live forever. For instance, in the realm of music there are a number of composers who were outstanding in their youth. Mozart at the age of 5 years wrote an incomparable piano concerto. This great musician lived only to the age of 35 years. Franz Liszt, when 10 years old, already played with the technique and the emotion of a mature virtuoso. Brahms, who was born in the slum districts of Hamburg, was something of a child prodigy. Chopin, who was very ill with tuberculosis at 20, had composed a great deal before this age; he died when he was 40. Schubert died at 31 and Mendelssohn at 38.

Examples from the physical sciences include the following: Copernicus (1473-1543), the famous astronomer, was appointed to the chair of astronomy in the University of Rome at the age of 26. Galileo (1564-1642), who was intended to devote his time to medicine, studied Euclid and turned his mind to geometry and philosophy. He made important discoveries before he became professor of mathematics at the age of 24 years at the University of Pisa. Isaac Newton (1642-1727), at 24, had discovered the binomial theorem and the principles of the integral calculus. He was appointed to full professorship in mathematics at Cambridge University when he was 27. Thomas Edison (1847-1931), the great inventor, received 40,000 dollars at the age of 23 years for one of his first inventions—the Edison Universal telegraphic printer. Guglielmo Marconi (1874-1937), at the age of 22 years, patented his new system of signalling—the world's first patent for wireless telegraphy. Svante Arrhenius (1859-1927), at the age of 24, read his preliminary paper which, with van 't Hoff's note, forms the basis of the modern conception of electrolyte dissociation and of osmotic pressure. Albert Einstein (1879-1955) published his Theory of Relativity when he was 26 years old.

In the history of medicine there are records of discoveries made by old and young. There are, however, few recorded instances of epoch-making discoveries by very young men, of the age of the medical student at present-day universities.

CONTRIBUTIONS TO MEDICINE

Examples will now be given of men well known in the history of medicine who made important discoveries early in life.[1,2,4,6,7] For the sake of interest and to limit the number considered, the age limit has been set at 26 years. With this limitation the discoveries of only twenty-three scientists, most of them well known to the medical profession, will be presented briefly. Some of the individuals to be mentioned have gained recognition through their assistance in team work, but most appear to have made important original contributions on their own.

Niels Stensen (1638-1686) made important contributions to anatomy at an early age. He discovered, when he was 22 years old (while dissecting the head of a sheep in the house of his professor), that he could pass a probe down a channel from the parotid gland. This was the parotid duct (Stensen's duct). He afterwards examined other glands such as the lacrimal glands, and was able to prove that all externally secreting glands have ducts. His contributions are so amazing as to be almost unbelievable. He described Peyer's patches and Fallot's tetralogy before these were re-described by the men whose names they now bear.

Regner de Graaf (1641-1673) was a pioneer in the study of pancreatic secretion. He experimented at the age of 23 on the living dog, and used a goose-quill to construct an external pancreatic fistula. He also dissected rabbits at varying intervals after coitus, discovered the corpus luteum, and traced the passage of the ova down the oviducts to the uterus. His epoch-making discoveries on ovulation were based on experiments performed on more than 100 rabbits and 40 goats, cows, dogs, cats, and other animals. At an earlier date he published a treatise on the male reproductive system. Among his fellow students at Leyden University was Niels Stensen. de Graaf never held an academic post, apparently because he was a Catholic.

Lorenzo Bellini (1643-1704), the Italian anatomist, was born of a poor family in Florence, but showed such promise that Duke Ferdinand II paid for his education. At the age of 20 he became professor of philosophy and of theoretical medicine at Pisa, and later in the same year, of anatomy as well. He is especially known for his classical description, at the age of 18 years, of the gross anatomy of the kidney, which he showed was a conglomerate of tubules including the renal excretory ducts, since known as the ducts of Bellini.

180 years later *William Bowman* (1816-1892), at the age of 26 years, published his report on the structure and function of the Malpighian bodies of the kidney, including Bowman's capsule which is named after him. He would have been greatly interested in the latest detailed descriptions of the structure of the capsule.

John Mayow (1643-1679), one of several famous Oxford physiologists, is best known for defining, at the age of 23, as a definite chemical entity (spiritus nitro-aereus), the substance we now know as oxygen. He concluded that the purpose of breathing is to take a fraction of air into blood as life-giving 'particles'.[8] He was a shy young man, easily hurt, and the failure of his contemporaries to appreciate his work might have been a factor in causing his early and unhappy death. The full significance of his studies was not recognized until after Lavoisier had announced the discovery of oxygen.[4]

Casper Bartholin the younger (1655-1738) was a member of one of the most celebrated medical families in history; at one stage in their history five of seven sons were professors in the University of Copenhagen. This particular Bartholin is said to have edited and published his father's *Dissertation on the Anatomy of the Swan* when he was 13 years of age. He became a medical student at 16, and three years later, while still a medical student, he was appointed professor of philosophy. At the age of 21 he published a book on the anatomy of the diaphragm. His name is best known to us for his description of the vulvovaginal glands, which are important from the clinical point of view because of their liability to become infected and to form abscesses.

Giovanni Battista Morgagni (1682-1771) was a precocious youth who wrote poetry and discussed problems of philosophy at the early age of 14. He received his medical degree at the age of 19 and devoted himself to anatomy, publishing his first work at the age of 24. He later became professor of anatomy, but it is for his work *De sedibus et causis morborum per anatomen indagatis libri quinque* (The seats and causes of diseases investigated by anatomy), published in 1761 when he was 79 years of age, that his name is inscribed among the greatest in the history of medicine. He has been called the 'father of pathology'.

Charles Blagden (1748-1820) carried out spectacular and well-conceived experiments in a heated room on the ability of the body to withstand dry heat and the importance of perspiration for maintaining constancy of body temperature. He published an account of his work at the age of 26.

Herbert Mayo (1796-1852), physiologist at Middlesex Hospital, London, clarified the problem of reflex-action, and described the functions of the nerves of the face (motor power in the VIIth, common sensibility in the Vth) in his publication which appeared in 1822. He deserves the credit for this finding instead of Bell, whose name is better known in this connection.[4]

Johannes Peter Muller (1801-1858) was the son of a cobbler, poor but not penniless, who was given a good education and became the greatest physiologist that Germany has produced. He made no epochal discoveries, but he enriched every field he touched. His important contributions to physiology included the important *Handbuch der Physiologie des Menschen.*

He was professor of anatomy and physiology in Berlin for 25 years from the age of 22. He was a great teacher and, unlike Claude Bernard who left no great pupils or disciples, he had pupils who became distinguished, for example Virchow, Helmholtz, Henle, and Schwann.

The ducts (Mullerian ducts) which give rise to female reproductive organs were first noted by him when he was 24.

Hermann L. F. von Helmholtz (1821-1894), a pupil of Muller and one of the greatest thinkers of all time, at 24 years of age measured for the first time the heat production of frog muscle. He had phenomenal powers of sustained abstract thinking. At the age of 26 he had already soared to extraordinary heights, as revealed in the publication of his celebrated essay on the Conservation of Energy. He became professor of physiology at 28. His major achievement was probably in physiological optics, including the mechanism of accommodation and the theory of colour vision. He was a skilled musician, and made contributions to the physiology of hearing.[4,6]

James Syme (1799-1870), the famous surgeon, never attended a course of lectures on surgery while a student at Edinburgh University, and in 1820 while still a final year medical student, 21 years old, he was appointed superintendent of the local fever hospital. He is best known for his amputation operation, essentially a disarticulation at the ankle joint, which he reported in 1844.

Henry Gray (1827-1861), well known to all who have studied anatomy, was lecturer in this subject at St. George's Hospital, London, and had gained prizes and published a number of original papers before he was elected to the Royal Society at the remarkably early age of 25 years. As a student he was a most painstaking and methodical worker, learning anatomy by making dissections for himself. His crowning achievement is of course the well known book, *Anatomy, Descriptive and Applied*, published when he was 31 years old. He died of smallpox at the age of 34.

William Osler (1849-1919), the great medical teacher, who interpreted disease in a functional manner, published many original works. He reported the relation of blood platelets to thrombi when he was 25 years old.

Paul Ehrlich (1854-1915), while still a student, became interested in lead poisoning and devised a stain to demonstrate lead in the tissues. This experiment convinced him that certain tissues had a selective affinity for certain chemicals, an idea which dominated all of his subsequent medical thinking. He described the mast cell at the age of 21 and distinguished it from plasma cells. He published an account of special staining methods for the differentiation of white blood cells and developed the differential blood-count technique when he was 25. His 'side-chain' theory was put forward when he was 31.

Ehrlich's work arose as a by-product of the dye-stuff industry; it laid the foundation of modern haematology and the beginning of a new chemical pharmacology in the provision of remedies which were to foreshadow the triumphs of chemotherapy of this century.

E. Aronsohn and J. Sachs were two medical students at the University of Berlin who demonstrated a centre of control of temperature in the brain in 1884, when they damaged in animals an area adjacent to the corpus striatum. This they showed a few months after Richet in Paris had also produced excessive body temperature by puncturing the brain and producing damage probably in the same region.[2]

Augusta Dejerine-Klumpke (1859-1927) was one of four brilliant sisters of a famous San Francisco family. In their day it was difficult for women to enter the medical profession, but she was accepted in the Medical Faculty of the University of Paris. She was brilliant and, while a student, she described the atrophic paralysis and sensory changes which follow lesions of the lower trunk or medial cord of the brachial plexus (Klumpke's paralysis, 1885). During her final year as a medical student she married the subsequently famous neurologist, Joseph Dejerine.

Walter Bradford Cannon (1871-1945), well known for his analysis of the mechanisms of the internal regulation of body activity (homeostasis), was also a pioneer in radiology. While still a medical student he realized, soon after roentgen rays had been discovered, that they could be used for the study of gastro-intestinal movements. He used bismuth as the radiopaque medium, and the first account of this work was given to the American Physiological Society in 1897.

Jay McLean was a second-year (sophomore) medical student in 1916 working with Howell, the distinguished American physiologist, at Johns Hopkins University. He was assigned the task of isolating certain phosphatides from heart and liver, for study of their thromboplastic effect compared with that of cephalin. Contrary to expectation he discovered an anticoagulant activity in the extracts. The active substance was later named heparin by Howell because of its predominant localization in the liver.

Charles Herbert Best (b. 1899) was associated with F. G. Banting (and J. J. R. Macleod) in the discovery of insulin. Banting was a young Canadian orthopaedic surgeon who obtained a post as demonstrator in physiology and became interested in diabetes mellitus. Best began his partnership with Banting on 16 May 1921, when he was a second-year medical student in the Department of Physiology in Toronto. There was no one in the laboratories at the time they began their work, except the caretaker and one or two friends. It was arranged they should have ten dogs and the use of the laboratory for eight weeks. Mr. Best and Mr. Noble were appointed as assistants to Banting, each to give four weeks. They tossed a coin to decide who would assist in the first four weeks and Mr. Best won the toss. At the end of the four weeks Noble did not return, Best stayed on and was associated throughout the entire work.

On 11 January 1922, eight months after they had begun their experiments, when Banting was 30 and Best 23, the first patients were treated in the Toronto General Hospital with extracts of the pancreas containing insulin, which revolutionized the treatment of diabetes mellitus. This discovery, important in its own way, was also important in giving a fresh and powerful impetus to the study of endocrinology.

Joshua Lerderberg (b. 1925) had already made significant contributions to genetics at the age of 21, and with his teacher, Edward Tatum, demonstrated that bacteria have a sort of sex life. At 27 he discovered, in collaboration with one of his own students, that bacteria infected with certain viruses may undergo hereditary changes (transduction) for which discovery he received the Nobel Prize in 1958. He is now interested in exobiology, a new science which attempts to obtain living material from other planets for comparison with that on earth.[9]

The last of the famous young investigators to be mentioned here is *Norman Urquhart Meldrum* (1907-1933) who died at the age of 26. He isolated the important enzyme carbonic anhydrase which facilitates the reaction between carbon dioxide and water to form carbonic acid. He described its preparation and properties. It is difficult to find any details about him, but his work is regarded as very important since his name and work are mentioned in the book entitled, *Some Founders of Physiology*,[6] which contains a galaxy of famous contributors to the growth of physiology.

The specific medical discoveries which have been cited were epoch-making in that they were milestones which marked new directions for investigators, but the road along these milestones cannot be ignored in realistic medical history.

Developments in medicine cannot be regarded as taking place in isolation. It must be remembered that they are inextricably bound up with the social process and with scientific developments in other fields. This important aspect is only mentioned in passing and cannot be considered in detail here.[3,8]

The brief account given here of the important discoveries by famous young scientific workers is fascinating and should inspire young people to solve the multitudinous problems which still confront us. The examples that have been cited from medical history should encourage our students to be interested in research at an early age. But research work is not easy and some general remarks on problems concerning the individual and the opportunities in his environment need to be presented.

DISCUSSION

Chance

Some great discoveries have been made by chance, for example penicillin and mercurial diuretics, but the dictum of Pasteur must be remembered: 'Chance favours the prepared mind'. The discovery of penicillin is often quoted to prove that important discoveries come by chance. The answer is that the particular combination that does the trick does come by chance, but that chance is multiplied by providing opportunities for discovery in the first place, and opportunities f r development by interested people in the second.[3] Seemingly trivial accidents have been turned to remarkably good advantage through the ability of an interested and properly equipped person to note nature's slightest deviation from what is expected of her.[5]

Hard Work

As a general rule all discovery, even that which at first sight seems to be the result of accident or good luck, is the result of laborious effort, constant and intelligent observation and experiment and, above all, of the individual's ability. Triumph comes to few, and even then it is based on hard work, patience, humility, and the courage to face disappointment and frustration. This is exemplified in the case of drugs which have been produced so abundantly in recent years. While chance still plays a large part in the discovery of new drugs, they are in general produced more rationally. Each new chemical compound is put through a series of tests designed to cover a wide range of pharmacological actions. Technicians, each trained to perform a single test, help to discover whether compounds have any future as drugs. When an interesting compound is found, details are worked out by specially designed experiments followed by well-designed therapeutic clinical trials. All this means hard work and expense.

Genius

Edison believed that there is no success without effort. Perhaps his best-known saying is his definition of genius: 'Genius is 1 per cent inspiration and 99 per cent perspiration', and he always worked according to this definition.

Science is not due solely to the genius of great men. Great men have had decisive effects on the progress of science, but no discovery of any effective kind can be made without the preparatory work of hundreds of comparatively minor and unimaginative scientists. These people accumulate the necessary data on which the great man can work.

Everyone is influenced by what he has learned from his predecessors, though his own experience, thought and experiment may enable him to advance knowledge by arriving at different conclusions from those held by his contemporaries. Many discoveries have not been dependent upon the work of especially gifted men. Yet there is even today a tendency in medicine, as in technology, to attribute progress romantically and falsely to individual genius, rather than to the efforts of thousands of persons in the past and present.

Students

Medical research, like most human activities, advances by virtue of contributions from many different types of individuals working at different levels. Greater recognition is therefore accorded to the 'little researcher'; and to foster this, education in modern times has at all levels been permeated with a tremendous concern for the adequate development of students, especially those who are gifted.

There is no reason why selected students should not take part in research programmes, especially in team work. Even the best scientists require aid and, for many adventures in research, friendly cooperation is required between individuals working under strict collective discipline. In a good deal of modern research many individuals take part in an enterprise and are responsible for joint conclusions.

Reference has already been made to medical students and other young investigators whose names are now famous in medical history. But fame, or notoriety, does not depend only on brilliant discovery; for example, although he did not discover ether it was W. T. G. Morton (1819-1869), a second-year medical student at Harvard Medical School who, after numerous experiments on himself, the family dog, cats, hens, and rats, used ether to anaesthetize a patient for Dr. J. C. Warren, Professor of Surgery at Harvard, in a public demonstration of 16 October 1846. When the patient was anaesthetized, Morton said those memorable words that have echoed through the years: 'Dr. Warren, your patient is ready,' and at the end of the operation Warren turned to his audience and said: 'Gentlemen, this is no humbug'.

In training students, teachers must constantly bear in mind that their subjects are so vast that the student is apt to become lost in a maze of factual knowledge if he is not provided with adequate guidance. Students must not only be instructed, but also guided and inspired. Prof. Noah Morris considered the teacher had failed if, at the end of his discourse, he was not mentally exhilarated and physically exhausted. The good teacher is forced to recognize the inevitable gaps in his own knowledge and understanding. As a good teacher he will stimulate his students to investigate these gaps.

We have to recognize that we are all ignorant about many matters, even in the common diseases with which doctors have to deal. Older men in control of research must be careful not to dominate or to dictate to younger men working with them. They must also not be isolated, aloof and inaccessible. They should be readily approachable as advisers.

We are all students and there is no sharp line of demarcation between us. Young people also have ideas, but this is not enough. Storm van Leeuwen said that he was weary of young men who could produce brilliant ideas; he was only interested in young men who were so troubled by a brilliant idea that they could not rest until they had demonstrated by experiment how true the idea was.[5] This admonition has general application as well as specific application to undergraduate students.

Research need not be confined to the laboratory. Many great discoveries in medicine have been made at the bedside by those rare individuals with the ability not only to see, but also to seek an explanation of a phenomenon which they and others have observed repeatedly in their patients.

Conditions

Certain conditions must be fulfilled if the advancement of science is to be encouraged to flourish and grow.[3]

1. The first condition is that the material support of scientific research should be on an adequate scale. Progress is halted by the lack of suitable materials and funds.

2. The individual scientific worker should get the conditions, opportunities, and incentives that will enable him to give his best service.

3. The basic condition for research to flourish is the human one. There is no real shortage of intellectual ability in the human race. The achievements already made have been the work of a handful of men, but by calling on men and women of all classes and peoples, the rate of advance of science should multiply manifold. University education must be made available to large numbers. A scientific education will provide the field from which will come the research workers who will build the science of the future.

4. Individuals do not do their best work alone. The best results occur when a number of people work together. Through mutual suggestion and emulation the chance of hitting on significant discoveries is enormously increased.

CONCLUSION

We are living in a stirring scientific era, and to be young in mind and spirit, even if not in years, is important if we are to participate in the interesting and exciting developments of our time. All of us who are privileged to be students must improve our knowledge and retain youthful enthusiasm for new discoveries. By being thus equipped we too may be able to assist others to make, or to make ourselves, a contribution to medical science.

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