The Young And The Bold.

Mrinal Dhawan[1], Aparajita Arora[1], Krishna Adit Agarwal[2], Pooja Pant

[1]Intern, [3]Secretary, Department of General Surgery, Sir Ganga Ram Hospital, New Delhi, India

[2]MBBS Student, Safdarjung Hospital, New Delhi, India

***Abstract**: As we stand today, on the threshold of a new era of Medicine, it is timely to look back upon the discoveries and developments that have brought us this far. Medical history has fascinating stories to tell. This paper highlights the lives of a few gifted Medical students, who with their curiosity, initiative, originality, and ruthless hard work made an immense contribution to medicine. These blazing young guns of medicine did not just live with the will to believe, but the wish to find out. Here are the stories of their great miracles.*

INTRODUCTION

> **"A discovery is said to be an accident meeting a prepared mind."**
>
> *- Albert Szent-Gyorgyi*
> *(Hungarian Biochemist,*
> *1937 Nobel Prize*
> *for Medicine, 1893-1986)*

Discovery in any field is a chance phenomenon. Great discoveries have come from looking at standard situations but seeing them differently. These miracle makers were ordinary men, who persevered, despite all their odds, as their stories will tell. Life threw opportunities at them in unusual ways- an insurmountable hurdle, or sometimes a cruel trick of destiny. These medical masterminds took chances, persevered till they got it right and changed the course of mankind.

HEPARIN

Heparin, one of the oldest drugs still in widespread clinical use, is a naturally occurring glycosaminoglycan whose main function is to inhibit the coagulation of blood. It was discovered almost a century ago and took many years to move from the laboratory to the bedside. There has been significant controversy regarding the distribution of credit its discovery.

JAY MCLEAN

In 1916, at Johns Hopkins Medical School, Baltimore, USA, a second year medical student, Jay McLean, (Fig 1) was working under the physiologist William Henry Howell.

Figure 1 : *Jay McLean*

The discovery of heparin came as a result of Jay McLean's determination to accomplish something by his own ability. The mile posts were the death of his father when he was 4 years old, the remarriage of his mother when he was 9 and the earthquake fire in San Francisco when he was 15. His stepfather was unsympathetic to his plans for a medical education at Johns Hopkins. Despite these handicaps, he made the decision to become a physician during his last year at Lowell High School in San Francisco[1]. William Henry Howell's main interests were the substances controlling blood clotting; He believed that the release of cephalin (so called because it was first isolated from canine brain) from platelets and leucocytes neutralized anti thrombin, permitting activation of prothrombin by calcium (Howell, 1912). McLean had come up to Baltimore the previous year and was assigned by Howell to examine the chemical purity of cephalin preparations, and to demonstrate that it was cephalin and not a contaminant in the preparation that accounted for the procoagulant activity. After finishing this work early, McLean extracted phosphatides (fat soluble compounds) from canine liver that appeared to demonstrate anticoagulant, properties in vitro and subsequently led to excessive bleeding in experimental animals. McLean then moved to the University of Pennsylvania to research cephalins further under Richard Mills Pearce. In October 1917, he returned to Baltimore but did no further research on the phosphatides he had isolated the previous year. Instead, he continued research on cephalin, feeling that work on a procoagulant rather than an anticoagulant, was better for the ongoing efforts in The Great War. Back in Howell's laboratories, work on anticoagulants continued. Alongside another medical student L. Emmett Holt Jr, Howell had isolated another fat-soluble anticoagulant apparently distinct from that isolated by McLean 2 years previously (Howell & Holt, 1918). The term 'heparin' was coined by Howell from the Greek 'hepar', or liver, the tissue from which it was first isolated. This water soluble heparin began to be produced commercially by a local pharmaceutical company in Baltimore, but studies conducted at Mayo Clinic, Minnesota demonstrated that this preparation caused side effects including headaches, fevers and nausea. Howell was concerned production would cease as its toxic effects might preclude widespread use[3]. Over the next 40 years, priority for the discovery of heparin became the subject of dispute. McLean returned to Baltimore and graduated in 1919. He entered private practice but his surgical career never thrived. He returned intermittently to his research on heparin. Much of his energy – lectures, correspondence and even a radio interview – was expended on his claim to priority in the discovery of heparin. McLean died of an ischemic heart disease at the age of 67 years[2].

Correspondence: Dr. Mrinal Dhawan, *163, Vigyan Vihar, Near Anand Vihar Colony, New Delhi-110092 Tel No. 8800427933*
e-mail*: mrinal255@gmail.com*

INSULIN

In 1920, Dr. Frederick Banting (Fig 2) wanted to make a pancreatic extract, which he hoped would have anti-diabetic qualities. In 1921, at the University Of Toronto, Canada, along with medical student Charles Best, they managed to make the pancreatic extract. Their method involved tying a string around the pancreas duct. When examined several weeks later, the pancreatic digestive cells had died and been absorbed by the immune system. The process left behind thousands of islets. They isolated the extracts from the islets and produced isletin. What they called isletin became known as insulin. Banting and Best managed to test this extract on dogs that had diabetes. They discovered insulin. In fact, they managed to keep a dog that had had its pancreas taken out, alive throughout the whole summer by administering it the extract (which was, in fact, insulin). The extract regulated the dog's blood sugar levels. At this point, Professor J. MacLeod, who had placed the laboratory at their disposal, said he wanted to see a re-run of the whole trial. After doing so he decided to get his whole research team to work on the production and purification of insulin. J.B. Collip joined the scientific team, which now consisted of Banting, Best, Collip and Macleod. They managed to produce enough insulin; in a pure enough form, to be able to test on patients. In 1922 the insulin was tested on Leonard Thompson, a 14-year-old diabetes patient who lay dying at the Toronto General Hospital. He was given an insulin injection. At first he suffered a severe allergic reaction and further injections were cancelled. The scientists worked hard on improving the extract and then a second dose of injections were administered on Thompson. The results were spectacular. The scientists went to the other wards with diabetic children, most of them comatose and dying from diabetic keto-acidosis. They went from bed to bed and injected them with the new purified extract - insulin. This is known as one of medicines most dramatic moments. Before injecting the last comatose children, the first started to awaken from their comas. Collip did not get on too well with Banting and Best apparently - and he soon left the project. Best continued trying to improve the extract and managed eventually to produce enough for the hospital's demand. Their work was privately published. The Eli Lilly Company soon got to hear about it and offered to assist. It was not long before the Eli Lilly Company managed to produce large quantities of refined pure insulin. In 1923 Banting and Macleod were awarded the Nobel Prize in Physiology or Medicine. Banting shared his prize with Best and Macleod shared his with Collip. The patent for insulin was sold to the University of Toronto for one dollar[4].

Figure 2 :*Dr. Frederick Banting*

ELCTRIC SYSTEM OF THE HEART

Why Does the Heart Beat?

This question-known as the myogenic versus neurogenic theory-dominated cardiac research in the 19th century. In 1839, Jan Evangelista Purkinje discovered gelatinous fibers in the ventricular subendocardium that he thought were muscular. Walter Gaskell, in 1886, demonstrated specialized muscle fibers joining the atria and ventricles that caused "block" when cut and found that the sinus venosus was the area of first excitation of the heart. By examining serial embryologic sections, Wilhelm His, Jr, showed that a connective tissue sheet became a bundle connecting the upper and lower cardiac chambers, the bundle of His. Sunao Tawara traced the atrioventricular (AV) bundle of His backward to find a compact node of fibers at the base of the atrial septum and forward where it connected with the bundles of cells discovered by Purkinje in 1839. Tawara concluded that this "AV connecting system" originated in the AV node, penetrated the septum as the His bundle, and then divided into left and right bundle branches that terminated in the Purkinje fibers[5]. 1906 was marked as the year of another major discovery "The Sinoatrial Node". Finalizing the discovery of the electrical system of the heart and providing an anatomical answer to the baffling mystery. Dr. Arthur Keith an anatomy lecturer at London Hospital along with Martin William Flack a medical student of the same hospital described histological in the right atrium of different mammalian including human hearts a structure which they called sino-auricular node and which they interpreted as the place where the heart beat originates. Flack because of Dr. Keith studied the hearts of trapped moles, mice and frogs and interestingly he found out a wonderful structure in the right auricle of the mole. Keith quickly sensed out that this structure which Flack had found closely resembled the AV node which had been identified the year before by Sunao Tawara a Japanese anatomist[6]. Thus Flack completed the electrical circuit of the heart. Following his graduation in 1909 he attained a fellowship which enabled him to work with the German physiologist Hugo Kronecker (1839-1914) in Bern and also with professor Léon Fredericq (1851-1935) in Lüttich, capital of the Belgian province Liege. He was a demonstrator of anatomy at the London Hospital Medical College from 1905-1911, and from 1911 to 1914 lecturer of physiology. He was appointed as the first director of Medical Research for Royal Air Force and he assessed physical fitness of pilots by his studies and researches on cardio respiratory physiology and developed techniques.[8,9] Flack had a history of childhood rheumatic heart disease which as a consequence he died of bacterial endocarditis in 1931[7].

Figure 3 : *Augusta Déjerine-Klumpke*

BRACHIAL PLEXUS

A Receiver and a distributor of nerves which gives directions for the functioning of the chest, shoulder, and arm in the form of Nerves. Formed by lower four cervical nerves and the first thoracic nerve, lies within a cave called as the Axilla, was discovered by a French neurologist, **Augusta Déjerine-Klumpke (**Fig 3**),** born October 15, 1859. San Francisco; died November 5, 1927, Paris. She was the first woman to be an intern in a Parisian hospital. She was known for a treatise about neuroanatomy.

AN AMERICAN IN PARIS

Augusta Marie was the daughter a prominent businessman. Her parents were separated, and in 1871 the mother moved to Germany with her six children[10]. Two years later they moved to Geneva, where Augusta attended tutorials for girls as well as courses in chemistry and the natural sciences at the academy of Lausanne. Augusta wanted to study medicine but, since there was no faculty of medicine in Lausanne, the family moved to Paris and she joined the faculty of Medicine[11], where Madeleine Bras in 1875, as the first woman in France, had been created a doctor of medicine. She was the student of notable figures as Ranvier (histology) , Charcot (neurology),diagnosed a brachial plexus palsy associated with Horner's syndrome. This actually formed the basis of her undergraduate thesis and her description of lesions of inferior roots of brachial plexus[12]. Despite the resistance of the dean of the faculty, Alfred Vulpian (1826-1887), Augusta was able to enter the study. In 1882 she won entrance to an externship, a hospital position without residence at the hospital. During her second and third year Augusta was connected to Vulpian's clinic. It was only due to intervention by minister of education, the physiologist Paul Bert (1830-1886), that Augusta in 1887 became the first woman in France to be appointed interne des hôpitaux. She was a skilled illustrator, drew up schematic diagrams and showed unexampled dexterity when slicing microscopic preparations from the central nervous system. Under her own name and with her colleagues she published a large number of neurological articles. In the year 1888, she married Jules Dejerine. The marriage was to become the beginning of a unique cooperation in neurological research.

Augusta's doctoral thesis on polyneuritis, lead toxicity and neuromuscular atrophies received great attention. During the First World War and subsequent following years she was a pioneer in the treatment and rehabilitation of the large number of soldiers afflicted by wounds of the nervous system and especially of the spinal cord. After the death of her husband Augusta Dejerine-Klumpke worked with her daughter and son in law, Étienne Sorrel, with the establishment of the Musée Dejerine with a laboratory and a library for the keeping of the scientific remains of the couple.

THE SPHINCTER

One of its kind. This is one of the best part fitted by God in the machine named as Human Beings. It's just a circular band of voluntary or involuntary muscle that encircles an orifice of the body or one of the hollow organs. One of the famous discoveries took place in the late nineteenth century when this Italian physiologist and anatomist **Ruggero Oddi** (Fig 4) (July 20, 1864 - March 22, 1913) described this small group of involuntary circular and longitudinal muscle fibers that wrapped around the end of the Bile and Pancreatic ducts. Ruggero Oddi was 23 year old, fourth year medical student at the University of Perugia. Oddi concluded that the sphincter controlled the intermittent flow of bile from the liver and pancreas to the duodenum. He continued his studies regarding the sphincter and measured pressure changes across the sphincter[13]t the University of Bologna and finally he gained his degree in medicine and surgery in Florence in the year 1889. Oddi married a 23 year old Teresa Bresciani Bartoli several months after their child was born[14]He became the director of Physiology institute in Genoa when he was just 29 years old. In Genoa Oddi had became friends with an influential; aristocrat named Stefano Capranica who owned a laboratory which Oddi used for his research. Oddi had some financial irregularities and he was also probably considered to be a drug addict. Following this oddi resigned. Later he moved to Brusselswhere underwent treatment for depression and then to Congo where he worked as a doctor. He came back to Perugia and he advocated people for the administration of Vitaline (a compound of glycerin, sodium borate, ammonium chloride, and alcohol) for infectious and malignant diseases. Later he was accused of manslaughter and illegal commerce of medicinal products[15]In 1911 he left for Tunisia where he died at the age of 48.

Figure 4 : *Ruggero Oddi*

PENICILLIN: THE FIRST WONDER DRUG

"While Fleming generally receives credit for discovering penicillin, in fact technically Fleming rediscovered the substance. It was this medical student named **Ernest Duchesne** (Fig 5) (May 30, 1874 – April 12, 1912) who originally discovered the antibiotic properties of Penicillium, but failed to report a connection between the fungus and a substance that had antibacterial properties, and Penicillium was forgotten in the scientific community until Fleming's rediscovery." He entered the Military Health Service School of Lyons in 1894. Duchesne's thesis "Contribution to the study of vital competition in micro-organisms: antagonism between moulds and microbes", that he submitted in 1897 to get his doctorate degree, was the first study to consider the therapeutic capabilities of moulds resulting from their anti-microbial activity. Duchesne had made his breakthrough by observing how the Arab stable boys at the army hospital kept their saddles in a dark and damp room to encourage mould to grow on them. When he asked why, they told him that the mould helped to heal the saddle sores on the horses. Intrigued, Duchesne prepared a solution of the mould and injected it into a series of diseased guinea pigs. All recovered. In a series of meticulous experiments, Duchesne studied the interaction between Escherichia coli and Penicillium glaucum, showing that the latter was able to completely eliminate the former in a culture containing only these two organisms. He also showed that an animal inoculated with a normally lethal dose of typhoid bacilli would be free of the disease if

JIMSA July-September 2013 Vol. 26 No. 3

the animal was also inoculated with Penicillium glaucum. This contrasts with the strain discovered by Fleming, Penicillium notatum, which did not affect the typhoid bacilli. Because he was 23 and unknown, the Institut Pasteur did not even acknowledge receipt of his dissertation. He urged more research but unfortunately his army service after getting his degree prevented him from doing any further work. Duchesne served a one year internship at Val-de-Grâce before he was appointed a 2nd class Major of Medicine in the 2nd Regiment de Hussards de Senlis. In 1901, he married Rosa Lassalas from Cannes. She died 2 years later of tuberculosis. In 1904, Duchesne also contracted a serious chest disease, probably tuberculosis. Three years later, he was discharged from the army. He died at the age of 37 on April 12, 1912.He was posthumously honored in 1949, and 5 years after Alexander Fleming had received the Nobel Prize.

Figure 5 : *Ernest Duchesne*

ETHER

Surgeries was a torture and like a journey to hell because of the pain involved in the procedures until this drug came into existence by again a medical student named as William E Clarke who became the first person to administer ether anesthesia for surgery. It was just like a dream come true for the operating dentist when he performed this painless tooth extraction in Rochester, New York, in January 1842. Apart from this medical student a doctor named Crawford Williamson Long (Fig 6) in Georgia used ether as the anesthetic drug and a painless surgery of excising a small cyst from his neck was undertaken[16,17]. By the late 1830s, physicist Humphry Davy's experiments had become widely publicized within academic circles in the northeastern United States. Wandering lecturers would hold public gatherings, referred to as "ether frolics", where members of the audience were encouraged to inhale diethyl ether or nitrous oxide to demonstrate the mind-altering properties of these agents while providing much entertainment to on-lookers. Four notable men participated in these events and witnessed the use of ether in this manner. They were William Edward Clarke (1819–1898), Crawford Long (1815–1878), Horace Wells (1815–1848), and William T. G. Morton (1819–1868).

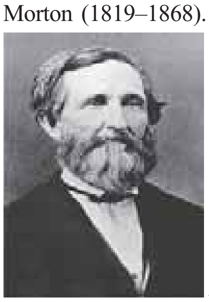

Figure 6 : *Crawford long*

SPERMATOZOA

This cell is responsible for the beginning of life...Johan Ham discovered these cells in 1677 when he was a medical student from Leiden. Ham was the first to suspect the relevance of spermatozoa in reproduction but without the observation of Antoni van Leeuwenhoek on the theory of generation he wouldn't be able to come up with a conclusion alone. Ham identified these spermatozoa which he called "animalcules with tails"(Fig7.) in a specimen of urethral discharge from a man with gonorrhea. He bought this specimen to Leeuwenhoek and Leeuwenhoek compared this specimen with a specimen of his own semen and he confirmed the presence of motile animalcules, less than a millionth the size of a course grain of sand with blunt round bodies and undulating transparent tails. Ham also noticed the absence of spermatozoa in the semen of a sterile man[18] and the fact that they did not survive for more than 24 hours[19]. Leeuwenhoek reported these findings in a Letter to the Royal Society in London and he gave credited Johan Ham for the discovery.

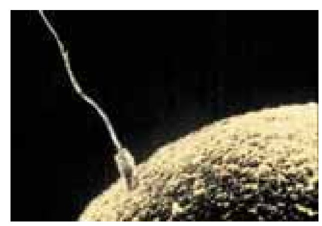

Figure 7 : *Spermatozoa*

COMMENTS

"The seeds of great discoveries are constantly floating around, but they only take root in minds well prepared to receive them."

— Joseph Henry

Nothing is as infectious as examples. Stories of these ordinary men achieving extraordinary feat make us believe that there is a hidden hero in all of us. Their ability to convert simple ideas to medical miracles has made a great impact on the practice of surgery. Their success is the sum of small efforts, repeated day in and day out. These young men inspire us to rise above our trials, seize every opportunity, and make it great.

REFERENCES

1. *Mclean J. The Discovery of Heparin. Circulation 1959;19:75-78.*
2. *Stringer MD, Ahmadi O. Famous Discoveries by Medical Students. ANZ J Surg. 2009;79:901-8.*
3. *Douglas W, David K. The story of the discovery of heparin and warfarin. BJH. 2008;141:757-63.*
4. *Simoni RD, Robert L. Hill and Martha Vaughan. The Discovery of Insulin: the Work of Frederick Banting and Charles Best. JBC. 2002; ASBMB*
5. *Silverman ME, Grove D, Upshaw CB. The Discovery of the Electrical System of the Heart. Circulation 2006;113:2775-2781.*
6. *Keith A, Flack MW. The auriculo-ventricular bundle of the human heart. Lancet 1906;2:350-64.*
7. *Silverman ME, Hollman A. Discovery of the sinus node by Keith and Flack: on the centennial of their 1907 publication. Heart 2007;93:1184-7.*
8. *Anon. Group Captain Martin Flack CBE, MA Oxon, MB, BchOxon Obituary. Be . Med J 1931;2:402-4.*
9. *Anon. Group Captain Martin Flack CBE, MB Oxf Obituary. Lancet 1931;2:430.*
10. *Bogousslavsky J. The Klumpke family-memories by Doctor Dejerine, born Augusta Klumpke. Eur. Neurol. 2005;53:113-20.*
11. *Satran R. Augusta Dejerine- Klumpke. First woman intern in Paris hospitals. Ann. Intern. Med.1974;80:260-4.*
12. *Klumpke A. Contribution a l'etude des paralysies radiculaires du plexus brachial. Paralysies radiculaires totales. Paralysies radiculaires inferieures. De la participation des filets sympathiques oculo-pupillaires dans ces paralysies. Revue de Medicine 1885;5:591-616.*
13. *Oddi R. Sulla tonicita dello sfintere delcoledocho. Archivio Per Le Scienze Mediche 1888;12:333-9.*
14. *Morelli A. Sorcetti F. Ruggero Oddi's life. Zeitschrift fur Gastroenterologie Verhandlungsband 1988;23:203-7.*
15. *Modlin IM, Ahlman H. Oddi: the paradox of the man and the sphincter. Arch Surg 1994;129:549-56.*
16. *Rutkow IM. Crawford Williamson Long. Arch.Surg.1999;134:578.*
17. *Thomas RK. Crawford William Lomg's discovery of anesthetic ether: mesmerism, delayed publication, and the historical record. Paper presented at the Key Brakley Symposium on the History of Psychology, Southern Society for Philosphy and Psychology, 17 April 2003, Atlanta , GA. (Cited 3 May 2008) Availaible from URL: http://rkthomas.myweb.uga.edu/LongSSPP.htm*
18. *Ruestow EG. Images and ideas: Leeuwenhoek's perception of the spermatozoa. J Hist Biol1983;16:185-224.*
19. *Lewenhoeck DA. Observations D. Anthonii Lewenhoeck, De Natis E Semine Genitali Animalculis . Philosphical Transactions 1678;12:1040-46.*