Haematology is the study of blood and blood forming organs. Blood is the connective tissue in the real sense, as it flows through different organs, connecting them structurally and functionally. It is unique in composition and function. Formed elements of blood are suspended in fluid medium, called plasma, having some peculiar physicochemical properties. It contains some electrolytes, sodium and chloride being the major component, as well as, some proteins, albumin, globulin and fibrinogen. Each component, along with, fluidity of the plasma plays some important role in maintaining milieu interne of the body. Plasma maintains the temperature and electrolyte balance and serves as acid base buffer of the body. It carries oxygen and other nutrients to different tissues, collects and carries waste products of metabolism to organs of excretion, like lungs, liver, kidney, carries hormonal substances to different organs for signaling their function. Plasma proteins are mainly of three types, albumin, globulin and fibrinogen. Albumin maintains osmotic pressure of blood and retains fluid in the intravascular compartment. Globulin, rather immunoglobulin, gives rise to protective antibodies. Fibrinogen helps in clotting of blood and repair of damaged endothelium.

Formed elements of blood are of three types, namely, red cells, white cells and platelets. Red cells carry oxygen to different vital tissues, through its haemoglobin content. White blood cells are defensive in function, neutrophils produce defense against acute infection, lymphocytes act against chronic infection and eosinophils and basophils are active in hypersensitivity reaction to foreign antigen. Platelets help in haemostasis and thrombus formation.

In addition to nutritive, excretory, and defensive function, blood carries different antigens to the target organ, triggers formation of both protective and damaging antibodies at the cellular level, and mediates antigen-antibody reaction.

The peculiarity of blood is that it is the tissue, which can be most easily transplanted (blood transfusion). Transplantation of blood forming tissue, bone marrow, or its component, stem cell, is one of the most recent advances in medicine. The procedure not only corrects malignant proliferation of haemopoietic cells but also causes arrest of some genetic disorders like thalassaemia or non-haematological disorders like Alzheimer disease or degenerative neurological disease.

Different haemopoietic growth hormones e.g. erythropoietin, granulocyte macrophage colony stimulating factors, are in current use to combat anaemia and infection, when they arise from defective haemopoietic tissue or as a result of chemotherapy for malignancy.
Haematology is one of the widest field of researches of molecular biology, as blood cells, in different stages of development can be directly visualized in the peripheral blood.

About one-fourth of total patients, attended in indoor or OPD of a general hospital, are affected by haematological disorder. Among the rest of the patients, about half may suffer from haematological complications e.g. vascular thrombosis, disseminated intravascular coagulation, microangiopathic haemolytic anaemia, as seen in hepatic disease, renal parenchymal disease or in obstetric patients with complications like abruptio placenta or eclampsia.

Any internist, hepatologist, nephrologist or even obstetrician must face haematological problem in day-to-day clinical practice.

1.1 DEVELOPMENT OF HAEMATOLOGY

Haematology in Ancient Medicine

Since ancient time, blood has been recognized as the essential component of life. In the Holy Bible, a universal truth about blood was mentioned that heart is the seat of the soul and blood is the source of energy for life. Ancient Romans hope to acquire vigor by drinking blood of the defendants at the end of the victory.

Before the invention of laboratory methods, Hippocrates formulated that four essential fluids of life are blood, black bile, yellow bile, phlegm and held the idea was that health is maintained by a balance of these four fluids. Thus in the days of Hippocrates, blood was thought to be one component of four essential “humours”. In the days of Galen haematopoiesis was presumed to be a process maintained by proper balance of body’s nutrients and body heat.

Examination of excavated skull in order to assess changes as a result of marrow hyperplasia is an essential component of modern haematology. Thalassaemia and Malaria are parts of Archeological diagnosis from ancient Greece.

At Lyndex Glencenstrshire, remains of a Roman temple of fourth century A.D. were excavated and remains of a unique arm and hand show kolionychia or spoon shaped nail, a condition caused by severe issue iron deficiency.

Development of New Concept

Thomas Sydenham (1624–1689) was known as English Hippocrates, for his study on clinical cases. For the treatment of iron deficiency anaemia, oral medication containing iron, was first prescribed by him. This recommendation was made 32 years before, Limzcy and Geffy demonstrated presence of iron in the ash of blood and 151 years before Paedlsch demonstrated deficiency of iron in chlorotic blood (1832). Sydenham did this unaided by laboratory. This is the first therapy suggested for world’s most common form of anaemia in ancient and even in modern time. Sydenham deserves the designation as the father of Modern Haematology.

Pythagorus and his followers realized that use of beans should be forbidden for maintaining health in certain parts of world. Today residents of southern Italy show the highest incidence of Mediterranean type of G6PD deficiency. It is probable the same genetic trait was present in ancient time which gives rise to favism i.e. explosive haemolytic anaemia, following ingestion of particular type of beans.
In the eighteenth century, blood was recommended for treatment of fits, depression, palsy, but not for pallor or bleeding.

Further Developments

Following renaissance, many physicians attempted various methods of administering blood directly or indirectly into circulation. Louis K Diamond (1780) made many unsuccessful attempts at transfusion. In 1901–02 Karl Landsteiner identified in the laboratory, four basic human blood groups, and this marked beginning of era of modern transfusion medicine. Faharacus (1921), a Swedish physician, who devised the erythrocyte sedimentation rate, observed the phenomenon of clotting of blood in a transparent container. This showed separation of blood into homogenous red fluid, dark red clot at the bottom with a thin layer of red cells above it. The concept of plasma as essential constituent of blood thus arises. Leeuwhoak (1632–1723) was able to describe the red corpuscles or erythrocytes. Improved methods for microscopy of blood in 1920s, and an increased knowledge of blood physiology and blood forming organs in the 1930s, subsequently gave rise to the concept of a number of blood disorders.

1.2 WOMEN PIONEERS IN THE DEVELOPMENT OF HAEMATOLOGY

An outstanding feature in the history of Haematology is that women pioneered a number of commendable studies in this subject. Some of them were research workers in Anatomy, Physiology or Community Medicine, while others were laboratory workers, technicians, or science graduates, rather than medical graduates only. Haematology is the product of endless intellectual attempts of people of different categories and women contribute a significant proportion in this respect.

When greater perils men environ, then women show a front of iron, and gentle in their manner, they do hold things in a quiet way.

—Thomas Dawn English (1819-1902)

Some of these researches are detailed below.

Wilfred Ashy (1879–1975) introduced serological method for estimating red cell life span in 1919. Born in London, graduated as a bachelor of science from Washington, this lady worked in the Rush Medical School of Chicago. She found that if a person is in good health the lifespan of transfused red cells is in excess of 120 days whereas in sick patients, it is shortened to one-half to one-third. Her findings resulted in serious debate, as some authorities argued that lifespan of a non-nucleated cell with little capability of metabolic activity (as then thought), should not be more than 2-3 weeks.

Florence Rena Sabin (1871–1953), granddaughter of a physician and daughter of a marine engineer, enrolled herself in New Medical Franklin School of John Hoffkins University, which offered a number of seats to women students at that time. She soon fell under the influence of Franklin P Mall, professor of anatomy. During internship she was attracted towards laboratory medicine rather than to clinical medicine and professor Mall readily offered her such a position. Sabin worked on developmental anatomy of lymphatic system. She demonstrated first that lymphatic system developed as a network derived from venous system. Then she commenced studies on development of blood cells, conducting studies on chick blastoderm, by initiating supravital staining and using early tissue culture methods. Morphology of cellular elements of blood as well as development of monocyte and its involvement in phagocytosis became thus evident. Dorothy Reed was another woman who graduated in 1900, the
same year as Sabin. She later became famous for her description of Reed Sternberg cells classically present in Hodgkin disease.

Lucy Wills (1888–1964) studied Botany in Newham College of Cambridge University in 1911. She travelled to South Africa as lecturer of Botany, returned to England, where she enrolled in London School of Medicine for Women. Graduated in 1929, she became more interested in biological aspect of Medicine and joined the department of chemical pathology at Royal Free Hospital. From late 1920 to 1930, she visited India on a number of occasions, where she worked on nutritional anaemia, supported by Lady Tata Fund of John Hopkins University. Lucy Hills discovered that macrocytic anaemia in pregnancy differed from pernicious anaemia because they do not have achlorhydria and responded to crude liver extract but not the pure liver extract. She postulated that there must be another factor responsible for macrocytic anaemia, other than vitamin B12. For some years this was called Willis factor and later shown up to be folic acid. Thus a cheap remedy for macrocytic anaemia in pregnancy in the tropics has been found. In 1938 she published the classical paper on “Tropical Macrocytic Anaemia: its relation to Pernicious Anaemia” and in 1939, at the end of the World War she established the first Haematology Department in Royal Free Hospital.

It is doubtful whether any haematologist could lay several foundations in haematological studies like Jennet Vaughan (1839–1993). At the London Hospital, the lady worked on Anatomy of Bone Marrow and its involvement in leucoerythroblastic anaemia. In 1934 she published a monograph on Anaemia. At Hammersmith she developed transfusion technique.

Virginia Minnich (1910–95) was a technician in the department of haematology of Ohio State University. Virginia’s knowledge of morphology of blood cells grew to legendary of proportion but she took part in early studies on iron deficiency anaemia, initially involving the variations in iron load, in women during pregnancy and menstrual cycle.

Virginia became essential component for training of technicians and medical students, evolved new tests, which led to eventual discovery of thalassaemia, caused by HbE.

She established haematological laboratory in Havana and Thailand.

Judith Pool (1919–75) was born in New York and gained her PhD in University of Chicago in 1946. She moved to Stanford University in California, where she became a member of Haematology Department in 1953. She first published a paper on blood coagulation. Her discovery was published in Nature in 1964, about high potency antihaeoophilic factor concentrate prepared from supernatant portion of plasma, after a single process of freezing and thawing.

These are few examples of leading women figures in haematology. They contributed towards its advancement at every level.

1.3 MODERN HAEMATOLOGY

Leukaemia

Robert Virchow (1858), a 24 year old graduate of Berlin Army School, studying pathology of phlebitis, confirmed the findings of D Hughes Bernmet, a physician, physiologist and teacher, who first described a case of chronic myeloid leukaemia and suggested the term thirty years before invention of staining methods. Virchow proposed two varieties of chronic leukaemia, splenic and lymphatic types. In 1995,
Leukaemia Research Fund and Royal College of Physicians held a symposium in Edinburgh, to commemorate the achievements in studies on leukaemia.

Since 1940, attempts to detect chromosomal abnormalities in leukaemic cells began. In 1960, Peter Norwell from University of Pennsylvania and David Hungerford, from Fox Chase Cancer Center Institute working on phlebothrombosis, described a minute acrocentric chromosome in cells cultured from blood of seven patients of CML. With consent of all the workers in this field this chromosome was named as “Philadelphia chromosome”, after the place where major work was conducted. The chromosome was also found in erythroid and megakaryocytic cells also. In 1995, a symposium on leukaemia was organized in Edinburgh by joint effort of Leukaemia Research Fund and Royal College of Physicians. In 1973, the chromosome was identified, as deleted portion of chromosome 9, translocated on chromosome 22, by Janet Rowby of Chicago University. In 1980s consequence of genetic material between two chromosomes was found to be production of protooncogene BCR-ABL, the fusion protein. “Abl” stands for Abelson, a leukaemia virus that carries a similar protein.

**Targeted Therapy**

A drug discovery programme started aimed at developing a drug to shut down the activity of BCR-ABL protooncogene i.e. signalling the proliferation of malignant cells. The compound Imatinib was developed in 1992. Studies show that this compound inhibits tyrosine kinase-mediated activity. In 1998 the drug was tested in patients suffering from CML. In clinical trials blood counts come down to normal. Imatinib is approved by US FDA in 2001. Unfortunately resistance to Imatinib appeared soon. This is due to mutation of BCR-ABL gene. The gene acts as the lock and the drug acts as the key. The lock changes, so the key doesn’t fit. Dasatinib and Nilotinib have been developed that can shut down the mutated form of gene.

**Multiple Myeloma**

In 1845, a patient, treated by Dr. Watson, for lumbar pain in the set up of extreme weakness, anaemia and albuminuria, was reported.

Dalrymple (1846) observed that cancellous parts of bones of such patients become filled up with gelatinous material, which was postulated as degenerated material excreted in urine as abnormal protein. Dr. Macintyre (1850), when consulted, found, in urine of this patient, a peculiar type of protein of specific gravity 1.035. This protein had peculiar property of developing haziness, when heated, and this disappears on addition of nitric acid, though precipitate appears after an hour of standing.

Henry Bence Jones, at about same time, confirmed the peculiar nature of protein, that it forms precipitate on cooling, which dissolves on heating, and clears on addition of nitric acid. He further corroborated that the precipitate was made up of hydrated detruxide of albumin. The protein was named after him.

The term “Multiple Myeloma was first introduced by J. von Rustizky (1873), while he was working in the Institute of Professor E. D. von Recklinghausen and studying a case of temple mass in a 47 year old man developing quadriplegia.

The first reported case of multiple myeloma in USA possibly was that published by Herrieck and Hketoen (1894) and they reviewed 412 cases in the literature since 1848. They estimated that multiple myeloma accounted for 0-3% of all malignancies and peak incidence is 55%.
Dr. Christian Roger (1898) made first antimortem diagnosis of multiple myeloma, 18 months after onset of symptoms. In this patient right clavicle enlarged and fractured without trauma. Microscopical examination of tumor shows that it consists of round lymphoid cells with large nuclei.

The term plasma cell introduced by Waldeyer (1875). He described large cells with granular cytoplasm.

Marschalky (1895) described characteristic features i.e. eccentric position of nuclei, perinuclear pale zone and spherical or irregular cytoplasm. Diagnosis of multiple myeloma was facilitated by reports of bone marrow aspiration by Arnium (1929), Rosenthal Vogel (1938).

Longsworth (1939) first applied electrophoresis to identify the monoclonal protein i.e. the protein with homogeneity. Later on with improved method of immuno-electrophoresis and immunofixation, it was possible to identify even small amount of monoclonal protein, to differentiate inflammatory (giving rise to polyclonal protein) and malignant disease.

Bone Marrow Transplantation

In early part of 20th century work of Alexis Carrel and others showed that allografts of skin or kidney would function for a time. Medawer and colleagues (1940) explained immunological basis of allograft rejection. Studies of Jacobson et al. (1949) showed shielding of spleen of the mice exposed to lethal irradiation permitted survival of the animal. This is the beginning of era of transplantation.

Immune rejection of grafted lymphoid cells (Billingham and Brent 1959) marks the understanding of graftversus host disease.

Development of concept of histocompatibility antigens came from demonstration of antibodies induced by transfusion or pregnancy, which reacted with antigens in human white blood cells. (Miescher and Faucomet 1954).

Galli et al. (1968) reported first successful allogenic marrow graft in a patient with severe immunodeficiency. In 1969 Seattle marrow transplant team began a series using HLA-matched sibling donors for patients of leukaemia and aplastic anaemia. The first patient was in blast stage of CML. In 1970 stem cell therapy was accepted as a treatment of malignant disease. During the years 1970–1986 long-term survival was attempted by ablating the malignant disease with chemotherapy. For treatment of haematological malignancy and solid tumour, autologous HCT (stem cell therapy) after high dose chemotherapy and / or irradiation was tried by Harowitz (1999).

Marrow transplant for non-malignant haematological diseases were attempted in thalassaemia (Thomas et al. 1982; Lucacelli et al. 1984) and in sickle cell disease (Johnson et al. 1984).

With progress of improved methods of blood banking, advent of newer antibiotics, understanding of chemotherapeutic agents, 5 year survival rate, after marrow transplant, gradually increases 10 to 20% per year after first successful transplant in late 1960s.

Dr. Edward Donall Thomas was awarded Nobel Prize for his pioneering work on bone marrow transplant.

Nobel prize in Physiology or Medicine was awarded jointly to Joseph E Murray and E Donall Thomas in 1990, for their discoveries concerning “organ and cell transplantation in the treatment of human disease”. Dr. Edward Donall Thomas was an American physician, who was an emeritus professor
of Medicine in Washington, USA. Born in 1920, he studied chemistry and chemical engineering from University of Texas and obtained MD from Harvard Medical School in 1946. He also received National Medal of Science in 1990.

Haematology has developed step by step to modern era. It involves all the fields of science like biochemistry, pathology, physiology, molecular biology, and genetics.

Various forms of therapy e.g. targeted therapy and stem cell therapy and bone marrow transplant thus evolved. Today, most of the haematological, even some non-haematological diseases are amenable to treatment, at least symptom-free survival or arrest of the disease process. Estimates suggest that, about 30,000 to 40,000 of transplants are performed yearly all over the world. Many more people are benefited by targeted therapy. More than 20,000 people have survived 5 years or more after a haemopoietic stem cell transplant. March of haematology is never complete, but will go forever to conquer the suffering of human being. It is difficult to think of such a subject in which so many advancements have been made in a century. It is wonderful to think that from an abnormal biochemical finding in urine, an malignant clone of cells and its secretion are found out, and finding of an abnormal chromosome in cells led to the discovery of targeted therapy.

History of discoveries in haematology is so vast that it can’t be covered in such a short span. This is only to create an interest in learning such an everdeveloping subject and also a humble tribute to the men and women who devoted their wholehearted attempts in the development of the subject.

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