CHAPTER

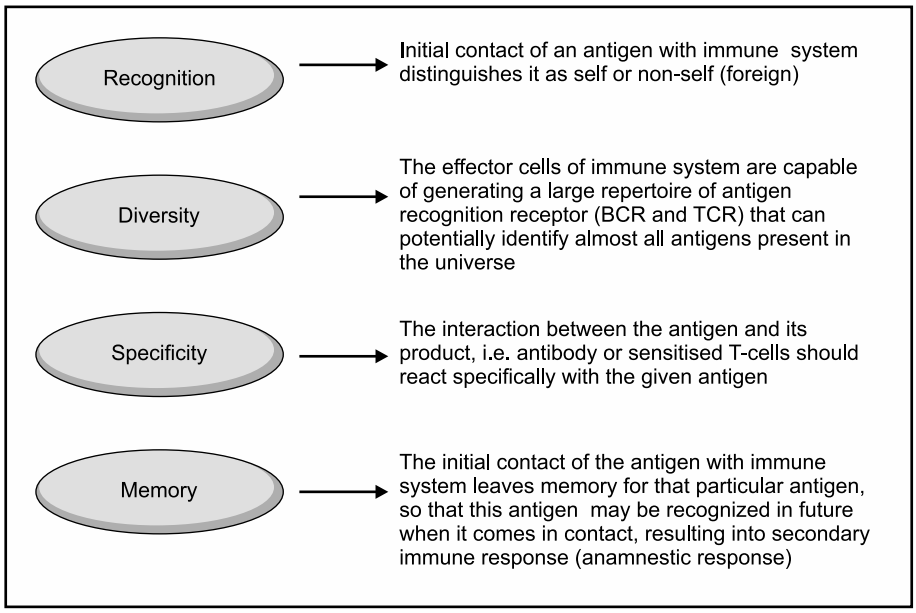
1

Historical Development of Immunology

The term immunology has been derived from the Latin word *immunis* means, to exempt and *logus* means discourse. Immunology is the study of the physiological mechanisms by which vertebrate animals (both human beings and animals) defend themselves from different microbial invaders, such as bacteria, viruses, protozoa and fungi. Immunology also provides insight into, how cell development is triggered and how cells stimulate and suppress one another. If a piece of skin or any other living tissue from one animal is grafted onto the same animal it is generally accepted by the body, on the other hand if the graft is taken from other animal of the same species or other species, it is usually not accepted by the body and after a few days it is rejected. The acceptance and rejection process of the graft is the reflection of the capacity of the immune system of the animal body to recognize the grafted material as self or non-self. This acceptance and rejection process is the function of immune system and the response is known as **Immune response.** The immune response is a self-defence mechanism that works to protect the host by distinguishing and neutralizing or destroying the non-self substances, such as abnormal cells (mutants or malignant) or invading various infectious agents. The study of various immune responses, their mechanism and consequences is known as **Immunology.** The field of immunology is attributed to the maiden and marvellous discoveries by Louis Pasteur and Edward Jenner. Four cardinal principles of immunology are:

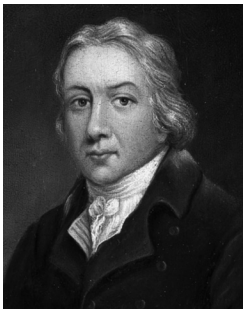
Historical Perspectives

Historical perspectives of any events (both arts and sciences) are important as these convey the excitement of discovery and the wonder of natural sciences. The history of immunology is also full of several excitements and wonders. As early as in 5th century B.C., in Greece, it was well known that persons recovered from infection with smallpox or plague are not likely to suffer from reinfection and this resistance was specific. Thus, this person was allowed to nurse the suffering individual in an outbreak. During 15th century inoculation with live microorganisms obtained from pustules of an individual with smallpox called 'variolation' was used to practice in India and China to achieve resistance to this dreadful disease. By the 17th century, the injection of material from active lesions as a prophylactic measure against smallpox was widespread and well documented in the Middle East. This method of prophylactic induction against smallpox was dangerous and undesirable.



In 1744 Benzamine Zesty, a Dorset shire farmer, inoculated his whole family with virus obtained from cowpox pustule with a needle in order to protect his whole family members against smallpox.

The work of the British Scientist Edward Jenner (1749–1823), who elaborated a highly method of inoculations against smallpox, proved to be of particular practical importance. In 1778 Edward Jenne observed that milkmaids who remained in contact with cow and had contracted cowpox (Jenner called the disease of cows 'variolae vaccinae') infection never suffered from smallpox in later life. This observation led to the discovery of the first useful substance (antigen) that could evoke immune response and gives rise to resistance against the highly communicable infectious disease. Lady Mary Montague, wife of the British Ambassador to Turkey brought scab of smallpox for vaccination ('variolation') to England about 250 years back and used the process of variolation onto her own 6 years old son. On 14th May, 1796 Jenner performed a most daring experiment by initially inoculating lymph from a cowpox pustule of a milkmaid, **Sarah Nelmes**, who suffered from cowpox lesion to **James Phipps**, a 8 years old boy of a gardener for the first time. After a few days of inoculation of content of cowpox, a further more daring step was taken by him, when he challenged James Phipps with the virulent poxvirus obtained from festering pustules of human smallpox. Neither any smallpox lesions were developed nor any manifestation of any symptoms of smallpox was observed and finally this boy survived. To explain his observation that previous infection with cowpox ward off the smallpox, Jenner assumed that there must be a relationship between the two disease. Finally in 1978 Jenner knew that he could prevent smallpox safely then only he made his knowledge public. James Phipps served the example of **first human guinea pig** in the history of immunology**.**


Edward Jenner

Pasteur coined the term vaccination (L.vacca-cow) in the honour of Jenner's initial discovery. Pasteur coined the term vaccination (L.vacca-cow) in the honour of

Jenner's initial discovery. Jenner's discovery created turbulence in the mind of many scientists.

In 1881 a chance discovery of Louis Pasteur turned him from Chemist to Microbiologist and later Immunologist. He observed that a virulent culture of *Pasteurella multocida* when injected into chickens caused fowl cholera in them. When this culture was inadvertently left on a bench at room temperature for a considerable period of time, it no longer caused classical disease in chickens. Again he prepared fresh culture from the left one bacterium and injected to chicken. To his astonishment these chickens also survived. This observation led Pasteur to think that aging has weakened the capacity of the bacteria to cause disease and this led to the development of method of **attenuation** (loss of virulence**)** of an organism and thus converting them to be used for useful vaccine which protected the chickens against the fowl cholera (Pasteur, 1880). This paved the way of protective inoculation or vaccination against the disease. He first applied this principle to the prevention of anthrax. Pasteur observed four methods, of attenuation and applied this technique for vaccination against Anthrax in sheep, Cholera in chicken and Rabies in man. The methods of attenuation were as follows:

- Aging of the culture (for chicken cholera)
- Cultivation at high temperature (for anthrax)
- Passage through another unrelated host (for rabies and swine erysipelas)
- Drying (for rabies).

Louis Pasteur injected and saved the first human case, a 9-year-old boy, **Joseph Meister,** who had been badly bitten by a rabid dog, with desiccated cord of rabid animal and thus established the utility of rabies prophylaxis in man. This boy served as a **second human guinea pig** in the history of immunology. As a token of grateful acknowledgement 'Pasteur Institute' was established in the every quarter of globe. Joseph Meister was appointed as gate porter at the Pasteur Institute, Paris. He was the first man to be survived after the bite of a rabid dog, but how vaccine could bring about protection against disease was not clearly known until 1890. In the same year E. Von-Behr **Louis Pasteur** ring (German scientist) and S. Kitasato (Japanese scientist) provided a clear evidence of the formation of antibody by injected into rabbits a very small dose of tetanus toxin, a deadly poisonous substance produced by the organism causing tetanus. These rabbits could withstand many lethal dose of tetanus toxin afterwards. They then proved that resistance of the rabbit towards this disease was due to the appearance of a class of serum protein called **Antibody.** Such antibody proteins have unique property of combining with the infecting agents and rendering them harmless. The substances which were used to produce antibodies were designated as **Antigen.** Later they prepared antitoxic sera against diphtheria toxin in horses which were found protective in men and animals. It was on Christmas eve in 1891, that diphtheria antiserum prepared from animals was administered to a German girl who was in state of shock and recorded first event of **passive immunization** and made Emil Von-Behering recipient of the First Nobel Prize in Medicine in 1901. With the discovery of anti-diphtheric sera and anti-tetanus sera, era of serotherapy started. Due to the adaptation of serotherapy, first village of Hamilton was declared free from diphtheria disease.

Louis Pasteur

In 1883 Emil Metchnikoff opined that the protection is not only caused by humoral factors, but certain cells also take part in immunity. As he was a zoologist, so he performed an experiment on a transparent water flea. He pinned a thorn on the water flea and next day he noticed the remarkable behaviour of certain movable cells in this primitive creature. He observed that these movable cells (later called phagocytes) which have gathered around the thorn were formed in the bone marrow and settled in the tissue. Its main function was to engulf the foreign material, which is later lysed by a hydrolytic enzyme present in them. Based on the observation Metchnikoff suggested that even marine invertebrates possess cells capable of ingesting and destroying foreign substances. The cells were later called **Macrophage** and enzyme **lysozyme**. So, relative importance of humoral and cellular immunity was complicated but in 1903, Almorth Wright opined that there are two arms of immune response and both have an important role to play.

In 1893, Buchner described another serum factor which can kill certain bacteria and the activity of this factor was found to be lost by heating at 56°C for a short-time. This bactericidal factor which has shown to have ability to lyse foreign cells after interaction with specific antibody was called **alexine,** meaning protective substance and later in 1895 it was named **complement** by Bordet.

In 1894, Richard Pfeffer (German scientist) working with *Vibrio cholerae* found that when immunized guinea pig was challenged with this organism intraperitoneally, it was lysed. In the same year Denys and Havit, the Belgian scientist observed that the whole blood of dog has bactericidal effect as compared to cell free plasma of that animal. They postulated that this effect may be due to the presence of leukocytes in the whole blood. This mechanism was further extended when Wright and Douglas in 1903 showed that a substance was present in the serum called opsonin which enhances phagocytosis. It was later shown that specific antibody immensely increased phagocytosis.

- In 1895, Bordet described the agglutination of bacteria by the sera of animals into which bacteria had been injected.
- In 1896, Charin and Rogers described agglutination (Widal) test for the diagnosis of enteric fever.
- In 1897, Kraus observed that the serum of an animal which had acquired immunity to the plague bacillus (*Pasteurella pestis*) or the *Vibrio cholerae* formed a precipitate when mixed with the filtrate of a culture of the organism concerned. Then only precipitation test came into existence.
- The 1900 onwards was the golden era of Immunology and thus several new concept relating to protection was propounded by different scientists at cellular and molecular level for which many of them were crowned with Nobel Prize.
- In 1901, Bordet and Gengou developed the complement fixation test**.**
- In 1902, Charles Richet and Paul Portier first introduced the concept of hypersensitivity. They observed that a subsequent sublethal dose of sea anemone extracts led to the death of an animal rather than protection and this type of an altered reactivity was called Anaphylaxis (Anti-against, Phylaxis-protection).
- In 1903, Obermayer and Pick were the first to observe antigenic diversity, when they attached NO_2 groups to rabbit serum protein and inoculated to rabbit. It was observed that antiserum reacted only with nitrated proteins of rabbit, horse and chicken serum but not with non-nitrated proteins.
- In 1903, Maurice Arthus described 'Arthus Phenomenon'.
- In 1908, Alexis Carrel proposed the concept of organ-grafting.

- In 1921, Carl Prausnitz and Henery Kustner demonstrated reagin type of antibody and demonstrated Prausnitz and Kustner (P-K) reaction.
- In 1925, Zinsser observed difference between immediate and delayed hypersensitivity.
- In 1930, Karl-Landsteiner—Father of Immunology, described ABO blood grouping and isohemagglutinin and certain drawbacks of Ehrlich's hypothesis.
- In 1934, Marrack proposed the Lattice theory of secondary aggregate of antigen and antibody.
- In 1937, Tiselius separated serum protein using technique of electrophoresis and observed that antibody activity lies in the gamma globulin fraction of the serum.
- In 1950, Rodney Porter used papain to digest IgG.
- In 1955, Bloom and Bennet described Macrophage Migration Inhibition test.
- In 1955, Jerne proposed Natural Selection theory of antibody formation.
- In 1956, Bruce Glick of Ohio state University described the role of bursa of Fabricius. His Chinese friend Chang took birds for demonstration of antibody. But some of the birds which lacked bursa did not produce antibody. This paved the way for the role of B-cell in production of antibody.
- In 1957, Alick Isaac described Interferon.
- In 1958, Sir McFarland Burnet and Niels Jerne gave Clonal Selection theory of antibody formation at Behring Institute.
- In 1959, James Gowans demonstrated function of lymphocyte.
- In 1960, Gerald Edelman used pepsin to digest IgG. In the same year Sir Macfarlane Burnet (Australian) and Peter Medawar (British) received Nobel Prize for their work on transplanting organ.
- In 1962, Jacques Miller showed the role of thymus in immune response to various antigens utilizing neonatal thymectomized mice, but it was Cooper in 1963, who defined the role of T- cells in cellular immunity. In the same year Good, Martin and Others showed that thymectomized newborn mice failed to induce transplantation reaction, showed impaired cell mediated immune response and antibody production against T-dependent antigen, i.e. sheep red blood cells.
- In 1963, Jacques Oudin and Henery Kunkel demonstrated Idiotypes.
- In 1965, Dreyer and Burnet proposed a two gene for one polypeptide hypothesis, one for variable (V) region and other for constant (C) region.
- In 1966, Harris and Hummeler provided conclusive evidence that lymphocytes are responsible for formation of antibody.
- In 1972, George M. Edelman (American) and Rodney Porter (British) gave chemical structure of antibody molecule and showed that antibody molecules consist of more than one kind of polypeptide chain which can be separated by chemical digestion.
- In 1977, Rosalyn Yalow gave Radioimmunoassay (RIA).
- In 1980, Baruj Benaceraf and George D. Snell (American) and Jean Dausset (French) discovered the genetic regulation of the body's immune system.
- In 1983, Kary Mullis working for Cetus Corporation in California while driving late at a moonlit night on California mountain road conceived the way of DNA sequencing. This revolutionized molecular genetics by making possible a whole new approach to the study and analysis of gene.
- In 1984, Niels Jerne (British), Georges Kohler (German) and Cesar Milstein (Argentine) described monoclonal antibodies for which they received Nobel Prize.
- In 1987, Susumu Tonegawa (Japanese) demonstrated how genes produce antibodies against specific disease agents and for this he was also honoured with Nobel Prize.

- In 1996, Peter C. Doherty (Australian) and Rolf M. Zinkernagael (Swiss) worked on the signals that alert white blood cells to kill virus infected cells. They showed that WBC of immune system look for changes in a key marker called self protein which identifies cells as belonging to ones, own body. Any alteration in this protein, tag the cell for destruction and for that they received Nobel Prize.
- In 2001, Timothy Hunt, Paul Nurse, and Lee Hartwell demonstrated about the Genes key regulation of cell cycle.
- In 2002, Sydney Brenner, H. Robert and John E. Sulstonthr worked on Genetic regulation of organ development and programmed cell death.
- In 2018, James P. Allison and Tasuku Honja demonstrate the process of treating cancer by realuring the existing break system within the human immune systems to fight cell and cancer cell. Two proteins are involved in break system. One is PD-1 and the other is CTLA-1. Both the proteins work as break in the immune system and T-cells stop fighting with the foreign body. Some cancer cells also contain these proteins which allow the cells to invade body without struggle.
- In 2019 William G Kaelin Jr, Sir Peter J. ratcliffe and Gregg, L. Semenza discovered how cells can sense and adapt to changing oxygen availability, They identified molecular machinery that regulates the activity of genes in response to varying level of oxygen. Their discoveries have also paved the way for promising new strategies to fight anemia, cancer and many other diseases.

The list of scientists who received Nobel Prize in the field of Medicine for Immunological work has been depicted in Table 1.1 in chronological order:

Table 1.1: List of Scientists who received Nobel Prize in the field of Medicine for immunological works

S.N.	*Year*	*Name of the Scientists*	*Field of work*
1.	1901	Emil von Behring (German)	Antiserum therapy
2.	1905	Robert Koch (German)	Discovering The tubercule bacilli and tuberculin
3.	1908	Paul Ehrlich (German) & Emil Metchnikoff. (Russian)	Role of phagocytosis in immunity
4.	1912	Alexis Carrel (French)	Organ grafting
5.	1913	Charles Robert Richet (French)	Anaphylaxis and allergy
6.	1919	Jules Bordet (Belgian)	Complement system and theories of Immunity
7.	1923	Sir Frederick Banting Candian) & John Macleod (Scottish).	Discovery of insulin
8.	1930	Karl Landsteiner (American)	Discovery of four human blood groups
9.	1946	Hermann J. Muller (American)	Production of mutation by means of X-ray radiation
10.	1951	Max Theiler (South African)	Yellow fever vaccine
11.	1955	Bloom And Bennet	Macrophage Migration Inhibition test
12.	1956	Bruce Glick	Role of bursa of Fabricius

Contd.

Table 1.1: List of Scientists who received Nobel Prize in the field of Medicine for immunological works (*Contd.*)

S.N.	*Year*	*Name of the Scientists*	*Field of work*
13.	1957	Daniel Bovet (Italian)	Antihistamine research
14.	1960	Sir Macfarlane Burnet (Australian) & Peter Medawar (British)	Clonal selection theory and existence of cell based immune tolerance
15.	1972	Gerald M. Edelman (American) & Rodney Porter (British)	Chemical structure of immunoglobulin
16.	1977	Rosalyn Yalow (American)	Radioimmunoassay (RIA)
17.	1980	Baruj Benacerraf, Georg G.D. Snell (American) & Jean Dausset (French)	Major histocompatibility complex and immunogenicity, distinction between self and non self
18.	1984	Niels Jerne (British), Cesar Milstein (Argentine) and Geroge E. Kohler (German)	Network theory and Monoclonal antibodies
19.	1987	Susumu Tonegawa (Japanese)	Molecular biology of immunoglobulin gene, diversity of antibodies
20.	1989	J. Michael Bishop & Harold E. Varmus (American)	Discovery of retroviral oncogenes
21.	1990	Joseph E. Murray & E. Donnall Thomas (American)	Transplanting human organ and bone marrow
22.	1991	Erwin Neher & B. Sakmann (German)	Cellular communication
23.	1995	Edward B. Lewis, Christiane -Volhard and Eric F. Wieschans	Genetic control of early embryonic development
24.	1996	Peter C. Doherty (Australian) & Rolf M. Zinkernagel (Swiss)	How MHC molecules are used by white blood cells to kill virus infected cells
25.	1997	Stanley Prusiner (American)	Discovery of prions
26.	1998	Joshuo Lederberg	Genetic diversity in microbes
27.	1999	Gunter Blobel	Signals that direct protein to their respective destination
28.	2001	Timothy Hunt, Paul Nurse, and Lee Hartwell.	Genes for the key regulation of cell cycle
29.	2002	Sydney Brenner, H. Robert and John E. Sulston	Genetic regulation of organ development and programmed cell death
30.	2010	Robert G. Edward	Father of test tube baby, as in 1978 he produced first test tube baby
31.	2011	Jules A. Hoffmann and Bruce Beutler Roulf M. Stunman	Activation of innate immunity, Toll like receptor, Innante immunity, discovery dendritic cell and adaptive immunity
32.	2012	John B. Gordon and Shiayna Yama naka	Stem cell research. They showed that if the specific cells of the body is kept in empty slat, these cells can be converted in any type of cell

Contd.

Table 1.1: List of Scientists who received Nobel Prize in the field of Medicine for immunological works (*Contd.*)

S.N.	*Year*	*Name of the Scientists*	*Field of work*
33.	2013	Shinya Yamanaka and John Gordon	On stem cell research. To change specific cell into blank cell which can be changed in an according to desire
34.	2015	William Campbell, Satosi Omura and Youyoc TU	Developed drug that reduced death from malaria and Rtemisinin for malaria
35.	2016	Yoshimori Ohsumi	Discovery of mechanism of autophagy which is the process cell destroy and recycle cellular immunology
36.	2017	Jeffrey C. Hall, Michael Rosbashand Michael W. Young	For discovery of molecular mechanism controlling the circadian rythym
37.	2018	James P. Allison and Tasukae Hongo	Cancer therapy by inhibition of negative immune regulation
38.	2019	William Kaelin Jr, Gregg, L.Semenza and Peter J. Ratcliffe	How cells sense and adapt to oxygen availability

N.B: Nobel Prize in Medicine was not awarded to any body in the year 1915, 1916, 1917, 1918, 1921, 1925, 1940, 1941 and 1942

MULTIPLE CHOICE QUESTIONS

Encircle the best answer among the points given below:

1. **Name the first human guinea pig who has been immortalized in the annals of immunology history:**
   (a) James Phipp (b) Robert Koch
   (c) Karl Landsteiner (d) John Pope
2. **In who's honour the term vaccination was coined by Louis Pasteur:**
   (a) Jacques Miller (b) Edward Jenner
   (c) Jules Bordet (d) Charles Richet
3. **All are the cardinal signs of immunology, except:**
   (a) Specificity (b) Memory
   (c) Recognition (d) Antigenicity
4. **Name the contribution of Alexis Carrol:**
   (a) Radioimmunoassay (b) Organ grafting
   (c) Complement (d) Ig structure
5. **Who gave structure of antibody molecule:**
   (a) Kraus (b) Karl-Steiner
   (c) Edelman & Porter (d) Bruce Glick
6. **Emil von-Behring paved the way of:**
   (a) Active immunization (b) Passive immunization
   (c) Both of the above (d) None of the above

7. **Who was the second human guinea pig in the history of Immunology:**
   (a) Forssman (b) Robert Koch
   (c) Joseph Meister (d) Bordet
8. **Name the discoverer of complement:**
   (a) Bordet (b) Baruj Benacerraf
   (c) Bruce Glick (d) None of them
9. **Attenuation of the organism can be achieved by:**
   (a) By passing the organism through unnatural hosts
   (b) By heat treatment (c) Aging of the culture
   (d) All of the above (e) None of the above
10. **Who proposed that besides humoral immunity cells also play important role in the protection of the body:**
   (a) Emil Metchnikoff (b) Richard Pfeffer
   (c) Henery Kustner (d) Carl Prusnitz
11. **Attenuation was a chance discovery observed by Louis Pasteur, when:**
   (a) He left the virulent culture of *Pasteurella multocida* on bench at room temperature
   (b) He observed that aging of *Pasteurella multocida* resulted in loss of virulence
   (c) Both of the above
   (d) None of the above
12. **For the first time for passive immunization:**
   (a) Antidiphtheric serum was used (b) It was tried on a German girl
   (c) Both of the above (d) None of the above
13. **Besides antibody there is one more factor in the serum of vertebrate animal, which has ability to kill bacteria, this was called:**
   (a) Properdine (b) Complement
   (c) Factor B (d) Factor D
14. **All the statement for bursa of Fabricius is correct, except:**
   (a) It is responsible for humoral immunity
   (b) It is responsible for B-cell production
   (c) It is responsible for T-cell production
   (d) It is found in birds only
15. **Enzymes used for the degradation of immunoglobulin are:**
   (a) Papain (b) Pepsin
   (c) 2-mercaptoethanol (d) All of the above

ANSWERS

1. (a) 2. (b) 3. (d) 4. (b) 5. (c) 6. (b) 7. (c) 8. (a)
9. (d) 10. (a) 11. (c) 12. (c) 13. (b) 14. (c) 15. (d)