Chapter 2

The Natural Immune System

"While lions pounce on zebras and robins peck at worms,
the leukocytes in our own body devour invading germs"
- Perspective in Biology and Medicine 32:61, 1988.

The body has many defense mechanisms, among others are the skin of the body, the membrane that covers the hollow organs and vessels and the immune system. The immune system reacts to a specific foreign body material or pathogenic material (referred to as antigen). During these reactions a 'memory' is built up of regular encountered antigen. The obtained memory speeds up and improves the reaction of the immune system to future exposure to the same antigen. Due to this reason defense reactions are divided into three types: non-specific defense reactions, inherited defense reactions and specific defense reactions [56]. The immune system forms part of the specific defense reactions. The classical view of the immune system is that the immune system distinguishes between what is normal (*self*) and foreign (*non-self* or antigen) in the body. The recognition of antigens leads to the creation of specialised activated cells which inactivate or destroy these antigens. The natural immune system mostly consists of lymphocytes and lymphoid organs. These organs are the tonsils and adenoids, thymus, lymph nodes, spleen, Peyer's patches, appendix, lymphatic vessels and bone marrow. Lymphoid organs are responsible for the growth, development and deployment of the lymphocytes in the immune system. The lymphocytes are used to detect any antigens in the body. The immune system works on the principle of a pattern recognition system, recognising *non-self* patterns from the *self* patterns [63]. Recently Matzinger [54, 55] introduced the *danger theory*. The main idea of the *danger theory* is that the immune system distinguishes between what is dangerous and non-dangerous in the body. The *danger theory* differs from the classical view in that the immune system does not respond to all

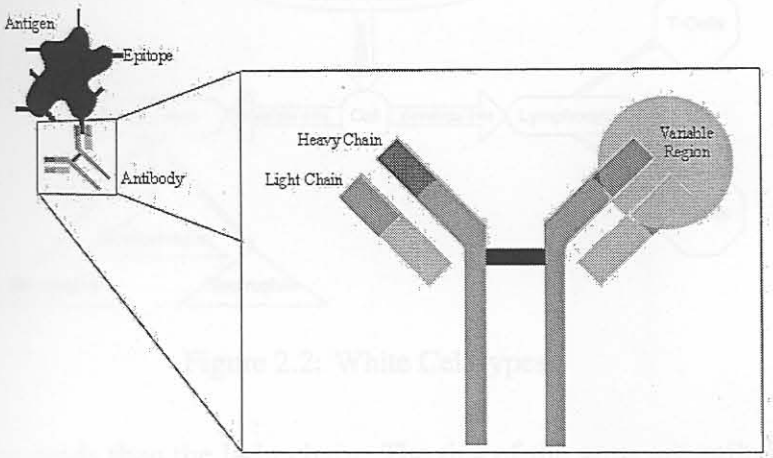

Figure 2.1: Antigen-Antibody-Complex

foreign cells, but only to those foreign cells that are harmful or dangerous to the body. The rest of this chapter explains the development of the different cell types in the immune system, antigens and antibodies, immune reactions and immunity types and the detection process of foreign body material.

2.1 Antibodies and Antigens

Within the natural immune system, antigens are material that can trigger immune response. An immune response is the body's reaction to antigens so that the antigens are eliminated to prevent damage to the body. Antigens can be either bacteria, fungi, parasites and/or viruses [71]. An antigen must be recognised as foreign (*non-self*). Every cell has a huge variety of antigens in its surface membrane. The foreign antigen is mostly present in the cell of micro-organisms and in the cell membrane of 'donor cells'. Donor cells are transplanted blood cells obtained through transplanted organs or blood. The small segments on the surface of an antigen are called *epitopes* (as shown in Figure 2.1). Epitopes trigger a specific immune response and antibodies bind to these epitopes [56].

Antibodies are chemical proteins. In contradiction to antigens, antibodies form part of *self* and are produced when lymphocytes come into contact with antigen (*non-self*). An antibody has a Y-shape (as shown Figure 2.1). Both arms of the Y consist of two identical heavy and two identical light chains. The chains are distinct into *heavy* and *light* since the heavy chain contains double

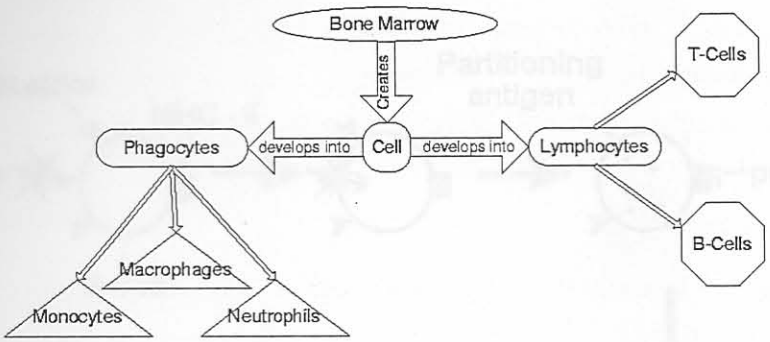

Figure 2.2: White Cell types

the number of amino-acids than the light chain. The tips of the arms are called the variable regions and vary from one antibody to another [71]. The variable regions enable the antibody to match antigen and bind to the epitopes of an antigen. After a binding between an antibody and an antigen's epitope, an antigen-antibody-complex is formed, which results into the de-activation of the antigen [56]. There are five classes of antibodies: IgM, IgG, IgA, IgE, IgD [56].

2.2 The White Cells

All cells in the body are created in the bone marrow (as illustrated in Figure 2.2). Some of these cells develop into large cell- and particle-devouring white cells known as phagocytes [71]. Phagocytes include monocytes, macrophages and neutrophils. Macrophages are versatile cells that secretes powerful chemicals and plays an important role in T-Cell activation. Other cells develop into small white cells known as lymphocytes.

2.2.1 The Lymphocytes

There are two types of lymphocytes: the T-Cell and B-Cell, both created in the bone marrow. On the surface of the T-Cells and B-Cells are receptor molecules that bind to other cells. The T-Cell binds only with molecules that are on the surface of other cells. The T-Cell first become mature in the thymus, whereas the B-Cell is already mature after creation in the bone marrow. A T-Cell becomes mature if and only if it does not have receptors that bind with molecules that represent *self* cells. It is therefore very important that the T-Cell can differentiate between *self* and *non-self* cells. Both T-Cells and B-Cells secrete lymphokines and macrophages secrete monokines. Monokines and lymphokines are known as cytokines and their function is to encourage cell growth, promote cell activation or destroy target cells [71]. These molecules on the surface of a

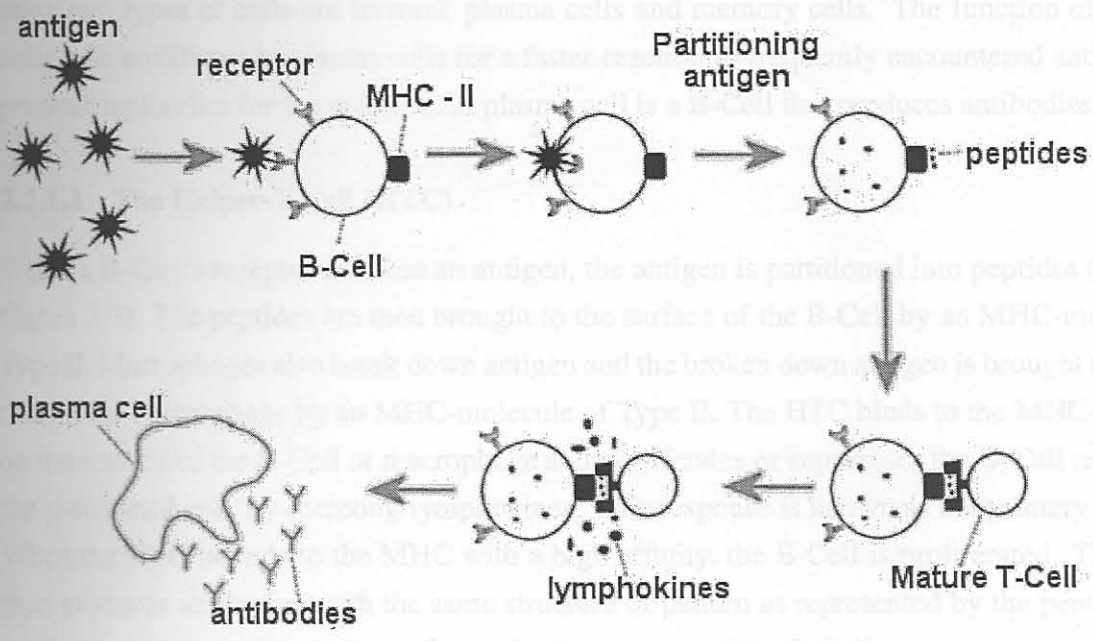

Figure 2.3: B-Cell develops into plasma cell, producing antibodies

cell are named the Major Histocompatibility Complex Molecules (MHC-molecules). Their main function is to bring to light the internal structure of a cell. MHC-molecules are grouped into two classes: Type I and Type II. MHC-molecules of Type I is on the surface of any cell and MHC-molecules of Type II mainly on the surface of B-Cells [63]. There are two types of T-Cells: The Helper-T-Cell and Natural-Killer-T-Cell. Each of these types of lymphocytes are described in detail below.

2.2.1.1 The B-Cell

The B-Cells are created in the bone marrow with monomeric IgM-receptors on their surfaces. A monomeric receptor is a chemical compound that can undergo a chemical reaction with other molecules to form larger molecules. In contrast to T-Cells, B-Cells leave the bone marrow as mature lymphocytes. B-Cells mostly exist in the milt and tonsils. It is in the milt and tonsils that the B-Cells develop into plasma cells after the B-Cells came into contact with antigens. After developing into plasma cells, the plasma cells produce antibodies which are effective against antigens [56]. The B-Cell has antigen-specific receptors and recognises in its natural state the antigens. When contact is made between B-Cell and antigen, clonal proliferation on the B-Cell takes place and is strengthened by Helper-T-Cells (as explained in section 2.2.1.2). During clonal prolifer-

ation two types of cells are formed: plasma cells and memory cells. The function of memory cells is to proliferate to plasma cells for a faster reaction to frequently encountered antigens and produce antibodies for the antigens. A plasma cell is a B-Cell that produces antibodies.

2.2.1.2 The Helper-T-Cell (HTC)

When a B-Cell's receptor matches an antigen, the antigen is partitioned into peptides (as shown Figure 2.3). The peptides are then brought to the surface of the B-Cell by an MHC-molecule of Type II. Macrophages also break down antigen and the broken down antigen is brought to the surface of the macrophage by an MHC-molecule of Type II. The HTC binds to the MHC-molecule on the surface of the B-Cell or macrophage and proliferates or suppresses the B-Cell response to the partitioned cell, by secreting lymphokines. This response is known as the primary response. When the HTC bounds to the MHC with a high affinity, the B-Cell is proliferated. The B-Cell then produces antibodies with the same structure or pattern as represented by the peptides. The production of antibodies is done after a *cloning process* of the B-Cell.

When the HTC does not bind with a high affinity, the B-Cell response is suppressed. Affinity is a force that causes the HTC to elect a MHC on the surface of the B-Cell with which the HTC has a stronger binding to unite, rather than with another MHC with a weaker binding. A higher affinity implies a stronger binding between the HTC and MHC. The antibodies then bind to the antigens' epitopes that have the same complementary structure or pattern. Epitopes are the portions on an antigen that is recognised by antibodies. When a B-Cell is proliferated enough, i.e. the B-Cell frequently detects antigens, it goes into a memory status, and when it is suppressed frequently it becomes annihilated and replaced by a newly created B-Cell. The immune system uses the B-Cells with memory status in a secondary response to frequently seen antigens of the same structure. The secondary response is much faster than the primary response, since no HTC signal or binding to the memory B-Cell is necessary for producing antibodies [63].

2.2.1.3 The Natural-Killer-T-Cell (NKTC)

The NKTC binds to MHC-molecules of type I (as illustrated in Figure 2.4). These MHC-molecules are found on all cells. Their function is to bring to light any viral proteins from a virally infected cell. The NKTC then binds to the MHC-molecule of Type I and destroys not only the virally infected cell but also the NKTC itself [63].

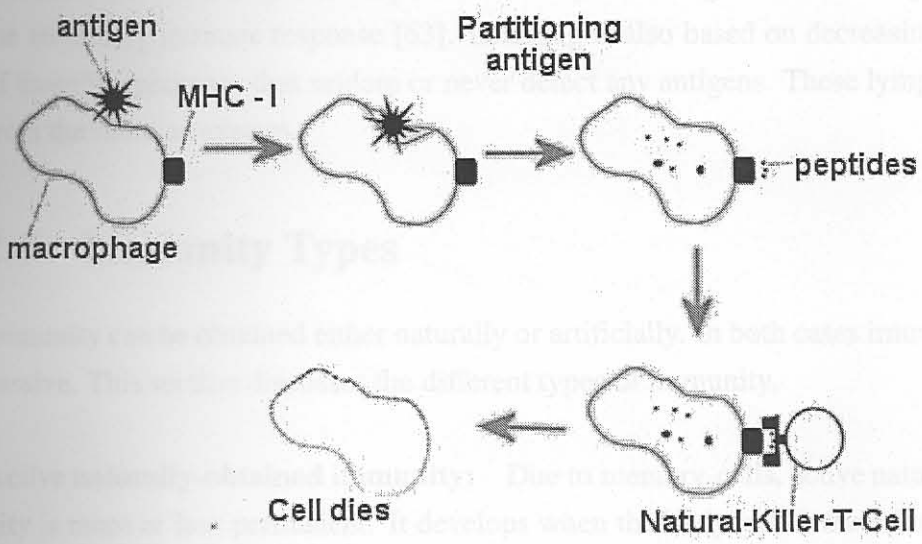

Figure 2.4: Macrophage and NKTC

2.3 The Cloning Process of the Lymphocyte

The cloning process is more generally known as *clonal selection*, which is the proliferation of the lymphocytes that recognise the antigens. The interaction of the lymphocyte with an antigen leads to an activation of the lymphocyte where upon the cell is proliferated and grown into a clone. Lymphocytes in a clone produce antibodies if it is a B-Cell and secrete growth factors (lymphokines) in the case of an HTC. Since antigens determine or select the lymphocytes that need to be cloned, the process is called *clonal selection* [56]. The fittest clones are those that bind to antigen best. For the process to be successful, the receptor molecule repository needs to be as complete and diverse as possible to recognise any foreign shape [63].

2.4 Learning the Antigen Structure

Learning in the immune system is based on increasing the population size of those lymphocytes that frequently recognise antigens. The immune system learns from experience the shape of the frequently encountered antigens and moves from a random receptor creation to a repertoire that represents the antigens more precisely. Since the total number of lymphocytes in the immune system is regulated, the increase in size of some clones decreases the size of other clones. This leads to the immune system forgetting previously learned antigens. When a familiar antigen is

detected, the immune system responds with larger cloning sizes. This response is referred to as the secondary immune response [63]. Learning is also based on decreasing the population size of those lymphocytes that seldom or never detect any antigens. These lymphocytes are removed from the immune system.

2.5 Immunity Types

Immunity can be obtained either naturally or artificially. In both cases immunity can be active or passive. This section discusses the different types of immunity.

Active naturally-obtained immunity: Due to memory-cells, active naturally-obtained immunity is more or less permanent. It develops when the body gets infected or receives foreign red blood cells and actively produces antibodies to deactivate the antigen [56].

Passive naturally-obtained immunity: Passive naturally-obtained immunity is short-lived since antibodies are continuously broken down without creation of new antibodies. New antibodies are not created because the antigens did not activate the *self* immune system. The immunity type develops from IgG-antibodies that are transplanted from the mother to the baby. The secreted IgA-antibodies in mothers-milk are another example of this immunity type and protect the baby from any antigens with which the mother came into contact [56].

Active artificially-obtained immunity: Active artificially-obtained immunity develops when dead organisms or weakened organisms are therapeutically applied. The concept is that special treated organisms keep their antigens without provoking illness-reactions [56].

Passive artificially-obtained immunity: Passive artificially-obtained immunity is obtained when a specific antibody which was produced by another human or animal, is injected into the body for an emergency treatment. Immunity is short-lived, since the immune system is not activated [56].

2.6 Conclusion

This chapter explained the working of the natural immune system and how the immune system protects the body against viruses, bacteria and any pathogenic material that can damage the body.

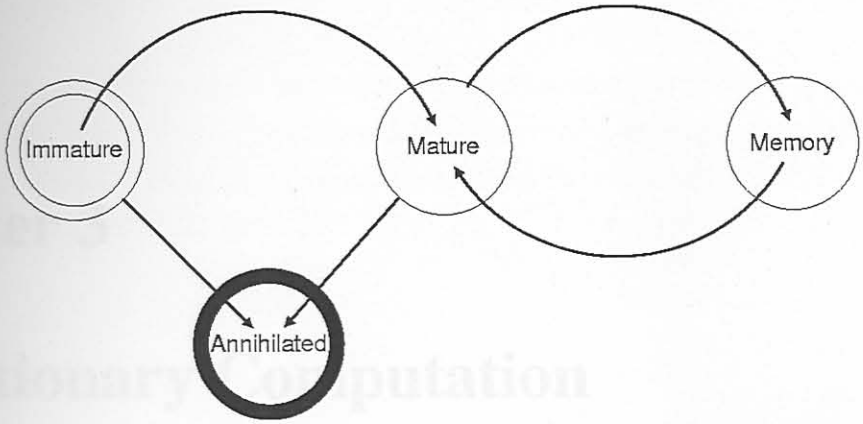

Figure 2.5: Life cycle of a lymphocyte

The different types of lymphocytes and molecules in the immune system were discussed. From this discussion it can be summarised that lymphocytes have different states: Immature, Mature, Memory and Annihilated (Figure 2.5 illustrates the life cycle of lymphocytes). The next chapter gives an overview of evolutionary computation (EC). An evolutionary algorithm (EA) is used in the Genetic Artificial Immune System (GAIS) developed in this dissertation (chapter 6) to evolve lymphocytes that can match non-self patterns with a higher affinity in a non-biological environment.