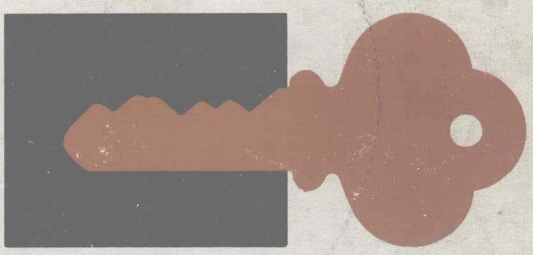
WILLIAM D. STANSFIELD

SEROLOGY & IMMUNOLOGY

A Clinical Approach



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A Clinical Approach

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To My Children, Lorrie, Lynn, and Bill

PREFACE

This text is primarily directed toward providing an introduction to the various disciplines of immunology (serology, immunity, immunopathology, immunochemistry, etc.) for students and practitioners in the human health professions. Special emphasis is given to the immunodiagnostic tests performed by medical laboratory technologists. The book should also provide a firm foundation for those interested in using serological techniques in research projects outside the field of immunology. Although human medicine is the main focus, the basic immunological principles are general enough to be useful to veterinarians and others concerned with the health of animals. Indeed, much of our knowledge about the workings of the human immune system have been obtained by using laboratory animals as models. For example, much more is known about the major histocompatibility complex (MHC) of mice than of humans, and for this reason the MHC of mice must be discussed in detail.

Immunology is seldom offered as a lower division course in colleges or universities because it is a discipline that requires a rather broad scientific background. There simply is not time in a quarter or semester immunology course to teach the fundamentals of subjects such as bacteriology, protein chemistry, Mendelian genetics, cytology, anatomy and physiology that are needed to understand many immunological principles. This book assumes that the reader has gained the required degree of sophistication in these basic sciences.

An attempt has been made to marry the theoretical and practical aspects of immunology wherever possible. Immunology is such a rapidly expanding field of science that some of the modern theories discussed herein may soon be obsolete. Nevertheless, it is hoped that the presentation of these ephemeral theories will serve to stimulate the reader to try to keep abreast of new developments in this exciting field.

Modern theories of immunology are but tips on the icebergs of fundamental knowledge accumulated largely since the time of Louis Pasteur, and we should remember that we are "standing on the shoulders of giants." However, no attempt has been made in this book to provide a historical frame of reference for modern theories, largely because of space limitations. For example, template theories of antibody production are not discussed because everything we presently know about protein synthesis renders these theories untenable. Likewise, other outmoded concepts will not be found in this volume, except perhaps for some archaic terms likely to be encountered in reading classical papers.

Heavy emphasis is given to the burgeoning vocabulary of immunology so that one may be equipped to launch into journal articles with a high degree of comprehension following mastery of the material in this book. As new terms are introduced and defined in the text, they appear in boldface. Likewise, the boldface citation of a term in the index is the location of its definition. In this way, the index can also function as a glossary. It has become common practice among professionals to freely use acronyms in communication (oral and written) with one another. One cannot hope to comprehend these discussions unless the language (terms and acronyms) is

known. An unusual feature of this book is its glossary of immunological acronyms widely used in the clinical laboratory.

For each type of diagnostic test, a thorough explanation is given of the basic principles, the controls that need to be run simultaneously, the interpretation of the results, and the pitfalls in performing and interpreting the tests. This is the kind of knowledge required of modern medical technologists to obtain licensure and for professional performance of daily tasks in the clinical laboratory. Furthermore, the mechanical and mathematical aspects of quality control are extremely important for the assurance of reliable test results. For this reason, an appendix has been added to the ten basic chapters that introduces the clinician to the mathematics of quality control.

An attempt has also been made to provide ample illustrations to help visualize abstract immunological processes. Careful study of these illustrations together with the detailed explanations in the text should aid in fixing the basic ideas in one's mind for long-term retention.

A self-evaluation section is included at the end of each chapter to provide the student with some immediate feedback on the degree of mastery of the subject matter. Three kinds of objective questions are available (terms, multiple choice, and true-false). There are 300 such items in this text, and collectively they and their answers should allow the student to gain a fairly accurate assessment of the need for restudy.

I especially wish to acknowledge the many helpful suggestions provided by my colleague David Grady. Thanks are also due to Cynthia Sommer and Duane Sears for their work in reviewing the manuscript. I would appreciate being informed of errors (both of commission and of omission) so that they may be corrected in any subsequent editions.

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Basic Principles

CHAPTER 1

CHAPTER OUTLINE

Immunology is that branch of vertebrate zoology concerned with the specific responses made by lymphocytes to foreign substances. **Serology** is a subdivision of immunology concerned with *in vitro* ("in the test tube"; extraorganismal) antigen-antibody reactions. Antibodies are found in the fluid portion of blood and in other fluids of the body. Approximately half of whole blood is cells (most are red blood cells called **erythrocytes;** some are white blood cells called **leukocytes**). The other half of blood is a fluid called **plasma.** The fluid remaining after blood clots in a test tube is called **serum.** The main difference between plasma and serum is that serum does not contain the protein fibrinogen. Serum is more commonly used than plasma in serological tests because serum will not clot when other materials are added to it. An **antigen** is any substance that can trigger specific responses from lymphocytes or that can react specifically with antibody. An **antibody** or functional **immunoglobulin** is a humoral (referring to body fluids) protein that is produced by a lymphocyte in response to an antigenic stimulus and that is capable of reacting specifically with that same antigen. **Immunity** is another subdivision of immunology involved with responses of lymphocytes that benefit the organism, as in prophylaxis (prevention) and therapeutics (treatment) of diseases caused by microorganisms. **Hypersensitivity** is a term that may be applied to lymphocyte reactions harmful to the body, as in allergies and graft rejections. Loose usage of the term "immune response" has been variously applied to either the beneficial or the detrimental aspects of immunology. Indeed, there are some instances where an immune response is neither completely beneficial nor detrimental. For example, invasion of host cells by certain viruses results in the appearance of new antigens on the cell membranes. Lymphocytes responding specifically to these new, foreign antigens may cause the destruction of virus-infected cells, limiting viral release and spread to uninfected cells. This activity produces some of the symptoms associated with the viral disease. Virally stimulated lymphocytes may also produce antiviral substances, such as an-

tibodies and interferons, that prevent attachment of viruses to host cells or inhibit replication of viruses within infected cells. Thus, the total effect of the immune response may be partly destructive and partly protective.

In the broad sense that includes hypersensitivity and immunity, the "immune response" of vertebrate animals can be defined as the acquired, transferable capacity of lymphocytes to react with specificity and memory to foreign substances. From this definition, it can be seen that true immune and hypersensitivity reactions have the following properties.

1. They are lymphocyte-mediated by products called antibodies and lymphokines.
2. These reactions are acquired only after contact between lymphocytes and the inciting antigen.
3. The response is directed specifically only at the inciting antigen. Antibodies combine with antigens as complementary molecular complexes analogous to the lock-and-key models of enzyme-substrate interactions.
4. They can be transferred from one individual to another via sensitized lymphocytes and/or antibodies.
5. Subsequent contacts with the inciting antigen produce more vigorous memory responses.
6. Self-components are distinguished from nonself-molecules so that these responses normally are made only to foreign substances. Autoallergies are an exception to the rule.

Nonsusceptibility

There are many communicable diseases that do not affect any member of a given species. Dogs, for example, do not suffer from measles, and humans do not contract canine distemper. **Nonsusceptibility** is the term that will be applied in this book to natural refractoriness of a species to infection by specific microorganisms. Although it has been common practice to refer to nonsusceptibility as nonspecific immunity, innate immunity, constitutional immunity, or genetic immunity, it is the opinion of the author that the word "immunity" should be restricted to the specific acquired activities of lymphocytes.

It is seldom known precisely why certain diseases are species-specific. Ultimately, genotypic differences between species must be held accountable, but this tells us nothing of the specific mechanisms involved. One of the best examples of how one kind of nonsusceptibility works was provided by Louis Pasteur in the nineteenth century. Anthrax is a disease found naturally only in mammals. Pasteur found that he could induce anthrax bacilli to infect chickens by artificially lowering their body temperatures from their normal 106°F down to the normal of many mammals (approximately 100°F). The genotype of the bird establishes a higher metabolic rate and consequently a higher body temperature. The anthrax bacillus can multiply *in vitro* at 42° to 43°C (108° to 110°F), but probably loses virulence *in vivo* (in the living organism) because one or more enzymes required for capsule

production are denatured (loss of native three-dimensional molecular shape) at these slightly higher temperatures. Encapsulated bacteria are generally more resistant to phagocytosis than unencapsulated forms of the same organism.

Nonsusceptibility provides complete protection (under normal conditions) for every member of the species without previously contacting the specific microorganism. Immunity, on the other hand, is acquired only after lymphocyte contact with an antigen (microorganism, foreign protein, etc.). Protection by immunity is variable from one individual to another within the species and from one time to another within the same individual. Even high levels of antimicrobial antibodies may not provide complete protection. The immune defenses can be overwhelmed by a sufficiently large inoculum of a pathogen so that clinical disease (or possibly death) ensues.

Three Lines of Defense

INTEGUMENTARY SYSTEM

The vertebrate body has, in addition to its immune response, two other major lines of defense against invasion by foreign substances. The first line of defense against pathogenic microorganisms includes the skin (integument) and the mucous membranes and their secretions. Most microorganisms cannot multiply *in vivo* and cause disease unless they can breach the barrier of the epithelial layers of these tissues. **Infection** is the result of microbial growth and/or multiplication at the expense of the host. Infecting microbes usually harm their hosts in one or more of three major ways: (1) by competing with host cells for essential nutrients, (2) by the elaboration of products that are toxic to host cells, and (3) by microbial products that promote the spread and persistence of pathogens without being directly toxic to host cells. These latter products, called **aggressins,** are exemplified by enzymes such as hyaluronidase, coagulase, collagenases, and fibinolysins.

The dry, thick, dead, cornified layer of the skin is normally an effective nonspecific barrier to the entry of most microorganisms. The moister, thinner epithelial linings of the mucous membranes found in the nasopharyngeal, gastrointestinal, and urogenital tracts would seem to provide a relatively easy route for microbial entry into the body. The gastrointestinal (GI) tract normally contains a massive microbial flora, but these bacteria are usually unable to infect the body because of the impermeable mucous layer covering the epithelial cells of the GI tract. The enzyme **lysozyme** is secreted by the nasal mucosa (also found in tears and sweat). Lysozyme digests some acetyl-amino sugars from the cell walls of many bacteria, weakening them and causing microbial death. Several other nonspecific antimicrobial substances are known to be present in blood and tissue fluids. A sticky coat of mucus tends to entrap foreign substances entering the nasopharyngeal passages. This layer of mucus is moved by ciliary action of epithelial cells to the throat and is usually swallowed. In the stomach, the action of hydrochloric acid and pepsin (a proteolytic enzyme) usually degrades accessible proteins on bacterial and viral surfaces.

RETICULOENDOTHELIAL SYSTEM

The second line of defense against microbes is the nonspecific **reticuloendothelial system** (RES), a group of cells in various tissues and organs with only one major property in common, viz., phagocytosis. **Phagocytes** are cells that engulf and digest foreign substances (such as microbes). They may be fixed (immobilized) as cells lining the sinusoids of "filtering organs" (liver, spleen, and lymph nodes), or they may be ameboid wandering cells in the tissue spaces (macrophages, histiocytes). How phagocytes recognize foreign materials is not well known, but their response is apparently nonspecific, attacking india ink particles as readily as microbes on first encounter. In both vertebrates and invertebrates, some phagocytes appear to exhibit specific responses in "experienced individuals" (i.e., those that have previously contacted the same antigen). This specificity could be partly acquired by phagocytes from the immune system of vertebrates via antibodies or lymphokines, but other explanations must be sought for this phenomenon in animals devoid of a lymphoid system.

Bacteria and injured tissues are thought to release chemicals that attract phagocytes. Such substances are called **chemotaxins.** These scavenger cells engulf bacteria and debris by surrounding the particles with pseudopod "arms" formed by sol-gel transformations of the cytoplasm. The enclosed phagocytic vacuole then coalesces with one or more lysosomes to form a **phagolysosome.** Digestion of the ingested particles is accomplished by activated lysosomal proteolytic enzymes. It is currently believed that singlet oxygen ($^1O_2$) generated by phagocytes is a more potent bactericidal agent than lysosomal enzymes. Singlet oxygen might be produced by decomposition of the superoxide radical (O_2^-) as a consequence of oxidation of reduced pyridine nucleotides or by other conceivable pathways. Carotenoid pigments are known to inactivate singlet oxygen, so that bacteria possessing these pigments tend to be protected against being killed within phagocytes. Many pathogenic bacteria of the genera *Mycobacterium* and *Brucella* are resistant to phagocytosis and are actually transported throughout the body by phagocytes, being thus protected from the immune system as long as they remain sequestered within the phagocytic cell. Bacteria possessing a polysaccharide capsule are commonly resistant to destruction by phagocytes. Still other bacteria such as the pyogenic (pus-forming) streptococci and staphylococci produce **leukocidins** that kill white blood cells (leukocytes) and the wandering tissue phagocytes called macrophages.

If a break should occur in the skin or mucous membranes, microbes may penetrate past the first line of defense. If not attacked by wandering phagocytes near the point of entry, they would likely be swept by either the bloodstream or the lymphatic system to and through the "filtering organs" where they would encounter the fixed phagocytes. The first and second lines of defense collectively constitute what is called **resistance.** Note that resistance mechanisms are nonspecific and that their strength in repelling invading microorganisms is quite variable. It is a well-known fact that when we fail to get enough sleep, fail to get adequate nutrition, suffer anxiety or depression, etc., we are more likely to succumb to colds and other common contagious diseases. We say that our resistance is low. This poorly defined physiological state implies that the nonspecific mechanisms of the

first and second lines of defense are subnormal. Resistance does not require prior contact with the antigens and is operative at various levels of effectiveness throughout our lives. Some immunologists use the term "specific resistance" or "acquired resistance" synonymously with "immunity," but the author of this text prefers to include only nonspecific protective mechanisms in the term "resistance."

IMMUNE SYSTEM

Should the invading microbes escape destruction by the second line of defense, there is still a chance that they can be destroyed by the action of the immune system, the third line of defense. The immune response involves interactions between antigens and lymphocytes and/or antibodies. There are three major limbs of the immune response (Figure 1.1). The **afferent limb** constitutes all of the functions involved in processing and delivery of antigens to the lymphoid tissues. The **central limb** comprises all of the changes that lymphocytes incur, as a consequence of the antigenic stimulus, to become transformed into effector cells and the subsequent release of effector substances called antibodies or lymphokines. Certain lymphoid cells become **primed** or specifically activated by an antigen and thereafter are referred to as **committed cells** or committed lymphocytes; these cells are destined to a particular line of development such as antibody production, immunologic memory, etc. The **efferent limb** of the immune response encompasses all of the processes that occur after the release of effectors. This involves specific interaction of lymphocytes or antibodies with inciting antigen that may, in turn, activate other cells or chemicals (such as macrophages and complement proteins) that tend to exacerbate or amplify the immune response. Table 1.1 summarizes the major differences between nonsusceptibility, resistance, and immunity.

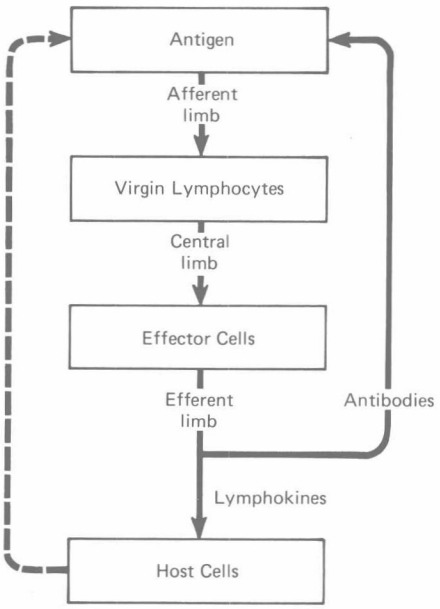

FIGURE 1.1. Three major limbs of the immune response.

Table 1.1 DISTINGUISHING FEATURES OF THREE MAJOR TYPES OF PROTECTION AGAINST PATHOGENIC ORGANISMS

Type of Protection	Responsible Agents	Requiring Prior Contact	Degree of Specificity	Degree of Protection
Nonsusceptibility	Heredity common to the species	No	High	Absolute
Resistance	Skin and mucous membranes; phagocytes	No	Low	Variable
Immunity	Antibodies, lymphokines	Yes	High	Variable

"Humoral" Immunity. Immunity in vertebrates depends on the cooperation of lymphocytes and phagocytes. Macrophages usually prepare or process antigens in ways that render them capable of binding to those lymphocytes that bear homologous cell-surface receptors. This antigenic stimulus causes certain immature lymphocytes (immunoblasts) to differentiate into mature antibody-producing immunocytes called **plasma cells.** Before antigenic stimulation, the antibodies made by a plasma cell are attached to the cell membrane, forming the antigen receptor sites. After stimulation by macrophage-processed antigen fragments, the plasma cell begins to release antibodies into the body fluids or "humors." Antibody-mediated immunity is therefore sometimes referred to as **humoral immunity.**

If the animal is encountering microbial antigens for the first time, some of its lymphocytes may be stimulated to produce antibodies. The interval from invasion to the time that specific antibodies can be detected in the serum commonly varies from a few days to a few weeks. Once these antibodies are released into the bloodstream, they can aid in the disposal of those same kinds of microbes by one or more of several mechanisms (lysis, agglutination, toxin neutralization, opsonization).

Antigen-antibody complexes may nonspecifically trigger activation of a series of normal serum enzymes known collectively as **complement** (Chapter 7). Although the mechanism is imprecisely known, it seems that the proteins at the end of the complement cascade (sequence of interacting complement components) is activated with the capacity to produce holes in the membranes of certain cells to which antibodies and complement have attached. Substances normally restricted from entry into cells may then flow through these holes and cause dissolution or **lysis** of the cell. Antibodies that can thus cause lysis of bacterial cells are called **bacteriolysins;** antibodies that can thus cause foreign red blood cells to rupture are called **hemolysins.** Some activated complement proteins are chemotactic, attracting lymphocytes and other white blood cells toward the site. The activities of these cells may contribute substantially to some inflammatory reactions, but not all inflammations are mediated by antigen-antibody-complement complexes.

Antibodies may cause **agglutination** or clumping of microbes, inhibiting their spread through the body and making phagocytic cells more efficient by allowing groups of microbes to be engulfed by a single psuedopodic movement of the cell membrane. The antigens involved in agglutination

reactions are known as **agglutinogens;** the corresponding antibodies are **agglutinins.** If agglutinating antibodies activate the complement system, cells such as gram-negative bacteria, foreign leukocytes, and erythrocytes can be lysed. However, many gram-positive bacteria, molds and yeasts, and most plant and foreign mammalian cells are resistant to complement-mediated cytolysis and might be agglutinated *in vivo.*

Antibodies may neutralize (render harmless) certain poisons and viruses. **Antitoxins** are antibodies that neutralize toxic bacterial products. **Antivenoms** are antibodies that neutralize the poisons of certain reptiles (mainly snakes) and certain arthopods such as spiders and scorpions. The diseases of diphtheria, tetanus, and botulism poisoning are apparently caused exclusively by the secreted toxic products of specific bacteria. One theory of antitoxin activity is that the attachment of antibody to the toxin occurs at a site other than the active site. Interaction of antitoxin with this other site (the **allosteric site**) causes a conformational change in the toxin molecule, altering either its toxic site and/or the site by which it attaches to and gains entry into the target cell (Figure 1.2). According to another theory, neutralization occurs by **steric hindrance.** If an antibody attaches at or near the toxic site, effective contact of the toxin molecule with the target cell is prohibited. In analogous but more complicated ways, antibodies may neutralize viruses by combining with their coat proteins whereby the viruses would normally attach to receptor sites on host cells. By either steric hindrance and/or allosteric transformation the antibody renders the virus unable to recognize or contact the receptors, and hence it becomes unable to infect the host cell (Figure 1.3).

Antibodies may enhance phagocytosis by poorly understood mechanisms other than agglutination. It seems that the attachment of antibodies to microbial cells tends to render them "sticky," perhaps by nullification of an electrostatic charge identical to that of the phagocytic cell. The name **opso-**

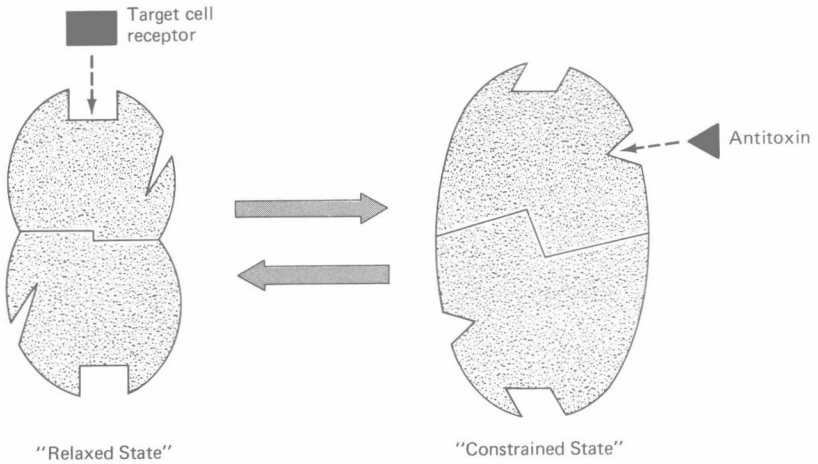

FIGURE 1.2. Model of an allosteric protein. If a protein consists of two identical subunits, it is inferred that an axis of symmetry exists. This model proposes that the protein may alternate between two structural states in which symmetry is preserved. In the "relaxed state," it can bind to target cells. In the "constrained state," it can bind antitoxin. Having bound antitoxin, the protein can no longer bind to the target cell receptor.

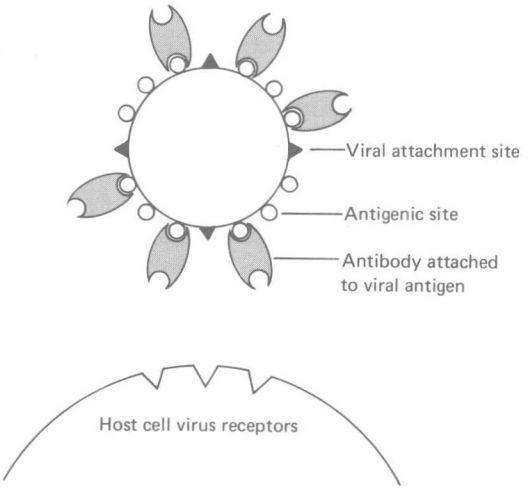

FIGURE 1.3. Diagram illustrating how an antibody complexed with a viral antigen near a viral attachment site prevents the virus from contacting receptors on a host cell by steric hindrance.

nin or opsonic antibody is given to antibodies that facilitate phagocytosis. The opsonic activity of a given antiserum can be quantitated by either an *in vitro* or an *in vivo* test. A **phagocytic index** can be calculated that expresses the average number of bacteria or inert particles ingested per phagocytic cell during a given time period. When this index is applied to bacteria subjected to prior treatment with an **antiserum** (a serum containing specific antibodies), an **opsonic index** can be obtained and compared with a replicate experiment in which the bacteria are not treated with an antiserum. The difference in the two experiments, if performed under the same conditions, is attributed to the enhancement of phagocytosis contributed by the opsonic antibodies.

After recovery from the infection, the animal has a reserve of antibodies ready to react with the antigens of that same kind of pathogenic microorganism. This is why subsequent infection with the same pathogen produces either no disease or a milder form of the disease, depending on such factors as the quantity or titer of specific antibodies present at the time of infection, the dosage of the pathogen, etc.

All antibodies are proteins having the molecular structure of immunoglobulins. The immunoglobulins are presently divided into five classes designated IgG, IgM, IgA, IgE, and IgD. The most common class of antibody (immunoglobulin G or IgG) consists of four polypeptide chains (Figure 1.4). Two of these chains, called heavy chains or H chains, are about twice as long as the other two, called light chains or L chains. These four chains are associated into a tetrameric or tetrapeptide structure that resembles the letter "Y." The arms of the Y-shaped antibody function in antigen recognition and binding; the tail of the immunoglobulin has effector functions that depend on the class to which it belongs. For example, antibodies of classes IgM and IgG can bind complement, those of class IgG can pass the placenta, etc. Antibodies of class IgM and some of class IgA exist as multiples of this basic tetrameric, Y-shaped structure. Further details of antibody structure, classification, and function are given in Chapter 2.

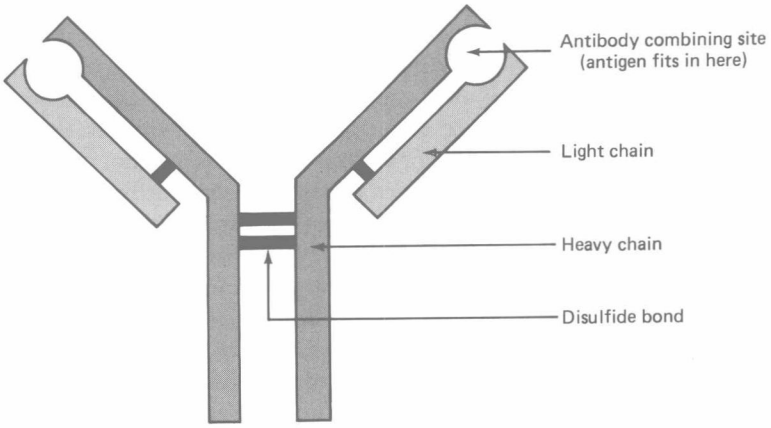

FIGURE 1.4. Model of a common immunoglobulin of class G (IgG).

"Cellular" Immunity. Some kinds of lymphocytes do not make an antibody response to antigens, but rather release chemicals called **lymphokines** that activate cells of the host. Some of these lymphokines cause mitotic activity in other lymphocytes; others attract macrophages or lymphocytes. Still other lymphokines cause the destruction of virally infected cells, etc. The protection afforded by these kinds of lymphocytes is sometimes called "cellular" immunity. This aspect of the immune system will be discussed in greater detail in Chapters 9 and 10. Each lymphocyte involved in either humoral or cellular immunity appears to respond specifically to one kind of antigen or to the molecular variants of an antigen that are nearly identical.

Types of Immunity

If the individual develops his own antibodies, he is said to have **active immunity.** If he receives antibodies or immune cells from another individual, this is **passive immunity.** Both forms of immunity may be attained **naturally** or **artificially.** Natural active immunity is developed when an immunologically competent individual contacts the antigen in his environment, as when he steps on a rusty nail or ingests microorganisms with his food. Natural passive immunity develops in mammals by one or two routes, both from the mother. Some antibodies may cross the placenta (only those of class IgG can do this), and some secretory antibodies of class IgA may cross the epithelium of the mammary ducts and be present in the mother's milk (especially in colostrum) and subsequently are absorbed by the newborn from its gastrointestinal (GI) tract. Artificial active immunity results from, for example, vaccination against smallpox (variola virus) by the purposeful introduction of cross-reacting cowpox (vaccinia) virus into the patient. Cowpox is probably the naturally occurring ancestor of human vaccinia virus. Artificial passive immunity can be conferred on an individual that receives specific antibodies in the serum from another individual of the same (homologous) or different (heterologous) species. For example, heterologous antitetanus antibodies made in a horse or goat or (preferably, if available) in a human should probably be administered to a person who has a puncture wound and who has not been immunized to tetanus within

the past five years. A major problem for an immunologically competent individual receiving passive immunity from another individual of the same species (and especially from another species) is the danger of a harmful systemic hypersensitivity response acquired as a result of contact with foreign serum. Foreign proteins are often potent antigens; antibodies from a different species behave as foreign protein antigens in the passively immunized recipient. The greater the degree of genetic difference between the two individuals, the greater the difference in protein structure is likely to be. Thus, receiving antibodies from members of one's own species is much more desirable for passive immunization than receiving them from another species. Furthermore, passive immunity is short-lived. Passively derived antibodies are degraded exponentially with time within the recipient, so that after several weeks or months the individual is once again susceptible to the disease and retains no "immunological memory" of the first encounter with the antigen. Table 1.2 summarizes the major attributes of active and passive immunities.

Table 1.2 Comparison of Active and Passive Immunities

	Type of Immunity	
	Active	Passive
Source	Self	Non-self
Immunizing agent	Antigen	Immune serum (antibodies)
Relative effectiveness in:		
Newborn	Low	Moderate to high
Adult	High	Moderate to low
Relative effective dosage required	Small	Large
Latent period (approximate time from immunization until it becomes effective)	5 days to 2 weeks	None (immediately effective)
Relative length of immunity	Long but variable (may be lifelong)	Short (up to 2 or 3 months)
Usual route of injection	Intramuscular or intradermal	Intravenous
Function	Prophylactic	Therapeutic and/or prophylactic
Undesirable effects attending:		
Natural immunity	Disease*	Usually none†
Artificial immunity	Usually none‡	Serum sickness (systemic hypersensitivity reaction)

* Most common infections are subclinical and detected only retrospectively in serological screening "field" studies.

† Rh disease (q.v.), antiplatelet antibodies and other exceptions are known.

‡ Some patients may develop a local hypersensitivity reaction to the foreign proteins of the animal in which a virus is grown (e.g., chicken egg proteins). Some vaccinations (e.g., typhoid, cholera) may be painful (due to presence of endotoxin lipopolysaccharide in antigen) at the injection site. This may cause nausea, generalized aches, fatigue, etc. With some infectious ("live") virus vaccines, generalized disease due to dissemination of the immunizing virus can occur in immunologically "compromised" (deficient) individuals.