Clinical Immunology and Allergy

SECOND EDITION

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Preface to the Second Edition

The second edition of *Clinical Immunology and Allergy* is practically a new book. It reflects the many changes in and the rapid accumulation of knowledge in the field of allergy and clinical immunology since the appearance of the first edition in 1962.

Our experience with an uninterrupted residency program in allergy for 28 years, with registrants for the annual course, Diseases due to Immune Mechanisms, and with the increasing emphasis placed by the allergy certifying boards on clinical immunology make it necessary to include in this book adequate information on immunologic problems encountered in clinical practice.

The following basic immunologic subjects are now presented in greater depth in Part I: the biochemical nature of antigen and antibody, antibody detection technics, normal and abnormal immunoglobulins, the morphology of antigen-antibody reactions, the role of the thymus in immunity, the antibody deficiency syndromes, transplantation immunity, and autoimmunity. Allergy to drugs, hormones, insects, and intestinal parasites as well as discussions of pulmonary function, spirometry, acid-base disturbances, nonatopic sensitivity diseases of the lungs, immunohematology, and immunoproliferative diseases are presented in Part II.

Pediatric allergy is covered in detail with topics such as immunization procedures, differential diagnosis in bronchial asthma and atopic dermatitis, rehabilitation of the asthmatic child, "cot" death, Aldrich and Heiner syndromes, and many other subjects of special interest to the pediatrician.

Clinical allergic conditions are considered under each of the four divisions of Part II. Some exceptions are made, however, in order to avoid repetition and to provide continuity. Thus, the topic of immunohematology, though included in the chapter on autoimmunity, embraces a discussion of some diseases that are immunologically induced but are not particularly autoimmune in nature. Similarly, a consideration of hypersensitivity diseases of the kidney in the same chapter comprises not only autoimmune renal conditions, but also nephritides in which other immune mechanisms may play a role.

Also in Part II is a new chapter on fungi by Glenn S. Bulmer, Ph.D.; he made valuable suggestions to the chapters on superficial and deep mycoses also. Finally, a new chapter on allergic diseases in small animals is included.

An outline precedes each chapter. No attempt is made to provide specific references, but a bibliography is supplied. A comprehensive index is also included.

The preparation of the subject matter in this text reflects the belief that in years to come the allergist will be oriented not only in internal medicine and pediatrics but also in clinical immunology.

The author is deeply grateful to Philip Fireman, M.D. for many helpful suggestions on basic immunology; to Winton Tong, Ph.D. for reviewing the chapter on acid-base balance; to Marvin Lewis, M.D. for suggestions on immunohematology; to Z. A. Zawadzki, M.D. for his help with the chapter on immunoproliferative diseases; and to Martin H. Lizerbram, M.D., Teaching Fellow in Clinical Immunology and Miss Romayne A. Teufel, B.A., M.T., his chief laboratory assistant, for their valuable contribution in proofreading. Grateful thanks are also due to the author's devoted secretary, Miss Rany M. Owens; to his wife, without whose continued patience and forbearance this book could never have been so completely rewritten. The author wishes to express his acknowledgments also to the many unnamed investigators from whose writings he has drawn freely in the compliation of this volume and to the publishers, Grune & Stratton, he expresses gratitude for their wholehearted interest and cooperation.

LEO H. CRIEP, M.D.

Preface to the First Edition

The field of hypersensitivity or allergy has made tremendous strides since the appearance of the author's last book, *Essentials of Allergy,* 15 years ago. This progress is particularly evident in the experimental phases of the immunology of hypersensitivity, an understanding of which has become essential for the enlightened allergist. A glance at modern medical literature and a review of the scientific programs of the various allergy societies indicate the extent to which clinical immunology has become a basic constituent of allergy. It is for this reason that the first part of this book is devoted to a consideration of fundamental immunology. This is written, not for the immunologist, but for the student, the resident, the internist, the pediatrician, the dermatologist and the allergist. It is intended to impart an understanding of the basic principles of immunology and an acquaintance with the immunologic tools employed in the study of hypersensitivity.

The second part of the book deals with the subject of hypersensitivity conveniently divided into four classes. These are the "immediate" response associated with circulating antibody; the "delayed" response, *not* associated with circulating antibody but with cellular sensitivity; the response resembling immunologic reactions associated with circulating antibody and/or cellular sensitivity; and finally, diseases characterized by morphologic and clinical similarity to immunologic reactions.

In many conditions, basic immunologic considerations are not subject to direct positive and dogmatic interpretation since our knowledge at the present is not conclusive. Hence, various shades of gray exist between what is considered black or white. This will account for the lack of general agreement among immunologists in many of the areas treated in this volume.

Ancillary subjects such as pulmonary function tests, corticosteroids, agammaglobulinemia, chronic vascular headache, diffuse connective tissue diseases, hematoimmunology, autoimmune disorders and rejection of homotransplants are discussed briefly and only to the extent to which they are of interest to the student of allergy. An effort is made to place the consideration of such topics within the framework of the classification given above. Insofar as it is possible, lengthy controversial discussion of various views and theories is avoided. Obviously, in a book of this scope, there are bound to be a number of omissions. Some subjects are presented briefly. For additional information, the interested reader is referred to recent reviews and to the list of reference books appended at the end of this volume. In the available space, we can present only a working version of these topics. In order to avoid much repetition, the reader is often referred to other sections of the book.

This volume covers modern and generally accepted concepts of diagnosis and treatment of allergic diseases. These conditions are considered important not only because of their relatively high incidence, but also because of their persistence and high morbidity.

The contents of this book truly reflect the ever-widening scope of allergy. The allergist is no longer content to concern himself only with the conventional concepts of clinical allergy. He has become aware that clinical immunology is an essential part of his domain. Through an understanding of the newer phases of hypersensitivity, he has grasped the significance of the ever-increasing list of subjects related to this field.

In writing this text, the author has drawn freely from the available literature as well as from his own experience. He therefore acknowledges his gratitude to the many named as well as the many unnamed collaborators and investigators without whose brilliant work the present volume could not have materialized.

The author owes gratitude to the Schering Corporation of Bloomfield, New Jersey, a grant from whom made printing of the color illustration possible.

The author is grateful as well to the editors and publishers of the medical journals with whose permission certain material is reprinted; and to Thaddeus Danowski, M.D., Hubert Bloch, M.D., Rudolph L. Baer, M.D. and Wallace N. Jensen, M.D., who have been very kind in critically reviewing parts of the book; to Miss Catherine M. Leslie, his secretary; his laboratory personnel, Miss Romayne A. Teufel, B.A., M.T., Miss Nada Cindrich, B.A., and to Mr. J. Mineo and Staff of the Medical Illustration Department of the Veterans Administration Hospital. Special acknowledgments are due to Frank J. Dixon, M.D., for his valuable assistance in carefully reviewing the part of the book dealing with fundamental immunology and the pathogenetic classification which is followed in the book; to E. R. Fisher, M.D. for writing on the anatomy and pathology of connective tissue diseases, and to P. A. Bromberg, M.D. for writing on the pathophysiology of bronchial asthma. The author expresses his indebtedness to his wife for her patience and help in reading the manuscript and proofs; and finally to his publishers for their kindness and cooperation.

LEO H. CRIEP, M.D.

CONTENTS

PART I

Fundamentals of Immunology

SECTION I TERMINOLOGY

1

Nomenclature

Hypersensitivity; hypersensitiveness; allergy; sensitivity; sensitiveness; specificity
Immunology; immunity; immunopathology; immunochemistry; immune response, immunization; sensitization
Isoimmune response; actively acquired immunity; passively acquired immunity; specific actively acquired immunity; natural or innate immunity; natural antibodies
Epitope; paratope; allotypes; allele
Homozygous; heterozygous; heterogenic; allogenic
Antibacterial immunity; antiviral immunity
Lysosomes; ribosomes; ribonucleic acid (RNA); mRNA; sRNA; deoxyribonucleic acid (DNA)
Pseudoglobulin; euglobulin
Properdin; interferon; haptene; anergy
"Immediate" and "delayed" hypersensitivity

As might be expected in the development of a comparatively new study, there exists a great deal of confusion in the literature on the terminology of allergy. This confusion is due to the fact that a variety of terms have been coined by various workers to denote the phenomena of hypersensitivity. For this reason, it seems advisable to clarify this nomenclature.

The terms *hypersensitivity* and *allergy* are used interchangeably, in an all-inclusive sense, to denote a state of specific sensitivity on the part of lower animals or of man to a substance which is harmless to most members of the same species. Thus, an individual is said to be hypersensitive or allergic to egg if the ingestion of a small amount of egg gives him unusual symptoms such as asthma. The terms *sensitiveness* and *sensitivity* are used synonymously with hypersensitiveness and hypersensitivity. General usage justifies the employment of the term hypersensitivity, redundant though it may be. The sensitivity in these instances is always *specific*. It results from exposure to a definite substance. An animal sensitive only to bovine serum albumin (BSA) will develop manifestations only if exposed specifically to BSA. The essence of the allergic reaction is altered tissue reactivity. Sensitized tissue reacts in a different manner from that of normal tissue when exposed to the sensitizing agent.

Immunobiologic reactions depend upon the property of molecular recognition by immunoglobulins. The immunologic mechanism can protect the individual against bacterial and viral infections, or it can damage tissues as in diseases of autoimmunity or allergy.

Immunology is the study of immunity. *Immunity* is the state of protection and resistance to disease or infection. *Immunopathology* is the study of the physiologic and morphologic changes which occur in a hypersensitive host animal exposed to the specifically related antigen. *Immunochemistry* is concerned with antigen-antibody reactions. It quantitatively measures antigens and antibodies and deals with the physical and chemical properties of antigens and antibodies at the molecular level. An *immune response* or *immunization* indicates the

production of antibodies and the resulting state of hypersensitivity or protection in response to exposure of the host to antigen. A true immune response is seen characteristically only in vertebrates. *Sensitization* is a term which is used synonymously with immunization.

An *isoimmune response* develops as a result of antigenic stimulation, the antigen being obtained from another individual of the same species. When sensitization is brought about by the injection of antigen, it is referred to as *actively acquired immunity*. However, when protection or sensitization is caused by the transfer of antibody-containing serum from the sensitized host or of sensitized cells to a normal recipient, it is referred to as *passively acquired immunity*. Active immunization lasts longer than passive immunity. *Specific actively acquired immunity* may result from previous exposure to a microorganism. This protection is against the specific microorganism. Thus, infection with measles virus protects the individual against measles. Acquired immunity may be passive when it is transmitted by the mother to the fetus. Immunity or protection of a nonspecific type may be determined by a genetic influence; for example, rats are immune to a great extent to diphtheria, whereas guinea pigs and man are very susceptible to this organism. There may be occasional instances of racial differences in immunity. *Natural or innate immunity* is the capacity of an organism to protect itself against invasion by pathogenic bacteria without the organism having experienced known previous exposure to such bacteria. *Natural antibodies* occur without a known previous disease or exposure to a given infection. These antibodies are not present at birth nor have they been transmitted from the mother, but must result from previous unrecognized mild exposure to the microorganism.

Epitope is the specific combining site of an antigen molecule. *Paratope* is the specific combining site occurring on the surface of the antibody molecule. *Allotypes* are genetically controlled variants of plasma proteins (gamma or beta globulins in different species). An *allele* is one of a pair or a group of genes with the same locus on homologous chromosomes.

Homozygous is a term applied to an individual in whom a given pair of genes are alike This is brought about through inbreeding. *Heterozygous* indicates an individual in whom there are many pairs of genes resulting from cross breeding. The two members of one or more pairs of genes are not similar. The term *heterogenic* or *allogenic* indicates a different genetic constitution.

Antibacterial immunity may occur as a result of infection. In the case of toxin-producing organisms such as tetanus or diphtheria, protective antitoxins (antibodies) are formed. Under different circumstances, however, exposure to living or nonliving antigens elicits an immunologic reaction which is not protective in nature. It produces undesirable manifestations, namely allergy or hypersensitivity. It causes demonstrable functional and morphologic changes which may be seen both in man and in lower animals. These changes vary in extent, severity, and duration, depending on the location of the reaction, the quantity of antigen and antibody, methods and route of exposure to antigen and the host response. It follows then that the manifestations of hypersensitivity are not caused by the toxic property of the antigen. These manifestations are entirely different from those elicited by exposure of a nonsensitive animal of the same species to the same antigen. Thus, an allergic individual responds with characteristic symptoms when exposed to substances to which he is sensitive, such as aspirin, pollen, or food. An anaphylactically sensitive animal responds with characteristic symptoms when exposed to the specific antigen. These symptoms are entirely different from those which aspirin, pollen, or foods elicit in nonallergic, nonsensitive, or normal individuals.

Antiviral immunity usually, though not always, follows exposure to and infection with a virus. This leads to immunity or protection. Herpes is an example of the exception to this statement. Humoral antibodies against the mumps, measles, and infectious hepatitis viruses have been demonstrated.

Lysosomes are polypeptides. They are a special group of cytoplasmic particles associated with various hydrolytic enzymes or hydro-

lases such as lipase and acid phosphatase. These enzymes are also found in the granules of polymorphonuclear leukocytes and eosinophils. They phagocytize and digest protein materials taken in by the cells and bring about partial degradation of the antigen. These structures are 0.5 to 2 microns in diameter. They have a lipoprotein membrane and may have something to do with autoimmunity. It is speculated that they may in some way denature or change native protein so that it becomes antigenic, thus producing antibodies which in turn react with normal tissues. No less than 20 different hydrolases have been identified. The function of lysosomes or enzymes is to take up antigen or some of our own tissue proteins and break them down into very small molecular fragments. This may bring about immunologic responses which are cross reactive with normal tissues. Lysosomes are affected by corticosteroids. The anti-inflammatory effect of corticosteroids may be due in part to their stabilizing effect on the lysosome membrane, thus interfering with the release of hydrolytic enzymes.

Protein molecules are formed on the small particulate material found in the cytoplasm, known as *ribosomes,* which consist of *ribonucleic acid* and protein. *RNA* is found in the cytoplasm and is a polymer of ribonucleotides. It is probably produced in the nucleus. There are two types of RNA—*messenger RNA (mRNA)* and *soluble* or *transfer RNA (sRNA).* The mRNA is produced in the nucleus by DNA and carries instructions from the DNA. These instructions determine the amino acid sequence, the folding of polypeptide chains, and the protein molecules synthesized by the cell. The sRNA also participates in this process. The RNA acts as a messenger for a code which determines the nature of the proteins produced by the ribosomes (Chapter 5). RNA is manufactured under the influence of *deoxyribonucleic acid* (DNA). DNA is a polymer of deoxyribonucleotides. It consists of a purine and pyrimidine base, a phosphate, and a sugar. The genetic factor depends on the formation of deoxynucleotides in the DNA molecule. The DNA are proteins found in the nucleus which go into the makeup of genes. The difference in amino acid sequence, therefore, is determined by the RNA, which in turn is controlled by the DNA.

Pseudoglobulin is a fraction of plasma globulin and includes part of gamma globulin, many beta, and some alpha globulins. It is soluble in distilled water and is precipitated by 33 to 46 per cent saturated ammonium sulfate.

Euglobulin is a plasma protein fraction which contains a part of the gamma globulin and the gamma 1 macroglobulin. It is insoluble in distilled water or in dilute salt solution.

Properdin occurs naturally in serum. It is produced by the combination of components of complement with euglobulin in the presence of magnesium ions. It is bactericidal to most of the gram-negative organisms, and is increased by the injection of endotoxin. There is some question as to the exact nature of properdin and as to whether it is actually responsible for nonspecific resistance to infection.

Interferon is a trypsin liberated by the cells in response to a virus infection. It interferes with the growth of viruses and, therefore, offers some protection. The relation of interferon deficiency to antiviral immunity is not clear, but these patients do not do well if they develop infectious hepatitis. *Haptene* is an incomplete antigen. *Anergy* is the absence of hypersensitivity.

The terms *"immediate"* and *"delayed" hypersensitivity* do not indicate the time necessary for induction of sensitivity, i.e., the time which elapses between initial exposure to antigen and the development of sensitivity, but denote the time of the reaction itself. This is shown for example by the interval in which a positive tuberculin skin reaction is obtained in tuberculin-sensitive individuals following the administration of tuberculin.

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Classification of Hypersensitivity

This chapter includes an immunologic and pathogenetic classification of hypersensitivity or allergy. Like most classifications dealing with a subject about which so much remains to be known, it is not entirely free of inconsistencies. Thus, homograft rejection is considered under the heading of cellular sensitivity even though there is suggestive evidence that in some instances ("first-set" reaction) circulating antibodies may play a causative role. Also, some autoimmune reactions are mediated by a delayed mechanism and others by circulating antibodies, but the entire subject is dealt with in one chapter.

I. *Reactions of hypersensitivity associated with circulating antibody (the immediate response)*
   A. Induced
      1. Anaphylaxis; antigen-antibody reaction in tissues; one reactant is fixed to tissue
         a. Systemic: direct, passive, reversed passive
         b. Cutaneous: direct, passive, reversed passive
      2. Arthus phenomenon; Antigen-antibody reaction in small blood vessel wall; no fixation of reactant to tissue
      3. Serum sickness: *protracted* interaction of circulating antigen with newly formed antibody resulting in circulating antigen-antibody complexes; experimental, clinical
   B. "Familial" or spontaneous—atopy associated with skin-sensitizing antibody
      1. Bronchial asthma; hay fever; urticaria; angioedema; atopic dermatitis; and miscellaneous conditions

II. *Reactions of hypersensitivity not associated with circulatingg antibody but with cellular sensitivity (delayed response)*
   A. Nonmicrobial
      1. Eczematous allergic contact dermatitis
      2. Fixed eruption
      3. Homograft rejection (transplantation immunity)
   B. Microbial: bacterial, fungal, viral, and parasitic infections
      1. Tuberculin-type reaction
      2. Id reaction

III. *Diseases of hypersensitivity resembling immunologic responses associated with circulating antibody and/or cellular sensitivity*
   Diseases of autoimmunity
      1. Solid organs: thyroid, central and peripheral nervous systems, testes, uvea, lens, liver, lung, adrenal, and kidney
      2. Formed elements of the blood: acute hemolytic anemia (AHA), leukopenia, idiopathic thrombocytopenic purpura (ITP)

IV. *Diseases of hypersensitivity characterized by morphologic and clinical similarities to immunologic reactions*
   Diffuse connective tissue diseases
      1. Polyarteritis nodosa
      2. Rheumatic fever
      3. Rheumatoid arthritis
      4. Systemic lupus erythematosus
      5. Progressive systemic sclerosis (scleroderma)
      6. Dermatomyositis and other conditions

SECTION II ANTIGEN

3

Antigen

Definitions: antigen; autologous antigen; homologous antigen; heterologous antigen; complete antigen
Composition: proteins; carbohydrates; lipids; the Forssman antigen; nucleic acid; DNA; RNA; haptene; "univalent" antigen; inhibitors
Boivin antigen
Conjugated antigen; Van der Waals forces
Simple chemicals; the immediate reaction
The Boivin antigen
Adjuvants: complete adjuvant; incomplete adjuvant; Freund's adjuvant
Antigenic specificity
Factors influencing antigenicity
Antigenic competition
Botanically and biologically related antigens
Species and organ-specific antigens
Blood types
Heterogenetic or heterophile antigens
Denaturation of antigen
Valence
Complex antigens
Cross reactivity
The fate of antigen

DEFINITIONS

Antigen is a substance which stimulates an immune response or the formation of antibody when introduced into a host. One must qualify this definition, because in delayed hypersensitivity, even though the condition is induced by antigenic stimulation, no circulating antibodies are demonstrable. Also, in immunologic paralysis, the administration of a large dose of antigen produces exactly the opposite effect (Chapter 13). To some extent the response to antigenic stimulation is a characteristic of the host. A host will not, as a rule, respond with the production of antibodies to self-antigens.

Autologous antigen is one obtained from the same individual; *homologous antigen* is obtained from another individual of the same species; and *heterologous antigen* is obtained from an individual of a different species. As a rule, antigens are always multivalent, whereas antibodies are always bivalent. A *complete antigen* is a functional antigen.

COMPOSITION

Proteins. Protein antigens may be of animal or plant origin. Examples are bovine serum gamma globulin (BGG), bovine serum albumin (BSA), lactalbumin, tissue protein, hemoglobin, enzymes, and hormones. They may be of plant origin, such as gluten and gliadin, or they may be of viral, bacterial, or fungal origin. Complete antigens are most often proteins in a colloidal state. Some proteins are better antigens than others. For example, ovalbumin, serum globulin, diphtheria, and tetanus toxoid are better antigens than hemoglobin or pollen.

The antigenicity of a given protein depends on the degree of its difference from the native protein. That is, it must be a foreign protein. It also depends on its susceptibility to being degraded (as in penicillin allergy) by the host into various immunogenic fractions. The degraded product is often the antigenic fraction.

Another factor which determines antigenicity is the capacity of a degraded protein to persist for a sufficient period so as to produce antibodies. Antigenicity is also dependent on the acid radicals in the determinant group, the special configuration and location of the determinant group, and the amino acids in the protein molecule.

Antigens are, as a rule, soluble in body fluid and may occasionally pass through the intestinal and respiratory mucous membranes and through the placenta. The serum passive-transfer test in man (Chapter 27 and 28) indicates that allergenic foods may pass unchanged through the intestinal mucosa and reach the sensitized skin area. On the other hand, there is no evidence that diphtheria antitoxin (DAT) antibodies present in the milk and serum of immunized cows are absorbed through the gastrointestinal tract of the infant following ingestion.

The protein molecule is composed of chains of polypeptides, which are combinations of amino acids (Fig. 1). The formula for an amino acid is shown in Fig. 2. Chains of amino acids in the protein molecule fold back on each other to form polypeptide chains. The simplest amino acid is glycine (Fig. 3). The NH_2 is basic. The COOH is acid. Another amino acid, alanine, is obtained by replacing one hydrogen with CH_3 (Fig. 4). In still another amino acid, tyrosine, the R group, which is any group attached in this position, is replaced with phenylhydroxyl. Free-reactive points such as amino (NH_2), carboxyl (COOH), and sulfhydryl (SH) are left on the surface of the protein molecule groupings. An analysis of the antigenic structure of the protein molecule indicates that there are several factors which determine its structure. These include the sequence of amino acids in the peptide chains, the folding of these chains, and the configuration of the

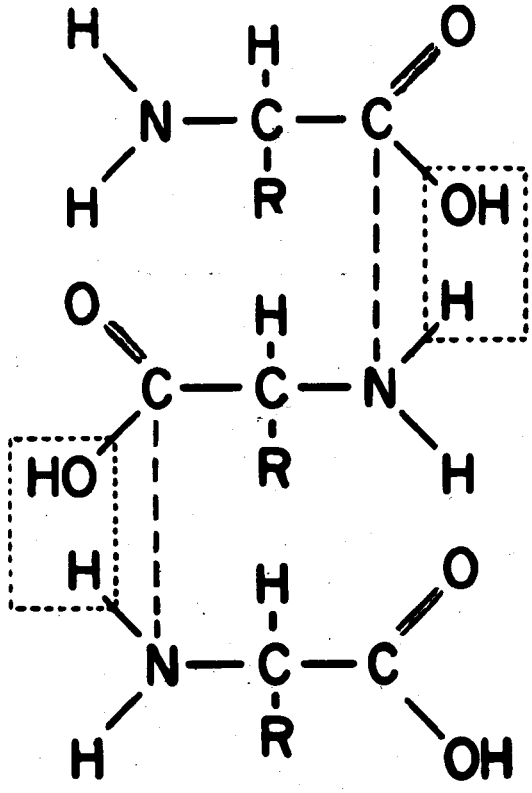

Fig. 1—Polypeptide.

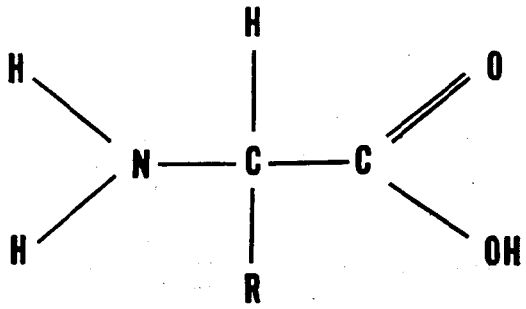

Fig. 2.—Formula for amino acid.

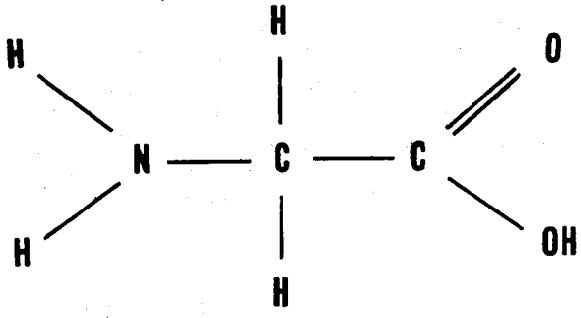

Fig. 3.—Glycine.

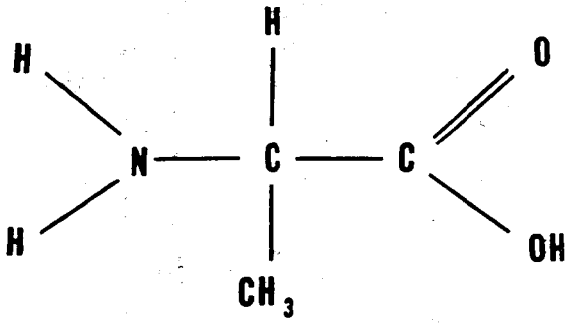

Fig. 4.—Alanine.

molecule. This configuration is brought about by a linkage of the side groups of several peptide chains by means of disulfide bonds. The reactive points found on the surface of the protein molecule no doubt determine its antigenicity. Some groupings which appear on the surface of the protein molecule are more antigenic than others.

The specific sites are polar groups on the surface of the molecule; examples are the carboxyl groups as in aspartic and glutamic acids, the amino group as in lysine and arginine, phenolic hydroxyl as in tyrosine, and the imidazole rings as in histadine. Blocking of these groups with specific substances modifies or abolishes their antigenicity. The word "determinant" is applied to the characteristics feature of the surface of an antigen molecule which is responsible for the specific combination with the related antibody. The disulfide bond is a covalently linked sulfide

grouping (—S—S—). It cross links the polypeptide chains of proteins. On reduction, when this bond is split, it yields 2 —SH (sulfhydryl groups). Sulfhydryl is the radical —SH which is usually attached to a carbon atom in the protein molecule. The SH group plays an important role in the activity of some enzymes. These enzymes are inactivated by oxidation or combination with heavy metals. SH groups, when combined, give rise to —S—S— (disulfide) bonds, which join polypeptide chains to one another and thus change the shape of the molecule.

Free reactive points found alone or in combination on the antigen molecule are the determinant groups which render the molecule specifically antigenic. These become electrically charged when the protein is placed in solution. As will be seen later, antibodies react and unite specifically with these free reactive groupings on the protein molecules, both because of their complementary physical configuration and because of their opposite electrical changes.

Antigenic protein molecules are usually large molecules with a molecular weight generally over 10,000; antigens with molecular weight of less than 40,000 are poor antigens.

Carbohydrates. Carbohydrates are found in bacterial cells, such as in the typhoid and tubercle bacillus and in the staphylococcus and pneumococcus. High molecular weight polysaccharides present in the capsule of the pneumococcus can stimulate the production of antibodies in man but not in rabbit. Glycoproteins are carbohydrates containing proteins found in the serum. Dextran is antigenic in man but not in the rabbit nor in the guinea pig. Polysaccharides are weak antigens. They become antigenic following conjugation with proteins or lipoproteins. The specificity determinant of the molecule resides in the nonreducing end of the sugar. This may include methyl, amino, or substituted hydroxyl groups. These determine the combining power with the related antibody.

Lipids. Certain lipids, particularly high molecular weight lipids such as cephalin and cholesterol, may be antigenic when combined with serum proteins. However, the exact antigenic role of lipids is not as yet established. Myelin is the antigenic determinant in experimental allergic encephalomyelitis (Chapter 70). The Wassermann antigen is a cardiolipin. The antigenic fraction of erythrocytes is the cell membrane or "stroma."

The *Forssman antigen* is a heterophile or heterogenetic antigen whose active portion is a lipid which includes a polysaccharide. It stimulates the formation of heterophile antibody. Heterophile or heterogenetic antigen is found in the red blood cells of sheep but not in their organs. It is also found in bacteria as well as in the tissues and organs of dogs, horses, and guinea pigs (kidneys), but not in their blood. Immunization of rabbits with extracts of these organs produces specific antibodies (agglutinins and hemolysins) against sheep red blood cells. The antiserum thus produced (Forssman antibody) is called "heterophile" or "heterogenetic." The lysin which it stimulates in the rabbit does not lyse ox red cells. The Forssman antigen must be injected in combination with some other substance, such as serum, in order to stimulate antibody formation. Hence, it is not a "complete" antigen, but rather a haptene; its activity is due to the lipoid-carbohydrate fraction of the organ which combines with the protein component.

Nucleic Acid. Deoxyribonucleic acid (DNA) is the chief constituent of genetic material in the chromosome of the nucleus. It can act as an antigen in combination with carrier proteins, that is, nucleoproteins. DNA is the genetic determinant dictating the nature of future development. It is probably instrumental in the synthesis of proteins. Ribonucleic acid (RNA) may produce anti-RNA antibody.

Sensitivity to DNA is in all probability a condition which is mediated by an immunologic mechanism. This condition is characterized by tender skin lesions and ecchymoses without a coagulation defect. This reaction can be reproduced on the trunk by DNA obtained from calf thymus and by autologous white blood cells.

Haptene. A complete antigen stimulates the formation of antibody and has the capacity of reacting with this antibody. However, antigens such as simple chemicals, while not by themselves capable of stimulating antibody forma-