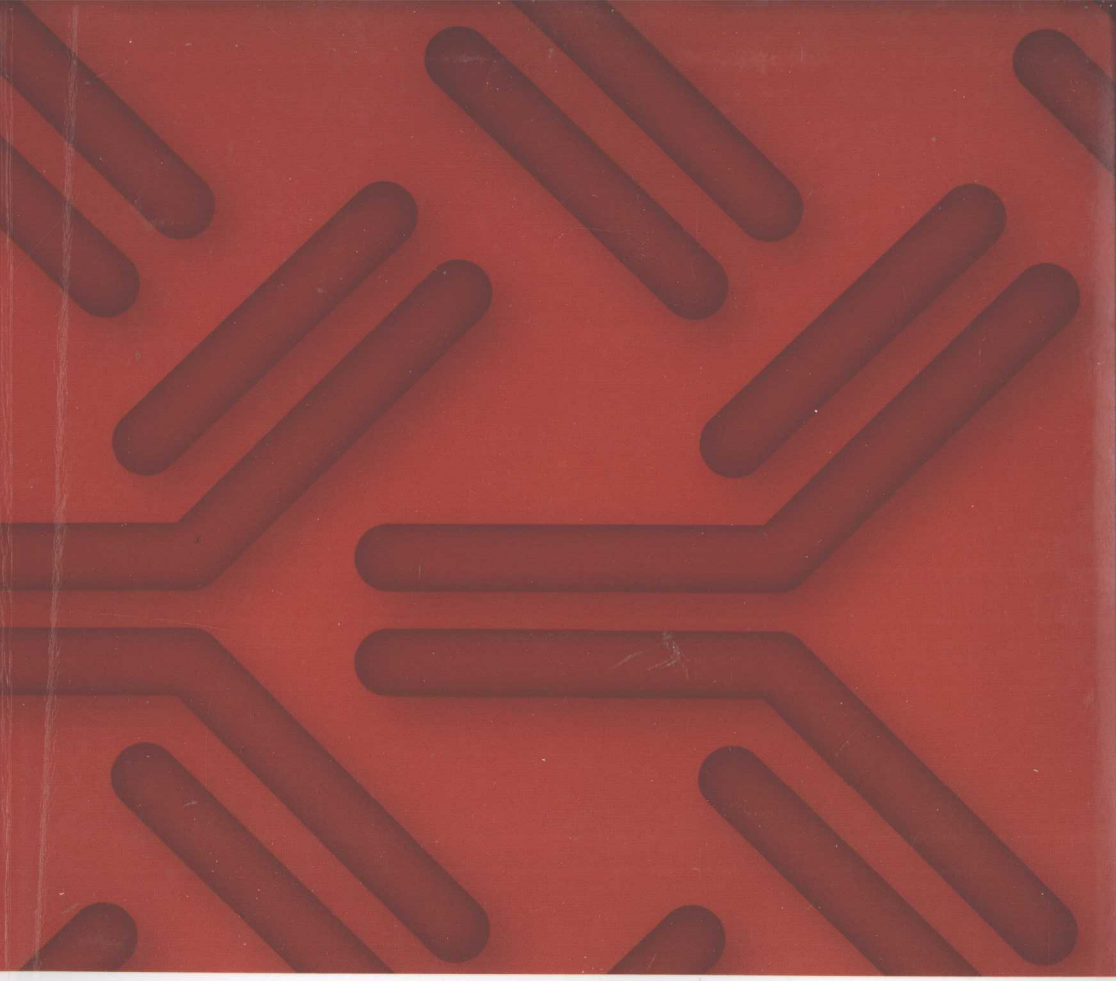

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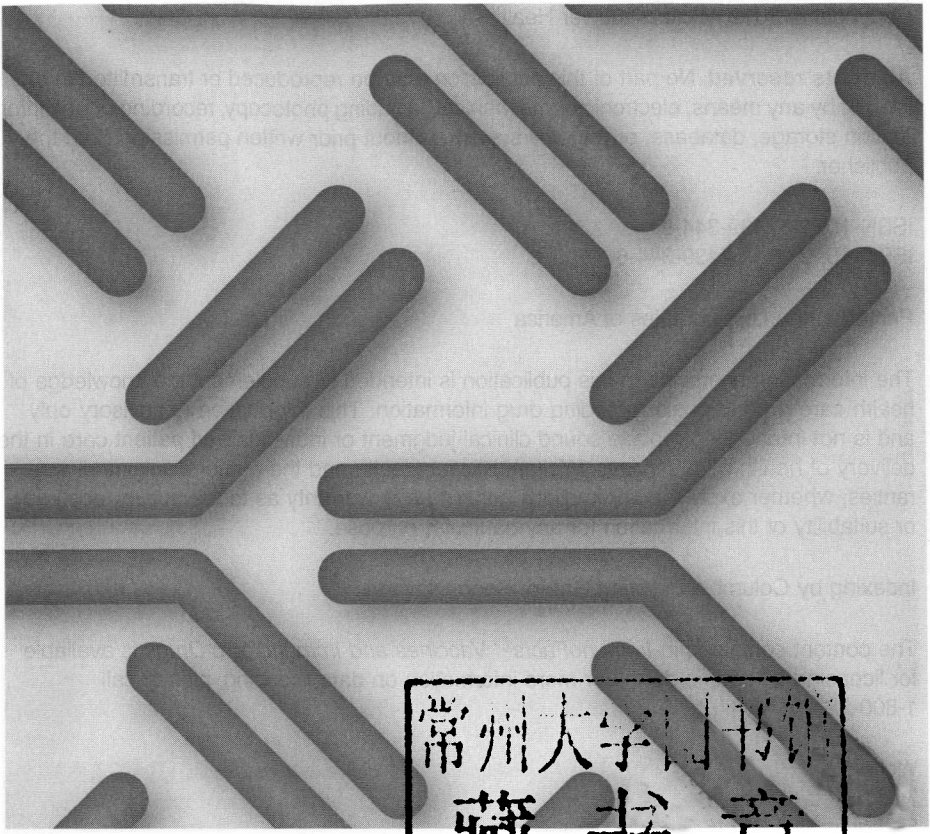

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About the Design: The front cover and chapter head pages of *ImmunoFacts* display an artist's rendition of an immunoglobulin molecule. The image of a double-stranded "Y" represents both the antibody products described in this book and the antibodies induced by vaccines described herein, as well as the entire pharmacopeia of immunologic drugs featured in *ImmunoFacts*.

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J.D.G.

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Emily's contribution to this book at age 13 months: gH jjqq j hui jj1r5c WU23TYT2T12R1 'R11R516T712UU

NOTE: The author is a pharmacist and epidemiologist employed by Merck & Co., Inc. He writes and edits this book in his private capacity, beginning more than 15 years before he joined Merck. No endorsement by any party is intended nor should it be inferred. Merck & Co., Inc. is not involved with and takes no responsibility for this work. The publisher coordinates independent review to ensure all content is presented in an objective manner.

Facts & Comparisons is very proud to bring you *ImmunoFacts®: Vaccines and Immunologic Drugs*, authored by John D. Grabenstein. This book continues Facts & Comparisons' unequaled reputation in publishing timely, current, and comprehensive references for the health professional.

ImmunoFacts® is a unique publication, providing detailed information on vaccines, antibodies, and other immunologic drugs. It is the most comprehensive source available in this field. Not only does it provide extensive information on vaccine products, there is also a great deal of information about related topics, such as investigational and international drugs, immunization documents, manufacturer addresses/phone numbers, drug interactions, and vaccine indications by risk group.

This publication also covers interferons, interleukins, immunomodulators/mediators, and monoclonal antibodies, to name a few. As new developments in the field of immunology continue to emerge, you can expect to find them discussed in detail in *ImmunoFacts®*. *ImmunoFacts®* will be of importance to any health professional who is concerned with prescribing, administering, dispensing, or monitoring patients receiving any immunologic drug.

This impressive compilation of immunologic information is largely the work of John D. Grabenstein, a pharmacist and renowned expert in this area. He, along with an equally dedicated and talented editorial panel of pharmacists and physicians, as well as the publishing staff, continue to provide the most up-to-date information in this field.

We are confident that this publication will be valuable to your practice. Please feel free to contact us with any comments, questions, or suggestions for *ImmunoFacts®*. We can only make it better with your input.

> "The literature of immunity, moreover, grows so amazingly that the analysis even of current works is a task of no mean proportions."
> - H.T. Ricketts, 1906

Ricketts could never have imagined the advances in immunology we appreciate today. But he was correct about the complexity of the science. The goal of *ImmunoFacts®: Vaccines and Immunologic Drugs* is to provide comprehensive drug information about this specific category of drugs. The format is intended to allow quick, reliable access to discrete pieces of information, while also helping readers compare and contrast information for similar products or uses.

ImmunoFacts® was first to bring together detailed information about the pharmaceutic and pharmacologic characteristics of immunologic drugs, along with authoritative recommendations for their use.

What is an immunologic drug? This deceptively simple question is the core issue in a series of decisions on which drugs to describe in this publication and which to exclude. The rationale for these decisions considers the following factors.

Inclusion Criteria

All licensed drugs whose action is wholly or largely immunological in nature are included. Also selected are unlicensed investigational drugs in human clinical trials, based on clinical significance and availability of information.

Immunologic drugs appear whether they are derived from biological sources or not. The construct of "biological" drugs is a fuzzy one that suffers from confusion over source and action. Biologicals are included only if their action is immunologic (eg, vaccines), but excluded if their action is not immunologic (eg, insulin, *Lactobacillus acidophilus*).

Several nonimmunologic drugs also have been included based on their close relationship to immunologic drugs. For example, epinephrine is included because it is the drug of choice for treating acute anaphylactoid hypersensitivity reactions associated with immunologic drugs. Histamine is a frequent positive-control reagent for allergen skin-test batteries. Botulinum toxin, while a microbial (and hence biological) product, is a neurotoxic drug, not an immunologic one; nonetheless, it is included to allow comparison with botulinum toxoid and antitoxin.

Exclusion Criteria

Drugs produced using biotechnology are excluded from this book unless their primary action is immunologic in nature. For example, epoetin (erythropoietin) is an erythrocyte colony-stimulating factor and is produced using recombinant DNA technology. Nonetheless, epoetin is indicated for stimulating hematopoiesis of red blood cells, whose primary actions are not immunologic.

This rationale leads to the inclusion of myeloid colony-stimulating factors (eg, filgrastim, sargramostim), but the exclusion of coagulation factors and alteplase (ie, tPA). Using this same approach, the human insulins, produced by recombinant DNA technology, also are excluded.

Organization

Immunologic drugs are grouped by major pharmacologic categories (eg, vaccines, antibodies, diagnostic reagents). Whenever a drug may logically fit into two or more categories, the ultimate location was chosen on the basis of the primary use of the drug. For example, IGIV is primarily an anti-infective drug, although it also can be used for hematologic purposes for the treatment of immune thrombocytopenic purpura (ITP).

Unfortunately, this scheme led to the separation of the two BCG products. Ticestrain BCG vaccine is included with the vaccines because of its long-standing indication for prevention of tuberculosis, but *TheraCys* and *Tice BCG* for intravesical use appear with the immunostimulants because it is licensed only for the treatment of bladder cancer, not tuberculosis prophylaxis.

Content

Most of the products listed in this publication are protected by letters of patent and their names may be trademarked or registered by the enterprise listed. The product distributor may or may not be the actual manufacturer or fabricator of the final doseform. Listing of specific products is an indication only of availability on the market and does not constitute an endorsement or recommendation. Drug product interchange is regulated by state laws; the listing of products together does not imply that they are therapeutically equivalent or legally interchangeable.

Use information derived from this book in conjunction with other clinical and printed data sources. The author and publisher have taken care to ensure that indications, contraindications, doses, and treatment schedules are correct and compatible with standards generally accepted at the time of publication. Readers are cautioned to apply their clinical judgment to individual patients for whom they care.

Editorial Review

The editorial panel of *ImmunoFacts®* includes recognized experts in clinical immunology, therapeutics, vaccinology, and drug information. Panelists review monographs and provide direction for the revision of *ImmunoFacts®*. In addition to the editorial panel, other authorities in government, academia, and the pharmaceutical industry are consulted as needed to provide information of the highest quality and reliability.

Table of Contents

Background

Immunology is the study of the body's defenses against infectious agents and other pathogens. The human immune system protects the body by eliminating or neutralizing materials recognized as different than the self. The wide range of immunologic responses and reactions affect essentially every organ, tissue, and cell of the body. The diversity of immune responses includes, but is certainly not limited to, antibody production, allergy, inflammation, phagocytosis, cytotoxicity, transplant and tumor rejection, and the myriad of signals that turn these responses off and on. Immunity is the state of being immune or protected from a disease. Immunologic drugs include any drug that stimulates, mimics, contributes, triggers, blocks, or modifies any kind of immune response.

The following sections provide a concise review of immunology, immunopharmacology, and immunopharmaceutics. First, the key participants and theories of immunology are briefly reviewed. The following two parts discuss immunopharmacology (the study of the effects of immunologic drugs on living organisms) and immunopharmaceutics (the study of the characteristics of immunologic doseforms and immunologic drug delivery).

This section is intended to satisfy readers' basic questions about the immune system. Consult detailed references for complete descriptions of human immunity and immune responses.

The Immune Response

The immune system is an intricate regulatory and defense system within the human body. Immune cells, tissues, mediators, and antibodies are involved in rejecting tumors; inactivating viruses, bacteria, and other microbes; neutralizing toxins; and performing other defense functions. In addition to these capabilities, the immune system is capable of remembering previous encounters with immunogens and mounting even stronger responses upon rechallenge. For example, once you have had measles, you will most likely never get it again. This section reviews the structure and function of the major arms of the immune response.

Immunogens, Antigens, and Allergens: Any substance that can evoke an immune response (eg, production of antibody) is called an immunogen. Vaccines must be immunogenic to be effective. Certain immunogens that can combine with antibodies are called antigens. The exposed 3-dimensional parts or chemical groupings on antigens to which antibodies attach are called determinant groups, haptens, or epitopes. Haptens also include certain low molecular weight compounds, nonimmunogenic by themselves, that can evoke an immune response when they combine with a larger carrier molecule.

For any organic molecule to be immunogenic, it must be recognized as foreign by the host. Most immunogens have molecular weights greater than 10,000 daltons, and most are proteins. Smaller molecules (eg, insulin, penicillin) may function as haptens if they combine with a carrier protein. For example, penicillin alone is antigenic, but poorly immunogenic. However, penicillin coupled to a protein can be highly immunogenic. Both antigenicity and immunogenicity are dependent on the 3-dimensional shape of the epitope. Changes to the conformation or accessibility of an epitope can increase, decrease, or negate that epitope's ability to combine with an antibody.

B-lymphocytes, macrophages, and other antigen-presenting cells (APCs) phagocytize immunogens. Immunogens are modified within those cells by denaturation, unfolding, and proteolysis. Eventually, epitopes of the immunogen are expressed on the surface of the APC. This allows activation of T-helper lymphocytes that, through the action of cytokines, activate

other B cells. These B-lymphocytes differentiate either into antibody-producing plasma cells specific for that epitope or into long-lived memory B-lymphocytes.

An allergen is an antigen (something recognized by the immune system) that causes allergy, the collection of diseases in which immune responses cause tissue inflammation and organ dysfunction. Antibody-mediated allergens induce the syndrome known as immediate hypersensitivity, which includes anaphylaxis. T-lymphocyte–mediated allergens induce delayed hypersensitivity, such as dermal reactions to tuberculin skin tests. Allergenic illness on exposure to an allergen requires an initial sensitization episode, where antigen-specific immunoglobulin E (IgE) antibodies are produced that attach to Fc (fragment, crystallizable [of immunoglobulin]) receptors on mast cells and basophils. Upon a second exposure, allergens combine with IgE bound to mast cells (followed by release of mediators such as histamine), form immune complexes with immunoglobulin G (IgG) or immunoglobulin M (IgM) (followed by complement activation), or combine with T-effector cells (followed by lymphokine release). Any of these 3 pathways can lead to inflammation. Allergists may use the term allergen to refer specifically to a substance that induces IgE production.

Antibodies: An antibody, synonymous with an immunoglobulin or immune globulin, is a glycoprotein molecule that produces the effects of humoral or circulating immunity. Although antibodies can act in a nonspecific fashion (eg, complement fixation, histamine release by mast cells), their most potent effects result from their specific interactions with antigens and with the host's own immune cells.

Humans possess 5 distinct classes or isotypes of immunoglobulins: IgG, immunoglobulin A (IgA), IgM, immunoglobulin D (IgD), and IgE. Characteristics of each isotype are described in the following table. "Gamma globulin" is an obsolete term for immunoglobulins, especially IgG. The term refers to the presence of immunoglobulins in the gamma region of serum separated by electrophoresis. It is a misnomer because some antibodies are found in the beta region and, hence, are beta globulins. IgG and IgA primarily exist as gamma globulins, although some are beta globulins. To further confound the issue, although most IgM and IgD molecules are beta globulins, some are gamma globulins. Nonetheless, common usage usually equates gamma globulin with IgG and often with intramuscular immune globulin (IgIM).

IgG is the most abundant of the immunoglobulins. It consists of 2 heavy polypeptide chains and 2 light chains, which, in 2 dimensions, looks like the capital letter Y on the cover of this book. In 3-dimensional actuality, an IgG molecule appears globular until it recognizes an antigen, at which time it looks more like a coiled spring resembling a Y. Specificity for a given antibody resides in the variable region at the 2 upper tips of the Y. This area comprises the first 100 amino acids from the amino-terminal end of each chain and is called the antigen-binding site. The whole molecule contains about 1,200 amino acids.

If the Y-shaped IgG molecule is enzymatically cleaved at the point of interchain disulfide bonds (at the junction of the Y), 2 antigen-binding fragments (Fab) and 1 cell-binding fragment (Fc, called the constant region of an IgG molecule) are produced. For example, the commercial product *Digibind* is composed of Fab fragments specific for digoxin molecules. If the Fc fraction is removed from IgG but both Fab fragments remain attached to each other, the combination is called a $F(ab)_2$ molecule.

IgG production represents one of the largest single forms of response to vaccination. Two different types of IgG response to an antigen can be noted. Upon first exposure to an antigen, circulating IgG antibodies are first detected in human serum after about 6 days, peaking after about 12 to 14 days. Antibody levels then plateau at a considerably lower level. But upon rechallenge or subsequent exposure to that same antigen, a strikingly quicker and larger IgG response results, with IgG concentrations tapering off only gradually. This secondary response is also called a booster, memory, or anamnestic response to an antigen. Consider the dosing strategy for the products containing tetanus toxoid: 5 doses are given to children as a basic