Introduction

It has been little more than a century since Emil von Behring and his colleagues (1890) showed that the blood of tetanus-immune rabbits contained a factor that could be transferred to nonimmune animals to protect them against tetanus. These observations, together with the work of Paul Ehrlich, started scientists on the long and complex path to our present understanding of the humoral, or B-cell, immune system. These early studies led to Nobel prize awards for von Behring (1901) and Ehrlich (1908), each of whom contributed much to our knowledge of the B-cell immune system. In the early 20th century it was recognized that the serum of individuals who had recently suffered an infection contained a protective humoral factor that could be transferred to a nonimmune person, thereafter affording that individual protection against the infectious agent that had caused disease. In 1933 McKhann and Chu reported that a placental extract containing the globulin fraction could modify measles. However, it was not until 1939 that Tiselius and Kabat demonstrated that the antibodies responsible for protection against these infectious disorders resided within the gammaglobulin plasma fraction. In a major step forward, Cohn in 1944 established a method for the fractionation and purification of this plasma gammaglobulin fraction. These procedures, which are based on cold ethanol precipitation of plasma, produce a readily adaptable, large-scale fractionation procedure that is still utilized to this day in the preparation of commercial gammaglobulin.

Initially, this gammaglobulin preparation was administered by the intramuscular route to prevent measles and hepatitis A by Stokes and his coworkers. In 1952, Col. Odgen Bruton described the first patient with agammaglobulinemia and recurrent infections. This and other similar patients were treated with Cohn's fractionated gammaglobulin by the intramuscular route to correct the hypogammaglobulinemia. Through the work of Fred Rosen, Charles Janeway, and Robert Good, a number of patients with humoral immune deficiencies was soon recognized and started on intramuscular gammaglobulin replacement therapy. Janeway and others even tried to use the Cohn-fractionated gammaglobulin by the intravenous

route, but this was met with serious side effects. Barandun reported that the treatment of agammaglobulinemic children with IM gammaglobulin by the intravenous route frequently led to serious adverse reactions. The need for a safe preparation of gammaglobulin for intravenous use soon became increasingly important as more patients with antibody deficiency syndromes were recognized and the requirement for larger doses of intramuscular gammaglobulin became evident in the treatment of older children and adults.

The reactions to this intramuscular preparation of gammaglobulin when given intravenously appeared to be caused by the presence of IgG aggregates. In the late 1960s and 1970s several approaches were used to try to overcome this problem using such methods as proteolytic digestion with pepsin or plasmin. The adjustment of the immunoglobulin solution to pH 4.0, together with the addition of small amounts of pepsin, seemed to remove the anticomplementary activity of the aggregates and provide a product that could be used by the intravenous route. This product appeared to retain, for the most part, its biological activity while minimizing the IgG aggregates that caused side effects. A number of other approaches were also used, including chemical modification and additional purification methods, to produce a gammaglobulin product safe for intravenous use. However, it was not until the late 1970s and early 1980s that a commercial product was available for intravenous use in the treatment of antibody deficiency disorders.

Since these original products became available, we now have "third generation" gammaglobulin products for intravenous use. These products are highly purified, >98% monomeric preparations of IgG that have retained their physicochemical properties for all the IgG subclasses as well as the biological functions of the native molecule. Since the first appearance of a commerical intravenous gammaglobulin product in the early 1980s, there has been an explosion in the therapeutic applications of intravenous immune serum globulin (IVIG), not only as replacement therapy in patients with antibody deficiency disorders, but also, as discussed in this treatise, as an immunoregulatory/immunomodulatory agent in the treatment of autoimmune disease. The first part of *IVIG Therapy Today* reviews the topics of primary and acquired humoral/B-cell immune deficiencies and IVIG as replacement therapy. The second

part will review the immunomodulatory effects of IVIG in autoimmune disorders.

In the first chapter of this treatise, Stanley A. Schwartz presents his perspective on the use of IVIG in the treatment of patients with primary immune deficiency disorders. This chapter contains a description of the commercially available IVIG products. In addition Schwartz outlines his approach with a helpful flow chart on the administration of IVIG in patients with primary antibody deficiency disease as replacement therapy.

Patients with acquired immunoglobulin deficiencies are another potential group that might benefit from IVIG replacement therapy. One of the largest groups of patients with acquired humoral immune deficiencies are the preterm infants who are born with hypogammaglobulinemia. Since the newborn infant acquires most of his/her IgG during the last trimester of pregnancy from the mother by the transplacental route, premature infants, particularly those born before 32 weeks gestation, are often hypogammaglobulinemic at birth and during the first 10 months of life. This places this group of infants at high risk for infection. Although the incidence of infection varies between neonatal intensive care units, it averages approximately 8–10% in this country, but may be as high as 40–50% in third-world countries. The increased morbidity and mortality from infection in the newborn period has prompted investigators to examine the efficacy of using intravenous immune serum globulin as replacement therapy in very low-birth-weight premature infants. Weisman and colleagues review the current status of intravenous immune serum globulin in the treatment of neonatal sepsis and as prophylaxis therapy in preterm infants against late-onset infections. Weisman presents a historical overview of the use of IVIG in preterm infants and briefly discusses some of the new placebo, controlled multicenter trials that should determine the efficacy of IVIG treatment in preterm infants and provide the appropriate protocols for therapy. The identification of specific bacterial pathogens responsible for infection in the newborn period has prompted studies on the development of specific antibody containing IVIG either derived from hyperimmune donors or from human monoclonal hybridomas. Along these lines, Hill and colleagues in their chapter describe the potential use of monoclonal

antibodies as therapeutic modalities in Group B streptococcal and *E. coli* infections of preterm infants. Although these studies are described for animal models, they will lead to the development of products for use in the human neonate.

Acquired humoral immune deficiency can also be seen in adults with lymphoproliferative diseases. Alan Winkelstein and Susan Jordan describe in their chapter the humoral immune deficiencies of patients with chronic lymphocytic leukemia (CLL) and multiple myeloma. The phenotypic characteristics of B-cell malignancies and the pathophysiology of the immune abnormalities in CLL and multiple myeloma are presented. The types of infections in patients with CLL and multiple myeloma are described and the studies of gammaglobulin replacement therapy in these two groups of patients are reviewed.

In the second part of this treatise, one of the most exciting applications for IVIG will be discussed—that in which IVIG is used as an immunoregulatory/immune modulatory agent in autoimmune disorders and in diseases of inflammation, e.g., Kawasaki's disease, polyneuropathies, and asthma. In the early 1960s Barandun observed that the hemolysis stopped and the Coomb's test became negative when patients with primary hypogammaglobulinemia and concommitant Coomb's positive hemolytic anemia were given IVIG. Subsequent serendipitous observations that IVIG could reverse thrombocytopenia was reported in two other patients with hypogammaglobulinemia and immune thrombocytopenia. In 1981 Imbach followed up on these initial observations and described the treatment of children with idiopathic immune thrombocytopenic purpura (ITP) with high dose IVIG. Subsequent studies by many other investigators have confirmed these initial observations, which has led to the use of IVIG as a firstline therapy in the treatment of children with ITP. In her chapter, Diane Nugent reviews the use of IVIG in the treatment of children with acute and chronic ITP and the autoimmune cytopenias. The pathophysiology of ITP, autoimmune hemolytic anemia, and the immune neutropenias are also discussed. Nugent presents her own clinical approach in the treatment of these hematological disorders and discusses what is known about the mechanism(s) by which IVIG reverses the hematological abnormalities. In a related theme, Kurtzberg and Dunsmore present

a discussion of the use of IVIG in neonatal isoimmune thrombocytopenia and alloimmunization thrombocytopenia. These clinical conditions can be associated with a significant bleeding diathesis in the neonatal period. The process of maternal alloimmunization to paternal platelet surface antigens and the development of thrombocytopenia is described. Kurtzberg and Dunsmore describe their experience in the use of IVIG in the neonatal period to prevent severe bleeding in patients with neonatal isoimmune thrombocytopenia and alloimmunization thrombocytopenia.

Turning our emphasis from the autoimmune hematological diseases to other autoimmune processes, Rowley and Schulman present an interesting discussion on Kawasaki's disease. Though of unknown etiology, Kawasaki's disease is associated with significant morbidity from coronary artery aneurysms. This may lead to thrombosis or stenosis, with myocardial infarction and sudden death in these children. Rowley and Schulman discuss the use of intravenous immune serum globulin in the treatment of these patients to reduce coronary artery disease. Apart from its clinical therapeutic effectiveness in the therapy of patients with Kawasaki's disease, the use of IVIG in this disease has led to important observations on the mechanisms by which IVIG may modify the inflammatory/immune process. Donald Leung describes in his chapter the immune abnormalities associated with Kawasaki's disease and proposes mechanisms by which IVIG may modify the immune perturbations and inflammatory processes in Kawasaki's disease. These studies will undoubtedly play an important role in designing future therapeutic protocols for IVIG in other immune-mediated disease in which there are perturbations of cytokine regulation. The experience in Kawasaki's disease set the stage for the use of IVIG in other autoimmune and inflammatory disorders.

Ann Parke explores her experience with the connective tissue disorder of the antiphospholipid antibody syndrome. The hallmark of this disease is thrombotic diathesis, fetal wastage, and thrombocytopenia associated with antibodies to phospholipids, e.g., the lupus anticoagulant. IVIG, together with anticoagulant therapy, appears to be of particular use in this syndrome in preventing fetal wastage and fetal loss. This treatment regimen has led to successful pregnancies in women who previously had adverse effects with prednisone treatment.

Arnold Levinson explores the use of IVIG in a number of neurologic disorders, some of which are autoimmune and others of which are inflammatory in nature. He reviews his strategy of IVIG therapy in myasthenia gravis and various demyelinating polyneuropathies, such as Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. Levinson also reviews the literature on IVIG in seizure disorders and proposes possible mechanisms by which IVIG might have an effect in these inflammatory neurological disorders.

Finally, in the last chapter of the treatise, Fireman and Friday review a new frontier for IVIG in clinical medicine: the possible role of IVIG in the treatment of severe steroid-dependent asthma. It has become increasingly clear over the past several years that asthma is an inflammatory disease with disregulation of not only IgE synthesis, but also certain inflammatory cytokines. Several groups have preliminary experience with IVIG as adjunct therapy in the management of severe asthma as an immunomodulatory agent. Fireman and Friday also review their experience with IVIG in asthmatic children and IgG subclass deficiency.

As we enter the second decade of IVIG therapy in a wide spectrum of clinical disorders, we must proceed cautiously and establish criteria by which we can judge the efficacy and cost-effectiveness of this modality of therapy. A theme that rings out from many of the chapters in this monograph is the need for proper randomized, placebo-controlled multicenter trials. This is particularly important for those disorders in which limitations of patient numbers require more than one study institution. Carefully designed studies will ensure the proper use of IVIG therapy as new approaches to disease management are planned. As with any new modality of therapy, one of the byproducts of careful investigation is a better understanding not only of the pathophysiology of the disease entities themselves, but of the immune-inflammatory network that is so important in the pathogenesis of disease. Knowledge of the mechanism(s) by which IVIG alters a disease process will allow us to design better treatment protocols and dosage regimens. This knowledge will also allow the exploration of the use of IVIG in other inflammatory/immune disorders.

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