Protein A Immunoadsorption
Clinical Potential

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Summary
Protein A is a staphylococcal bacterial cell wall component that binds certain subclasses of IgG, other classes of mammalian immunoglobulins and immune complexes. Initial studies in tumour-bearing animals and in patients with cancer were based on the early premise that circulating immune complexes function as suppressor factors of anticancer immunity. Subsequently, the use of protein A in various autoimmune disorders was explored. All these early studies utilised protein A-bearing staphylococci as an extracorporeal immunoadsorbent to remove IgG and immune complexes. Although promising clinical responses in cancer and various autoimmune illnesses were observed, there was also substantial toxicity. We now understand this toxicity to be due to leakage of protein A and enterotoxins from the formalin-fixed Staphylococcus aureus. As a result, more stable protein A matrices were developed.

The 2 leading extracorporeal protein A devices, the Immunosorba® and Pro-
sorba® columns, utilise highly purified protein A covalently coupled to a relatively inert solid phase matrix. Although these devices differ in design and utilisation, both have demonstrated clinical effectiveness in several autoimmune illnesses, with manageable adverse effects. The Immunosorba® column has been licensed in the US for the treatment of immune-mediated haemophilia, and the Prosorba® column is approved for the treatment of idiopathic thrombocytopenic purpura. Use of the Prosorba® column in various other autoimmune disorders, including rheumatoid arthritis and renal graft rejection, is under investigation. There is also some evidence that certain cancers may respond to immunoadsorption therapy, provided that concomitant chemotherapy is used.

In addition to its reported clinical benefit, protein A immunoadsorption may provide further insights into the clinical pathogenesis of immune-mediated disorders and certain cancers. Analysis of the composition of immune complexes from patients during therapy, including the nature of bound antigen, may substantially further our understanding of the role of these immune complexes in these disorders. Indeed, different modes of action may be operative depending upon the type of illness.

1. Staphylococcal Protein A

Protein A is a staphylococcal bacterial wall component with the distinctive ability to bind certain subclasses of immunoglobulin G (IgG) via the Fc region of the molecule.\textsuperscript{1,2} This important characteristic of the protein A molecule has made it an extremely valuable tool for the rapid purification of IgG from various mammalian species.\textsuperscript{1,2} Moreover, protein A appears to have a higher affinity for immune-complexed IgG.\textsuperscript{2} Thus, when protein A is part of a solid matrix, it can be used as an effective agent for the removal of IgG-containing immune complexes from sera or plasma. It is this latter characteristic of the protein A molecule that has been exploited by various investigators to isolate and characterise IgG-containing immune complexes from pathological sera and plasma.\textsuperscript{2}

From the ability of protein A to bind IgG-containing immune complexes, it was reasoned that a solid phase protein A matrix could be utilised as a system to remove IgG and IgG-containing circulating immune complexes (CIC) from plasma in order to modulate the immune response. This was based upon the early premise that CIC function as suppressor factors in tumour-bearing animals.\textsuperscript{3,4} Consequently, initial studies were performed on naturally occurring tumours in animal models, wherein solid phase extracorporeal protein A immunoadsorption was utilised to remove IgG and CIC. The encouraging results of these studies prompted investigators to explore the clinical potential of protein A immunoadsorption in human diseases.

Most of these early studies were performed by perfusing plasma over heat-killed and formalin-stabilised protein A–bearing Staphylococcus aureus Cowan I strain. More sophisticated systems employing purified protein A bound to various matrices (charcoal, glass beads, agarose, silica and other solid phases) emerged over the years, and were tested in small numbers of patients with cancer and autoimmune diseases.

2. Studies with Early Protein A Devices

2.1 Animal Studies

One of the first studies to assess the interaction between protein A and specific blocking factors, presumably CIC, was performed by Steele et al.\textsuperscript{5} These investigators used rats with transplanted polyoma virus–induced tumours to study the effects on their sera after incubation with protein A–bearing staphylococcus. They observed that specific blocking factors were removed by protein A, and that antibodies could subsequently be detected in treated