Trauma, Stress and Immunity in Anaesthesia and Surgery

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Preface

'Trauma, stress and immunity in anaesthesia and surgery' was conceived to supply a need of the clinician, predominantly the anaesthetist and surgeon, for a single, short volume embracing all aspects of the immunology involved in preoperative and postoperative care of the surgical patient. As our writing progressed we became increasingly aware that much that is casually accepted as immunological response is in reality the body's stress response to trauma. The trauma is usually predominantly surgical, but under certain conditions anaesthesia and psychological factors may assume a disproportionate role. Equally, the sequelae of the body's stress response may be haematological rather than 'immunological', causing various coagulation problems postoperatively. The situation does not become easier with the realization that activation of the coagulation mechanism involves mediators, for example complement proteins, conventionally associated with host immunity. To do justice to this complex field it became evident that our volume would have to become a multiauthor work, involving established workers in specialized fields, both clinical and research.

In Part 1 we have given an overview of immunology in a manner particularly pertinent to the anaesthetist and surgeon, which requires no previous knowledge of immunology. The chapter on anaesthetic drug action incorporates much new data on the action and availability of new local anaesthetic agents. The section concludes with a sensible examination of the practical methods available for investigating altered immunological parameters and the likely pitfalls in their interpretation. The laboratory investigations are described in considerable technical detail and are backed up by an extensive and modern bibliography. We recommend this section for any clinician, budding clinical immunologist or senior medical student.

Part 2 deals with the body's stress response to anaesthesia and surgery. This section begins with a description of general changes in the blood and possible coagulation problems arising as a result of trauma, which is followed by chapters on the more specific endocrine and metabolic changes and their clinical significance.

Part 3 is devoted to the immune sequelae of anaesthesia and surgery, and considers three groups of patients:

1. 'Normal' patients undergoing surgery.
2. Cancer patients, in whom immunity may be compromised before surgery.
3. Patients in whom immunity has been deliberately suppressed before organ transplantation.

The section also outlines specific clinical problems that may be encountered pre- and postoperatively, and their possible solutions. Immediate adverse reaction to drug administration is also discussed.

The final section, Part 4, which discusses the psychological factors influencing the patients' response to surgery, is probably unique to this volume.

We are only too aware that there are omissions from this book. These include a detailed treatise on the role of the mononuclear phagocyte system (the reticuloendothelial system) and its interplay with coagulation, and also the role of the central nervous system in the responses to injury. Our chosen experts were simply not available to produce this volume within the time limits which we had set ourselves, but we hope we have compromised by citing extensive biblographies.

Finally, we gratefully acknowledge the help of friends and colleagues in the preparation of this book. We are grateful to Miss Heather Waldron and Dr R. Cookson of Janssen Pharmaceutical Limited, UK, for their help in setting up a Symposium in Bath last year (Watkins and Glynn, 1980), thus allowing our ideas to crystallize into this final format; and to the staff of Butterworths, who encouraged us to develop the concept of this book in the first place.

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Contents

General introduction

John Watkins and Matti Salo

Although it is widely accepted that surgical or mechanical trauma combined with anaesthesia are major factors contributing to stress-induced endocrine and metabolic changes in the surgical patient, the effects of psychological stress, even before hospitalization, are rarely considered. The central nervous system induced manifestations are the result of the various traumas but their relative contributions may well be expected to change between different 'surgical groups' reflecting, for example, the severity of the surgical procedure and also the patient's psychological response to malignant and to non-malignant situations requiring an 'equivalent degree' of surgery. The plethora of changes in endocrine balance, metabolism and parameters of immunity in such patients encourages us to concentrate upon each separately rather than to examine the interrelationship between each.

Adequate host immunocompetence is the limiting factor of all hospital procedures, surgical or otherwise, since there is little point in the patient surviving an unpleasant procedure only to succumb to a minor infection. Thus interest must ultimately centre on the degree to which the various traumas compromise host immunity, both in the 'normal' patient and in patients in whom immunity may be already severely compromised by disease or design (i.e. immunosuppressive therapy). Unfortunately, the measurement of such interaction poses considerable practical problems.

Paradoxically, in the biological sciences increasing specialization and the pursuit of the finer structures and mechanisms of the organism leads both to less appreciation of the being as a whole – a case of not seeing the wood for the trees – and an almost naïve and unquestioning acceptance of the statements and dogmas of other specialists in adjacent areas of research. Although we are indebted to the pioneers of immunological research for their careful and painstaking work, particularly on animal models, we must be prepared to accept what we really see and not that which we have been conditioned to see from our knowledge of such models. Thus while the immunological changes which occur in the individual undergoing anaesthesia and surgery certainly involve the cells, proteins and chemical effectors of classical immunology, the sequence and relative importance of their activation is often grossly different from the classical

concept. 'Trauma' itself is a composite function with contributions from anaesthesia, surgery and various psychological factors; the relative contributions probably differ in different individuals. Whatever we understand by the stress response it does produce measurable biochemical manifestations such as the stimulation of adrenocorticotrophine, cortisol, catecholamines and growth hormone. These changes in turn influence other parameters, particularly cell metabolism. All these effects are brought about by rapid changes in the 'normal' hormone balance of the individual, mediated through the central, hypothalamic and pituitary axis of the brain.

The biochemical changes may severely modify leucocyte distribution and behaviour and lead to serious misconceptions of immune disturbance, since we cannot measure the individual's immunity in a physical, direct sense but only in terms of the various parameters which we have accepted as 'normal' in the non-traumatized, healthy individual. 'Neutropenia' is merely an observation, which is visually identical whether it be produced by endotoxin shock, complement activation or whatever.

The patient undergoing surgery usually possesses an underlying immunopathology which may well activate or alter normal body processes so that they react in a totally unexpected, adverse manner both to drugs and to surgery. Patients on high-dosage steroids and immunosuppressive regimens, for example in transplantation surgery, will acquire additional advantages and disadvantages from this regimen during and after surgery, since the therapy will interact with other biological systems as well as reducing immune surveillance.

Various practical approaches have been made to reduce the magnitude of the biochemical changes associated with the stress response, notably the introduction of neuroleptanalgesia and neuroleptanaesthesia (the latter achieved by adding nitrous oxide and oxygen to the technique since there seems little point in keeping a patient awake during a major operation). The technique was originally designed to provide an alternative anaesthesia for major surgery, avoiding severe central nervous system or circulatory depression, and depending upon the use of two types of drugs, a powerful tranquillizer and narcotic analgesic. Early usage of the phenothiazines as tranquillizers led to undesirable side effects and it is worth noting that (under admittedly different conditions of administration) the phenothiazines sometimes cause immunological and coagulation disorders in psychotic patients. Even with the 'safer' neuroleptic drugs, individual susceptibility occurs and some subjects receiving clinically effective doses of these substances may exhibit restlessness, agitation and hallucination. Although neuroleptanalgesia constitutes a valuable addition to the armoury of the anaesthetist, whether it contributes significantly to the stability of the individual's immunity remains debatable – even stability itself may not always be desirable.

Finally, what do we mean by immunity? In general terms we imply host resistance to infection and disease but this is not the sole function of immunocompetent cells and their specific protein products, the antibodies. Although in the laboratory the use of antibodies in diffusion, immunoelectrophoresis,

immunofluorescence and radioimmunoassay procedures provides valuable and precise *in vitro* diagnostic aids in a variety of diseases, *in vivo* the situation is much more complicated. Irrespective of the individual's ability to produce high titres of avid antibody to invasive antigen the host who cannot mobilize the secondary effector mechanisms such as complement will not mobilize the macrophage and tissue repair systems in a satisfactory manner, and cannot be described as immune competent. Conversely, complement (C3) has direct action against invasive pneumococci in the absence of antibody response. We shall see later that these highly important secondary effector systems also interact with blood coagulation systems and profound effects may be induced by anaesthetic and surgical techniques. It must be emphasized that the laboratory measurement of any parameter of immunity by itself does not constitute a statement of the host's overall immune status, but significant changes in the parameters after anaesthesia and surgery may provide valuable clues to stress mechanisms and lead to improved techniques, both surgical and anaesthetic.

Immunity is, in essence, an *in vivo* phenomenon which involves both the surveillance and direct response of the body (in terms of the production of specific proteins, the antibodies) against invading organisms and their toxic products, and also the 'inflammatory response', the function of which is basically to remove and destroy the identified and located foreign material. This latter process is carried out by 'signals' initiating from antibody combined with foreign materials, i.e. to antigens. Impairment of any individual stage, surveillance, immune response or inflammatory response will result in the impairment of immunity of the host. The situation is complicated by the fact that surveillance and inflammatory response effectors may, in some circumstances, be identical, e.g. phagocytic cells, and that the *immediate* level of any individual's immunity is effectively in the 'mind', since the latter controls the endocrine balance dictating cell metabolism. Overall, of course, immunity is controlled by interacting inherited genetic factors such as the immune-response genes, but it is the phenotypic expression of immunity which anaesthetist and surgeons are concerned with, since temporary disturbances of immunity, acceptable in the population as a whole, may have far-reaching consequences in certain groups of individuals with underlying immunopathology such as neoplasia, autoimmune disease and familial defects of the immunity systems, in addition to the deliberately immunocompromised patient involved in transplant surgery. Disturbances of immunity arise immediately from the assault of anaesthetic and surgical trauma, the relative effects of which may be further modified by the psychological state of the patient, the latter in turn modified by physiological considerations such as pain and malnutrition (often with associated fears of cancer), and frankly altered metabolism and immunity resulting from metastatic and cirrhotic diseases. The psychological trauma may be so intense in certain individuals that it overrides the surgical and anaesthetic trauma; one feels that some of the deaths associated with dental anaesthesia may well involve this factor, and in such individuals it is no less a disease than those associated with aberrations of immunity.

In planning this book we have attempted to consider the requirements of anaesthetists and surgeons for a clear and concise account of the theoretical and practical aspects of immunity which they encounter from day to day. This is not a book of specialized techniques, such as tissue typing, but it is a practical reference to the immunological techniques currently used in evaluating changes in immunity, and also to the areas in which at present the reader should use caution both in interpreting the results of such experiments and in the use of prophylactic and therapeutic measures to counter the supposed harmful effects underlying the experimentation. It is appropriate to commence this book with a review of the immunology most relevant to anaesthesia and surgery, and thus introduce the terminology which will recur throughout the ensuing chapters.

Part 1

Basic concepts

1

An introduction to immunology relevant to anaesthesia and surgery

John Watkins

Immunology: The past and the present

Immunology is a new science which borrows heavily from both the theory and practical skills of the bacteriologist, the histopathologist, the haematologist and not least from the physical biochemist. Thus any standard textbook on the subject contains sections which would not be out of place in textbooks of their parent disciplines. If we accept this view, the unfortunately slightly mysterious and esoteric veil of reputation which immunology has acquired for itself recently begins to slip and then immunology becomes of more practical and immediate use for clinicians in adjacent disciplines.

The emergence of immunology as a science

Although virtually all the subject encompassed by the term 'immunology' has been recorded in the past 100 years it is only in the last 30 years or so that the subject has emerged as an individual science. The first deliberate attempt at the manipulation of immunity, however, dates from smallpox vaccination introduced by Jenner in 1800. From then until the end of the nineteenth century immunology developed more or less spasmodically, boosted predominantly by Pasteur's work in bacteriology and by the important recognition of the involvement of nucleated white blood cells in 'immunity' (Metchnikoff, 1845–1916). Immunology at this stage was characterized by bickering between two rival groups; those who believed that immunity was totally dependent on phagocytic cells and those who subscribed to a non-cellular, humoral theory. Fuel to the controversy was added by Behring, who in 1890 observed that the antitoxic (antibody) activity which inactivated diphtheria and tetanus exotoxins resided in the cell-free, humoral fraction of blood. However, differences between the antagonists were somewhat reconciled by Wright in 1903, who realized that both cellular and humoral factors played a role in immunity. He drew attention to the fact that although many bacteria are phagocytosed readily, some are remarkably

resistant unless first coated with serum substances which functioned by aiding the phagocytosis of bacteria. These he and Douglas termed 'opsonins'. Other plasma proteins (complements) also have opsonizing activity even in the absence of antibody but this was, of course, not appreciated at the time.

The 1900s were also characterized by the dawning realization that under certain conditions the immune response might be harmful to the host. The French scientists Portier and Richet injected dogs with an extract prepared from sea-anenome tentacles and found to their surprise that sublethal quantities (based on first exposure), when injected into *previously sensitized* dogs, caused convulsions and collapse and often terminated in death. These scientists proposed the term 'anaphylaxis' to describe the phenomenon, as a contradistinction to the beneficial prophylaxis brought about by vaccination. However, even the latter caused some misgivings. Von Pirquet and Schick, working in Vienna with antidiphtheria antiserum raised in horses, discovered that *systemic* reactions in children, including fever and transient arteritis, often followed 8 days after a second injection of the antitoxin. This response – serum sickness – is now known to be mediated by circulating immune complexes; we shall see other problems that originate from such complexes later in this volume (*see* Chapter 9). Serum sickness originates from complexes containing excess *antigen*; the parallel situation of excess *antibody-containing* complexes was discovered, but not understood, by Arthus at about the same time as Pirquet and Schick's observations on systemic reactions and included the formation of erythematous local skin lesions after repeated injection of foreign serum (Arthus reaction). *Figure 1.1* shows a most unusual Arthus type reaction to the anaesthetic drug thiopentone. This was superimposed upon a severe systemic anaphylactic reaction.

Figure 1.1 (*bottom right*) Fixed drug reactions on the arm of a patient who exhibited a marked anaphylactoid reaction to thiopentone. The flared areas correspond to the precipitation of specific antibody–drug complexes on the sites of previous venepunctures and not to the site of administration of the anaesthetic (dorsum of hand). The patient had received a previous exposure to the drug uneventfully. (Photograph by kind permision of Dr P. Latto, Anaesthetic Department, University Hospital of Wales, Cardiff and reproduced with permission of the author and publishers of the *British Journal of Anaesthesiology*, 1979; **51**, 51.) This situation should not be confused with more common physicochemical precipitation effects after thiopentone administration to patients with chronic infections, or after viral infections. Pre-existing (i.e. non-drug specific) immune complexes are precipitated locally in these patients by the high initial concentration of the drug bolus, producing a flare along the injection vein and sometimes local urticaria near the puncture site (*top right*). This particular patient had chronic pelvic inflammation. She exhibited only this local untoward response to anaesthesia which was otherwise uneventful, unlike the other patient (*bottom right*), in whom the cutaneous effects were secondary to a clinically severe hypotensive response. (Photograph by kind permission of Dr C. J. Levy, Anaesthetic Department, Royal Hallamshire Hospital and Mr A. Emery, Medical Photography Department, Northern General Hospital, Sheffield.)

In addition to such 'man-made' diseases several workers had also recognized the existence of autoimmunity, and in 1904 Donath and Landsteiner described the first red-cell autoantibody.

A further 30 or 40 years were to elapse before technology was sufficiently advanced to pursue the initial observations and to obtain a full understanding of the mechanisms involved. For example, until 'pure' proteins could be isolated little progress could be made regarding the structure and synthesis of antibodies, and indeed the term 'immunoglobulins' was only used by Heremans in 1959. Nevertheless, this had not prevented men of vision like Paul Ehrlich (1854–1915) from providing the foundations of modern theoretical immunology, with his discoveries and theories of primary and secondary immune response, the transference of immunity from mother to offspring and the theory of antibody formation based on cellular receptors. The latter is still largely acceptable today. A theoretical model of antigen–antibody reactions based on the multivalence of each was proposed by Marrack in 1934. He postulated that a lattice could be created of alternating antigen and antibody molecules joined through *specific* reactive groups. Such a lattice requires that the antibodies have a minimum of two antigen-combining sites, and this was confirmed by the demonstration of the biochemical structure of the immunoglobulin now known as IgG (Porter and Edelman, 1960).

The period, however, was not without its share of 'red-herrings', of which the 'instructive theory' of antibody synthesis deserves comment. The chemical experiments of Landsteiner and others, who coupled aromatic compounds such as dinitrobenzene to carrier proteins and polysaccharides and produced antibodies in animals directed against these determinants (haptens), made it difficult to accept Ehrlich's views that the body had preformed antibodies (or antibody precursors) whose release into the plasma and further production was stimulated by the entry of antigen into the body. After all, such chemical determinants were most unlikely to occur in nature; therefore in the 1930s an alternative theory to that of Ehrlich developed known as the 'instructive' or 'template' theory. This theory proposed that antigen entered specific cells capable of synthesizing antibody and that they acted instructively as a template around which a standard unfolded gamma-globulin chain was moulded to produce the appropriate complementary shape; this shape was then locked in permanently by disulphide and hydrogen bonding. Although plausible at the time in terms of the available knowledge of protein structure, it was almost completely discredited by the late 1940s on the basis of newer discoveries of immunity, particularly the new concept of immunological tolerance (Burnet and Fenner, 1949) and the phenomenon of immunological memory (i.e., that after antibody response to a first administration of antigen has disappeared, a second challenge with that antigen provokes a disproportionately greater and more rapid antibody response).

Modern trends

By 1955 the work of Coons and his colleagues had established that the lymphocyte is transformed in the presence of antigen to an antibody-producing