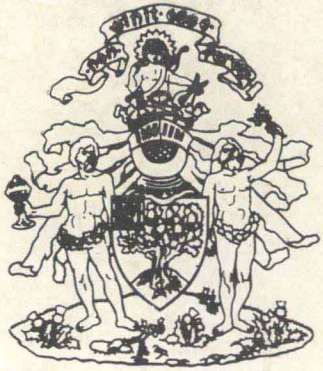

ROYAL COLLEGE OF PHYSICIANS
EDINBURGH

# CURRENT MEDICINE

## 2

*Edited by*
*D. H. Lawson*

Churchill Livingstone

# Current Medicine 2

## Royal College of Physicians of Edinburgh

Edited by

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# Foreword

In 1988 the Royal College of Physicians of Edinburgh produced an update on recent advances in medicine in easily readable form intended primarily for its own Fellows and Collegiate Members. *Current Medicine 1988* was very well received and it clearly achieved its main objectives. The Council of the College has therefore decided to proceed with a series on an approximately biennial basis and I am very pleased to introduce *Current Medicine 2*. This will again go to Fellows and Collegiate Members, but on this occasion we shall make it available to the wider profession through medical bookshops.

Professor D. H. Lawson has edited *Current Medicine 2* on behalf of the College and is to be commended on having brought together excellent contributions on everyday problems which all physicians face and to which recent advances in knowledge can be applied. With *Current Medicine 1988* several of our Fellows expressed disappointment about the lack of reference to children's disorders; this has received attention and the Council of the College will keep the matter under review and ensure that a good balance is maintained in the future.

Again, there is a section summarizing the 'best management' of common therapeutic dilemmas which proved popular in *Current Medicine 1988*. This time an appreciation of one of our great Scottish physicians and teachers, Sir Derrick Dunlop is added; this will give great pleasure to the many who knew him and learned from him.

The Royal College of Physicians of Edinburgh has always had as one of its main purposes the maintenance of the highest standards of clinical practice wherever the College had influence at home and overseas. I am sure that *Current Medicine 2* will be seen to follow in this tradition.

1990 J.R.

# Preface

Advances in medicine occur so frequently nowadays that physicians find considerable problems in keeping up-to-date in their own chosen specialties. The bulk of clinical practice, both in Scotland and beyond, is still carried out by the general physician, who, although usually having an area of particular expertise, nonetheless has to deal with a wide variety of clinical problems as they present de novo to the clinic or wards. Such physicians face a daunting task in maintaining their practical knowledge at a sufficiently high level to allow them to practise good clinical medicine. The subjects which comprise *Current Medicine 2*, were chosen to assist such practitioners in keeping abreast of areas of development in medicine. It is also hoped that they will be useful to candidates for the Membership examination of the Royal Colleges of Physicians in the UK.

The book is divided into three sections. In the first, 11 distinguished authors have produced topical reviews on areas of their expertise. Their reviews range from preventative medicine in the form of an essay on the use of vaccines old and new, to treatments for major clinical problems such as diabetic pregnancy, osteoporosis and cardiac dysrhythmias. Young patients are not forgotten and we have essays on asthma and wheezing, on the aetiology and management of acute renal failure and on poisoning with household products.

The second section of the book comprises five essays by distinguished clinicians who give their personal views on the best management of a major clinical problem. This section was given a personal focus deliberately in the hope that authors would go beyond the perspective of the standard textbooks and address some of the more controversial issues which frequently face clinicians.

It is a salutary lesson to look back at the way our treatments change over the years. Sometimes our endeavours, for the best of reasons, are subsequently seen to be less than optimal. I have asked Dr A. Ross Lorimer and Professor Michael Lee to explore the management of severe hypertension from an historical perspective. The resulting article will, I am sure, be of great interest both to those of us who recall the dramatic benefits which were achieved following introduction of the ganglion-blocking agents and

also to those who now see so little accelerated hypertension as to feel uncomfortable with its management.

Finally, I have introduced a historical section to this series. I hope that in future editions, my successors will continue this section. To begin the series, I have asked two distinguished physicians to write from the basis of their personal knowledge and perspective, about one of our greatest 20th century Scottish physicians — Sir Derrick Dunlop. Too often, in the frenzy of clinical practice, we ignore the historical perspective. There is much to learn from a study of the past and no more appropriate starting point than with that great teacher and clinician, Derrick Dunlop. The current moves towards uniformity in education of our physicians together with the increasing expectations of patients in our health care system, tends towards eliminating 'characters' in medicine. Such a move is to be resisted where possible. Individualists with flair and clinical acumen are rare in our community and should be encouraged and fostered at all costs. Sir Derrick was clearly both a 'character' and a most distinguished teacher and clinician and I am grateful to Drs Smith and Lambie for their thoughtful and gracious tribute to their renowned mentor.

If this series is to be successful as a reference work for our Fellows and Members throughout the world, the contents of future editions should reflect the needs of these physicians. I am sure the College would welcome comments on particular areas which could be addressed in forthcoming editions of *Current Medicine*. In particular, I hope that we will be able to incorporate more articles from abroad in future editions of this series.

No book can be written without the enthusiastic collaboration of a number of people. My thanks are due to our contributors, who have adhered to tight schedules, my secretary, Mrs Ann Rodden, who has orchestrated the entire exercise from beginning to end, and our publishers whose assistance and expertise have been of the highest calibre.

Glasgow, 1990 D. H. L.

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D.H.L.

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# Contents

SECTION 1

# Topical reviews

# 1. Immunizing agents and vaccines, old and new

*J. G. Collee*

A vaccine is any preparation that is used to confer active immunity. The word has its origin in Jenner's work with cowpox and the cross protection that this afforded against smallpox, though Jenner was not the first to discover and exploit the principle of active immunization. Our common terminology has evolved loosely in this field. At the outset, it is important to distinguish clearly between passive and active immunization.

## PASSIVE IMMUNIZATION

This denotes the passive acquisition of preformed protective antibodies. *Natural passive immunity* is conferred on a fetus when maternal antibodies cross the placental barrier. Some antibodies are also passed naturally to the newborn in colostrum. *Artificial passive immunity* is acquired when serum containing protective antibody is injected. This immunizing serum may be derived from an animal (heterologous) or from man (homologous) who has been actively immunized with an appropriate antigen, or from the pooled sera of individuals who have naturally acquired immunity. The injection of heterologous animal serum carries a risk of untoward reactions including serum sickness and anaphylaxis. Accordingly, refined homologous antisera from human donors have largely, but not completely, replaced animal sera for human use. Problems associated with the use of human sera include the transience of passive protection and occasional adverse reactions; there are stringent precautions to minimize the risk of transmission of infective agents such as those of hepatitis B, non-A non-B hepatitis, AIDS and cytomegaloviruses and the 'unconventional agents' or 'scrapie-like agents' that may be associated with conditions such as Creutzfeld-Jacob disease, kuru and other encephalopathies. Blood or blood products (or other tissues) destined for clinical use or incorporated into products that may be injected parenterally should be obtained from identified and suitably screened donors. Sera are currently screened for evidence of hepatitis B and HIV infection. The recognition of bovine spongiform encephalopathy (BSE) as a scrapie-like disease of cattle has added anxieties about the use of bovine products in vaccines and other preparations for parenteral use or implantation in man.

## Immunoglobulin preparations

Unmodified IgG preparations are not suitable for intravenous use as they may contain aggregates that cause adverse reactions. Various refining procedures avoid this problem and stabilize the product; this is especially important for intravenous preparations. The following are for intramuscular injection and must not be given intravenously (Table 1.1). Details are given in the British National Formulary (1988).

*Human normal immunoglobulin* derived from the pooled plasma of blood donors contains significant amounts of protective antibody to measles, hepatitis A and some other viruses. Preparations of human normal immunoglobulin (HNIG) are available in Britain for the passive protection of intending travellers against hepatitis A or to protect individual contacts. HNIG may also be used to prevent measles temporarily in immunocompromised children after contact with a case or to attenuate the disease. HNIG offers an uncertain degree of passive postexposure protection against mumps, and it does not give assured postexposure protection against rubella.

*Specific human immunoglobulin* preparations are available in Britain for passive protection against tetanus (Human Tetanus Immunoglobulin, HTIG), hepatitis B (HBIG), rabies (HRIG), and varicella-zoster (ZIG).

Limited amounts of antivaccinia immunoglobulin (AVIG) are held for the treatment of generalized vaccinia (which may occur after vaccination of workers who may have to deal with suspected smallpox) or for emergency protection of workers handling vaccinia virus in research laboratories.

**Table 1.1** Immunoglobulin preparations and antisera currently available for intramuscular use* in Britain. (The abbreviations are explained in the text)

| Product | For temporary protection against: |
|---|---|
| *Pooled human normal IgG* (HNIG) | Hepatitis A<br>Measles in immunocompromised contacts |
| *Specific human IgG* | |
| HBIG | Hepatitis B |
| HTIG | Tetanus |
| HRIG | Rabies |
| ZIG | Varicella-zoster infections |
| AVIG | Generalized vaccinia |
| *Antisera produced in animals* | |
| Diphtheria antitoxin | Diphtheria |
| Botulinum antitoxin | Botulism |

**Notes*: 1. Anti-D (Rho) immunoglobulin is also available for intramuscular use.
2. Special preparations of immunoglobulin for *intravenous* use are available for the treatment of primary hypogamma-globulinaemia and in some cases for idiopathic thrombocytopenic purpura.

Preparations of specific heterologous antiserum raised in animals are available for use in suspected cases of diphtheria and botulism, with careful precautions to check for hypersensitivity by prior trial dose.

### Duration of passive immunity

Natural passive immunity protects the infant for a few months. Some immunoglobulin preparations may give comparable protection (e.g. HNIG against hepatitis A), but artificial passive immunization with homologous antiserum generally protects for only a few weeks; and heterologous antiserum gives even less durable protection.

### Anti-D (Rho) immunoglobulin

Mention should be made of this preparation that prevents the formation of maternal antibodies to rhesus-positive cells released during childbirth or abortion into a rhesus-negative mother's circulation from a rhesus-positive fetus. An injection of this immunoglobulin given to the mother as soon as possible within 72 hours of the event blocks the released antigen and thus avoids the development of antibodies that would cause haemolytic disease of the newborn in a subsequent pregnancy.

### Monoclonal antibodies

Fusing a mouse myeloma cell with a lymphocyte from an immunized animal can produce a hybrid cell line that may be successfully cloned and passaged to produce large amounts of a specific 'monoclonal' antibody. The hybrid clone can then be grown indefinitely in vitro to give antibody levels of 5–50 $\mu$g/ml. Alternatively, passage of the hybrid clone in vivo in the mouse peritoneal cavity will result in hybridoma (tumour) production with ascites fluid containing as much as 5–15 mg antibody/ml (but see below). Monoclonal antibodies are widely used for the analysis of microbial antigens, for the large-scale production of specific immunoglobulins that may be used as diagnostic or therapeutic agents, and for much related biomedical research. They have a role in many commercially useful procedures, including the separation, purification and concentration of antigens and proteins of pharmaceutical interest.

Possible clinical uses of mouse-derived monoclonal antibody preparations in man raise anxieties that range from transmission of mouse viruses to anaphylactic and other adverse reactions that may be attributed to cytokines or to heterologous proteins transferred to man from the mouse peritoneal fluid. The latter problem can be avoided by making mouse/human hybridomas and growing them in vitro so that the monoclonal antibody produced is essentially human. The exclusion of possible murine viruses and cell products associated with the oncogenic potential of the mouse cell

component requires demanding technical control of the production process and the final product.

### Immunotherapy for infections with Gram-negative bacteria

There has been much interest in the possible use of sera directed against the lipopolysaccharide of Gram-negative bacteria in the treatment of patients with so-called 'Gram-negative sepsis'. The lipopolysaccharides of coliform bacteria carry specific 0 side chains; protective antibody directed against these is type-specific. However, the endotoxic part of the molecule lies in the lipid A within the core region, and anticore antibody has been shown to be protective and not type-specific. As the core structure is similar in most Gram-negative bacteria, hyperimmune anticore antibody holds promise as a broad-spectrum therapeutic agent. The topic is very well reviewed by Cohen (1988). We do not yet have clear evidence that this approach will transform the clinical management of septic shock, but monoclonal antibody developments may provide the next step forward.

### Antibody-mediated reversal of drug toxicity

If a drug hapten conjugated with human serum albumin is injected into an animal, drug-specific antibodies may be produced. These may be of practical value in neutralizing a toxic drug. The use of refined antibody fragments rather than large antibody molecules can circumvent problems of dealing with the clearance of these complexes in vivo (see Hewick 1989). Digoxin-specific antibody preparations are commercially available for clinical use.

### Antigen-targeted drugs

The discovery of tumour-associated antigens in the last two decades, with evolving knowledge and development of tumour-specific polyclonal and monoclonal antibodies, is being exploited in cancer therapy. If an antigen is tumour-specific or is expressed in much greater amount by tumour cells, a specific antibody-cytotoxin conjugate is likely to be usefully selective. The antibody may be conjugated with a drug or a toxin or a radionuclide. Similar developments are proceeding for the scintigraphic imaging of tumours. There are still many technical problems in this difficult field.

## ACTIVE IMMUNIZATION

Active immunization involves the use of vaccines prepared as: 1. toxoids derived from a few bacterial toxins; 2. suspensions of inactivated (killed) bacteria or viruses; and 3. suspensions of non-inactivated (live, attenuated), bacteria or viruses. Recently, modifications and refinements have evolved