HAEMOLYTIC DISEASE OF THE NEWBORN AND ITS PREVENTION

L A Derrick Tovey

History and incidence

Philip Levine.

Fifty years ago a paper was published in the *Journal of the American Medical Association* entitled "An unusual case of intra-group agglutination" by Philip Levine and Rufus Stetson. The title was unlikely to interest the casual reader, and yet it was a historic paper. Professor J J van Loghem called it "a milestone in the history of medical science" when it was reprinted in *Vox sanguinis* in 1980. That article was the first of many about what was later defined as "Rhesus haemolytic disease of the newborn," in those days an important cause of fetal and neonatal mortality and morbidity. For example, at Queen Charlotte's Hospital, London, between 1946 and 1949, 11 035 babies were delivered and 34 died because of Rh antibodies, an incidence of 3.2/1000 births. One in 200 pregnant mothers developed Rh antibodies, and of those 20% lost their infants in their first affected pregnancy, and 40% in subsequently affected pregnancies.

Rh haemolytic disease of the newborn was therefore a serious cause of misery and distress for many Rh negative mothers. Some improvement in fetal survival was achieved by the introduction of exchange transfusions, intrauterine transfusions, intensive plasma exchange, and early induction of labour. These measures, often heroic, reduced the mortality for Rh positive fetuses but it was not possible at that time to reduce the numbers of mothers who become sensitised.

The breakthrough came in the early 1960s. In a report of a meeting of the Liverpool Medical Institution on 18 February 1960 Dr Ronald Finn of the department of medicine, University of Liverpool, "tentatively suggested that it might be possible to destroy any fetal cells found in the maternal circulation following delivery by means of a suitable antibody. If successful, this would prevent the development of erythroblastosis." This, another historic prediction, was made possible by the studies of the mechanics of Rh sensitisation carried out in the department of medicine at Liverpool under the direction of Professor Sir Cyril Clarke.

Just before that the Kleihauer technique had been described; this allowed research workers to detect fetal red cells in maternal blood, and the workers in Liverpool found a correlation between the number of fetal red cells in the maternal circulation and the incidence of Rh sensitisation. In other words, Rh negative mothers became sensitised by small "transfusions" (fetal leaks) of their infants' Rh positive cells into their circulations during pregnancy. These leaks usually occurred during the last trimester.

The second fact that they considered was the effect of ABO incompatibility between mothers and children on the incidence of Rh sensitisation. Not all Rh negative mothers are equally at risk. If the father is ABO incompatible (for example, group O mother, group A father) then the mother's chances of developing antibodies are reduced by a factor of eight. The mechanism of this protection was explained along the lines outlined below.

Perinatal deaths/1000 births caused by anti-D haemolytic disease of the newborn.

Mechanism of Rh sensitisation and effect of ABO incompatibility.

- The Rh antigen is complex
- It is the result of the activity of three pairs of allelic genes: Cc Dd Ee
- The commonest cause of haemolytic disease of the newborn is the D antigen
- A Rh negative mother is usually cde/cde and "Rh positive" refers to those who carry the D antigen (for example, CDe/cde)
- Anti-D is therefore the commonest antibody causing haemolytic disease of the newborn

A mother who had extensive plasma exchange during pregnancy with her healthy baby, sitting in front of the machine used for the plasma exchange.

The group O mother has naturally occurring anti-A and anti-B in her serum, and if her infant is group A or B then as soon as any fetal red cells leak into her circulation they are destroyed by the maternal anti-A or anti-B and the chances of sensitisation are reduced.

Unfortunately most matings are compatible so there is no natural protection. The Liverpool workers then argued that the only fetal red cells that need to be destroyed are the Rh positive ones—whether they are ABO compatible or not—as Rh negative cells cannot sensitise because they lack the D antigen. Thus if an anti-D antibody was injected it would destroy all fetal cells that were capable of sensitising the mother. Ironically their weapon—which they hoped would wipe out Rh disease altogether—was the causative antibody itself; a preliminary clinical trial showed that their reasoning was correct.

Coincidentally a group of American workers had conceived the idea of giving anti-Rh immunoglobulin to prevent Rh sensitisation by a totally different route. They started with the premise that giving a passive antibody at about the same time as the subject is exposed to the corresponding antigen will prevent active immunisation, and so they gave passive anti-D to volunteers and found that it was protective. Whether the anti-D simply acts non-specifically by removing D positive cells, or whether there is a more specific immunological action as postulated by the American workers, is still not clear. Whatever the mechanism, giving anti-D soon after delivery does lead to a reduction in the number of mothers sensitised, and prophylactic regimens have been in practice in most countries for many years.

Rh prophylaxis in Rh D negative mothers in Great Britain using anti-D immunoglobulin

A Kleihauer test should be carried out on the maternal blood, and if the fetal leak of red cells is above normal (more than one fetal cell/500 adult cells), a larger dose of anti-D immunoglobulin should be given.

Points to note:

- It is necessary to give anti-D after every Rh positive pregnancy unless the patient has shown evidence of active immunisation.
- Anti-D is only necessary if the infant is Rh D positive. If, however, the infant's anti-D group is in doubt, anti-D should be given.
- If the mother is reported as D⁺, anti-D is not necessary.
- Although anti-D should be given within 72 hours, it has been shown to give some protection if given up to 12 days after delivery.

It is not well known that abdominal trauma to a pregnant woman can result in a leak of fetal red cells, resulting in Rh sensitisation. Doctors attending such cases should determine the patient's Rh group, and if she is D negative should give anti-D immunoglobulin. If there is any doubt about whether anti-D immunoglobulin should be given, a haematologist or director of a transfusion centre should be consulted.

Kleihauer staining to show fetal red cells (dark staining) among maternal red cells (pale "ghosts").

Incidence of anti-D sensitisation/1000 births, 1970-86.

The introduction of Rh prophylaxis caused a sharp decline in the number of pregnant mothers with evidence of Rh sensitisation, but this decline has now almost ceased. The reasons for the continuing incidence of Rh haemolytic disease of the newborn in spite of a decade of immunisation after delivery are:

The original decrease was due not only to Rh prophylaxis but also to a change in patterns of behaviour. Mothers developing antibodies were more likely to request sterilisation or contraception than have further affected babies.

During pregnancy

Anti-D should be given after any potentially sensitising episode, including:

- Amniocentesis
- External cephalic version
- Abdominal trauma
- Antepartum haemorrhage
- Ectopic pregnancy
- Chorionic villus sampling

Dose: before 20 weeks' gestation 50 µg (250 IU)
after 20 weeks' gestation 100 µg (500 IU)

After delivery

100 µg anti-D should be given:

- Within 72 hours if the infant is Rh (D) positive
- If the Rh (D) type of the infant cannot be determined
- If the screen for fetal cells is > 4 ml additional anti-D should be given

Abortions

Anti-D should be given for:

- All therapeutic abortions
- Spontaneous abortions if there is surgical intervention
- Spontaneous abortions after 12-13 weeks' gestation
- Threatened abortions after 12-13 weeks' gestation

Dose: before 20 weeks' gestation 50 µg (250 IU)
after 20 weeks' gestation 100 µg (500 IU)

• *Failure to give the injection*—Some mothers fail to receive the injection, despite being eligible. Sometimes this is because they have antibodies other than anti-D (for example, anti-Kell); it is a fallacy therefore to assume that anti-D is not necessary. Doctors or midwives may be distracted by more acute and pressing clinical problems at the time of delivery. Occasionally a sample of cord blood is taken incorrectly and a Rh positive infant is grouped as Rh D negative because the blood is mainly the mother's. Thus the mother is mistakenly thought not to need injection. Some mothers refuse anti-D immunoglobulin either for religious reasons or because they are not convinced that it is safe. It is important to disseminate the information that no case of transmitted viral infection (including HIV) has been reported after injection of anti-D immunoglobulin.

Recent data from the Yorkshire region emphasise that abortion is a sensitising factor, and therefore the woman needs Rh prophylaxis. In my opinion all women having surgical terminations should receive an intramuscular injection of 50 µg (25 IU) of anti-D immunoglobulin, although some obstetricians consider that it is not necessary for therapeutic abortions before 13 weeks' gestation. In cases of spontaneous or threatened abortion an injection is definitely necessary after 13 weeks. In the case of spontaneous or threatened abortion before 13 weeks the need for anti-D has not been proved, but a good rule is "if in doubt give anti-D."

• *Failure of protection*—Some mothers develop anti-D before delivery, so the injection of anti-D immunoglobulin after delivery is too late. This is particularly dangerous in those having their first babies, of whom roughly 1% of Rh D negative women develop antibodies in pregnancy—usually during the last trimester. Often a second Rh D positive infant is severely affected. These are the so called "hyper-responders" to the D antigen, and these mothers lose a proportionally higher percentage of infants than those who respond normally.

Antenatal prophylaxis

Stillbirth with hydrops fetalis caused by Rh antibodies.

Infant with kernicterus (brain damage caused by jaundice).

To reduce the number of women who became sensitised during pregnancy, workers in Canada introduced antenatal prophylaxis. A recent survey showed that in 40% of all new cases of anti-D sensitisation, antibodies were first detected between 30 weeks' gestation and delivery and thus the patients may well have been protected by antenatal prophylaxis.

The prophylactic anti-D immunoglobulin is usually given at 28 and 34 weeks' gestation. Some people give it only at 28 weeks, but in Great Britain it is recommended that both injections are given. The standard dose is 100 µg (500 IU), and if the infant is Rh D positive a similar or higher dose is given after delivery as in the standard postnatal regimen.

The chances of a mother becoming sensitised are much greater in first and second Rh positive pregnancies. Because of this it is recommended that antenatal prophylaxis is given at least in the first pregnancy. Excluding other causes of fetal loss, the mother is thus "guaranteed" two unaffected infants. This programme is particularly relevant if anti-D immunoglobulin is in short supply. Most obstetricians will have encountered sad cases of hyper-responders who developed antibodies in a first pregnancy, lost the child for other reasons, and then had a severely affected baby. Such women are in danger of never having a living child.

At present antenatal prophylaxis is not practised universally, principally because of doubt about its cost effectiveness. A detailed study from Canada has questioned this, however, and claimed that antenatal prophylaxis—particularly in first pregnancies—is economically worth while. Others consider that the dangers of injecting foreign red cells to immunise or boost Rh negative volunteers do not justify providing the increasing amount of anti-D immunoglobulin that is necessary for antenatal prophylaxis. This argument carries particular weight now, when HIV and hepatitis B virus can be transmitted by blood products. Although it is not possible to eliminate these risks completely, careful selection of donors restricts them to a minimum.

Anti-D immunoglobulin.

Haemolytic disease caused by blood group antibodies other than anti-D

The picture of Philip Levine appeared in The discovery of Rh haemolytic disease (*Vox Sang* 1984;47:187-90) and is reprinted by kind permission of S Karger A G, Basle. The figure showing prenatal deaths caused by anti-D haemolytic disease of the newborn is from: Tovey LAD. The contribution of antenatal anti-D prophylaxis to the reduction of the morbidity and mortality in Rh haemolytic disease of the newborn (*Plasma Therapy and Transfusion Technology* 1984;5:99-104) and is reproduced by kind permission of Pergamon Press plc. The colour illustrations are reproduced by courtesy of the Audiovisual Department, St James's University Hospital, Leeds, except that of the anti-D immunoglobulin, which is reproduced by courtesy of Dr A M Jackson, Scarborough Hospital.

Dr L A Derrick Tovey was formerly director, Yorkshire Regional Transfusion Centre, Leeds.

Some obstetricians have claimed that there are insufficient data to reassure them that antenatal prophylaxis is safe, either for mother or infant. A recent study in Yorkshire, however, found no ill effects and these results bear out those of the Canadian (and other) workers.

One encouraging aspect of Rh haemolytic disease of the newborn is that, although we have been able to reduce the incidence of Rh sensitisation by only 70%, greatly improved obstetric management and neonatal intensive care have reduced the number of deaths as a result of Rh incompatibility by 90%.

Although anti-D is by far the most common blood group antibody that causes haemolytic disease of the newborn, the disease can also be caused by other antibodies. Luckily few cause severe haemolytic disease, but anti-c and anti-Kell must be treated seriously and managed in a similar way to anti-D. Finally, although anti-A and anti-B antibodies do not normally pass the placenta, immune forms (IgG) do occur and result in ABO haemolytic disease, a common cause of neonatal jaundice particularly when the mother is group O and the infant group A.

BOOKS RECEIVED

Nuclear medicine

Developments in Nuclear Medicine. Vol 16. "Scintigraphy of Inflammation with Nanometer-sized Colloidal Tracers." M de Schrijver. (Pp vi+212; figs; £42.) Dordrecht: Kluwer Academic, 1989. Distributed by MTP Press. ISBN 0-7923-0272-9.

Nursing

Nurses: the Inside Story of the Nursing Profession. D Gould. (Pp viii+196; £3.99 paperback.) London: Unwin Paperbacks, 1989. ISBN 0-04-440-518-9.

Oncology

Lung Cancer: the Evolution of Concepts. Vol 1. Ed J G Gruhn, S T Rosen. (Pp xii+249; figs; £48.50.) New York: Field and Wood, 1989. Distributed by W W Norton and Company. ISBN 0-938607-10-3.

Ophthalmology

Acute Hemorrhagic Conjunctivitis: Etiology, Epidemiology and Clinical Manifestations. Y Uchida, K Ishii, K Miyamura, S Yamazaki. (Pp xiii+438; figs; colour plates; £133.40.) Basel: Karger, 1989. Distributed by John Wiley and Sons. ISBN 3-8055-4997-0.

Clinical Anatomy of the Eye. R S Snell, M A Lemp. (Pp xi+364; figs and colour plates; £29.50 paperback.) Boston: Blackwell Scientific, 1989. ISBN 0-86542-086-6.

Differential Diagnosis of Hereditary Vitreoretinopathy. A Spallone. (Pp xv+106; figs and colour plates; £70.) Milan: Fogliazza, 1989. ISBN 88-85904-11-4.

Extracapsular Cataract Microsurgery and Posterior Chamber Intraocular Lenses. L Buratto. (Pp xi+756; figs; colour plates; £320.) Milan: Centro Ambrosiano Microchirurgia Oculare, 1989. Distributed by Fogliazza. ISBN 88-85904-06-8.

Glaucoma: a Colour Manual of Diagnosis and Treatment. J J Kanski, J A McAllister. (Pp viii+151; figs; colour plates; £45.) London: Butterworth Scientific, 1989. ISBN 0-407-01644-9.

Laser Microsurgery of Glaucoma. L Buratto, A Ricci, D Vitali. (Pp xiii+

248; figs; colour plates; £120.) Milan: Fogliazza, 1988. ISBN 88-85904-05-X.

Orthopaedics

Back Pain and Spinal Manipulation: a Practical Guide. C Kenna, J Murtagh. (Pp viii+407; figs; £35.) Sydney: Butterworth Scientific, 1989. ISBN 0-409-49259-0.

Pathology

Gastrointestinal and Oesophageal Pathology. Ed R Whitehead. (Pp xiii+850; figs; £125.) Edinburgh: Churchill Livingstone, 1989. ISBN 0-443-03589-X.

Perinatal care

Drugs and Human Lactation. Ed P N Bennett. (Pp xiv+589; figs; £223.75.) Amsterdam: Elsevier, 1988, for WHO Regional Office for Europe. ISBN 0-444-90361-5.

Pharmacology

Anti-inflammatory Steroid Action: Basic and Clinical Aspects. Ed R P Schleimer, H N Claman, A L Oronsky. (Pp xvii+564; figs; £110.) San Diego: Academic Press, 1989. Distributed by Harcourt Brace Jovanovich. ISBN 0-12-625145-2.

Antiviral Drugs: Basic and Therapeutic Aspects. Ed R Calio, G Nisticò. (Pp x+220; figs; £37.50.) Milan: Pythagora Press, 1989. ISBN 88-85852-03-3.

Clinical Pharmacology. Vol 14. "Adverse Reactions to Drug Formulation Agents. A Handbook of Excipients." M Weiner, I L Bernstein. Series editor M Weiner. (Pp x+466; £150.) New York: Dekker, 1989. ISBN 0-8247-7944-4.

Ellis Horwood Series in the Biomedical Sciences. "Handbook of Renal-Independent Cardiac Glycosides: Pharmacology and Clinical Pharmacology." N Rietbrock, B G Woodcock. General editor A Wiseman. (Pp xxi+328; figs; £54.) Chichester: Ellis Horwood, 1989. Distributed by John Wiley and Sons. ISBN 0-7458-0640-6.

Keyguide to Information Sources in Pharmacy. B Strickland-Hodge, M H Jepson, B J Reid. (Pp x+178; £30.)

London: Mansell, 1989. ISBN 0-7201-1966-9.

Psychiatry

Development and Psychopathology: Studies in Psychoanalytic Psychiatry. C Yorke, S Wiseberg, T Freeman. (Pp ix+243; £22.50.) New Haven: Yale University Press, 1989. ISBN 0-300-04419-2.

Developmental Breakdown and Psychoanalytic Treatment in Adolescence: Clinical Studies. Ed M Laufer, M E Laufer. (Pp viii+217; £19.95.) New Haven: Yale University Press, 1989. ISBN 0-300-04437-2.

Health Services Planning and Research: Contributions from Psychiatric Case Registers. Ed J K Wing. (Pp ix+126; £7.50 paperback.) London: Gaskell, 1989. ISBN 0-902241-30-3.

Life Events and Illness. Ed G W Brown, T O Harris. (Pp xvi+496; figs; £35.) London: Unwin Hyman, 1989. ISBN 0-04-445426-0.

New Library of Psychoanalysis. 9. "Psychic Equilibrium and Psychic Change. Selected Papers of Betty Joseph." Ed M Feldman, E B Spilius. General editor D Tuckett. (Pp x+230; £14.95 paperback.) London: Tavistock/Routledge, 1989. ISBN 0-415-04117-1.

Schizophrenia: a Guide to What It is and What Can Be Done to Help. J M Atkinson. (Pp 144; £4.99 paperback.) Wellingborough: Thorsons, 1989. ISBN 0-7225-1990-7.

Understanding Women in Distress. P Ashurst, Z Hall. (Pp x+237; £12.95 paperback.) London: Tavistock/Routledge, 1989. ISBN 0-415-01833-1.

Rheumatology

Inflammatory Disease and Therapy. Vol 1. "Methotrexate Therapy in Rheumatic Disease." Ed W S Wilke. Series editor D E Furst. (Pp xiii+317; figs; £119.50.) New York: Dekker, 1989. ISBN 0-8247-8115-5.

New Clinical Applications: Rheumatology. "Infections and Arthritis." Ed J J Calabro, W C Dick. (Pp ix+171; figs; £35.) Dordrecht: Kluwer Academic, 1989. Distributed by MTP Press. ISBN 0-7462-0052-8.

Sociology

Early Life Series. "Family Obligations and Social Change." J Finch. (Pp viii+269; £9.95 paperback.) Oxford: Polity Press, 1989. ISBN 0-7456-0324-6.

Surgery

Atlas of Spinal Surgery. C A Fager. (Pp ix+247; figs; colour plates; £62.35.) Philadelphia: Lea and Febiger, 1989. ISBN 0-8121-1172-9.

Plastic Surgery of the Facial Skeleton. S A Wolfe, S Berkowitz. (Pp xviii+796; figs; £150.) Boston: Little, Brown, 1989. Distributed by Churchill Livingstone. ISBN 0-316-95105-6.

Surgery: Diagnosis and Therapy. 1989-90. Ed R M Stillman. (Pp xii+663; £9.95 paperback.) Connecticut: Appleton and Lange, 1989. Distributed by Prentice Hall International. ISBN 0-8385-8734-8.

Surgical Audit. A Pollock, M Evans. (Pp xiv+167; £19.50.) London: Butterworth Scientific, 1989. ISBN 0-407-00823-3.

Surgical Practice Illustrated—2. "Atlas of Congenital Cardiac Surgery." P A Ebert. Series editor D B Skinner. (Pp xiv+138; figs; £85.) New York: Churchill Livingstone, 1989. ISBN 0-443-08532-3.

Thoracic Trauma. R M Hood, A D Boyd, A T Cullford. (Pp x+460; figs; £67.50.) Philadelphia: Saunders, 1989. Distributed by Harcourt Brace Jovanovich. ISBN 0-7216-2353-0.

Surgery—transplantation

Developments in Surgery. "International Handbook of Pancreas Transplantation." Ed J M Dubernard, D E R Sutherland. (Pp xi+552; figs; £105.) Dordrecht: Kluwer Academic, 1989. Distributed by MTP Press. ISBN 0-89838-399-4.

Ultrasound

Developments in Cardiovascular Medicine. "Clinical Echocardiography." M Iwase, I Sotobata. (Pp xi+304; figs and colour plates; £76.50.) Dordrecht: Kluwer Academic, 1989. Distributed by MTP Press. ISBN 0-7923-0004-1.

Intravascular Ultrasound: Techniques, Developments, Clinical Perspectives. Ed

N Bom, J Roelandt. (Pp x+218; figs; £32.) Dordrecht: Kluwer Academic, 1989. Distributed by MTP Press. ISBN 0-7923-0387-3.

Series in Radiology. Vol 20. "Magnetic Resonance Imaging of Bone and Soft Tissue Tumors and Their Mimics: a Clinical Atlas." A M A De Schepper, H R M Degryse. (Pp 130; figs; £48.) Dordrecht: Kluwer Academic, 1989. Distributed by MTP Press. ISBN 0-7923-0343-1.

Urology

Atlas of Urologic Surgery. F Hinman Jr. (Pp xxx+1057; figs; £118.) Philadelphia: Saunders, 1989. Distributed by Harcourt Brace Jovanovich. ISBN 0-7216-1749-2.

The Prostate. Ed J M Fitzpatrick, R J Krane. (Pp xiv+449; figs; £60.) Edinburgh: Churchill Livingstone, 1989. ISBN 0-443-03558-X.

Miscellaneous

The Body and the French Revolution: Sex, Class and Political Culture. D Outram. (Pp x+197; figs; £22.) New Haven: Yale University Press, 1989. ISBN 0-300-04436-4.

Celebration. M Spufford. (Pp 126; £2.95 paperback.) London: Fount Paperbacks, 1989. ISBN 0-00-627449-8.

Cholesterol and Children: the Parent's Guide to Giving Children a Future Free of Heart Disease. R E Kowalski. (Pp 240; £8.95.) Wellingborough: Thorsons, 1989. ISBN 0-7225-2145-6.

Doctors and Doctors' Wives. F Roe. (Pp 336; £11.95.) London: Constable, 1989. ISBN 0-09-469280-7.

Fantastic Women: Sex, Gender, and Transvestism. A Woodhouse. (Pp xv+157; £25.) London: Macmillan, 1989. ISBN 0-333-44669-0.

Genius: the History of an Idea. Ed P Murray. (Pp x+235; figs; £25.) Oxford: Basil Blackwell, 1989. ISBN 0-631-15785-9.

"I have done my duty": Florence Nightingale in the Crimean War 1854-56. Ed S M Goldie. (Pp xii+326; figs; £12.95 paperback.) Manchester: Manchester University Press, 1989. ISBN 0-7190-2628-8.