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Finn R, Clarke C A, Donohoe W T A, McConnell R B, Sheppard P M, Lehane D & Kulke W. Experimental studies on the prevention of Rh haemolytic disease. *Brit. Med. J.* 1:1486-90, 1961.[Dept. Med. and Sub-Dept. Genet., Univ. Liverpool; Liverpool Regional Blood Transfusion Serv.; and Radio-Isotope Unit, Liverpool Radium Inst., England]

Experiments on Rhesus (Rh)-negative male volunteers injected with Rh-positive cells showed that Rh immunisation could not be prevented by injecting 19S anti-Rh antibody, although about 60 percent of the cells were eliminated. When 7S antibody was substituted for 19S,[1] the way was clear for preventing Rh haemolytic disease. In addition, the Kleihauer technique enabled the size of any feto-maternal haemorrhage to be determined. [The SCI® indicates that this paper has been cited in over 200 publications.]

Experimental Prevention of Rh Immunisation by Injecting Anti-D

Sir Cyril A. Clarke
43 Caldy Road
West Kirby
Wirral, Merseyside L48 2HF
England

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About 1 in 7 marriages are between Rh-negative women and Rh-positive men, and yet only in about 1 in 20 of such unions is the woman immunised. There are three principal reasons for this: first, the husband may be heterozygous, in which case half the offspring will be Rh negative; second, there may have been no transplacental haemorrhage; and, third, where there is ABO incompatibility as between mother and fetus (which occurs in about 20 percent of cases), this is protective. R.R. Race and R. Sanger[2] were the first to suggest this last, since they thought that the naturally occurring maternal 19S anti-A or anti-B would eliminate any fetal cells before they had time to stimulate the production of Rh antibodies. This suggestion was responsible for our trial of 19S anti-D given to Rh-negative male volunteers who had been injected with Rh-positive cells. However, this failed since only about 60 percent of the injected cells were eliminated, and controls and "treated" were immunised in equal numbers. The result was quite different[1] when we switched to the 7S ("incomplete") Rh antibody, which inactivated (by "coating") all the injected red cells, and the male volunteers were fully protected. Trials followed in women using incomplete anti-D gamma globulin, which were again successful. Other countries joined in the work and the excellent results are shown in the table.[3]

Surprisingly, the results were not quite so good with our "low risk" trial, in women with no or very few fetal cells. This turned out to be because a few women are immunised during pregnancy, and, though any fetal cells are eliminated, the antibodies cannot be detected by standard procedures, and so the women enter the trial as nonimmunised. To overcome this problem, antenatal anti-D given at the 28th and 35th weeks of pregnancy as well as after delivery was suggested in Canada[4] and elsewhere, and there was an excellent trial in this country in Yorkshire[5] that showed that antenatal plus postnatal anti-D got rid of almost all the failures of prophylaxis.

The effect of anti-D on Rh baby deaths has been monitored since 1977 by the Research Unit of the Royal College of Physicians of London[6] and more recently via the Department of Community Health in the University of Liverpool (Professor Peter Pharoah and Dr. Ruth Hussey). The deaths were ascertained from the Office of Population Censuses and Surveys (OPCS) and amplified from the case notes kindly lent to us by the obstetricians. We found that the number of deaths from haemolytic disease due to anti-D fell progressively from 106 in 1977 to 25 in 1984; it thereafter remained approximately constant for three years but fell again in 1988 (20 deaths). Interestingly, the number of deaths due to anti-c has remained approximately constant—three to four per year, except in 1984, when it was five; in 1987, when it was 0; and in 1988, when it was four again. One might have expected these deaths to have dropped since improved obstetric care is thought to be rescuing more hemolytic disease of the newborn (HDN) babies than in earlier years.

The number of deaths registered on the death certificates as due to HDN but found by us to have some other cause fell progressively—the number was 45 in 1977 but only 6 in 1988—clearly due to our frequent discussions with the OPCS resulting in more accurate death certification.

The failure rate remained much the same—i.e., around 10 per year—and this can probably only be reduced by the wider application of antenatal anti-D, which at present is only given in a few centres in this country, principally because of shortage. However, with the coming of monoclonal anti-D, this will be overcome, as will the current fear of jaundice and AIDS. Nevin Hughes-Jones informs me that first testing of monoclonals in male volunteers has resulted in excellent clearance of the coated cells.[7] The future looks bright.

Table *Combined results: subsequent pregnancies (all centres) up to June 1967. Rh positive ABO compatible infants*

	Control				Treated		
	Total	Immunised	Not immunised	% Immunised	Total	Immunised	Not immunised
Liverpool group (first trial)	26	4	22	15	21	0	21
Germany	7	3	4	43	9	0	9
Columbia, New York	14	4	10	29	21	0	21
Long Beach, California	14	3	11	21	13	0	13
Cornell, New York	1	1	0	100	2	0	2
Edinburgh	1	0	1	0	0	0	0
Totals	63	15	48	24	66	0	66

From Clark,[3] reprinted by permission of the publisher.

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4. **Bowman J M, Chown B, Lewis M & Pollock J M.** Rh isoimmunisation during pregnancy: antenatal prophylaxis. *Can. Med. Assn. J.* 118:623-7, 1978. (Cited 55 times.)
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6. **Clarke C A & Mollison P L.** Deaths from Rh haemolytic disease of the fetus and newborn, 1977-87. *J. Roy. Coll. Phys. Lond.* 23:181-4, 1989.
7. **Hughes-Jones N.** Personal communication. 1990.

IA-20