of heavy and light chains were scrambled to create new, artificial antibodies not represented in the population of human B cells from which the genes were derived. At first sight this may seem to be a disadvantage, but these artificial antibodies may be more likely to recognise human “self” components, as B cells with this property are generally deleted or suppressed by the intact immune system. Many cancer “antigens” and most targets for antibody mediated immunosuppression (lymphocyte surface markers and circulating cytokines) fall into the category of self. The random combinatorial phage library may therefore be a richer source of therapeutically useful antibodies than one that faithfully reproduces the human immune system from which it was derived. Antibodies to human tumour necrosis factor and human immunoglobulin have already been fished out of the library, suggesting that the artificial pairing of antibody variable domains on phage particles really does

allow us to step outside the constraints of the human immune system.

Phage antibody libraries therefore represent a new and potentially limitless source of readily accessible human antibodies against virtually any desired molecular target. Libraries of increasing size and diversity will surely be constructed, with the added possibility of automated production of human monoclonal antibodies. The challenge now is to convert this new technology into clinical benefit without undue delay.

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- 1 Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 1975;256:495-7.
- 2 Waldmann TA. Monoclonal antibodies in diagnosis and therapy. *Science* 1991;252:1657-62.
- 3 Winter G, Milstein C. Man-made antibodies. *Nature* 1991;349:293-9.
- 4 Jones PT, Dear PH, Foote J, Neuberger MS, Winter G. Replacing the complementary-determining regions in a human antibody with those from a mouse. *Nature* 1986;321:522-5.
- 5 Riechmann L, Clark M, Waldmann H, Winter G. Reshaping human antibodies for therapy. *Nature* 1988;332:323-7.
- 6 Hale G, Clark MR, Marcus R, Winter G, Dyer MJS, Phillips JM, et al. Remission induction in non-Hodgkin lymphoma with reshaped monoclonal antibody CAMPATH-1H. *Lancet* 1988;iii:1394-9.
- 7 Mathieson PW, Cobbold SP, Hale G, Clark M, Oliviera DBG, Lockwood CM, et al. Monoclonal antibody therapy in systemic vasculitis. *N Engl J Med* 1990;323:250-4.
- 8 Gorman SD, Clark MR, Routledge EG, Cobbold SP, Waldmann H. Reshaping a therapeutic CD4 antibody. *Proc Natl Acad Sci USA* 1991;88:4181-5.
- 9 Queen C, Schneider WP, Selick HE, Payne PW, Landolf NF, Duncan JF, et al. A humanized antibody that binds to the interleukin 2 receptor. *Proc Natl Acad Sci USA* 1989;86:10029-33.
- 10 Kettleborough CA, Saldanha J, Heath VJ, Morrison CJ, Bendig MM. Humanization of a mouse monoclonal antibody by CDR-grafting: the importance of framework residues on loop conformation. *Protein Engineering* 1991;4:773-83.
- 11 Tempest PR, Bremner P, Lambert M, Taylor G, Furze JM, Karr FJ, et al. Reshaping a human

- monoclonal antibody to inhibit human respiratory syncytial virus infection in vivo. *Bio/technology* 1991;9:266-71.
- 12 Co MS, Deschamps M, Whitley RJ, Queen C. Humanized antibodies for antiviral therapy. *Proc Natl Acad Sci USA* 1991;88:2869-73.
- 13 Skerra A, Pluckthün A. Assembly of a functional immunoglobulin Fv fragment in Escherichia coli. *Science* 1988;240:1038-41.
- 14 Orlandi R, Güssow DH, Jones PT, Winter G. Cloning immunoglobulin variable domains for expression by the polymerase chain reaction. *Proc Natl Acad Sci USA* 1989;86:3833-7.
- 15 Marks JD, Tristram M, Karpas A, Winter G. Oligonucleotide primers for polymerase chain reaction amplification of human immunoglobulin variable genes and design of family-specific oligonucleotide probes. *Eur J Immunol* 1991;21:985-91.
- 16 McCafferty J, Griffiths AD, Winter G, Chiswell DJ. Phage antibodies: filamentous phage displaying antibody variable domains. *Nature* 1990;348:552-4.
- 17 Clackson T, Hoogenboom HR, Griffiths AD, Winter G. Making antibody fragments using phage display libraries. *Nature* 1991;352:624-8.
- 18 Burton DR, Barbas CF III, Persson MAA, Koenig S, Chanock RM, Lerner RA. A large array of human monoclonal antibodies to type I human immunodeficiency virus from combinatorial libraries of asymptomatic seropositive individuals. *Proc Natl Acad Sci USA* 1991;88:10134-7.
- 19 Marks JD, Hoogenboom HR, Bonnett TP, McCafferty J, Griffiths AD, Winter G. By-passing immunization: human antibodies from V-gene libraries displayed on phage. *J Mol Biol* 1991;222:581-97.

Seat belts in pregnancy

Above and below the bump, not over it

Seat belts are thought to save about 200 lives and 7000 serious injuries a year in the United Kingdom.¹ With the possible exception of symmetrical shoulder constraints and a lap belt² the diagonal shoulder strap with a lap belt (three point harness) gives the best protection.^{3,4}

A review of the use of seat belts in pregnancy concluded that all occupants of motor vehicles, but especially pregnant women, should always wear three point restraints.⁵ Typical of these studies is that reported by Crosby and Costiloe.⁶ Of 441 pregnant women involved in road traffic accidents, only one in seven was wearing a seat belt at the time. Maternal mortality was 33% in women ejected from the car and only 5% in those not ejected. Fetal mortality was 47% and 11% respectively.

Despite this evidence Griffiths and colleagues report in this week's journal that fewer than half the maternity units that they surveyed taught women about the use of seat belts during pregnancy, although all units felt able to give advice (p 614).⁷ As three point harnesses dissipate the energy of the impact over the chest wall and the pelvis the diagonal strap should pass over the shoulder between the breasts and the lap strap should lie on the upper thighs.⁸ In pregnancy this means above and below the bump and not over it. Both Griffiths *et al*'s study and a study from a military institution in America, where the wearing of seat belts is mandatory,⁹ showed that the advice given was often at variance with this and may have been

so incorrect as to be dangerous. In the American study some 133 women (22%) wore the lap strap at the level of the umbilicus or high over the pregnancy swelling.⁹

The commonest reason for not wearing seat belts is the fear of increasing the risk of injury to the fetus.⁹ Studies on pregnant baboons showed a significant reduction in fetal mortality among animals restrained with three point harnesses.¹⁰ The most important factor in fetal injury was deceleration, followed by forced flexion of the maternal body over the lap belt with subsequent uterine compression and distortion. Modern seat belts can prevent maternal flexion, but deceleration may cause placental abruption. This, however, is unusual, although cases are usually reported under dramatic titles.¹¹

Abruptio results from deformation of an elastic uterus about a relatively inelastic placenta. It is estimated to occur in 1-5% of minor injuries and 20-50% of major injuries,¹² with the lower figures coming from series with a high proportion of women using seat belts. In severe injuries the uterus may rupture, which almost invariably causes fetal death. Maternal death occurs in about 10% of such cases and usually results from concomitant injuries.¹²

The management of women surviving road traffic accidents is mainly concerned with resuscitating the mother as this is also the best means of resuscitating the fetus. Severely injured pregnant women should undergo radiological studies or

surgery as for their non-pregnant counterparts, although if they are in the second half of pregnancy they should be nursed in the left lateral position to prevent supine hypotension caused by the weight of the pregnant uterus on the inferior vena cava.

The fetus should be monitored by cardiotocography, probably for four hours.¹² Abnormalities of the fetal heart rate usually permit early diagnosis of a placental abruption, which in many cases is not accompanied by vaginal bleeding. In the acute phase ultrasonographic examination will not usually be helpful until the abruption is clinically obvious, but mothers find ultrasonography reassuring. Delayed abruption may occur four to five days after the accident,¹³ which suggests that patients should probably be kept in hospital for five days.

Other effects on the pregnancy may be preterm labour, premature rupture of the membranes, and fetomaternal haemorrhage. Haemorrhage should be sought with a Kleihauer test, and if the patient is rhesus negative anti-D gammaglobulin should be given. Any fetal anaemia resulting from fetomaternal haemorrhage is rarely severe enough to threaten the fetus. Pelvic fractures in pregnancy may be associated with substantial retroperitoneal bleeding, causing hypovolaemic shock, or injuries to the urinary tract or uterus. In the absence of severe deformity delivery through a recently fractured pelvis is not usually accompanied by serious complications. There is little or no evidence on the effect of seat belts on the occurrence of these complications.

Strong evidence therefore exists to support the use of seat

belts in pregnancy; they should be worn over and under the bump. There is also evidence that health care professionals do not routinely educate pregnant women in the correct use of seat belts and that some carers give dangerous advice. Finally, there is evidence that when pregnant women receive advice from trained instructors they are more likely to wear seat belts.¹⁴

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- 1 Seat belt regulations retained. *BMJ* 1986;292:286.
- 2 McCoy GF, Johnstone RA, Nelson IW, Duthie RB. Facial injuries to restrained drivers caused by steering wheels. *Lancet* 1988;iii:456.
- 3 Gallup BM. The assessment of facial injury to fully restrained drivers through full-scale car crash testing. *J Trauma* 1987;27:711-8.
- 4 Campbell BJ. Safety belt injury reduction related to crash severity and front seat position. *J Trauma* 1987;27:733-9.
- 5 Stuart GCE, Harding PGR, Davies EM. Blunt abdominal trauma in pregnancy. *Can Med Assoc J* 1980;122:901-5.
- 6 Crosby WM, Costiloe JP. Safety of lap-belt restraint for pregnant victims of automobile collisions. *N Engl J Med* 1971;284:632-6.
- 7 Griffiths M, Usherwood MMCD, Reginald PW. Antenatal teaching of the use of seat belts in pregnancy. *BMJ* 1992;304:614.
- 8 American College of Obstetricians and Gynecologists. *Automobile passenger restraints for children and pregnant women*. Washington, DC: ACOG, 1983. (Technical Bulletin 74.)
- 9 Hammond TL, Mickens-Powers BF, Strickland K, Hankins DV. The use of automobile safety restraint systems during pregnancy. *J Obstet Gynecol Neonat Nursing* 1990;19:339-43.
- 10 Crosby WM, King LC, Stout LC. Fetal survival following impact: improvement with shoulder harness restraints. *Am J Obstet Gynecol* 1972;112:1101-4.
- 11 Chetcuti P, Levene MI. Seat belts: a potential hazard to the fetus. *J Perinat Med* 1987;15:207-9.
- 12 Pearlman MD, Tintinalli JE, Lorenz RP. Blunt trauma during pregnancy. *N Engl J Med* 1990;323:1609-13.
- 13 Higgins SD, Garite TJ. Late abruptio placenta in trauma patients: indications for monitoring. *Obstet Gynecol* 1984;63:10S.
- 14 Chang A, Magwene K, Frand E. Increased use of safety belts following education in childbirth classes. *Birth* 1987;14:148-52.

Missing women

Social inequality outweighs women's survival advantage in Asia and north Africa

In Europe and North America women tend to outnumber men. For example, in the United Kingdom, France, and the United States the ratio of women to men exceeds 1.05. In many Third World countries, however, especially in Asia and north Africa, the female:male ratio may be as low as 0.95 (Egypt), 0.94 (Bangladesh, China, and west Asia), 0.93 (India), or even 0.90 (Pakistan). These differences are relevant to an assessment of female inequality across the world.¹⁻⁶

Everywhere about 5% more boys than girls are born. But women are harder than men and, given similar care, survive better at all ages—including in utero.⁷ There are other causes for this preponderance of women—for example, some remaining impact of the deaths of men in the last world war and more cigarette smoking and violent deaths among men. But even taking these into account, women would still outnumber men if given similar care.⁷

Social factors must therefore explain the low female:male ratios in Asian and north African countries. These countries would have millions more women if they showed the female: male ratios of Europe and the United States.⁴ Calculated on this basis, China is missing more than 50 million women.

Using European or American ratios may not, however, be appropriate. Because of lower female mortality in Europe and America the female:male ratio rises gradually with age. A lower ratio would therefore be expected in Asia and north Africa partly because of a lower life expectancy and higher fertility rate. There are several ways of adjusting for this. One is to adopt the female:male ratios of sub-Saharan Africa, where there is little female disadvantage in terms of relative mortality but where life expectancy is no higher and fertility

rates no lower than those in Asia and north Africa. Using the sub-Saharan ratio of 1.022 yields an estimate of 44 million missing women in China, 37 million in India, and a total of more than 100 million worldwide.⁵

Using population models based on Western demographic experience it is possible to estimate roughly how many women there would be without any female disadvantage in survival, given the actual life expectancy and the fertility rates in these countries. Coale estimates 29 million missing women in China, 23 million in India, and an overall total of 60 million for selected countries.⁶ Though lower, these numbers are still enormous.

Why is overall mortality for females higher than that for males in these countries? Consider India, where age specific mortality for females consistently exceeds that for males until the fourth decade. Although the excess mortality at childbearing age may be partly due to maternal mortality, obviously no such explanation is possible for female disadvantage in survival in infancy and childhood. Despite occasional distressing accounts of female infanticide, this could not explain the extra mortality or its age distribution. The comparative neglect of female health and nutrition, especially—but not exclusively—during childhood, would seem the prime suspect. Considerable direct evidence exists of neglect of female children in terms of health care, admission to hospitals, and even feeding.^{8,9}

Even though the position in India has been more extensively studied than that in other countries, similar evidence of relative neglect of the health and nutrition of female children may be found in other countries in Asia and north Africa. In China some evidence suggests that the extent of neglect may