reported series resolution took an average of 14-30 days, and about 5-20% of patients still required laparotomy.^{30,31}

What is the prognosis after an ectopic pregnancy? Among 55 American women treated by salpingectomy or salpingostomy and followed up for three to 41 months 30 became pregnant again: 24 pregnancies were intrauterine and six were repeat ectopics.³² In a four to eight year follow up of 110 Finnish women (42 treated by conservative surgery and 68 by salpingectomy) 71 went on to have normal deliveries, 22 had recurrent ectopic pregnancies, and 16 were infertile.³³ The outlook was better in patients aged under 30, those using an intrauterine device at the time of their ectopic pregnancy, and those who had conservative surgery. Among women treated in Israel by conservative microsurgery 14 (56%) of 25 women with two tubes achieved an intrauterine pregnancy and three (12%) had a repeat ectopic pregnancy: for 26 women with one tube the figures were 12 (46%) and 10 (39%) respectively.³⁴ These authors concluded that despite the high risk of another ectopic pregnancy conservative surgery is justified because the rates of intrauterine pregnancy are higher than those achieved by in vitro fertilisation. As most of the women who became pregnant did so during the first year after operation the authors recommended that patients try to conceive again without delay.

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Hepatitis B virus "escape" mutants

A rare event which causes vaccination failure

The protection given by vaccination has considerably reduced the morbidity and mortality from acute viral diseases. For many years vaccination was an empirical procedure, and dead or live attenuated whole organisms were used with little knowledge of the responses required to provide protection. Modern refinements have been introduced after scientific study of the immunological basis of effective prophylaxis. Thus in some cases live attenuated vaccines have superseded dead preparations and the specific antigens that induce immunodominant responses have been mapped. Safe preparations are now being made using molecular biological techniques to produce recombinant proteins or synthetic peptides known to induce protective responses.

Protection against persistent or latent viral infections is more complicated than that against acute infections, particularly if infection occurs perinatally, when early intervention is essential. Nevertheless the protection given by vaccination against such infections is now being assessed.

In the early 1980s trials of vaccines against hepatitis B virus were begun using hepatitis B surface antigen (HBsAg) derived from plasma of asymptomatic chronic carriers. Trials among people at high risk showed that these preparations were safe and effective in preventing transmission to susceptible people in the 95% of vaccinees who develop adequate

antibody titres to HBsAg. These preparations, and the newer recombinant HBsAg vaccines, are now recommended for all high risk groups in the developed world. In some parts of the developing world, however, up to one fifth of the apparently healthy population are chronic carriers of the virus. Progression to cirrhosis or hepatocellular carcinoma occurs in 25-30% of these people. Mothers who are chronic carriers may transmit the virus to their offspring in the perinatal period, and these babies then become chronic carriers themselves. Transmission rates of up to 90% have been recorded in China and Japan, but the rate is much lower in African countries. This sequence of events is preventable by passive immunisation of the baby within 12 hours of birth with simultaneous administration of vaccine—so called active-passive immunisation. The passively administered hepatitis B immunoglobulin does not interfere with the active immune response to vaccine if given at a different site. This strategy, which has been encouragingly successful so far, aims at preventing the maternal virus reaching the infant liver and thereby preventing replication and chronic infection.

In recent trials of hepatitis B virus in a high risk area in southern Italy Carman *et al* reported that 44 of the 1590 vaccinees showed evidence of viral replication (HBsAg), although all had developed protective titres of antibody.¹ The

most likely explanation is that the vaccinees were incubating the virus at the time of vaccination; and this was probably true for most patients in this study, in whom HBsAg was detectable for only a short while. One child developed severe, chronic disease, however, and this child was investigated in detail. The child was born to a carrier mother and had been given hepatitis B immunoglobulin at birth and one month later. Vaccination was performed at 3, 4, and 9 months of age. After this regimen, and despite adequate serum concentrations of antibodies to HBsAg, the child developed a severe infection with persistent antigenaemia with both surface and e antigens. Studies on the virus isolated from the mother and from the child at two time points four years apart showed that a stable mutation had occurred in the isolates from the child. This took the form of a single amino acid substitution in the HBsAg which had caused a configurational change in an external loop. The change was such that the antibodies provoked by the vaccine could not bind to the modified virus antigen, so allowing the virus to replicate in the face of a normal antibody response induced by vaccination.

During the replication of any virus mutant forms are continually being produced; their survival depends, firstly, on their ability to maintain a high replication efficiency and, secondly, on the selective pressure engendered by the immune response. In the influenza virus system—the best studied example of this phenomenon—mutations giving rise to antigenic drift regularly lead to the emergence of variants, which can then infect the susceptible population. The mutant hepatitis B virus described by Carman *et al* probably arose from the maternal strain during replication in the child under selection pressure from the vaccine induced immune response.¹ The delay of three months before administration of the vaccine to the child must have allowed replication of hepatitis B virus in the liver to proceed, with the mutant emerging possibly even before vaccination. The antibody response to vaccination would then have imposed the selec-

tion pressure necessary to allow the “escape” mutant to replicate unrestricted. It is perhaps surprising that a single antibody binding structure (epitope) should be so dominant, and remarkable that this epitope should be essential in inducing neutralising antibody, as apparently it plays no part in essential virus functions such as cellular binding and entry—the mutant has clearly maintained these functions. What remains to be seen is whether this is an isolated case or whether mutations at this site will be commonplace.

A few reports have now appeared of patients maintaining viral replication after vaccination² and of mutant^{3,4} and variant^{2,5} hepatitis B viruses arising in chronically infected patients. We will have to await detailed analysis of the DNA genomes in such cases before passing judgment on the clinical relevance of the present finding. If, however, this mechanism does emerge as a common cause of vaccination failure, alternative strategies will have to be considered such as the inclusion in the vaccine preparation of other epitopes to stimulate B and T cells. Clearly, as the scope of vaccination widens to include other chronic, persistent, and latent virus infections more such problems may emerge. But they will certainly not be a reason for doubting that vaccination is the method of choice for preventing many of the infectious diseases that still devastate the developing countries.

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BCG vaccination in children

Routine vaccination of schoolchildren is not cost effective and could be stopped

For the past 40 years one of the main planks of the public health strategy against tuberculosis in Britain has been BCG (bacille Calmette-Guerin) vaccination for tuberculin negative schoolchildren aged 10-14. Uptake rates of 75% have been consistently achieved over the past decade. BCG is still recommended for this age group and for children at any age at high risk of infection, such as neonates of Indian ethnic origin and children with a family history of tuberculosis. Vaccination is also recommended for tuberculin negative immigrants from the Indian subcontinent as soon as possible after their arrival in Britain and for contacts of patients with active respiratory tuberculosis.¹⁻⁵

BCG vaccination provides effective protection against active tuberculous infection for a minimum of 20 years.⁶ It is also safe. Early and late local cutaneous and regional complications are rare when a defined, age dependent dose of freeze dried vaccine is given by staff well trained in proper techniques.^{3,7-9} Hypertrophic scarring and keloid formation may be minimised by injection at or below the insertion of the deltoid, or by using the less accessible sites—the inner aspect of the arm, the thigh, or the buttock.¹⁰ Serious hypersensitivity reaction, osteitis, and intrathoracic and intra-abdominal lesions have been reported only rarely and often without full

bacteriological or histological confirmation. Disseminated BCG infection is rare and occurs only in patients with serious defects in cell mediated immunity.^{7,8}

Since the introduction of mass BCG immunisation of schoolchildren the incidence of tuberculosis in all ethnic groups—in tuberculin positive and tuberculin negative, vaccinated and unvaccinated groups—has steadily fallen.^{2,11} The annual decrease in notifications of tuberculosis attributed to the protective effect of BCG, at a maximum 4.1% from 1965-71, fell to 1% in 1978-83.¹² Thus, despite its safety and efficacy BCG is no longer uniformly offered to all British schoolchildren, and district health authorities have inconsistent vaccination policies.¹³ The present low risk of infection for young white adults in England and Wales¹⁴ depends more on higher living standards, effective chemoprophylaxis, and chemotherapy than on vaccination.^{15,16} The BCG school vaccination programme has not been cost effective since the mid-1970s,¹⁷ and if it were to be stopped altogether there would be no disaster, only a temporary slowing in the rate of decline in new notifications.¹⁴ These assertions are based on clear evidence from countries where routine BCG vaccination has been stopped.¹⁸

If, then, the arguments favour abandoning the continued