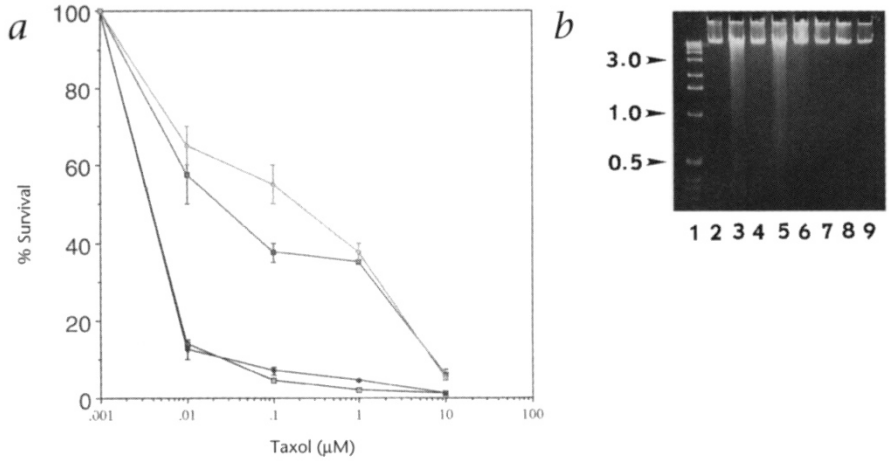

Fig. 2 Loss of p53 leads to Taxol resistance in teratocarcinoma cells. *a*, %-Clonogenic survival of parental PA-1 cells (□), G418-resistant PA-1/Neo cells (◆) and the two E6-transfected clones PA-1/E6-5 (■) and PA-1/E6-10 (◈) is shown as a function of Taxol dose. Clonogenic survival was determined as previously described[2]. *b*, Integrity of genomic DNA derived from parental PA-1 cells (lanes 2, 3), PA-1/Neo cells (lanes 4, 5), PA-1/E6-5 cells (lanes 6, 7) and PA-1/E6-10 cells (lanes 8, 9) is shown either in the absence (lanes 2, 4, 6, 8) or presence (lanes 3, 5, 7, 9) of 0.3 μg/ml adriamycin for 48 h. Isolation of genomic DNA was performed as previously described[3]. DNA size markers (in kilobases) are indicated by arrows corresponding to appropriate bands on a "1.0-kb ladder" (lane 1).

parental, neo and E6-transfected cells (data not shown).

We checked the chemosensitivity of the E6-expressing clones as compared with parental or a neo-clone and found that they not only became more resistant to adriamycin, carboplatinum and etoposide (not shown), but surprisingly (given the recent report by Wahl *et al.*[1]) also to the antimicrotubule agent Taxol (Fig. 2*a*). These ovarian teratocarcinoma cells became more than 100 times as resistant to Taxol following targeted degradation of wild-type p53 through expression of E6. We also checked the E6-expressing H460 lung cancer cells[2] for their sensitivity to Taxol, and again surprisingly did not observe a two log enhancement in chemosensitivity as has been reported by Wahl *et al.*[1] for normal fibroblasts lacking wild-type p53 function (data not shown). We correlated the increased resistance of the E6-expressing ovarian carcinoma clones with decreased apoptosis induction following chemotherapy (Fig. 2*b*). Endonucleolytic cleavage of DNA was only observed in PA-1 parental cells (Fig. 2*b* lane 3) or G418-resistant PA-1 cells (Fig. 2*b* lane 5) but not in E6-transfected clones (lanes 7 and 9) following exposure to chemotherapy.

Our observations suggest that there may not only be tissue-specific differences in the relationship between p53 status and chemosensitivity[2], but there may be a difference between loss of wild-type p53 function in normal fibroblasts versus cancer cells. It is not therefore obvious that the acquisition of p53 mutations associated with cancer progression would have predictable consequences with respect to sensitivity to Taxol therapy. It may be of interest to study the effects of p53 loss in the normal precursors of the ovarian teratocarcinoma cells. It is clear that disruption of wild-type p53 function by HPV16 E6 did not increase Taxol sensitivity in PA-1 ovarian teratocarcinoma cells. More work needs to be done to better understand these relationships in ovarian as well as other cancer cells.

GEN SHENG WU & WAFIK S. EL-DEIRY
Howard Hughes Medical Institute
Department of Medicine and Genetics
University of Pennsylvania
School of Medicine
415 Curie Boulevard, CRB 437
Philadelphia, Pennsylvania 19104, USA

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Edward Jenner 200 years on

To the editor — At a time when infectious diseases are in the headlines and continue to threaten mankind, there is a bicentennial that, surprisingly, is being forgotten, yet lends itself to some reflection.

On 14 May 1796 Edward Jenner injected an 8-year-old boy, James Phipps, with the pustules of cows harboring a disease similar to smallpox, the first vaccine. This event occurred after a cultural debate that spanned the whole eighteenth century. Now, 200 years and a worldwide effort have eradicated small pox.

It is interesting to note that the triumph of the smallpox vaccine occurred in the absence of a sound theory of immunity. It was based on careful epidemiological weighing of the risk-to-benefit ratio of vaccination. This should prompt some thought in those who view progress in science as founded mainly on formulation and disproving of general hypotheses. It is also interesting that at the time of Jenner's experiment, the social soil was most apt to accept vaccination. Years of debate had involved the most vivid intellects of the century (Voltaire in France, Beccaria and Parini in Italy), as well as politicians and royalty. Of course, the way vaccination was introduced and practiced in the eighteenth century can be criticized (orphans and slaves were widely used for experimentation); however, all in all, a social attitude must underlie the development of vaccines and the accompanying political debate. Molecular biology and immunology now offer potent conceptual and molecular tools, but are we, as industrialized societies, ready to invest a decent amount of financial and intellectual resources in tackling the infectious diseases that still plague most of the world? Social concern was, and still should be, an integral component of medicine.

Finally, Jenner's paper was rejected by the Royal Society and published at his own expense. Rejection of Jenner's paper by the most prestigious forum of the time should serve as a warning against excessive fetishism surrounding journal impact factors and other citation measures.

ALBERTO MANTOVANI
Istituto di Ricerche Farmacologiche "Mario Negri"
Laboratory of Immunology
Via Eritrea 62, 20157 Milan, Italy
University of Brescia, 25123 Brescia, Italy