later elaborated by Knudson. The supposed monoclonal origin and time scale of development of papillomas are entirely consistent with current views.

Unfortunately, we do not know why this research was not continued. The war or some other misfortune may have prevented it, but that work, being 30 years ahead of the papers usually cited, shows great imagination.

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## Treatment for glioma

Sir—If a new treatment for recurrent glioma, however ingenious, is followed by a median survival of only 31 weeks, compared with 23 weeks in controls, should this really be described as “an effective treatment” in the way that Brem and colleagues (April 22, p 1008) do in their abstract? Having told us that those treated in this way live a few weeks longer than untreated controls, why do they not just leave it at that? Readers can then decide for themselves whether to call this an effective treatment—or a treatment that is having very little effect.

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## Glutathione S-transferase alpha as marker for hepatocellular damage in pre-eclampsia and HELLP syndrome

Sir—Pre-eclampsia and the syndrome of haemolysis, elevated liver enzymes, and low platelets (HELLP) represent major causes of maternal and perinatal morbidity and mortality. Correct assessment of hepatocellular damage is crucial in the clinical management of these patients. Glutathione S-transferase alpha (GSTa) is a cytosolic enzyme found in high concentrations in the liver (3 mg/g wet weight) with a short plasma half-life of 2 h. Since no clinical conditions other than hepatic diseases are known to cause raised plasma concentrations of GSTa, plasma measurements of this enzyme may therefore provide a fast, specific, and sensitive index of acute hepatocellular damage.1

We studied plasma concentrations of GSTa and alanine aminotransferase (ALT) in 21 patients with pre-eclampsia (phase IV diastolic blood pressure >100 mm Hg and proteinuria >500 mg per 24 h, median 30 and range 26–39 weeks’ gestation), 8 of whom had developed HELLP syndrome according to the criteria of Sibai.2

Plasma GSTa concentrations were measured with a sandwich ELISA. The assay uses an anti-human GSTa mouse monoclonal as catching antibody and rabbit anti-human GSTa antisem, both developed in our laboratory, as the source of the detecting antibodies.3 The assay has no cross-reactivity with other human GSTs and the variations within and between assays are 2±5% and 7±3%, respectively. An upper normal reference value of 10±0 ng/mL was calculated by use of plasma samples from 225 healthy blood donors. In 71 women during the third trimester of uncomplicated pregnancy, plasma GSTa values were always below 10±0 ng/mL. The upper limit of the reference range

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Figure: Plasma concentrations of GSTa and ALT expressed as multiples of upper normal reference value in 2 patients (A and B) with HELLP syndrome

for ALT in our hospital is 30 IU/L. 16 women had raised ALT values (median 4·2 times upper normal reference range, 1·5–35·7). In all these patients GSTa values were also raised (median 37±0 times the upper normal reference value, range 1·5–35·7). In all these patients GSTa concentrations was between 100 and 1000 times greater than that of ALT.

In addition 2 nulliparous women (A and B) who developed HELLP syndrome were studied prospectively after admission at 26 and 28 weeks’ gestation (figure). Both women had substantial rises in plasma GSTa during recurrent periods of severe epigastric pain. The rises preceded those of ALT by several hours and the relative magnitude of the abnormality of GSTa was remarkably greater (almost 10 times) than that of ALT.

For ALT 5 of 16 patients had mean values above the upper reference limit (30 IU/L). 14 patients had mean values above the upper reference limit for GSTa (2×5 times the upper reference limit of 15 ng/mL).

Measurement of plasma GSTa might provide an earlier and much more sensitive indicator of acute hepatocellular damage, as well as of its resolution, in pre-eclampsia and the HELLP syndrome than the aminotransferases. Better
Thyrotropin-releasing hormone for prevention of neonatal respiratory disease

Sir—the ACTOBAT group report (April 8, p 877) the results of their trial of thyrotropin-releasing hormone (TRH) for prevention of respiratory disease in premature infants. Their findings seem to differ from previously published findings, including our trial.1 The ACTOBAT trial is an important contribution in view of the large sample size and analysis by intention-to-treat. With respect to the failure to demonstrate efficacy, it should be noted that although not statistically significant, there was a trend in the ACTOBAT analysis by intention-to-treat. With respect to the failure to find the ACTOBAT results, we did not find a significant increase in maternal blood pressure, defined as an increase greater than 20 mm Hg, with a lower level of existing maternal hypertension as an exclusion criterion.1 We are undertaking a large US collaborative trial of antenatal TRH with our previous treatment protocol, plus routine postnatal surfactant as clinically indicated, and we will analyse by intention-to-treat as for the ACTOBAT trial. We are doing serial measurements of thyroid hormones and a TRH stimulation test to investigate suppression and responsiveness of the thyroid axis. Our results together with those of the planned European trial should elucidate the risks and benefits of this treatment. In the meantime we agree with the conclusion of the ACTOBAT investigators that antenatal TRH cannot be recommended for routine clinical use at present.

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Sir—the ACTOBAT group study of antenatal TRH for prevention of neonatal respiratory disease used a lower dose (200 μg) than that administered in previous trials. In fetal sheep, glucocorticoids alone can enhance lung maturation, but a better effect than that of glucocorticoids is observed only with a combination of glucocorticoids, triiodothyronine, and prolactin.1 Thus the efficacy of TRH may depend on its ability to maintain raised fetal concentrations of triiodothyronine and prolactin. Furthermore, fetal TRH concentrations themselves may be important if part of the beneficial effects of this hormone are mediated through its direct neurotransmitter action. We have shown that 400 μg TRH can increase both triiodothyronine and prolactin in preterm human fetuses.2 However, this effect lasts only 6—8 h—hence the recommendation to use 400 μg every 8 h in antenatal efforts to mature the fetal lung. A lower dose, such as that used in ACTOBAT, does not stimulate prolactin release in the preterm human fetus.3 Our preliminary findings on the dose-response to TRH in preterm human fetuses also suggest that, whereas maternal administration of 200 μg may result in increases of fetal triiodothyronine which are comparable with those observed after 400 μg, the increase in the pituitary hormones thyrotropin and prolactin are lower.4 Although we do not know how far the concentrations of fetal TRH are modified by maternal administration of this hormone, lower doses of TRH probably result in lower fetal levels as well. Thus it is quite likely that ACTOBAT used less TRH than is necessary to provide optimum increases of fetal hormones to mature the fetal lung.