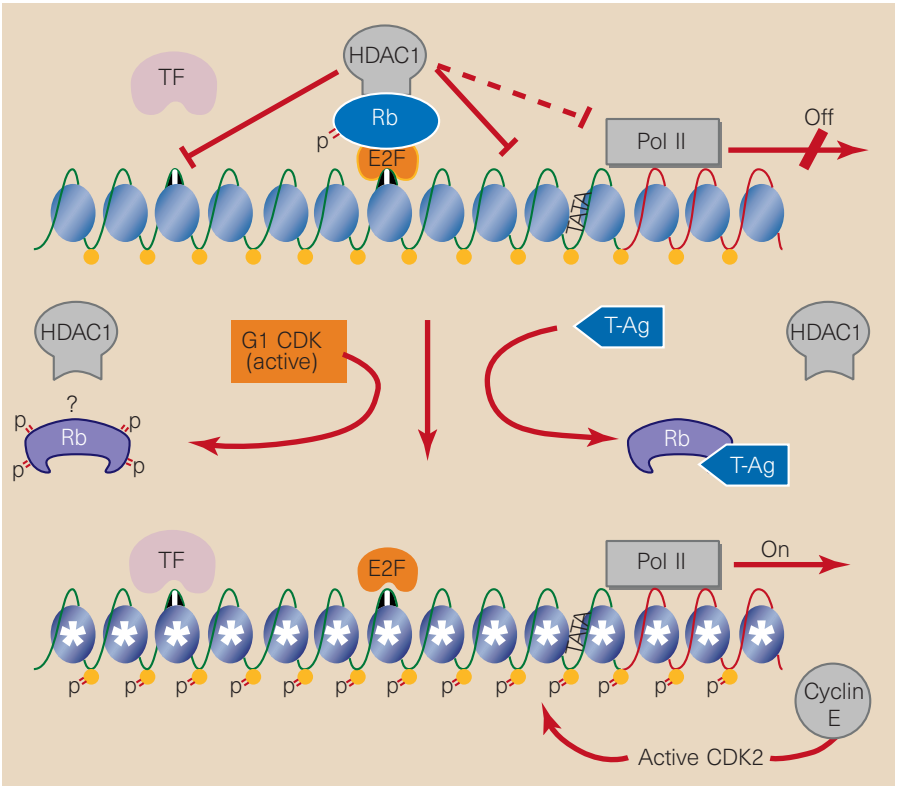


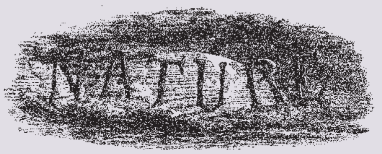
Figure 1 **Retinoblastoma and the road to cancer. Retinoblastoma (Rb) is a tumour-suppressor protein that represses gene expression by modulating the architecture of chromatin. Brehm *et al.*[3] and Magnaghi-Jaulin *et al.*[4] have found that Rb tethers the E2F protein to the histone deacetylase HDAC1, to form a complex that prevents expression from E2F-bound promoters. HDAC1 may facilitate the removal of highly charged acetyl groups (white asterisks) from core histones, causing a tighter association between the DNA and nucleosomes, and preventing transcription factors (TF) from gaining access to the DNA. This repression is released when, on exposure to proliferative signals, G1 cyclin-dependent kinases (CDKs) phosphorylate Rb. Viral oncoproteins such as T-Ag may also bind Rb, causing it to dissociate, and allowing transcription to occur from the E2F-bound promoters. (Figure provided by Lynda Chin.)**

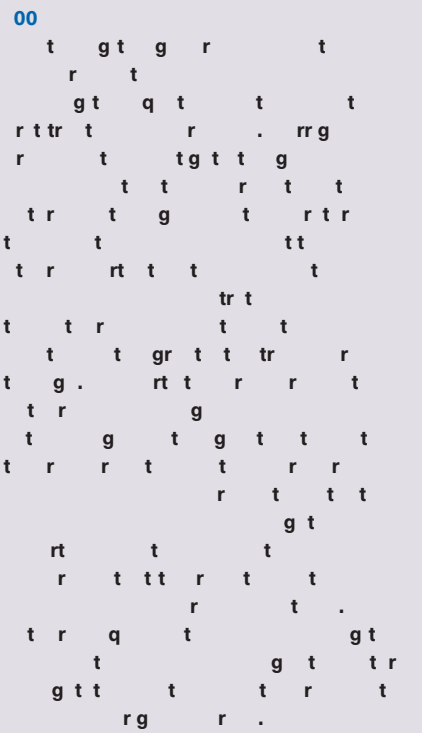
cycle control because Rb and HDAC1 can act together to repress the cyclin E promoter, and trichostatin A (a potent inhibitor of HDAC1) can alleviate this repression.

The issue of how HDAC1 represses an E2F-regulated promoter remains open. The widely held view is that HDACs mediate the removal of highly charged acetyl groups from core histones. This causes a tighter association between DNA and nucleosomes, thereby impairing the access of transcription factors to DNA-recognition elements[9]. Conversely, histone acetyltransferase-mediated acetylation would destabilize nucleosomes, increasing the accessibility of promoters[9]. Non-histone proteins may also be affected by HDAC1, particularly those involved in the regulation of gene expression. Such speculations are supported by the fact that basal[10] and sequence-specific[11] transcription factors are targets of acetylation.

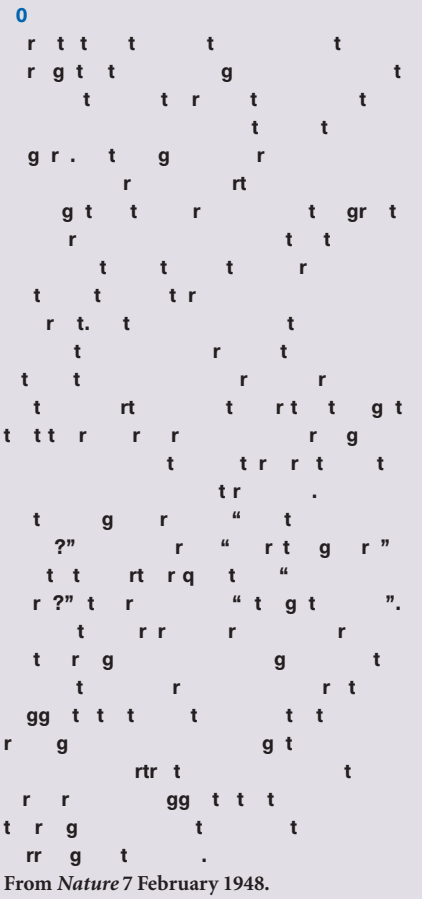
The findings reported by Brehm *et al.*[3] and Magnaghi-Jaulin *et al.*[4] join an expanding number of studies that implicate chromatin modulation in the genesis or suppression of cancer. For example, the E1a oncoprotein can stimulate proliferation by disrupting the growth-suppressive interaction between p300/CBP and another histone acetyltransferase, P/CAF (ref. 12). A further example of the cancer–chromatin connection comes from observations that the potent anti-oncogenic activities of the Mad(Mxi1)/Sin3 complex correlate with its ability to recruit HDAC (ref. 13).

Repression of E2F-bound promoters by Rb is considered to be one of the key mechanisms by which Rb induces growth arrest[1]. As such, the interaction between HDAC1 and Rb may represent a main point of attack for the oncogenic process. To test this hypothesis, Brehm *et al.* and Magnaghi-Jaulin *et al.* conducted two types of experiment. One showed that tumour-derived point mutations and deletions that impinge on the A/B pocket abolish both Rb-induced repression and Rb-associated deacetylase activity, correlating with increased transactivation through E2F. The other experiment documented that specific viral oncoprotein sequences can disrupt the interaction between Rb and HDAC1[3,4], and displace deacetylase activity from Rb *in vitro*[3]. This finding is significant because viral oncoproteins invariably target and inactivate the critical components of growth-suppressor





From *Nature* 3 February 1898.



From *Nature* 7 February 1948.