



Figure 1 B- and T-cell development. Immunoglobulin (Ig) heavy-chain and T-cell receptor (TCR) β -chain genes are assembled by *V(D)J* recombination in pro-B and pro-T cells, respectively. Heavy and β chains then pair with 'surrogate' receptor subunits to generate the pre-B-cell receptor (pre-BCR) and pre-TCR, respectively. These receptors are critical for developmental and proliferative events leading to pre-B and pre-T cells. Here, a second wave of recombination occurs, assembling immunoglobulin light-chain and TCR α -chain genes, and allow expression of the complete BCR and TCR. Expression of the *RAG1* and *RAG2* genes continues in TCR-expressing thymocytes until the cells either receive a positive selection signal or they die. Expression of the *RAG* genes was previously thought to be terminated in immature B cells (dotted line), but the results of Yu *et al.*³ and Monroe *et al.*⁴ indicate that expression drops gradually as the cells develop further.

RAG2 protein. In contrast, Monroe and colleagues' RAG2-GFP protein appears to be appropriately regulated. But it could conceivably be relatively unstable, and, because it is expressed at only modest levels, detection of cells with low expression of the gene is a problem.

Both groups detected a subset of RAG-expressing B cells in the spleen. Expression of the *RAG* genes was previously thought to terminate in the bone marrow, but it now seems that expression decreases relatively slowly as B cells mature, and continues in at least some splenic B cells (Fig. 1). Yu and colleagues also show that adoptively transferred mature splenic B cells that do not express the *RAG* genes do not reactivate expression of GFP or RAG when stimulated by antigen or cytokines. How, then, can one explain earlier results showing rapid induction of *V(D)J* recombination in splenic and lymph-node B cells? Yu *et al.* propose that, when a developing B cell encounters a low-affinity antigen, the maturation process is slowed down, prolonging the time that the B cell expresses the *RAG* genes. This implies that rapidly induced recombination occurs in immature B cells which have never stopped expressing *RAG*, and that it occurs without an increase in *RAG* expression lev-

els. It is not clear how to reconcile this idea with the increased *RAG* expression triggered by cytokines or antigen in B cells in the lymph nodes^{8,14}. Nor is it easy to explain the extensive *V(D)J* recombination in stimulated splenic B cells if, indeed, they continue to express the very low levels of *RAG1* and *RAG2* seen in unstimulated cells.

Perhaps the greater mystery is how to explain the delayed appearance of *RAG*-expressing B cells in splenic germinal centres^{7,10}. Monroe *et al.*⁴ show that such cells have many phenotypic properties of pre-B cells, and these authors advance some intriguing theories to account for this. One possibility is that, during an immune response, some mature B cells reacquire immature characteristics (including expression of *RAG*), as originally proposed by Han *et al.*⁷. But Yu and colleagues' results argue against this idea. Alternatively, these mysterious cells may be true pre-B cells that either arose in the spleen or were recruited from the bone marrow. Recruitment of pre-B cells to sites of an active immune response would be a new and unexpected phenomenon.

Finally, Yu *et al.*³ and Monroe *et al.*⁴ extend the striking parallels between B- and T-cell development by showing that, in both lineages, termination of *RAG* expression



100 YEARS AGO

It should not be necessary at this time of day to emphasise the fact of the imperial character of the Royal Gardens, Kew, still it would appear there are many inhabitants of Great Britain whose notion of the value of this establishment is limited by their desire for a local public park suited to the recreation of dwellers in and about London. Several incidents have of late shown this – witness the recent preposterous proposal brought forward in the House of Commons to throw the gardens open to cyclists! Suggestions of this kind are on the face of them, to those aware of the true character of the gardens, too absurd for discussion, yet there is an element of danger in this appeal to the selfish instincts of that large body of pleasure-seekers who are veritable Gallios in their contempt for science, especially when its just claims place an obstacle to the gratification of their pleasure whims. From *Nature* 10 August 1899.

50 YEARS AGO

Now that the long-established mechanical unit, the joule, is to assume so much greater importance, there is one matter ... that should be decided, and that is how the word is to be pronounced. There was not long ago a correspondence on the subject in *Nature* which revealed the most surprising disagreement, and more recent inquiries among various people in Manchester confirm these doubts. Some make the great man's name rhyme with 'cool', some with 'cowl', and some even with 'coal'. Thus, Sir Arthur Schuster called him 'Jowl', while Prof. H. B. Dixon, who had a curiosity in such matters, said the name was disyllabic as 'Jo-ull', which would be nearly 'Joal'. On the other hand, Osborne Reynolds in his memoir on him, though he never states how the name is spoken, mentions that it derives from the village of Youlgreave in Derbyshire from which his family came, which would make it 'Jool', and this is the preference of at least some of the surviving family. However all this may be, the word is now to be international, and it is unreasonable to make foreigners suffer from the horrors of English orthography; it therefore seems best that the joule as a unit of heat should rhyme with the word 'cool' – of course, giving the initial 'j' its proper English value. From *Nature* 13 August 1949.