100 YEARS AGO

The average child is capable of a quality of thinking that leads its elders, when they try to follow it, into an intellectual quagmire of inconsistency and absurdity from which they beat an inglorious retreat by angrily bidding it "not to ask silly questions". If they bid themselves not to give silly answers their request would be just… I once heard a child ask its mother, "What makes the flowers grow?" Promptly came the answer, "Jesus!" No wonder when children's intellects are muddled with such unprovable assertions that they cease to think… Granting that the results of a mother's pernicious training can be remedied in later life, it is obviously waste of valuable energy, time and money to organise an elaborate system of education to undo that which ought never to have been done. And therefore I urge that our national progress depends very largely upon "the hand that rocks the cradle": if it rocks with an intelligent purpose, it will be well with our future men; if not, then England, like Tyre, Venice and Rome… "must be led, through prouder eminences, to less pitied destruction."

From *Nature* 11 April 1901.

50 YEARS AGO

May I reply to Mr. Tyman's letter in *Nature* of February 10, p. 245? The Swedish alphabet has twenty-eight letters, of which Å is the twenty-sixth. This letter is not a modified 'A'. The relation of 'Å' to 'A' is somewhat analogous to that of 'W' to 'U'. Unfortunately the British Committee of 1937, oblivious of this, recommended the use of 'A' as an abbreviation for the ångström. The half-dozen examples quoted by Mr. Twyman of the use of 'A' in reports and books written in English since 1937 merely show that the recommendation of this Committee has quite naturally been followed. There will soon appear two English reports on symbols superseding that of 1937. One of these is sponsored by the Royal Society, the Faraday Society and the Physical Society; the other is sponsored by the British Standards Institute. Until these new reports are published, I cannot state with complete certainty what symbol they will recommend for the ångström. I can, however, affirm that both Committees charged with preparing these reports are aware of the distinction between the letters 'Å' and 'A' in Swedish.

From *Nature* 14 April 1951.

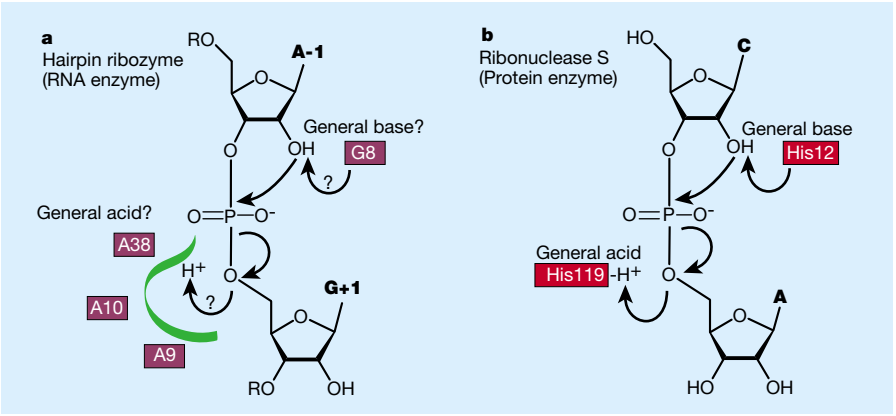

Figure 1 **RNA and protein enzymes. Possible similarities between the reaction mechanisms of** a, **the hairpin ribozyme, and** b, **the protein enzyme ribonuclease S (RNase S). In the RNase S reaction mechanism, two active-site histidines (His 12 and His 119) promote general acid–base catalysis while a lysine (not shown) provides charge neutralization. Guanine and adenine bases at specific positions (G8, A9, A10 and/or A38) might have similar functions in hairpin-ribozyme catalysis. The newly solved crystal structure[1] shows that G8 contacts the 2′-OH nucleophile and the three adenines line a pocket (green) near the 5′-oxygen leaving group.**

that are each interrupted by a stretch of non-complementary sequence, termed stems A and B, which end in loops (see Fig. 1b of the paper on page 781). Juxtaposition of these stems results in an RNA secondary structure that resembles a hairpin, hence the ribozyme's name.

The hairpin is small, but deciphering its catalytic mechanism has been diabolically difficult. Without insight from structural studies, it was initially assumed that the ribozyme promotes its chemical reaction using active-site metal ions by a mechanism similar to that of protein-based polymerases or phosphatases[2]. This idea had a reassuring symmetry, in that it suggested that the RNA and protein worlds are chemically equivalent at their catalytic centres. The principle appears to be true for some larger ribozymes. But it does not apply to the hairpin and other small self-splicing ribozymes because they are fully active in the absence of metal ions[3,4]. Although this result implied that nucleotides within the hairpin's loops are directly involved in catalysis, it was not clear how they might contribute.

Given this mechanistic uncertainty, Rupert and Ferré-D'Amaré's high-resolution crystal structure[1] comes as a boon. The hairpin ribozyme was crystallized in its docked conformation with an inhibitor at the cleavage site to prevent reaction. As seen repeatedly in other RNA structures, the loop segments are not loops at all, but are closed by a series of non-canonical interactions between the bases. These interactions create wide minor grooves that are used for tight helical packing near the active site. Both stem structures were previously solved in isolation by nuclear magnetic resonance spectroscopy[5,6], but their conformations are altogether different in the docked structure. For example, only two of seven non-canonically paired bases in the isolated stem B structure are retained in the docked complex. This difference suggests that dramatic conformational rearrangements occur in both loops upon active-site assembly, a prediction supported by biochemical data[7].

But what does the structure tell us about the catalytic mechanism of this ribozyme? As expected, the active site is devoid of metal ions and is composed entirely of RNA functional groups. Of particular importance, alignment of the two loops orients the reactive phosphate of G + 1 (guanosine + 1) for 'in line' attack by the nucleophile, the 2′-OH of A − 1 (adenosine − 1) (Fig. 1a; the numbers refer to the base distance from the reactive phosphate). This is a strong indication that the crystallized ribozyme is in its active conformation. This alignment results from the startlingly irregular geometries adopted by G + 1 and A − 1, which leave the bases unstacked from each other and rotated in opposite directions. Proper orientation of the nucleophile and leaving group may explain much of the hairpin's catalytic potential.

The structure of the hairpin ribozyme's active site does not resemble that of a protein polymerase, but is there another protein enzyme to which the hairpin can be compared? Rupert and Ferré-D'Amaré suggest that the distorted conformation around the reactive phosphate is reminiscent of ribonuclease S (RNase S), a protein that catalyses an equivalent reaction and induces similar distortions at the nucleotides surrounding the reactive phosphate[8]. However, in addition to nucleophilic alignment, RNase S uses a general acid–base mechanism of catalysis[9]. One histidine in its active site abstracts a proton from the 2′-OH nucleophile (general base catalysis), while the second donates a proton to the 5′-oxyanion leaving group (general acid catalysis) (Fig. 1b).