



100 YEARS AGO

It is evident that the moors, valleys and plains of Yorkshire have been depopulated in comparatively recent times. The disappearance of so many conspicuous species is commonly attributed to the glacial period, but I think that the action of man has been still more influential. The extinct animals are such as man hunts for profit or for his own safety. Many of them, among others the cave-bear, *Machairodus*, Irish elk, mammoth and straight-tusked elephant, are known to have lasted into the human period. That so many of them were last seen in the company of man is some proof that he was concerned in their death.

The journey to Tomsk, in Siberia, promises to become quite a pleasant one under the new organisation of the direct trains. The train, which left St. Petersburg on July 31, offered even more comforts to the travellers than the best American trains... It had also, in addition to the usual luxurious fittings of the best Pullman saloon cars, a piano in the first class saloon, a free library provided with a good selection of works on Siberia, as well as with all papers which appear in the towns passed by the train during the journey; a pretty outlook-saloon at the back of the train, with meteorological instruments in it; and even a dark room for amateur photographers, arranged in the second class lavatory. All the furniture is covered with a special material which can be washed with a disinfecting fluid without being injured.

From *Nature* 25 August 1898.

50 YEARS AGO

The curriculum for 'applied medicine', if it can so be called, is always immediately affected by changes in fundamental medical knowledge... Not surprisingly, the medical course has in consequence increased over the past thirty years or so from four to six years. If the same process were to continue, and the strong claims of new interests were admitted, there is no saying how many years would have to be allowed for the training of a doctor in twenty years time.

From *Nature* 28 August 1948.

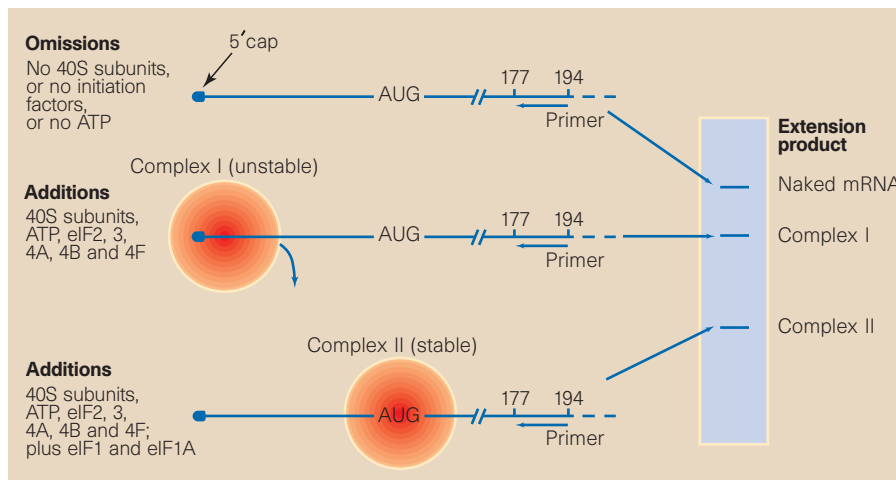


Figure 1 The toeprinting assays used by Pestova *et al.*² to map the position of the bound 40S ribosomal subunit on β -globin messenger RNA. First, initiation complexes were formed by incubation of the components listed on the left; mRNA and Met-tRNA_i were present in all assays, as was a non-hydrolysable analogue of GTP (this stage of initiation needs GTP as a co-factor, but not GTP hydrolysis). Then the primer was added and extended by incubation with reverse transcriptase and radiolabelled dNTPs. The complementary DNA primer extension products were resolved by gel electrophoresis, and the results are shown on the right. The diagram is roughly to scale in terms of the positions of the leading edge of the 40S subunit and of the AUG initiation codon relative to the 5' end.

(itself a component of the pre-initiation complex) and which also has a subunit that binds to the 5' cap.

The 40S ribosomal subunit then scans the mRNA, the scanning being coupled to or immediately following unwinding of the RNA: both eIF4F and 4A have RNA helicase activity dependent on ATP hydrolysis and on initiation factor eIF4B. It is unclear whether the ATP hydrolysis required for initiation is entirely ascribable to the action of these helicases, or whether it is due, in part, to the movement of the 40S subunit itself being driven by ATP hydrolysis. After the AUG initiation codon has been recognized (presumably by pairing with the anticodon of Met-tRNA_i associated with the 40S subunit), the final steps are GTP hydrolysis, the release of all initiation factors associated with the 40S subunit, and the joining of the large (60S) ribosomal subunit. Translation of the mRNA to synthesize the encoded protein then begins.

Why no mention of eIF1 and 1A in this scheme? The reason is that when the initiation pathway was elucidated in the late 1970s, it was found that omission of these two small proteins from the assays caused only a small reduction in initiation efficiency. No well-defined function has been ascribed to either of them and they have often been taken to be non-essential. Nevertheless, the genes encoding both of these factors are necessary for viability in yeast^{4,5}, and so it may be that there was some cross-contamination of the preparations used in the earlier assays.

Pestova *et al.*² have revisited those experiments of the late 1970s, but with three important refinements: they used recombi-

nant eIF1, 1A, 4A and 4B expressed in bacteria; the multi-subunit factors (eIF2, 3 and the eIF4F complex) were from mammalian sources but were almost certainly purer than the earlier preparations; and, instead of studying the interaction of the 40S ribosomal subunit with mRNA solely by sucrose density gradients, the authors used toeprinting assays (Fig. 1) to determine the location of the bound 40S subunit on the mRNA (natural β -globin mRNA).

The striking result was that, when the reaction included ATP and all of those factors thought to be strictly necessary for initiation (eIF2, 3, 4A, 4B and the eIF4F complex), the resulting 40S/mRNA complex (complex I) not only tended to fall apart on sucrose gradient centrifugation, but the toeprinting assay showed that the leading edge of the 40S subunit was positioned just 21–24 nucleotides downstream of the 5' cap (Fig. 1). This implies that the subunit was centred just a few residues from the cap and had not scanned far, if at all. Moreover, complex I must undergo cycles of spontaneous dissociation and (re)formation, because the delayed addition of excess competitor mRNA resulted in the disappearance of complex I formed on the original mRNA.

Most surprisingly, both of the 'Cinderella factors', eIF1 and 1A, were required to produce a complex (complex II), which was not only stable to sucrose gradient centrifugation and to challenge by competitor mRNA, but which had the 40S subunit centred over the authentic initiation codon (Fig. 1). Neither factor alone produced this outcome.

So, is complex I the elusive intermediate in the scanning process? The answer, unfor-