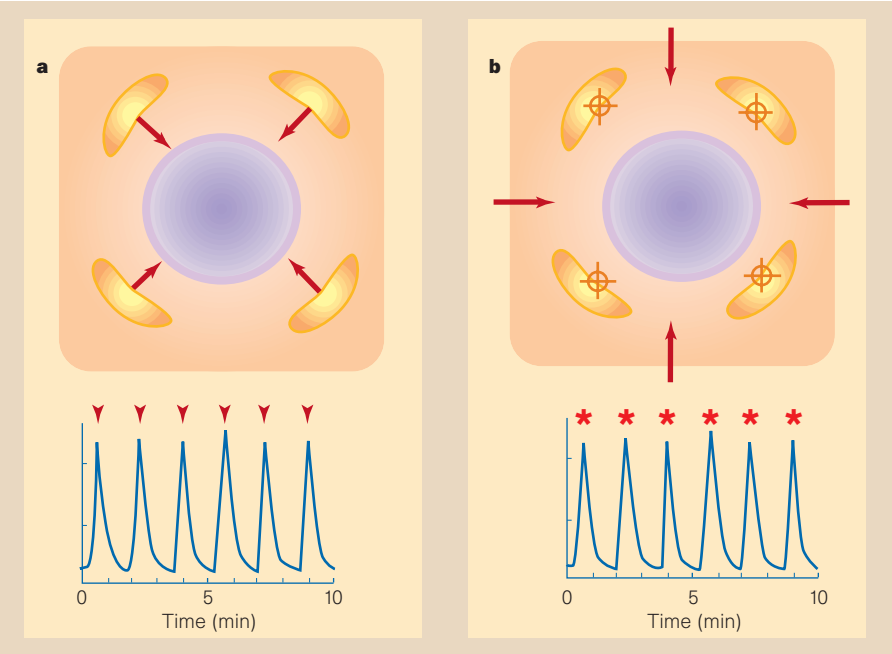

Figure 1 **New procedures for generating homogeneous oscillations in the concentration of cytosolic Ca^{2+}.** a, **The method developed by Li *et al.*[4]. Cells are loaded with a caged version of inositol-1,4,5-trisphosphate, which is released by rhythmic flashes of ultraviolet light (arrowheads). Activation of the corresponding receptor in the endoplasmic reticulum leads to the release of Ca^{2+} to the cytosol (arrows) in an oscillating manner.** b, **The method developed by Dolmetsch *et al.*[3]. Irreversible blockade of SERCA, a Ca^{2+} pump in the endoplasmic reticulum, by thapsigargin (⊕) prevents accumulation of Ca^{2+} within intracellular stores, so these become depleted. The resulting increase in the permeability of the plasmalemma to Ca^{2+} (due to activation of the store-dependent CRAC channels; arrows) is used to generate oscillations in the concentration of cytosolic Ca^{2+}. These oscillations are driven by rises in the concentration of Ca^{2+} in the incubation medium (asterisks).**

the case of the faster frequencies, this may have been due to desensitization of the $Ins(1,4,5)P_3$ receptor[4].

Dolmetsch *et al.*[3] took a completely different approach — rather than stimulating $Ins(1,4,5)P_3$-sensitive Ca^{2+} stores, they depleted them. Jurkat T cells were exposed to thapsigargin, which irreversibly blocks the specific Ca^{2+} pumps known as sarcoplasmic–endoplasmic reticulum Ca^{2+}-ATPases (SERCAs). This resulted in activation of the store-operated Ca^{2+} (CRAC) channels in the plasmalemma, leading to a stable increase in permeability of the cells to Ca^{2+}. Using this procedure, oscillations of controlled amplitude (generated by rapidly changing the concentration of Ca^{2+} in the incubation medium) were dynamically clamped. So, these oscillations were generated at the cell surface, without any involvement of intracellular receptors (Fig. 1b).

Dolmetsch *et al.* used this system to compare the effects, on NF-AT-induced gene expression, of oscillations and stable responses of similar average amplitude. They then looked, in parallel, at the activation of three Ca^{2+}-activated transcription factors — NF-AT, Oct/OAP and NF-κB. In each case, activation was monitored by the expression of reporter genes driven either directly or through the promoters of specific cytokines. Again, oscillations proved to be more efficient than stable increases — but only when the average concentration of cytosolic Ca^{2+} remained below ~300 nM. Moreover (and even more excitingly), whereas the three transcription factors were activated in parallel with stable increases in the concentration of Ca^{2+}, such parallel activation was observed for the oscillations only if they occurred with a period of 400 seconds or less. With oscillations of a lower frequency, only NF-κB seemed to be stimulated. These low-frequency oscillations are thought to be triggered by intercellular signalling events, so they are important in cell physiology.

How can these results be explained? Activation of the three transcription factors studied by Dolmetsch *et al.* is mediated by a Ca^{2+}-dependent phosphatase called calcineurin. The transcription factors exist as complexes in the cytoplasm, and they are dephosphorylated by calcineurin. This induces dissociation of the complexes, followed by migration of the active subunits to the nucleus[6,7]. The ensuing expression of specific genes is not controlled directly by Ca^{2+}, but it keeps going as long as the transcription factor remains in the nucleus. During oscillations, therefore, the work of transcription factors does not decline with the decreasing concentration of cytosolic Ca^{2+} — it can persist for longer. Moreover, because NF-AT returns to the cytoplasm

100 YEARS AGO

Striking is the difference in appearance between a Solpuga fasting and a Solpuga full fed. In the former the abdomen shrivels up, the segments shrinking one within another like the several pieces of a half-closed telescope; in the latter the expansion is carried to such an extent that the distended abdomen much resembles a short thick sausage, far surpassing in size and weight the rest of the body and limbs. This is brought about by the imbibition of water and of the fluid and semi-fluid tissues of their prey. In support of their water-drinking propensities, the following passage, written by the Soudan war correspondent to the *Standard* (October 19, 1897), may be cited: "One day in my tent [at Kerma] I heard a rustle like that of a silk dress. A big, ugly, yellow hairy beast, with nippers like a crab, was moving fast as a mouse over the moist ground near the zeer [porous water jar] in the corner of my tent. At last he settled down to suck the water from the sides of the jar." The writer of the passage just quoted had previously spoken of this animal as the "famous abu-shabat, the terror of the Soudan in the way of spiders, as large as your hand and ten times more venomous than a scorpion."

From *Nature* 28 April 1898.

50 YEARS AGO

Mainini has described (*Semana Medica*, 64, 337, March 1947) a pregnancy test in which, following injection of pregnancy urine into the male toad (*Bufo arenarum* Hensel), liberation of spermatozoa into the urinary bladder occurs within three hours; the same animal can be used again after five days. Drs. Octavio Rodrigues Lima and Oswaldo Gelli Pereira, of the Obstetrical Clinic, Medical School of Rio de Janeiro, University of Brazil, state in a communication submitted to the Editors that they have confirmed this work, using as test animal the male toad (*Bufo marinus*), as the species used by Mainini was not available to them. ... Sixty tests were carried out with the urine of amenorrhœic women. Positive results were found between half an hour and two hours, and were confirmed clinically in all cases. The test appears to be simple, economical and reliable.

From *Nature* 1 May 1948.