a calcium storage site, by showing that Ca^{2+} accumulation occurs even at low Ca^{2+} concentrations at which mitochondria cannot accumulate calcium or when mitochondrial calcium uptake is inhibited[10,15]. Thus ER in liver cells, synaptosomes and macrophages has been shown to accumulate Ca^{2+} at the low concentrations required of a physiological regulator. A more direct approach has been to visualize, through electron microscopy, sometimes combined with electron-probe X-ray microanalysis, the deposits of calcium (or strontium, which acts as a more electron-opaque substitute for calcium) oxalate in the ER of synaptosomes[5], squid axons[13], photoreceptor cells[16] and endothelium[17].

For the ER to regulate cell Ca^{2+}, it must have not only a mechanism of calcium uptake, but also one of calcium release. On stimulation of cells by hormones or transmitters, the signal for Ca^{2+} release may be mediated by a change in the properties of the surface membrane, most commonly depolarization, and/or by a diffusible intracellular second messenger. The feasibility of the first mechanism is suggested by the close (about 10–20 nm) proximity of ER subsurface cisterns to the plasma membrane. These structures, which resemble the 'surface couplings' of cardiac, smooth and some skeletal muscles, have been observed in some non-muscle cells[18-20] and may be present in all eukaryotic cells. There is also evidence that electrical stimulation of the surface membrane of fibroblasts, known to contain subsurface cisternae, can release calcium from an intracellular source, probably the subplasmalemmal ER[20]. The second possibility, that an endogenous intracellular messenger releases calcium from the ER, has recently received strong support. Thus in pancreatic cells[21], in isolated hepatocytes[22] and in insulinoma cells[23], a phosphatidylinositol metabolite, inositol trisphosphate, has been shown to release intracellular Ca^{2+} from a non-mitochondrial site, presumably the ER. It was further observed that caffeine releases intracellular Ca^{2+} from a non-mitochondrial source in rat nerve cells[24], reminiscent of the caffeine-induced Ca^{2+} release from the SR of skeletal muscle[25]. Caffeine-induced Ca^{2+} release from the ER has also been observed in macrophages[8], but not in liver[15].

The first inkling that mitochondria might not have a significant role in the regulation of cytoplasmic Ca^{2+} followed the observation that, in the presence of physiological Mg^{2+} concentrations, the affinity of isolated mitochondria for Ca^{2+} is too low[26]. In the normal cell, Ca^{2+} fluctuates, at most, from 5×10^{-8} to 5×10^{-6} M between rest and maximal activation, while the Ca^{2+} concentration required for a half-maximal rate of calcium transport by mitochondria is 10^{-5} M or higher[17,26]. Furthermore, in intact cells, the calcium content of mitochondria is relatively low compared with that of the SR and even after sustained increases of Ca^{2+} within the physiological range in maximally contracted muscle, mitochondrial calcium content is not increased[17]. On the other hand there is no question that in the presence of inorganic phosphate (P_i), mitochondria can accumulate massive amounts of calcium and, perhaps, become initial sites of pathological calcification when cell Ca^{2+} (and P_i) rises to abnormally high levels due to cell damage. In injured cells, mitochondria may serve as the final low-affinity/high-capacity buffer for Ca^{2+}, and moderate loading of mitochondria by Ca^{2+} may be an alternative to cell death. It remains to be shown that such cells survive and that mitochondria can discharge their excess Ca^{2+} to the extracellular space via the various surface-membrane-mediated calcium transport mechanisms that must ultimately maintain the steady-state calcium content of cells. One candidate for a naturally occurring 'transmitter' that can release mitochondrial calcium has been identified: sodium can discharge calcium from mitochondria isolated from heart, brain and skeletal muscle, although not from liver, kidney and smooth muscle mitochondria[2].

What, then, is the physiological role, if any, of the complicated mitochondrial calcium transport system so passionately pursued by biochemists for nearly 20 years? One possibility is that, although mitochondria do not have the capacity to regulate cytoplasmic Ca^{2+}, they themselves can respond to changes in cytoplasmic Ca^{2+} concentrations by producing very small changes in the Ca^{2+} of the mitochondrial matrix space[27]. A number of the mitochondrial enzymes (dehydrogenases) are sensitive to Ca^{2+} in the range 0.1–10 μM. Therefore, small changes in mitochondrial Ca^{2+}, achievable by even a relatively inefficient (low-affinity) calcium transport system, could have important effects on oxidative metabolism.

While far from complete, the case (even in plants) for the ER as the major intracellular regulator of Ca^{2+} has clearly become much stronger during the last few years. The lumen of the ER communicates with the perinuclear space where, in some instances, high concentrations of calcium (or strontium) have been demonstrated. Perhaps an ER system, capable of accumulating calcium against a gradient in the nuclear membrane, was acquired with the nucleus when cells became eukaryotes. Unfortunately for biologists, living systems often evolve to use different structures and mechanisms to solve the same problems (photoreceptor systems and contractile regulation are but two examples), and grand unifying schemes with fundamental principles applicable to 'all cells' are rare. In the regulation of cell Ca^{2+} by the ER in all nucleated cells, we may have a rare example. □

1. Fiskum, G. & Lehninger, A.L. in *Calcium and Cell Function* Vol. 2, 39 (Academic, New York, 1982).
2. Carafoli, E. & Crompton, M. *Ann. N.Y. Acad. Sci.* **307**, 269 (1978).
3. Otsuka, M., Ohtsuki, I. & Ebashi, S. *J. Biochem.* **58**, 188 (1965).
4. Trotta, E.E. & DeMeis, L. *Biochem. biophys. Acta* **394**, 239 (1975).
5. Blaustein, M.P. *et al. J. Physiol., Paris* **76**, 459 (1980).
6. Immelmann, A. & Soling, H.-D. *FEBS Lett.* **162**, 406 (1983).
7. Moore, L. & Pastan, I. *Ann. N.Y. Acad. Sci.* **307**, 177 (1978).
8. Hirata, M. *et al. J. Biochem., Tokyo* **94**, 1155 (1983).
9. Black, B.L. *et al. J. biol. Chem.* **256**, 322 (1981).
10. Martonosi, A.N. in *Muscle and Nonmuscle Motility* Vol. 1 (ed. Stracher, A.) 233 (Academic, New York, 1983).
11. Tsudzuki, T. *J. Biochem., Tokyo* **86**, 777 (1979).
12. Heilman, C. *et al. Biochem. biophys. Res. Commun.* **114**, 584 (1983).
13. Henkart, M.P. *et al. Science* **202**, 1300 (1978).
14. Tiffert, T. & Brinley, F.J. Jr *Cell Calcium* **2**, 89 (1981).
15. Burgess, G.M. *et al. J. biol. Chem.* **258**, 15336 (1983).
16. Walz, B. *J. ultrastruct. Res.* **81**, 240 (1982).
17. Somlyo, A.P. *et al.* in *Calcium Phosphate Transport Across Biomembranes* (eds Bronner, F. & Peterlik, M.) 87 (Academic, New York, 1981).
18. Rosenbluth, J. *J. Cell Biol.* **13**, 405 (1962).
19. Gardiner, D.M. & Grey, R.D. *J. Cell Biol.* **96**, 1159 (1983).
20. Henkart, M.P. & Nelson, P.G. *J. gen. Physiol.* **73**, 655 (1979).
21. Streb, H. *et al. Nature* **306**, 67 (1983).
22. Joseph, S.K. *et al. J. biol. Chem.* **259**, 3077 (1984).
23. Prentki, M. *et al. Nature* **309**, 562 (1984).
24. Neering, J.R. & McBurney, R.N. *Nature* **309**, 158 (1984).
25. Weber, A. & Herz, R. *J. gen. Physiol.* **52**, 750 (1968).
26. Scarpa, A. & Graziotti, P. *J. gen. Physiol.* **62**, 756 (1973).
27. Denton, R.M. & McCormack, J.G. *FEBS Lett.* 119, 1 (1980).

Andrew P. Somlyo is at the Pennsylvania Muscle Institute, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania 19104.

100 years ago

ARRANGEMENTS have been made by the Council of the Scottish Meteorological Society for the completion this season of the Observatory of Ben Nevis. The first portion of the Observatory was, it may be remembered, opened in October last, and since the observers went into residence continuous hourly observations have been made of the conditions of the atmosphere at the top of the Ben, with special reference to temperature, pressure, humidity, and motion. From the discussion of these, and what were daily made by Mr Clement L. Wragge in the summers of 1881 and 1882, by the Secretary, Mr Buchan, the Council have been fully confirmed in the high expectations they had formed concerning the value of a high-level station, both in its bearing upon general meteorological problems, and also with reference to possible forecasts for the British Islands. The additions to be made to the Observatory will just double its size, and enable the three observers — who during the winter have been considerably cramped in their one apartment — to work under more comfortable conditions. On the south of the present doorway there is to be erected a shelter for tourists. The estimated cost of the completion of the Observatory will be 800l., which is, however, irrespective of a heavy item of charge for conveying on horseback the materials to the top of the hill. It is understood that the cost of equipment and maintenance of the Observatory heretofore has been heavier than was anticipated. The directors intend shortly to make a fresh appeal for funds to the public, which will no doubt be as liberally responded to as was their last.

From *Nature* **30**, 179, 19 June 1884.