the weak base within 4 min of warming cells with adherent virus to 37°C.

The low *p*H of endosomes may bring about dissociation of ligand and receptor protein. In experiments reported by Anne Hubbard (Johns Hopkins University), liver galactose receptor–ligand complexes are endocytosed at 16°C, a temperature at which endosome–lysosome fusion is impaired[5]. However, ligands still dissociate from receptors and the latter return to the cell surface, despite the absence of ligand degradation. It may be that these endosomes represent the elusive sites of receptor recovery — an acid wash through which regular 'preening' of the cell surface can be achieved.

The fate of the ligands and soluble content of endosomes is clearer — they are transferred to secondary lysosomes and degraded, which for them is a one-way trip. Exceptionally, certain receptors, for epidermal growth factor or the Fc portion of immunoglobulin, also enter lysosomes. Whether this is because their affinity for ligands is unaffected by the low *p*H in the endosome or because of intrinsic differences in the molecular structures of such receptors, remains an open question.

Equally enigmatic is the direction taken by the receptors which do recycle following the dissociation of their ligands or their normal recovery during membrane recycling in the absence of a specific ligand. Specific labels are lost at this stage and anti-receptor immunocytochemistry can only demonstrate the total cellular distribution, not the pathways of recycling. However, the endocytosis of cationized ferritin (CF), a positively charged, electron-dense marker which binds tightly and non-specifically to membranes, has provided some indirect evidence of how receptors recycle.

Kinetic studies of the endocytosis of CF by pituitary cells and lymphocytes made over a number of years by Marilyn Farquhar[9,10] show that after its appearance in endosomes, CF enters the trans elements of the Golgi stacks. After 30 min, CF appears on the inner membrane of secretion granules and therefore on the exocytotic leg of its journey through the cell. Autoradiography of iodinated surface membrane proteins suggests essentially the same route — although slow techniques such as conventional fixation and electron microscopy provide images which reflect rate-determining stages in the flux through a cell, so this picture may be incomplete.

In at least one case there is good evidence that CF follows the same route as receptors. Richard Rodewald (University of Virginia) has described transcytosis or diacytosis (passage through a cell) of maternal IgG across the intestinal epithelium of new-born rats[11]. The immunoglobulin is bound by Fc receptors at the gut lumen and is discharged into the neonatal circulation. Efficient segregation of IgG–Fc receptor complexes from soluble markers occurs in the endosomes near the sites of absorption (coated pits). The integrity of the receptor–ligand complex may be favoured in this case by low *p*H, since the neutral *p*H of the neonatal blood affects dissociation of the complex when it appears at the basolateral cell surface. CF accompanies the ligand through the same pathway and is exocytosed, still in membrane-bound form, at the sites of IgG release.

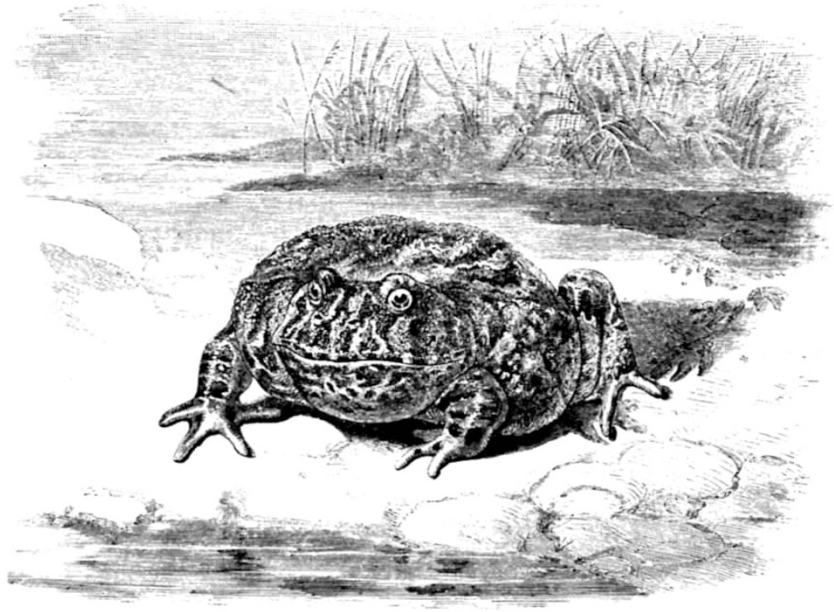
Considerable advances have been made in this popular area of cell biology, to which an increasingly 'molecular' approach is being applied. There remain, of course, major problems. We still need to account for the fast recycling times of cell membrane (seconds in the neuromuscular junction) and certain receptors (a minute or less for low-density lipoprotein receptor). Do these membrane components have time to follow the pathways described above? The relationship between endocytosis of membrane components through coated and uncoated regions is also unclear. Most telling of all, however, is the degree of our ignorance of the nature of the signals which direct this extensive traffic of receptor proteins and orchestrate the flow of cellular membrane. To understand these, we need techniques which allow us to observe the membranes from within the cell itself. □

1. Willingham, M.C. & Pastan, I. *Cell* **21**, 67 (1980).
2. Bretscher, M.S., Thomson, J.N. & Pearse, B.M.F. *Proc. natn. Acad. Sci. U.S.A.* **77**, 4156 (1980).
3. Goldstein, J.L., Anderson, R.G.W. & Brown, M.S. *Nature* **279**, 679 (1979).
4. Willingham, M.C. & Pastan, I.H. *Cell* **21**, 67 (1980).
5. Wall, D.A. & Hubbard, A.L. *J. Cell Biol.* **90**, 687 (1981).
6. Geisow, M.J., Hart, P., D'Arcy & Young, M.R. *J. Cell Biol.* **89**, 645 (1981).
7. Maxfield, F.R. & Tycko, R. *J. Cell. Biol.* **91**, 212a (1981).
8. White, J., Matlin, K. & Helenius, A. *J. Cell Biol.* **89**, 674 (1981).
9. Farquhar, M.G. *J. Cell Biol.* **77**, R35 (1978).
10. Ottensen, P.D., Courtoy, P.J. & Farquhar, M.G. *J. exp. Med.* **152**, 1 (1980).
11. Rodewald, R.D. & Abrahamson, D.R. *J. Cell Biol.* **91**, 270 (1981).

100 years ago

Amongst the batrachians exhibited at the Zoological Society are several species of gigantic size when compared with their puny representatives in this country, such as the Agua Toad (*Bufo agua*) of Brazil and the Ocellated Bladder-Frog (*Cystignathus ocellatus*) of Buenos Ayres. But by far the most remarkable of these forms in the series is the Adorned Ceratophrys, or "Esquerzo" of the natives of the Argentine Republic — a large toad of brilliant colours and extraordinary form, of which a figure (Fig 16) is now given, taken from a water-colour sketch prepared by Mr Ernest Griset.

The Esquerzo was discovered by Mr Darwin during the celebrated voyage of H.M.S. *Beagle*, and first described by the late Prof. Bell in the "Zoology of the Voyage of the *Beagle*." This monster inhabits the pampas of Buenos Ayres, and is said to feed chiefly on its smaller brethren of the same class. Mr Ernest William White, F.Z.S., to whom the Society is indebted for one of the two specimens now in the Gardens, specially mentions it in his lately-published "Cameos from the Silver-Land" as one of the characteristic forms of the grassy plains of the Argentine Republic. "In the damp grass," he says, may often be perceived the leering eyes and mottled black and green body of the huge Esquerzo (*Ceratophrys ornata*), whose gaping mouth crammed with the body of an unfortunate sapo (toad), and surmounted by threatening horns, inspires terror. This said Esquerzo bears an awfully spiteful character, and is credited with the deaths of many children.



THE ESQUERZO, OR BARKING TOAD

From *Nature* **25**, 393; February 23 (1882).