sets should allow the changes in temperature and moisture to be bounded.

How are we to solve this problem? We definitely need more studies like that of Bonnefille *et al.*, exploring tropical and semi-tropical palaeo-temperatures at a range of elevations and at widely separated locations. From the modelling end, we need to determine why the different GCMs produce different tropical responses to increases in CO_2. The uncertainty in tropical climate sensitivity emphasizes that we do not yet understand global climate sensitivity, and makes dynamical and regional predictions for the coming century that much more difficult. □

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CELL BIOLOGY

Trawling for receptors

Graham Warren

ENDOCYTOSIS is the process whereby substances on cell surfaces are enclosed in membrane-bound vesicles and taken into the cell. These substances then pass through the cell in what is usually thought of as an orderly itinerary of discrete stages (Fig. 1). But video images of living cells show that the endocytic pathway may be more interconnected than was previously thought. In the conventional picture, receptors that cluster in clathrin-coated pits in the plasma membrane pass through a series of internal, membrane-bound compartments[1], the first of which is the early endosome. Transferrin receptors are recycled almost immediately from this compartment back to the cell surface[2] whereas receptors for epidermal growth factor pass to late endosomes. In the process, these receptors become incorporated into budding vesicles that pinch off and congregate within what can then be called a multi-vesicular body[3] (Fig. 2). These are processed further[4] and are eventually delivered to lysosomes. There is general agreement that each compartment in the endocytic pathway is a discrete, separate entity. In fact, it is difficult to see how parts of the pathway could function were this not the case. But on page 335 of this issue[5], Hopkins *et al.* report observations that strongly suggest that the early part of the endocytic pathway is a network of interconnected tubules.

What Hopkins *et al.* have done is to use different fluorescent tags to follow both the transferrin and epidermal growth factor (EGF) receptors in living cells using video recording at low light levels. At steady state, the transferrin receptor reveals an interconnected, tubular network, through which occasional pulses of receptor appear to be moving at high speed (up to 1 $\mu m\ s^{-1}$). The network is very extensive but has not been seen before because it is labile: sensitive to low levels of ultraviolet light, lowered temperature and the chemical fixatives that are normally used to prepare samples for immunofluorescence and electron microscopy.

The effect of adding EGF is particularly dramatic as anyone who has seen the video will confirm. The network grows and the EGF receptors appear rapidly in boluses that move along the tubes at speeds of around 0.05 $\mu m\ s^{-1}$. Electron microscopy confirms that these boluses are multi-vesicular bodies (MVBs). The MVB has always been thought of as a discrete organelle and any tubular extensions have been short and thought to be

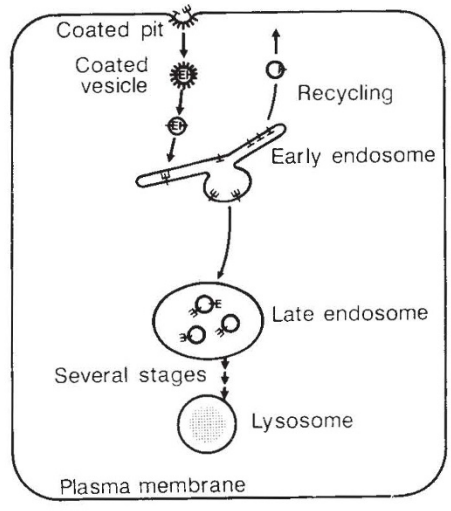

FIG. 1 The usual picture of receptor-mediated endocytosis. EGF receptors (—**E**) and transferrin receptors (**T**) are ingested by the cell and pass through a series of stages before being respectively destroyed or recycled. Multivesicular bodies can form at almost any stage from maturing endosomes or early lysosomes.

Ann Bishop (1899–1990)

THE death on 7 May of Ann Bishop marks the end of an era during which the direction of British protozoology was influenced by three remarkable women — Doris Mackinnon (1887–1956), Muriel Robertson (1883–1973) and Ann Bishop herself.

A Manchester zoologist by training, Bishop worked all her life in Cambridge and made numerous and diverse contributions to protozoology including the nuclear and ciliary structural biology of the ciliate *Spirostomum* and various aspects of the biology of *Trichomonas* and *Entamoeba* species. She was involved in the discovery that the causative agent of blackhead in turkeys was *Histomonas meleagridis*, but it was as a malariologist that she became best known.

In the years overlapping the Second World War, Bishop made vitally important contributions to the understanding of drug resistance in malaria. In the late 1930s, as new antimalarial drugs were becoming available, there was great concern that these might easily evoke resistance as had happened with antibiotics. But there were few procedures or protocols that had been laid down for the investigation of this problem, and Bishop had to develop experimental systems to assess resistance. Her choice was *Plasmodium gallinaceum* in chickens, and by 1938 she had demonstrated resistance to proguanil. She also discovered the time at which resistance occurred, that it persisted even after mosquito transmission and, more importantly, that there was cross-resistance between proguanil and other dihydrofolate reductase inhibitors which she later discovered extended to pyrimethamine. A decade later, with the availability of rodent malarias, she turned her attention to these and established procedures, which have now become standard in laboratories all over the world. Bishop also set herself the task of discovering how drug resistance occurs, a problem that remains unsolved. She also began to investigate the trigger for gametocytogenesis in malaria parasites, a question that 25 years later is still unanswered.

From 1942 to 1964, she was director of the Medical Research Council's Chemotherapy Research Unit at the Molteno Institute in Cambridge where many British and foreign scientists trained in experimental parasitology and benefited from her wide experience. Her work was recognized by her being elected to a Fellow of the Royal Society in 1959, a rare accomplishment for a woman at that time, especially for one engaged in essentially medical research. Those who knew Ann Bishop will remember her with affection as a great scientist and a gracious lady. F. E. G. Cox

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