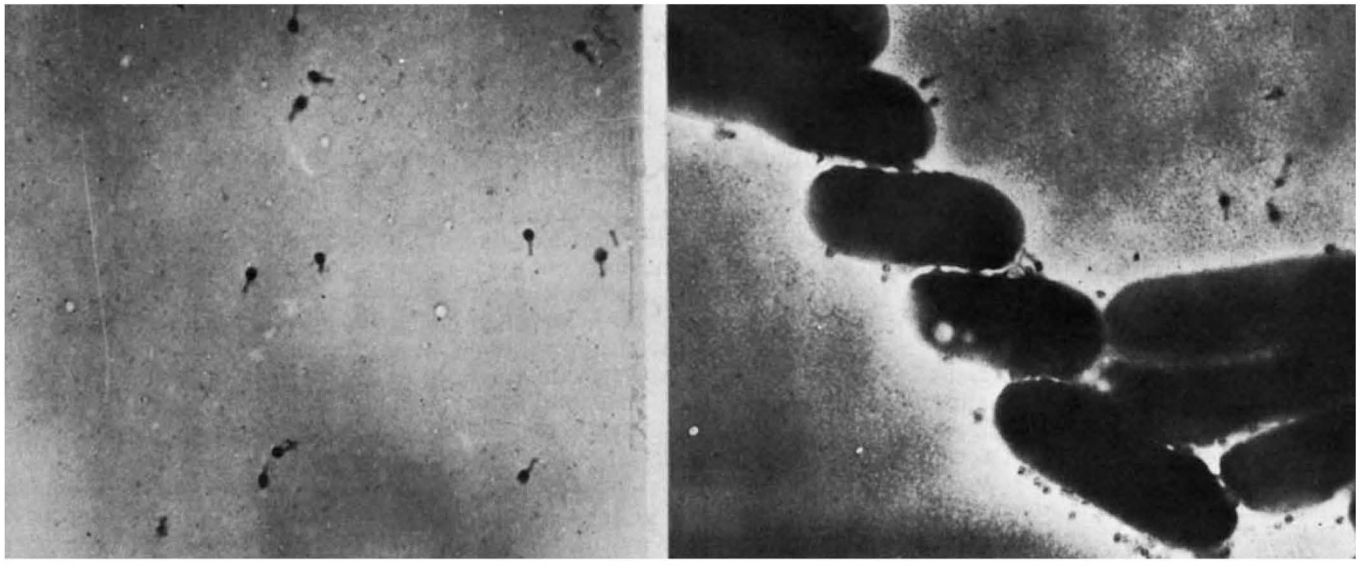
# The virus verified

UNTIL the advent of the electron microscope, viruses were to the biologist what atoms had long been to the physicist: entities which could not be seen on account of their small size but which proved exceedingly fruitful in accounting for observed phenomena.

The earliest electron micrographs to reveal unmistakably the head-and-tail structure of viruses were of the viral strain originally called 'anti-coli PC', and now known as bacteriophage T2, taken by Thomas Anderson(RCA Research Laboratories) and Salvador Luria (Columbia University) in the week of 2 March 1942 and published the same year in *Proceedings of the National Academy of Sciences U.S.A.* (**28**, 127). Anderson recorded the phage particles at a magnification of x45,000 (below left) and their attachment to the gamma or PC strain of *Escherichia coli* bacilli at x50,000 (below right), both on Kodak Lantern slide glass plates using an RCA model B electron microscope and very highly concentrated stocks of bacteriophage.

A typical bacteriophage T2 particle possesses a head 60–80 μm in diameter and a tail 120–130 μm long and 20 μm thick. In the right-hand micrograph, the bacteriophage is seen attaching itself to the cell walls of a bacterium, living up to its name of 'bacterium eater'. With hindsight, Anderson describes the ensuing viral attack as follows: rather like a hypodermic syringe, the "attachment causes the tail sheath to contract which drives the needle [an extension of the neck below the head, invisible on the 1942 micrographs] into the bacterial wall, which somehow induces the DNA contained in the head to pass through the needle into the bacterium. There the DNA takes over the synthetic machinery of the bacterium to make some 100 daughter phage particles in 20 minutes. The bacterium then lyses to release the daughter particles into the medium where each of them can encounter a fresh bacterium to repeat the life cycle". The infecting phage particles adsorbed onto the bacterial wall remain stuck fast, their delivery complete and their role fulfilled. **Jon Darius**

*Selected from* Beyond Vision *by Jon Darius of the Science Museum (Natural History), London (to be published in April by Oxford University Press). Micrographs reproduced by courtesy of T.F. Anderson, now at the Fox Chase Institute for Cancer Research.*



insulin they will secrete the unprocessed molecule (R. Kelly, University of California, San Francisco). Conversely, AtT-20 cells, which inducibly process and secrete adrenocorticotropic hormone, can also be induced to process and secrete insulin after transfection with the proinsulin gene. Unstimulated AtT-20 cells will secrete the unprocessed hormones at low levels, presumably via the constitutive path. This is suggestive, though not strictly conclusive, evidence for two separate vesicular pathways.

And the most recent work of Schekman and his colleagues suggests that yeasts also have distinct secretory paths — although the evidence in this case concerns only constitutive secretion. Schekman and his co-workers find that isolated secretory vesicles contain all the secretory enzymes of yeast but only a subset of the plasma membrane proteins. If the membrane proteins are travelling by different routes, however, they converge at the final step: mutations affecting the last stage in secretion also prevent the appearance of any membrane protein at the cell surface.

For vesicle traffic originating at the cell surface — and particularly concerning the recycling of membrane receptors — there is some hope that human mutants may soon provide important insights. Receptor recycling has already been reviewed in *Nature*[10] and elsewhere[11,12] and it is now generally accepted that surface receptors enter the cell via clathrin-coated pits whence they may either return to the cell surface after releasing their ligand, or progress to the lysosomes for degradation.

With the discovery that some forms of familial hypercholesterolaemia are due to mutations that interfere with the biosynthesis or post-translational processing of low-density lipoprotein (LDL) receptors[11], it has become clear that defects in cholesterol uptake may make it possible to identify and understand branchpoints in intracellular vesicle pathways. J.L. Goldstein and his colleagues (University of Texas, Dallas) have, for example, identified a mutant receptor that binds cholesterol normally but fails to aggregate in coated pits; and they are now in the process of cloning LDL receptor cDNA, which will enable them to analyse such defects at the molecular level.

Mutant receptors, and mutant viruses borrowing cellular secretory paths, may help to reveal mechanisms that for the time being can only be inferred from morphological and kinetic studies. But the most powerful approach should lie with the temperature-sensitive mutants of yeast: first, because they may affect components of the selective mechanism rather than the selected molecule; and second, because their temperature sensitivity makes it possible to examine defects that would otherwise be lethal. □

*Miranda Robertson is an associate editor of Nature.*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