
## 50 Years Ago

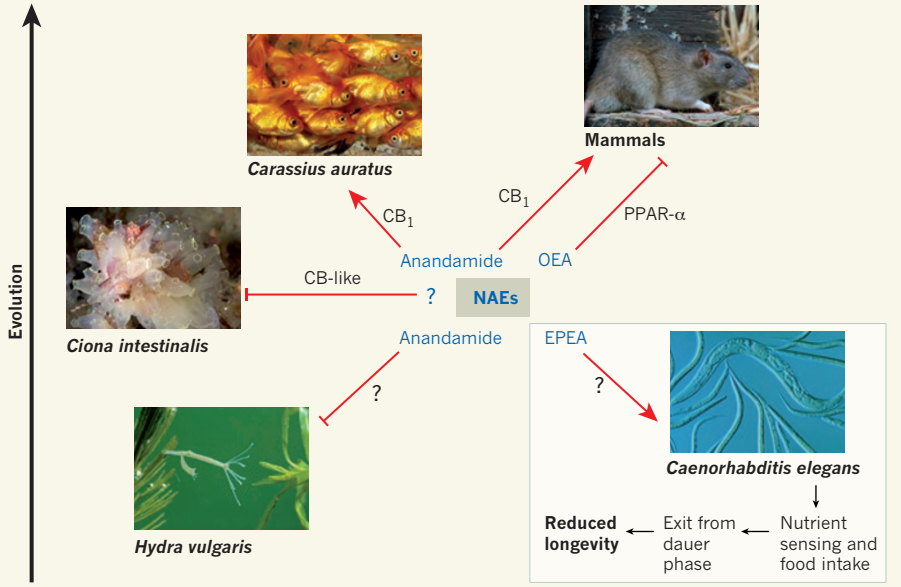
The [World Health Organization] programme for the eradication of malaria from the world is reported as having made significant progress in various fields, although handicapped by a persistent shortage of funds. Sixty-one countries are now fully engaged in this programme; in another nineteen, planning has reached an advanced stage, and, in seventeen other areas—mainly in Africa—the Organization is assisting with preliminary work … The World Health Organization's assistance to Governments for the control of yaws, smallpox and tuberculosis, leprosy and various diseases increased significantly during the year. Medical research was intensified on practically all communicable diseases, the main co-ordinated effort being centred on virus diseases and on bilharziasis [schistosomiasis].

**From *Nature* 13 May 1961**

## 100 Years Ago

Whatever may be thought of Mr. Willett's so-called daylight-saving scheme, it is impossible not to admire the persistence with which he pursues the idea, and secures support for it from city corporations, town councils, chambers of commerce, members of Parliament, and other people who are attracted by the advantages offered, and do not realise how unscientific the scheme is, or the gravity of the objections to the adoption of a variable standard of time-reckoning. We do not believe for an instant that the Government is likely to give facilities for legislation on the lines of the Summer Season Time Bill … The scheme is unworthy of the dignity of a great nation … We cannot think that the Government will lend its support to proposals which … would make us the laughing-stock of the enlightened people of the world.

**From *Nature* 11 May 1911**




FROM BOTTOM: K. WOTHE/MINDEN PICTURES/FLPA; S. STAMMERS/SPL; K. TELNES/IMAGEQUESTMARINE.COM; G. LACZ/FLPA; REINHARD/ARCO/NATUREPL.COM

**Figure 1 | *N*-Acylethanolamines, feeding behaviour and lifespan.** *N*-Acylethanolamines (NAEs) are evolutionarily conserved lipids: they occur in a wide range of organisms, including the coelenterate *Hydra vulgaris*, the chordate *Ciona intestinalis* and the fish *Carassius auratus*. In all cases, these small lipids either inhibit (blunt-ended arrows) or enhance (pointed arrows) feeding behaviours. In mammals, $CB_1$ and PPAR-α receptors mediate the effects of NAEs such as anandamide and *N*-oleoylethanolamine (OEA), respectively, although NAE receptors in some of the other species are unknown (black question marks). Inset: Lucanic *et al.*[2] show that in the nematode *Caenorhabditis elegans*, *N*-eicosapentaenoylethanolamine (EPEA), the most abundant NAE in this organism, enhances feeding behaviour. This leads to exit of the animals from the dauer phase — which they originally enter when faced with food shortage — and to reduced longevity.

Using other types of mutants, the authors further show that NAE deficiency and dietary restriction extend *C. elegans* lifespan through the same developmental effects (see below and Fig. 1).

Conversely, supplementing the worms' diet with *N*-eicosapentaenoylethanolamine (EPEA), the most abundant NAE in *C. elegans*, inhibited dietary-restriction-induced lifespan extension in wild-type worms; it also had the same effect in more long-lived mutants in which nutrient sensing was impaired because they lacked the signalling molecule TOR, which is necessary for food intake. Lucanic *et al.* propose that NAE-mediated signalling, which is presumably acting in the pharynx, coordinates nutrient sensing and energy status with the metabolic and developmental changes that ultimately determine lifespan in worms.

Rodents cope with prolonged semi-starvation by — among other things — reducing the levels of appetite-inducing endocannabinoids in their hypothalamus (the brain area that mediates homeostatic control of energy intake)[4]. Instead, in the face of dietary restriction, *C. elegans* enters a quiescent and low-energy-consuming state known as the dauer phase, in which NAE levels are at their lowest[2]. Lucanic and co-workers[2] show that administration of exogenous EPEA can bring the nematode out of the dauer phase, and they propose that it does so by providing "a false signal of high nutrient availability" and by reversing "the metabolic adaptation to reduced food availability that confers lifespan extension".

Perhaps the only missing information in the researchers' extensive study is the receptor through which EPEA, and possibly other NAEs, produce their effects in *C. elegans* — like most other invertebrates, this animal does not express the equivalent of cannabinoid receptors[8]. The authors did look at 'indigenous' members of the several classes of receptor that are activated by these lipids in mammals, including orphan G-protein-coupled receptors, nuclear receptors and ligand-activated ion channels[9]. But genetic deletion of proteins related to such potential NAE targets in *C. elegans* did not affect the ability of EPEA to rescue the worm from the dauer phase[2], leaving the identity of the receptor mediating NAE signalling in this animal a mystery.

Nevertheless, apart from the discovery of novel molecular mechanisms underlying dietary-restriction-induced developmental changes in *C. elegans*, the elegant work of Lucanic and colleagues' sends another noteworthy general message: across nearly all types of living organism, NAEs are of fundamental importance as signalling molecules that act through different receptors (with sometimes more than one receptor mediating the effects of a particular NAE)[9], and have diverse biological actions.