

Maternal age and traits in offspring

The timing of a mouse's first litter influences the development of her pups.

We have investigated the effect of the age at first pregnancy in mice on maternal steroid hormone levels and how these influence the growth and sexual maturation of their pups. We find that early-adolescent and middle-aged pregnant mice have less serum oestradiol and a different pattern of serum testosterone compared with young-adult pregnant mice. Grown offspring of early-adolescent and middle-aged mothers have lower body weight and delayed puberty, and males have smaller reproductive organs than those produced by young adults. Female offspring themselves produce pups whose birthweight depends on the age at pregnancy of their grandmothers. Changes in a female's physiology during ageing can thus alter the growth and reproductive traits not only of her own offspring but also of subsequent generations.

We measured the concentration of steroid hormones in serum from pregnant CF-1 females between gestation day 16 and the last day of pregnancy, when the reproductive organs of fetuses are undergoing differentiation (Fig. 1). Serum testosterone was significantly lower in middle-aged than in either early-adolescent or young-adult pregnant females, and peaked significantly later (at gestation day 18) in the young-adult females. Serum oestradiol was significantly lower in early-adolescent and middle-aged pregnant females relative to the young adults, whereas serum progesterone did not differ significantly as a function of maternal age (Fig. 1a).

Offspring (F_1 generation) are designated by maternal age at mating in early adolescence (EA), young adulthood (YA) or middle age (MA). As young adults, YA males had significantly greater body weight and heavier testes and epididymides than EA or MA males (Fig. 1b). Maternal age seemed to influence testicular sperm production and storage, irrespective of its effect on the body weight of male offspring. The small size of MA male offspring was surprising, given that they were born in litters containing 40% fewer pups than YA males (Fig. 1a, legend) and all animals were delivered by caesarean section and reared by young-adult foster mothers.

Body weight at weaning (23 days old) of EA female offspring (12.1 ± 0.2 g) was significantly lower than for YA females (13.3 ± 0.3 g) and MA females (12.9 ± 0.4 g), which did not differ significantly. After being weaned, F_1 females were paired with a stud male until visibly pregnant. Based on the age at delivery of young and a 19-day pregnancy, the age at which the EA females

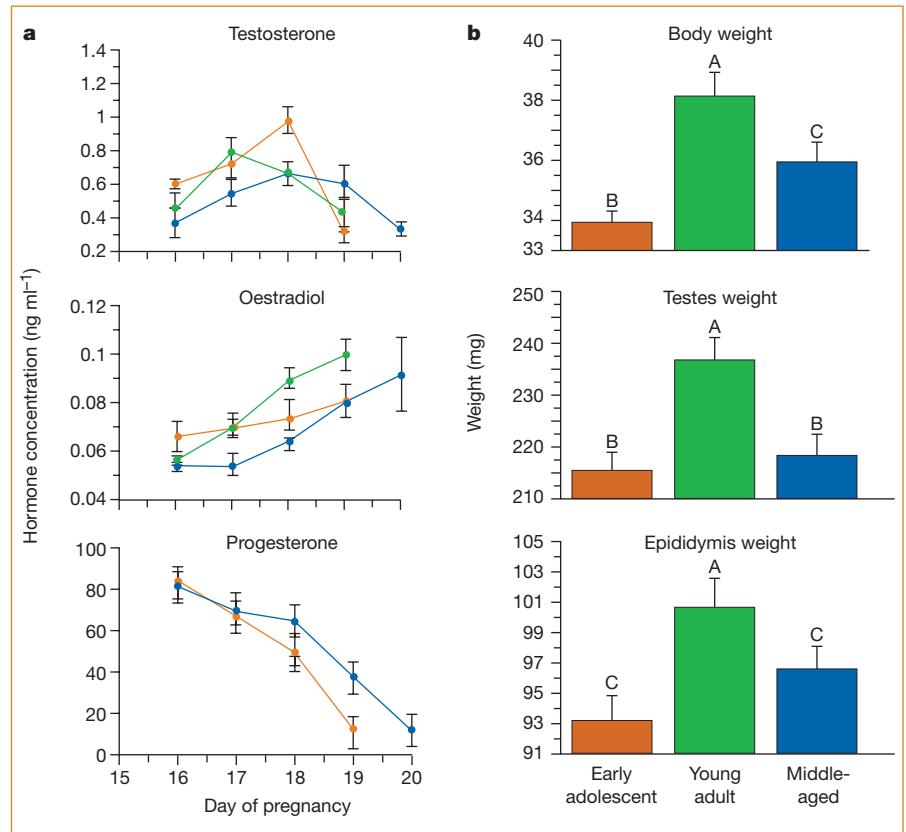


Figure 1 Maternal serum steroid-hormone concentrations and traits of male offspring. **a**, Pregnant mice were mated at 35 days old (early adolescent; red), at 3 months old (young adult; green), or at 9 months old (middle aged; blue). Maternal serum was collected on gestation day 16 (mating, day 0) through to the day of normal parturition. For middle-aged females, parturition was delayed by one day and this was associated with a delay (not statistically significant) in the decline in progesterone at the end of pregnancy. The number of live pups at birth differed significantly, with young-adult mothers producing more pups (12.1 ± 0.5) than early-adolescent females (10.3 ± 0.5), who produced more pups than middle-aged females (7.5 ± 0.5); data are means \pm s.e.m.; n was 7–11 per group per day. **b**, Mean body weight (\pm s.e.m.), and mean weight of testes and epididymides for 3-month-old male offspring (F_1 generation) of mothers of different ages. Early-adolescent, $n=25$; young-adult, $n=32$; and middle-aged, $n=23$. Body weight of males differs as a function of maternal age; the means for weight of testes and epididymides are adjusted for differences in body weight by analysis of covariance. A versus B, $P < 0.01$; A or B versus C, $P < 0.05$.

(35.2 ± 1.2 days old) and MA females (34.0 ± 1.3 days old) completed puberty (ovulated and mated) was significantly delayed relative to YA females (31.1 ± 0.8 days old). A small increase in oestradiol or other oestrogens during fetal life in female mice is also associated with advancement of puberty^{1,2}. Body weight and the age at puberty can both influence reproductive fitness and affect population dynamics³.

To investigate whether the effects of age at first pregnancy could be passed on to subsequent generations, we measured the body weight of the male and female pups (F_2 generation) produced by the F_1 females; litter size and sex ratio did not differ significantly. F_2 pups with young-adult grandmothers weighed 1.60 ± 0.01 g at birth and were significantly heavier than pups with grandmothers that had become pregnant in

either early adolescence (1.51 ± 0.01 g) or middle age (1.50 ± 0.01 g).

Maternal-age effects on human offspring have not been investigated, apart from those related to genetic abnormalities associated with ageing oocytes^{4,5}. Maternal differences in circulating oestradiol and testosterone associated with the timing of first pregnancy are also seen in rats⁶. The levels of oestradiol and testosterone in the mother during sexual differentiation in the fetus may be related to certain traits in human offspring, such as undescended testes and, subsequently, testicular cancer^{7–9}; these hormones *in utero* may permanently 'imprint' the function of cells in reproductive organs, the brain and many other tissues^{1,10,11}. The influence on offspring of age-related changes in the maternal reproductive and endocrine systems calls for further investigation as very

early (soon after puberty) and very late (approaching menopause) pregnancies are common in humans.

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Intelligence

Maze-solving by an amoeboid organism

The plasmodium of the slime mould *Physarum polycephalum* is a large amoeba-like cell consisting of a dendritic network of tube-like structures (pseudopodia). It changes its shape as it crawls over a plain agar gel and, if food is placed at two different points, it will put out pseudopodia that connect the two food sources. Here we show that this simple organism has the ability to find the mini-

mum-length solution between two points in a labyrinth.

We took a growing tip of an appropriate size from a large plasmodium in a 25 × 35 cm culture trough and divided it into small pieces. We then positioned these in a maze created by cutting a plastic film and placing it on an agar surface. The plasmodial pieces spread and coalesced to form a single organism that filled the maze (Fig. 1a), avoiding the dry surface of the plastic film. At the start and end points of the maze, we placed 0.5 × 1 × 2 cm agar blocks containing nutrient (0.1 mg g⁻¹ of ground oat flakes). There were four possible routes (α 1,

α 2, β 1, β 2) between the start and end points (Fig. 1a).

The plasmodium pseudopodia reaching dead ends in the labyrinth shrank (Fig. 1b), resulting in the formation of a single thick pseudopodium spanning the minimum length between the nutrient-containing agar blocks (Fig. 1c). The exact position and length of the pseudopodium was different in each experiment, but the path through α 2 — which was about 22% shorter than that through α 1 — was always selected (Fig. 1d). About the same number of tubes formed through β 1 and β 2 as the difference (about 2%) in their path lengths is lost in the meandering of the tube trajectory and is within experimental error.

The addition of food leads to a local increase in the plasmodium's contraction frequency, initiating waves propagating towards regions of lower frequency^{1–5}, in accordance with the theory of phase dynamics⁶. The plasmodial tube is reinforced or decays when it lies parallel or perpendicular, respectively, to the direction of local periodic contraction⁷; the final tube, following the wave propagation, will therefore link food sites by the shortest path.

To maximize its foraging efficiency, and therefore its chances of survival, the plasmodium changes its shape in the maze to form one thick tube covering the shortest distance between the food sources. This remarkable process of cellular computation implies that cellular materials can show a primitive intelligence^{8–10}.

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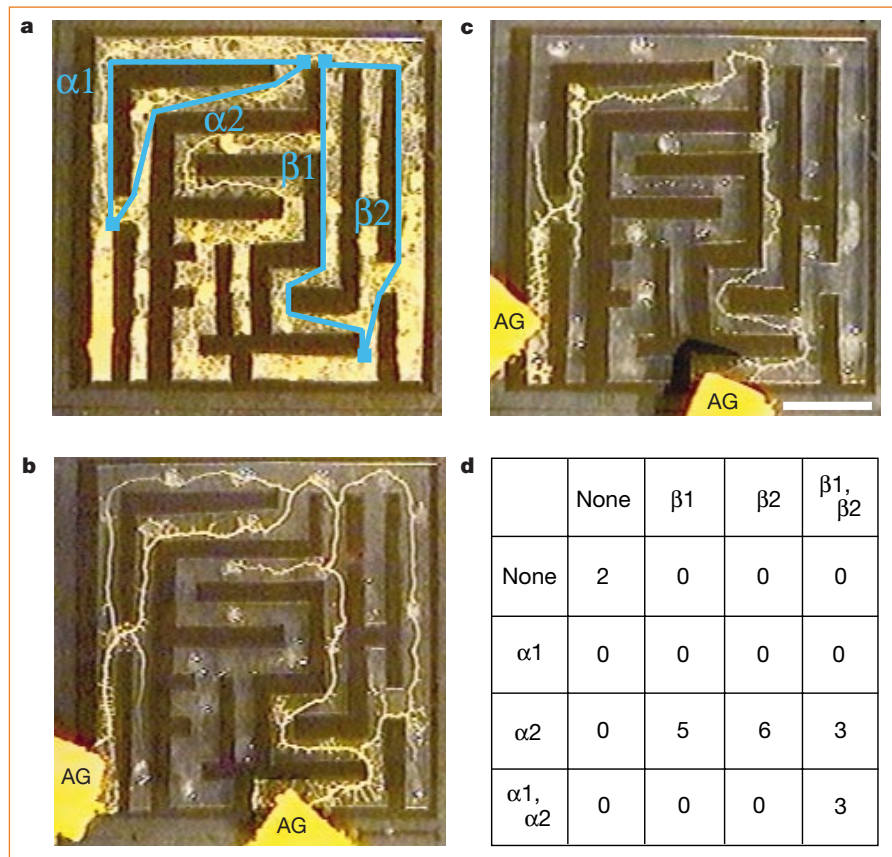


Figure 1 Maze-solving by *Physarum polycephalum*. **a**, Structure of the organism before finding the shortest path. Blue lines indicate the shortest paths between two agar blocks containing nutrients: α 1 (41 ± 1 mm); α 2 (33 ± 1 mm); β 1 (44 ± 1 mm); and β 2 (45 ± 1 mm). **b**, Four hours after the setting of the agar blocks (AG), the dead ends of the plasmodium shrink and the pseudopodia explore all possible connections. **c**, Four hours later, the shortest path has been selected. Plasmodium wet weight, 90 ± 10 mg. Yellow, plasmodium; black, 'walls' of the maze; scale bar, 1 cm. **d**, Path selection. Numbers indicate the frequency with which each pathway was selected. 'None', no pseudopodia (tubes) were put out. See Supplementary Information for an animated version of **a–c**.

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Supplementary information is available on Nature's World-Wide Web site (<http://www.nature.com>).