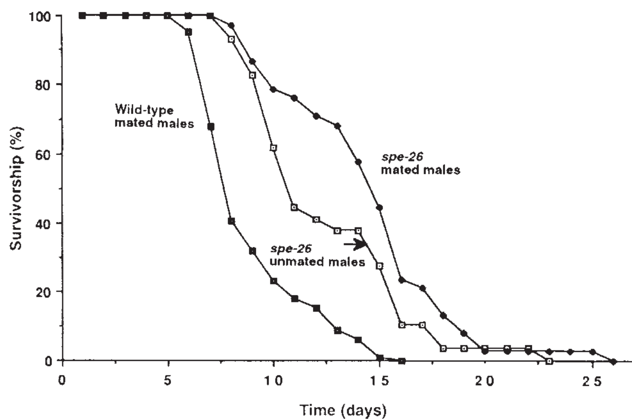

FIG. 4 Survivorship of mated and unmated *spe-26(hc138ts)* males. Lifespans of *spe-26* mated males are significantly greater than wild-type mated males. $Z=6.9$, $P<0.00005$, $N=137$. Mean lifespan of mated males = 13.6 days, s.d. = 3.9 days, $N=37$. Mean lifespan of unmated males = 11.7 days, s.d. = 3.7 days, $N=28$. Nearly 50% of the progeny were male in both mutants, indicating mutant *spe-26* males were successfully mating[16]. Mean lifespan in mated *spe-26* males is slightly greater than unmated *spe-26* males. $Z=1.9$, $P=0.03$, $N=67$.

male are equivalent in volume to about 6 oocytes, and the increased sperm production due to mating is equivalent in volume to only a few additional oocytes. Despite this apparently small amount of energy devoted to sperm production, my results show that increased sperm production reduces male lifespan, and reduced sperm production increases worm lifespan. Note that the mutations reported to increase lifespan in *C. elegans* also cause fourfold reductions in *C. elegans* fertility[15], which may be caused by defective sperm production in these mutants[27].

Another unexpected result of this study is that mating did not reduce hermaphrodite lifespan. A mated hermaphrodite produces additional oocytes which exceed in number and volume the entire somatic cell content of the animal. Despite this apparently large additional energetic expense, mating did not reduce hermaphrodite lifespan. *C. elegans* lifespan appears to be much more tightly linked to spermatogenesis than oogenesis. This conclusion is further supported by the large increase in lifespan of mutant *spe-26* hermaphrodites and mated males with reduced sperm production.

Life history theory predicts that increased lifespan should be selected for in male worms but not hermaphrodites[28,29]. By day 10 almost 90% of mated males are dead. Yet mated males of this age still contained hundreds of sperm. Therefore males with increased lifespans could potentially mate later in life and pass on more of their genes before dying. Increasing lifespan in hermaphrodites, in contrast, would not increase their fitness. Unmated hermaphrodites complete egg laying by day 5 and mated hermaphrodites complete egg laying by day 8, long before their average age at death (11.8 days). Thus, hermaphrodites are post-reproductive for a significant portion of their life and there is no selective advantage in their increased lifespans.

Although it appears that increased lifespan should be of selective advantage to male *C. elegans*, laboratory studies must be interpreted with caution. Important ecological factors such as animal density, predation, and food supply were artificially controlled in these experiments. *C. elegans*' reproductive output parameters indicate that they have been selected for rapid reproductive and short generation time[12], traits characteristic of organisms living in unstable environments with a high probability of the organisms dying in any given time. In their natural environment *C. elegans* may die well before reaching their maximum potential lifespan, minimizing the selective pressures for increased lifespans.

A basic assumption of sexual selection and life history theories is that gamete production is generally of minor cost to males. My results show that clearly this is not the case in *C. elegans*. Spermatogenesis rather than oogenesis is the major factor influencing worm lifespan. □

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Viscous fingering of HCl through gastric mucin

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THE HCl in the mammalian stomach is concentrated enough to digest the stomach itself, yet the gastric epithelium remains undamaged. One protective factor is gastric mucus, which forms a protective layer over the surface epithelium[1–4] and acts as a diffusion barrier[5,6] Bicarbonate ions secreted by the gastric epithelium[7] are trapped in the mucus gel, establishing a gradient from pH 1–2 at the lumen to pH 6–7 at the cell surface[8–10]. How does HCl, secreted at the base of gastric glands by parietal cells, traverse the mucus layer without acidifying it? Here we demonstrate that injection of HCl through solutions of pig gastric mucin produces viscous fingering patterns[11–18] dependent on pH, mucin concentration and acid flow rate. Above pH 4, discrete fingers are observed, whereas below pH 4, HCl neither penetrates the mucin solution nor forms fingers. Our *in vitro* results suggest that HCl secreted by the gastric gland can penetrate the mucus gel layer

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(pH 5–7) through narrow fingers, whereas HCl in the lumen (pH 2) is prevented from diffusing back to the epithelium by the high viscosity of gastric mucus gel on the luminal side.

Viscous fingering[11-18] is the process by which a complex interface develops when a fluid of lower viscosity is injected into a more viscous one; the driving fluid may penetrate, rather than grossly displace, the stationary fluid, with some of the more viscous fluid remaining behind the interface in lacunae, or 'fjords'. To study viscous fingering, HCl was injected into the solution of mucin in a Hele-Shaw cell[11,15], and a highly branched pattern characteristic of viscous fingers was observed (Fig. 1*a–c*). To confirm that this is indeed viscous fingering, we also did experiments in a flat capillary geometry. The shape of the fingering is dependent on the shape of the cell, and Fig. 1*d* confirms the usual morphology found in the 'channel' geometry. For further confirmation of viscous fingering phenomena, we studied the reverse flow of (high-viscosity) mucin into (low-viscosity) acid; as expected, the interface is then stable against perturbations and develops symmetrically (Fig. 1*e*).

We also did fingering experiments at a mucin concentration of 30 mg ml^{-1}, which is the concentration *in vivo*[19] in the pig stomach. At this higher concentration, the viscosity of the mucin solution (41 centipoise (cP)), measured by falling ball microviscometry[20], is about 12 times that of the 10 mg ml^{-1} solution (3.6 cP), and we expect non-newtonian viscous effects to be more dramatic. The fingers observed (Fig. 2*a*) are indeed narrower and more widely spaced than in the 10 mg ml^{-1} mucin solution (Fig. 1*c*). This effect becomes more pronounced at high flow rates of acid (Fig. 2*b,c*), where the tips of the fingers retain their integrity as they propagate: tip-splitting is suppressed. This type of finger, with its apparently parabolic tip, is referred to as 'dendritic' because of its resemblance to the branches which appear during solidification processes (for example, the branches of a snowflake)[13,14].

The injection velocity of HCl was $\sim 4 \text{ cm s}^{-1}$ (Fig. 1*a–c*). Experiments with initial velocities as high as 40 cm s^{-1} revealed that, as fluid velocity increases, finger spacing increases and finger width decreases. In contrast with the lower mucin concentrations and HCl velocities shown in Fig. 1, Fig. 2*b,c* shows that this trend is followed for a mucin concentration of 30 mg ml^{-1}, and an acid velocity of $\sim 3.5 \text{ cm s}^{-1}$ at a radial distance of 0.5 cm. These parameters are comparable to those *in vivo*.

We also observed viscous fingering with partially purified mucin containing non-mucin proteins and lipids, and thus closer in composition to the mucus gel layer that exists *in vivo*[21]. The

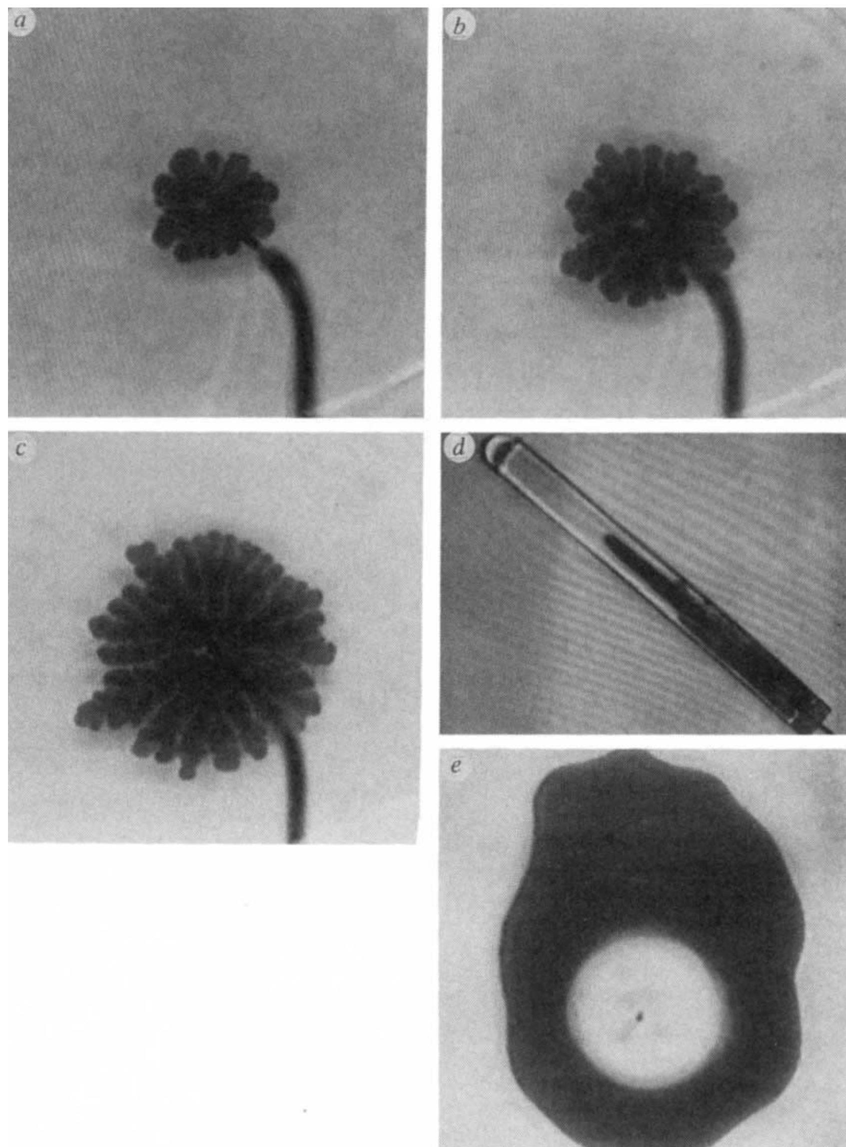

FIG. 1 Viscous fingers formed by HCl (dark) injected into solutions of gastric mucin (white). The patterns were recorded with a video CCD camera (for details see ref. 28). Several frames are shown: *a–c*, fingering pattern for HCl into mucin (10mg ml^{-1}, pH 7) at successive time intervals. For tip-splitting fingers, constant injection rate results in a decrease in interfacial velocity with time. The increase in finger packing may be due to this variation. *d*, Single finger produced by injection of HCl (dark) into mucin (white) in the channel geometry. *e*, Mucin (white) injected into HCl (dark) does not produce viscous fingers but rather results in complete symmetric displacement. In the experiment illustrated on the cover, HCl without added trypan blue was injected into mucin solution containing the acid indicator dye bromophenol blue, which turns yellow at acidic pH. The absence of colour change indicates that during the passage of HCl, hydrogen ions are confined to the boundary of the fingers and do not diffuse into the mucin solution.

METHODS. The component primarily responsible for the viscoelastic properties of gastric mucus is mucin, a glycoprotein (80% carbohydrate and 20% protein) of large molecular mass ($>2\times10^6$) secreted by the epithelial cells. For our studies we used mucin isolated from pig stomach mucosal scrapings, purified by gel filtration on a Sepharose 2B column followed by density gradient ultracentrifugation in a CsCl gradient according to standard methods[29]. Viscous fingering experiments were done in a Hele-Shaw cell consisting of two square glass plates ($10\text{cm}\times10\text{cm}$) separated by $\sim 300 \mu\text{m}$ and clamped on all four corners. Mucin solution was layered between the plates through a hole in the top plate. HCl(0.1M), containing 0.04% trypan blue to aid visualization of acid migration, was injected through the top hole (diameter 0.5 mm), using an infusion pump, at a constant rate of volume flow (0.0186 ml s^{-1}). In the absence of dye, turbidity due to aggregation of mucin at low pH[20] outlines the finger making it visible, and similar highly branched patterns are observed. Channel flow experiment (*d*) was done in a flat capillary ($5 \text{ cm}\times0.4 \text{ cm}\times0.04 \text{ cm}$). After mucin solution was aspirated into the capillary, one end was sealed with 'Sealease'. A 30.5 gauge needle was inserted through the seal and acid injected as in the above experiments.

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formation of viscous fingers was also strongly dependent on mucin solution pH (Fig. 3). Viscous fingering patterns developed at pH 7 and 5 (Fig. 3*a*,*b*), but at pH 4 the bulk of the injected HCl remained on the periphery of the mucin solution and only small, poorly formed fingers were observed (Fig. 3*c*). In mucin solutions at pH 2, the acid did not enter the mucin at all (Fig. 3*d*), but instead flowed around the sample, as predicted by our previous observation[20] that solutions of gastric mucin undergo profound aggregation and increased viscosity below pH 4, the pH at which viscous fingering begins to disappear.

To simulate the *in vivo* situation where secreted HCl travels toward the lumen through a layer of mucus, we also studied acid migration through a column of mucin solution in a test tube (Fig. 4). When HCl was injected into water alone, it diffused irregularly throughout the tube (upper panel). When HCl was injected at the same flow rate into a solution of gastric mucin, the acid travelled in a discrete 'channel' to the top, where it then layered horizontally on top of the mucus layer and did not diffuse downward into the solution (lower panel). When simultaneously injected from two syringes, the acid travelled in two discrete 'channels' which remained separate.

On the basis of hydrodynamic theory, viscous fingering is expected when a low-viscosity liquid is driven under pressure into a high-viscosity liquid. Thus viscous fingering offers a physically plausible mechanism whereby 250 ml h^{-1} of HCl[22] can traverse a protective mucus volume of 30–50 ml without causing major disruption of the 500 μm thick mucus layer[23] between the crypt opening and the gastric lumen. The opossum gastric mucosa[24] contains smooth muscle strands and varicose nerve endings near gastric glands, suggesting muscle contraction could give rise to hydrostatic pressure within the crypt during acid secretion. Our results complement the recent *in vivo* observations in rats[25], where secreted acid travelled through the mucus layer into the lumen only at restricted regions or channels directly above gastric crypts. We argue that HCl secreted under pressure by gastric glands forms viscous fingers in the mucus gel layer; as the acid passes through the mucus layer it may form a gelled or aggregated mucus boundary around the finger, preventing gross acidification of the surrounding layer of mucus. Such fingers may correspond to the channels suggested in ref. 25. Once free in the lumen, the acid causes the layer of mucin on the luminal side to become more viscous[20]. In the absence of hydrodynamic pressure on the luminal side, reverse fingering of acid does not occur and passive back-diffusion of acid would be impeded by the high viscosity of this boundary layer.

Although our experiments were not done *in vivo*, we believe there are sufficient supporting data favouring the physiological relevance of our *in vitro* studies of HCl migration through solutions of gastric mucin. The use of mucin is justified because it is the major viscoelastic component of gastric mucus and the higher concentration used in our studies (30 mg ml^{-1}) is comparable to the reported *in vivo* concentration[19]. Acid fingers which were relatively thick and closely spaced at 10 mg ml^{-1} became

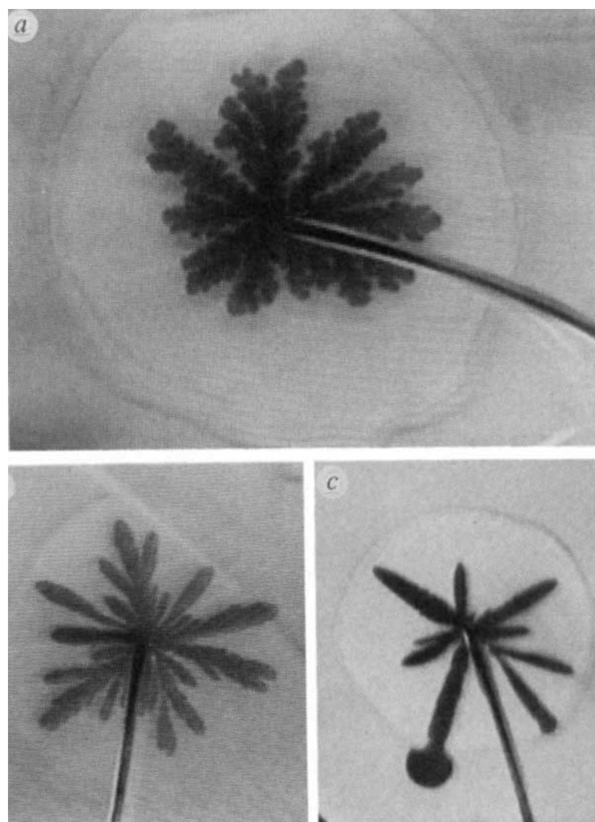

FIG. 2 Viscous fingers formed by HCl (dark) injected into 30 mg ml^{-1} solutions of mucin (white). Effect of increasing acid flow rate and temperature: *a*, injection at 0.0186 ml s^{-1}, results in narrower fingers, the fjords, white areas between the dark acid fingers, are more prominent, indicating less disturbance to the mucin layer; *b*, for same mucin concentration as in *a*, injection of HCl at 0.33 ml s^{-1} results in thinner, more widely spaced fingers; *c*, same experiment as *b* done with both mucin solution and acid at 37 °C (other data shown were taken at ambient room temperature).

METHODS. To estimate the HCl secretion velocity at the mouth of the crypt, we assume Poiseuille flow, and approximate the crypt as a cylinder of length $l = 1{,}000$ μm, and radius $r = 20$ μm[30]. The pressure in the middle of the rat crypt was measured by Agren and Holm[31] as 19 mm Hg in the resting state, and 22 mm Hg after pentagastrin stimulation. These authors report a relative pressure in the lumen of 0 mm; others[32] have reported the luminal pressure as 5 mm Hg. For simplicity, we assume that at rest a 14–19 mm pressure drop occurs across the mucin layer as opposed to a muscular constriction of the neck of the gland. Such a tensile load is below the critical yield stress of mucin[33]. The excess pressure gradient G after stimulation is then about 3 mm Hg per 500 μm. From the Poiseuille formula, and using our measured viscosity of HCl of $\eta = 1.0$ cP, the mean flow velocity is $Ga^2/8\eta = 4$ cm s^{-1}. This acid velocity agrees roughly with the ~1 cm s^{-1} flow velocity calculated using the model crypt dimensions of 1.3×10^{-6} ml, and the frequency of pressure oscillation (0.1 Hz) also reported by Agren and Holm[31].

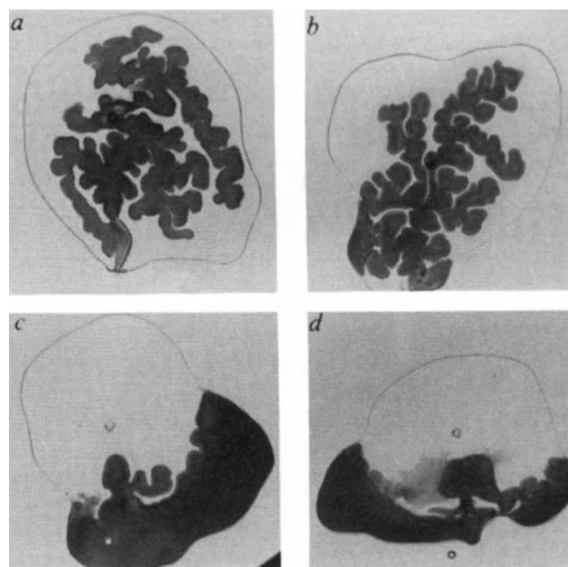

FIG. 3 Viscous fingering of HCl in gastric mucin, where the injection is now from the periphery (as opposed to the central hole). Effect of varying pH of mucin solution. Acid-formed fingering patterns in mucin solutions at *a*, pH 7 and *b*, pH 5. In striking contrast, acid barely penetrated mucin at *c*, pH 4 or *d*, pH 2.

METHODS. Mucin, 10 mg ml^{-1} in 10 mM phosphate buffer. HCl (0.1M) containing 0.04% trypan blue injected at the same flow rate in all four experiments. Partially purified mucin obtained by Sepharose 2B gel filtration was used.

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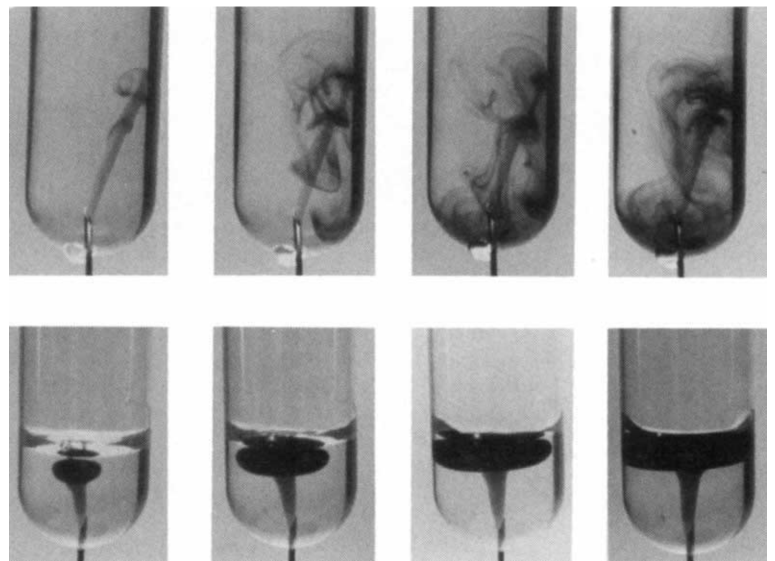

FIG. 4 Lower panel, HCl injected into a column of gastric mucin of concentration 2.5 mg ml^{-1} in 0.1M NaCl, pH 6.5. HCl (flow rate 0.01 ml s^{-1}) forms a discrete channel. The four pictures show the channel at successive increasing time intervals (left to right). Upper panel, Control experiment with water under the same conditions shows the rapid diffusion of acid.
METHODS. Acid (0.1M) containing trypan blue (0.04%) injected through a needle pierced into the bottom of the tube containing mucin solution. Flow rate controlled using an infusion pump.

more distinct and widely spaced on increasing mucin concentration to 30 mg ml^{-1}. Thus the studies at lower mucin concentrations served to establish the trend in viscous fingering morphology and suggest that if the *in vivo* concentration were greater than 30 mg ml^{-1}, the fingers would be even finer and less disruptive of the mucus layer. Ever since Heatley[3] proposed the barrier theory of gastric mucus in 1959, the question of whether mucus represents an effective barrier or not has been the subject of considerable investigation. Although the ability of the mucus gel layer to maintain a pH gradient is a subject of controversy[26,27], the notion that gastric mucus impedes the diffusion of H^+ has been supported by many *in vitro* and *in vivo* experiments[5,6,8]. Our *in vitro* studies offer a physical-chemical basis for the barrier function of gastric mucus *in vivo*. □

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Possible blindsight in infants lacking one cerebral hemisphere

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PATIENTS with damage to the striate cortex have a subjectively blind region of the visual field, but may still be able to detect and localize targets within this region[1,2]. But the relative roles in this 'blindsight' of subcortical neural systems, and of pathways to extra-striate visual areas, have been uncertain[3]. Here we report results on two infants in whom one cerebral hemisphere, including both striate and extra-striate visual cortex, needed surgical removal in their first year. Single conspicuous targets in the half-field contralateral to the lesion could elicit fixations, implying detection and orienting by a subcortical system. In contrast, binocular optokinetic nystagmus (OKN), for which a subcortical pathway has often been thought adequate, showed a marked asymmetry. In normal neonates, fixation shifts and OKN have both been taken to reflect subcortical control[4]; our results are consistent with subcortical control for fixation but not for OKN.

Hemispherectomy surgery, to relieve intractable myoclonic seizures caused by congenital unilateral megalencephaly (Fig. 1), was performed on infant P.P. (right hemisphere) at 4 months of age and on infant L.A.H. (left hemisphere) at 8 months. The complete removal of one hemisphere was confirmed by the neuropathologist's examination of removed tissue in each case. The tests we report followed these operations by 3-7 months (P.P.) and 8-10 months (L.A.H.).

In the week before surgery, both infants (then heavily medicated to alleviate their seizures) showed very poor visual behaviour. P.P. showed no consistent shifts of gaze to a target; L.A.H. showed some visually guided reaching but poor shifts of gaze, and acuity around 1 cycle deg^{-1} (equivalent to a newborn). But in postoperative testing, both children were visually alert with full eye movements, although each showed intermittent strabismus. Their visual acuity was in the normal range for 11-15 month infants (8-12 cycle deg^{-1}, tested by preferential

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