# Wireless capsule endoscopy

The discomfort of internal gastrointestinal examination may soon be a thing of the past.

We have developed a new type of endoscopy, which for the first time allows painless endoscopic imaging of the whole of the small bowel. This procedure involves a wireless capsule endoscope and we describe here its successful testing in humans.

The invention of fibre-optic endoscopy[1] made visualization of the whole stomach, upper small bowel and colon possible. The procedures used to examine these (gastroscopy, small-bowel endoscopy and colonoscopy, respectively) cause discomfort because they require flexible, relatively wide cables to be pushed into the bowel — these cables carry light by fibre-optic bundles, power and video signals. Small-bowel endoscopy in particular is constrained by problems of discomfort and limitations of how far enteroscopes can be advanced into the small bowel. There is a clinical need for improved methods of examining the small bowel and colon, especially in patients with recurrent gastrointestinal bleeding.

The invention of the transistor made it possible to design swallowable electronic radio-telemetry capsules for the study of gastrointestinal physiological parameters. These capsules were first reported in the 1950s and were used to measure temperature[2], pressure[2,3] and pH[3,4]. We have developed and tested a new type of video-telemetry capsule endoscope that is small enough to be swallowed (11 × 30 mm) and has no external wires, fibre-optic bundles or cables. By using a lens of short focal length, images are obtained as the optical window of the capsule sweeps past the gut wall, without requiring air inflation of the gut lumen. The capsule endoscope is propelled by peristalsis through the gastrointestinal tract and does not require a pushing force to propel it through the bowel.

The video images are transmitted using UHF-band radio-telemetry to aerials taped to the body which allow image capture, and the signal strength is used to calculate the position of the capsule in the body (see Supplementary Information); the images are stored on a portable recorder. This system allows more than 5 hours of continuous recording. The patient need not be confined to a hospital environment during the examination and is free to continue his or her daily routine.

The design of the video capsule was made possible by progress in the performance of three technologies: complementary metal oxide silicon (CMOS) image sensors, application-specific integrated circuit (ASIC) devices, and white-light-emitting diode (LED) illumination. Novel optical design, better energy management and overall system design were also important in creating the capsule.

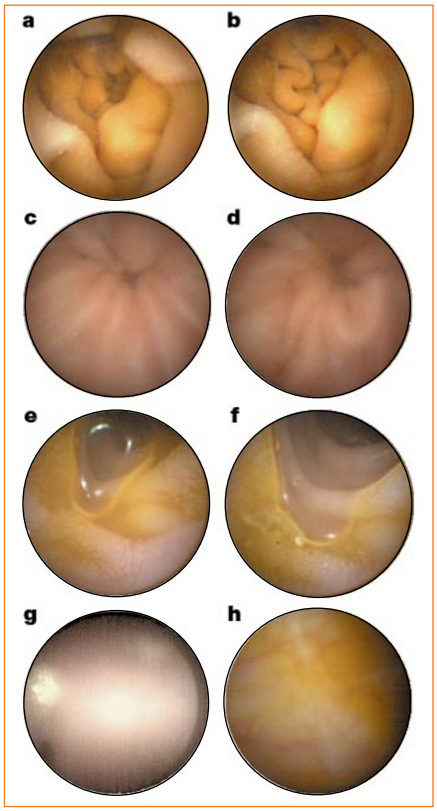


**Figure 1** Samples of images of the small bowel acquired by the capsule endoscope during human *in vivo* studies. **a,b,** Gastric folds in the body of the stomach; **c,d,** villous pattern of the small bowel enhanced by the presence of a little water and an air bubble in the lumen; **e,f,** airless images of normal jejunum, viewed with the lumen closed in front of the optical dome of the capsule; **g,h,** views of the terminal ileum.

The addition of a buffer amplifier on each pixel reduced the output noise that was initially associated with CMOS image sensors and has allowed CMOS chips to achieve an image quality comparable to those of charge-coupled device image sensors[5], but using much less power.

Advances in ASIC design allowed the integration of a very small video transmitter of sufficient power output, efficiency and bandwidth into the capsule. Synchronous switching of the LEDs, the CMOS sensor and the ASIC transmitter minimize power consumption. By careful design of the optics, we were able to eliminate internal reflections which are a common problem when the illumination and imager are incorporated under the same dome.

With ethical committee approval, the first studies were performed on ten normal human volunteers. The capsule was easily swallowed and caused no discomfort. Propelled by peristalsis (see Supplementary Information), it successfully transmitted video images (Fig. 1) from the stomach, small bowel and caecum (mean gastric transit time was 80 min, range 17–280 min; mean small-bowel transit time was 90 min, range 45–140 min; mouth-to-evacuation time was 24 h, range 10–48 h). High-quality images were received throughout the video transmissions, lasting up to 6 hours.

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**Supplementary information** is available on *Nature*'s World-Wide Web site (http://www.nature.com) or as paper copy from the London editorial office of *Nature*.

Cell biology

## Non-thermal heat-shock response to microwaves

Exposure limits set for microwave radiation assume that any biological effects result from tissue heating[1]: non-thermal effects have been reported but remain controversial. We show here that prolonged exposure to low-intensity microwave fields can induce heat-shock responses in the soil nematode *Caenorhabditis elegans*. This effect appears to be non-thermal, suggesting that current exposure limits set for microwave equipment may need to be reconsidered.

Heat-shock proteins (HSPs) are induced in most organisms by adverse conditions (such as heat or toxicants) that cause damage to cellular proteins, acting as molecular chaperones to rescue damaged proteins[2]. To detect HSP responses, we have pioneered the use of transgenic *C. elegans* strains carrying reporter-gene constructs (encoding β-galactosidase in strain PC72 or green fluorescent protein (GFP) in strain PC161) regulated by homologous *hsp16* heat-shock promoters[3]. When exposed to diverse stressors at 20–25 °C,

these worms express readily detectable reporter products, whereas controls show minimal expression[4].

Worms were exposed overnight to continuous-wave microwave radiation at 750 MHz and 0.5 W in the transverse electromagnetic (TEM) cell described previously[5]. Figure 1 shows temperature profiles for reporter expression in both irradiated and control (foil-shielded) worm cultures. In microwave-exposed cultures, expression is comparable to that of controls at 24.0 °C ($P > 0.05$), but then rises steeply through 24.5 and 25.0 to 25.5 °C ($P < 0.001$). In non-exposed controls, heat-induced reporter expression follows the pattern for HSP16 (ref. 6), increasing sharply only above 27 °C (to a maximum at 30 °C). There is thus a disparity of 3 °C between exposed and control induction profiles.

A thermal explanation for this disparity would require that the exposed worms become 3 °C warmer than controls — or more if only a minority of worms/tissues is affected. We reject this thermal explanation on several grounds, not least the diffusion of heat over 18 hours.

First, no temperature difference is detectable between control and exposed cultures after irradiation[5]. This is also true for concentrated (50% w/v) worm suspensions incubated for 18 h at 25 °C alongside a saline solution alone, under exposed versus control conditions (24.68 ± 0.116 °C s.d., $P = 0.28$, for all 16 measurements under four conditions using a sensitive copper–constantan microthermocouple). Temperature differences of 0.5 °C (that is, worms 1 °C warmer than the saline) would have been easily detectable in this experiment.

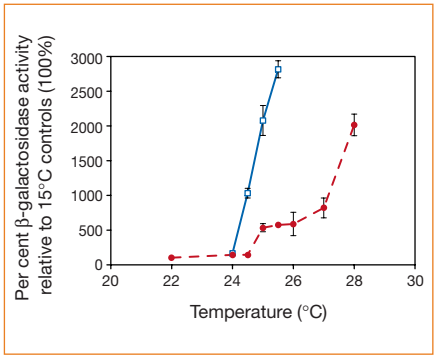


**Figure 1** Saline[9] suspensions of young adult PC72 worms grown synchronously at 15 °C (ref. 10) were split between three conditions for a total of 18 h: (1) exposed to microwaves (in TEM cell at 750 MHz and 0.5 W; ref. 5) within a Leec LT3 incubator; (2) temperature controls shielded with aluminium foil in the same incubator; (3) baseline controls at 15 °C. Incubator temperatures of 24.0, 24.5, 25.0 and 25.5 °C were tested using 12 replicates for each condition; controls only (6 replicates of condition 2) were also run at 22, 26, 27 and 28 °C. All worm samples were assayed fluorometrically[4,5] for β-galactosidase activity. Enzyme activities were normalized against 15 °C baseline controls (100%) within each batch to allow comparison of reporter induction at different temperatures. Squares, blue solid line; reporter activities (± s.e.m.) in microwave-exposed cultures. Circles, red dashed line; control reporter activities (± s.e.m.) at each temperature.

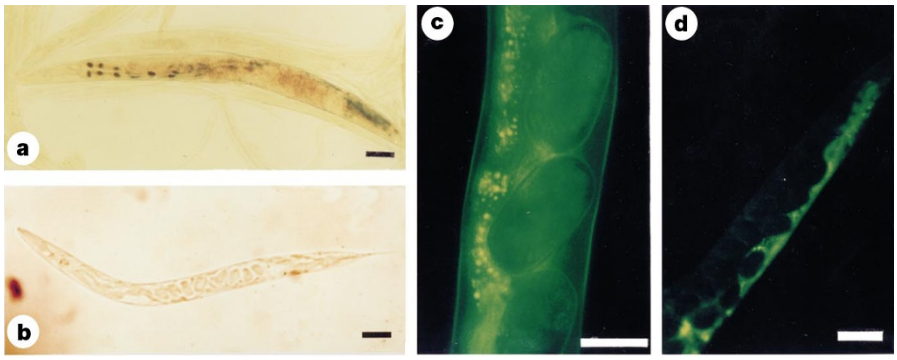


**Figure 2** PC72 and PC161 (similar to PC72, but carrying an additional GFP reporter under *hsp16* control) worms were either exposed for 18 h at 25 °C to microwaves (750 MHz, 0.5 W) or kept as 25 °C controls, then reporter expression was localized *in situ* by staining with X-gal (PC72) or viewing under ultraviolet light on a fluorescence microscope (PC161). **a,** Exposed PC72 worm, showing nuclear staining for β-galactosidase throughout the gut; **b,** typical PC72 worm under control conditions: no observable staining; **c,** exposed PC161 worm, showing GFP fluorescence throughout ovoid embryos; **d,** typical control PC161 worm, showing yellowish gut autofluorescence (also in **c**) but no GFP fluorescence in embryos. Note that many worms in **a** and **c** show little reporter expression. Scale bars, 50 μm.

Second, *in situ* detection of reporter products shows that *lacZ* is expressed throughout the gut in PC72 worms (Fig. 2a,b), and also that GFP is expressed in many embryos within adult PC161 worms (Fig. 2c,d). These expression sites together constitute about half of worm tissues.

Third, the field at the centre of our TEM cell is 45 V $m^{-1}$, and the measured permittivity of concentrated worm suspensions (at 615 MHz) gives a conductivity of about 0.48 $\Omega^{-1}$ $m^{-1}$. The calculated specific absorption rate (SAR) is only 0.001 W $kg^{-1}$, which is much less than published values[7] for mobile phones (0.02–1.0 W $kg^{-1}$). Mobile-phone manufacturers claim that SARs in this range are insufficient to cause measurable tissue heating within the human head, and we are not disputing this.

We suggest instead that the induction of heat-shock proteins described here could involve non-thermal mechanisms. These could include microwave disruption of the weak bonds that maintain the active folded forms of proteins; enhanced production of reactive oxygen species (known to be inducers of HSPs[8]); or interference with cell-signalling pathways that affect HSP induction (by heat-shock-factor activation). All these mechanisms are testable using the functional genomic tools that are available in *C. elegans*. Because of the universality of the heat-shock response[2], a similar non-thermal induction might also occur in human tissues exposed to microwaves, a possibility that needs investigation.

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Structural biology

## Proton-powered turbine of a plant motor

ATP synthases are enzymes that can work in two directions to catalyse either the synthesis or breakdown of ATP, and they constitute the smallest rotary motors in biology. The flow of protons propels the rotation[1] of a membrane-spanning complex of identical protein subunits, the number of which determines the efficiency of energy conversion. This proton-powered turbine is predicted to consist of 12 subunits[2–4], based on data for *Escherichia coli*[5]. The yeast mitochondrial enzyme, however, has only 10 subunits[6]. We have imaged the ATP synthase from leaf chloroplasts by using atomic force microscopy and, surprisingly, find that its turbine has 14 subunits, arranged in a cylindrical ring.