

Son et lumière meets surgery

Biomedicine: "Non invasive" surgical techniques based on sound and light could be much easier on the body than ordinary surgery

TOT SO long ago, newly qualified doc-N tors in the West would take the Hippocratic oath. Along with promises to look after the interests of their tutors, to do no harm to their patients and not to procure abortions, they also swore not to "cut for stone". It was actually an early form of restrictive practice. The oath's wording makes it clear that stone-cutting (removing kidney stones) was reserved for surgeons, with their separate guilds and separate fees. But the latest technology makes the distinction irrelevant. These days, kidney stones and similar calciferous accumulations in other parts of the body can be dealt with by using a dose of shockwaves to break up the offending concretion-with no cutting required.

Shockwave therapy, as it is known, is just one of a range of non-invasive techniques that reduce the need to slice people open in order to treat them. Such techniques promise to blur still further the once-sharp distinction between physician and surgeon that the Hippocratic oath sought to preserve. As with all technological destruction of restrictive practices, though, this one has one clear beneficiary: the customer—or, as he is generally known in medical circles, the patient.

Shockwaves are a particular sort of sound wave. More gentle sound waves (or, strictly, ultrasound waves, since their pitch is too high to be heard by the human ear), have long been used to peer inside the body and produce images of, for example, developing embryos. More powerful and focused forms of these waves are now being adapted for surgical purposes.

Just as light rays focused by a lens can create searing heat, so too can ultrasound waves that are generated from a specially designed transducer. Concentrated in this way, they cause the tissues at the focus to vibrate and heat up dramatically.

A sound change

One company developing this technology is InSightec, based in Haifa, Israel. In-Sightec's system, called ExAblate, uses magnetic-resonance imaging (MRI) to guide the operator in focusing the ultrasound on the tissue (usually a blood clot or tumour) that needs to be destroyed. Besides showing the patient's internal anatomy, MRI is able to map the local temperature and thus indicate exactly where the ultrasound is arriving and how much heat is being delivered to the target.

The ultrasound itself is produced by an array of 211 transducer elements that generate beams that converge on the target. According to Wladyslaw Gedroyc, medical director of magnetic resonance imaging at St Mary's Hospital, London, the accuracy of MRI-based systems like InSightec's makes it possible to attack difficult targets like brain tumours, in addition to bone cancers, liver tumours and clots.

The reliance on MRI, however, makes this approach expensive and long-winded. Lots of scans have to be taken from different angles to assemble the image. The result is precision, but the patient may have to sit still for hours. In the search for cheaper, quicker alternatives Mirabilis Medica, a maker of medical devices based in Seattle, has settled on ultrasound to look at the target as well as to destroy it. An adapted version of a fetal scanner is used to locate the tissue to be cooked. It is then zapped using a transducer array similar to InSightec's.

The difference in cost is huge: around \$50,000 compared with \$1m for the MRIbased system (in addition to the cost of the MRI scanner itself). The all-ultrasonic approach is also quicker because the image can be examined directly by the operator of the zapper, rather than being laboriously constructed from multiple slices inside a computer. When he sees the target in the image he brings it under a set of metaphorical crosshairs and presses a "fire" button, rather like playing a video game. The destruction of a tumour in the uterus takes less than 30 minutes using the Mirabilis Medica technology, whereas the InSightec system requires three to four hours.

But the image produced by ultrasound is of lower resolution than the MRI picture, so if pinpoint accuracy is required, MRI is better. When removing a uterine tumour, a bit of collateral damage is not too serious. When targeting the brain, though, every cubic millimetre destroyed unnecessarily risks diminishing the outcome for the patient. Also, MRI imaging casts no shadows, whereas there are some places inside the body that are hard to see with ultrasound because, say, a lot of bone is in the way.

Regardless of the exact method used, though, ultrasonic excision of this sort is expected to revolutionise treatment of both benign and malignant tumours, since many of them develop in places that conventional surgery cannot reach without **>>**

"Non-invasive techniques reduce the need to slice people open in order to treat them."

risking substantial injury to the patient. "Focused ultrasound appears to be the real deal," says Christopher Rose, technology chief at Vantage Oncology, a radiationtherapy provider based in Los Angeles. Once America's Food and Drug Administration approves the technology for widespread use (the InSightec device is currently approved for some treatments) it could prove competitive with the radiation treatment that is currently used to destroy tumours, he says.

Destroying diseased tissue is a traditional role of surgery. Stimulating it so that it works properly is a rather newer idea. It, too, though, is becoming common. The tissue in question is usually in the brain. Deep-brain stimulation, in which a patient's skull is cut open, electrodes are inserted, and nerve cells are stimulated, is already used to treat Parkinson's disease, and the same approach is also being tested for the treatment of comas, epilepsy, depression and even Alzheimer's disease. It is, however, tricky and dangerous. For this reason, some researchers have started looking into the idea of using ultrasound to tinker with brain activity instead.

Nerves propagate information electrically-hence the use of electrodes for deepbrain stimulation. The actual electric current in a nerve cell, though, is caused by a flow of ions (electrically charged atoms) rather than electrons, which carry current in a wire. These ions pass in and out of the cell in waves, and the waves are propagated along protrusions from the cell. These electrical waves are stimulated originally by the arrival at a cell of a chemical called a neurotransmitter. When the electrical wave arrives in a region where one nerve cell abuts another, it likewise stimulates neurotransmitter production and thus allows the signal to jump across the gap from one cell to the next.

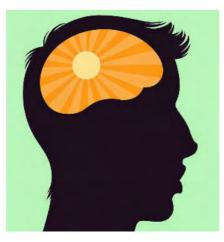
The idea behind ultrasonic stimulation of the brain is to shake open the pores that let ions in and out of nerve cells, and thus enhance the production of neurotransmitters. And that is what SynSonix, a firm based in Tempe, Arizona, is attempting to do. The ultrasound in question, produced by a machine developed by William Tyler at Arizona State University, is of much lower intensity than that used to zap tumours and blood clots, but it seems, in preliminary experiments, to do the job. And as well as saving patients the grief of open brain surgery, SynSonix's treatment is expected to be much less expensive, costing \$20,000 instead of the \$60,000 typically needed for electrode surgery.

Nor are sound waves the only way to replace electrodes. Karl Deisseroth, a psychiatrist and bio-engineer at Stanford University, is looking at ways of making nerve cells react to light. Dr Deisseroth's work makes use of light-sensitive proteins found in single-celled algae and in archaebacteria, an obscure group of micro-organisms. His chosen alga is unusual because when it is exposed to blue light, certain proteins within the algal cell respond by allowing sodium ions into the cell. This ionic movement causes a flagellum (a small propeller) on the outside of the alga to begin rotating. which propels the cell towards the light, allowing it to photosynthesise better. In the archaebacterium, yellow light causes proteins to start pumping chloride ions into the cell, as part of its energy-generation mechanism.

Seeing the light

The reason these mechanisms are of interest to neurologists is that bringing sodium ions into nerve cells initiates electrical activity, while bringing in chloride ions shuts activity down. Dr Deisseroth and his colleagues are therefore incorporating the genes which encode the relevant proteins into viruses that have been engineered to find and infect specific types of nerve cell in the brain. Once in those nerve cells, the virus-transported genes permit the manufacture of proteins that will either flood the cell with sodium ions when it is exposed to blue light or with chloride ions when exposed to yellow light.

The advantage of Dr Deisseroth's technique is that it is selective. Only cells susceptible to the virus are affected—and the virus can be "tuned" to those involved in the type of disease to be treated. The drawback is that the technique works only with visible light, and this does not penetrate



flesh. It therefore requires a small hole to be drilled in the skull, so that a fibre-optic cable can be used to shine light inside. To make the process completely non-invasive, Dr Deisseroth is trying to tweak the hijacked proteins so they respond to different frequencies of infra-red light which, unlike the visible colours of blue and yellow, passes through the body easily.

The fact that infra-red light passes harmlessly through the body is also being put to use by researchers who are trying to employ it to control blood flow. Weihong Tan at the University of Florida and his colleagues have created a molecular "clasp" designed to open or close, depending on the frequency of light it is exposed to.

The clasp consists of two parts: a molecule that responds to light, and a short, single strand of DNA. In its natural state, the DNA binds with an enzyme called thrombin, which regulates blood clotting. When in contact with thrombin, the DNA deactivates the enzyme, and this allows blood to flow freely. However, when the clasp is exposed to a specific frequency of light, the DNA folds itself into a curved, closed shape that stops it binding to the thrombin. This activates the enzyme, triggering clotting. Exposure to a different frequency of light causes the DNA to relax into its natural shape again, deactivating the thrombin.

The technology is still in its early days, but the goal is to inject patients with the microscopic clasps and use different frequencies of infra-red light to activate and deactivate the clotting clasps in specific locations. That will allow clots to be manufactured deliberately—for example, to cut off the blood supply to a tumour.

The upshot will, if all goes well, be yet another way to avoid the surgeon's knife: an internal ligature that can be switched on or off using light-and thus another diminution of the surgeon's trade. In truth, of course, the distinction between surgery and other branches of medicine has been blurred for years, despite the British affectation of newly qualified surgeons dropping the hard-won appellation "Dr" in favour of "Mr", "Mrs", "Miss" or "Ms". Traditional surgery is unlikely to disappear completely, of course, but Dr Gedroyc is optimistic that the sort of non-invasive techniques that he and his colleagues are working on will soon see surgeons relegated to dealing with problems like organ torsion and twisted bones, which have to be dealt with physically. Sawbones they were, and sawbones they will become once again. Hippocrates would no doubt have approved.