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Ultrasonic boom

Scientists find vibrations good for a variety of uses

By Jennifer Nagorka
Staff Writer of The Dallas Morning News

The sounds that humans can't hear are helping scientists create novel chemicals, view hidden tumors and control the release of drugs.

Using equipment that fits on top of a desk, a chemistry professor can produce, in ordinary liquids, flashes of heat that rival the temperature of the sun's surface. Miniature ultrasound

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probes allow cardiologists to look at the cracked, plaque-coated inner walls of patients' arteries.

Ultrasound gained fame for its ability to produce dim, blurry images of a fetus in the womb. But a handful of household gadgets also exploit the properties of these ultra-high-frequency sound waves — such as dog whistles, insect traps and jewelry cleaning baths.

Because the field of ultrasound research is relatively new, researchers expect its applications to multiply.

Ultrasound "will take its place as one of the routine techniques in synthetic chemistry," predicted Kenneth Suslick, a pioneer in the field of sonochemistry and a professor at the University of Illinois at Urbana-Champaign. "Ultrasound provides us with an entirely new way of interacting energy and matter."

Robert Langer, a professor at the Massachu-

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Ultrasound finds wide variety of uses in chemistry, medicine

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setts Institute of Technology, studies how ultrasound affects drug implants. "It opens up whole new possibilities for delivering drugs," he said.

And unlike many other types of sophisticated lab or medical imaging equipment, ultrasound is cheap and safe.

"No significant biological effect has ever been reported or reproduced in the clinical setting," said radiologist Robert Lerner of the University of Rochester.

Even though it can't be heard, ultrasound is sound. Sound waves are compression waves — they travel by alternately expanding and compressing the medium through which they move, whether air or water or metal.

The frequency of a sound wave equals how many times the wave rarefies and contracts each second. Frequency corresponds to pitch. Humans hear frequencies ranging from 16 to 20,000 cycles per second. Dogs can hear up to 40,000 cycles per second.

Extremely low frequencies — the lowest bass notes on a pipe organ — are felt, rather than heard.

Ultrasound is a lump term for all frequencies of sound above the range of human hearing. In the 1960s, sports medicine doctors began using ultrasound to treat damaged tissue. In the late 1970s, fetal sonograms became available. A doctor passes an ultrasound probe over the mother's belly and the pattern of echoes constructs an image of the fetus.

Ultrasound devices grew more powerful and compact in the 1980s. Sonochemistry floundered until these high-intensity ultrasound generators became available, Dr. Suslick said.

High-intensity ultrasound can be used instead of heat or light or radiation to induce or speed up chemical reactions. It can produce awesome microenvironments when it travels through liquids or particle-liquid slurries. In tiny regions of a liquid, temperatures shoot up to about 9000 degrees Fahrenheit and pressures increase to 500 atmospheres — about the same pressure as the bottom of a deep ocean.

The heat flash is accompanied by a momentary flare of light, called sonoluminescence. Particles in solution may slam into each other at speeds of about 1,000 miles per second. Each effect vanishes within a microsecond, the time it takes for a lightning bolt to strike.

"It's kind of cute," Dr. Suslick said.

Bubbles are the basis of sonochemistry. Alternating cycles of compression and rarefaction spawn bubbles. During rarefaction, molecules are allowed more elbow room. Gases especially like to spread out, forming minute bubbles.

If conditions are right, bubbles grow until they can't maintain their size. Liquid rushes in and the bubbles implode, generating heat, light and high pressure. The surrounding liquid stays cool because the heat is extinguished much faster than any gas could conduct it. Scientists dub this process of bubbles forming and collapsing "cavitation."

The heat generated by cavitation lasts long enough to produce useful effects. For example, Dr. Suslick said, technicians can use ultrasound to separate crude oil into commercially valuable fractions, such as gasoline.

The collapsing bubbles also generate shock waves — "microscopic depth charges," as Dr. Suslick calls them. These shock waves drive particles at high speeds through the liquid. Colliding particles melt, exposing fresh new metal primed for further chemical reactions.

Ultrasound could improve or simplify manufacturing in the petroleum and chemical industries, Dr. Suslick wrote in a recent issue of the journal *Science*. Pharmaceutical manufacturers could use it to synthesize molecules because chemicals subjected to ultrasound sometimes combine differently than when exposed to heat or light. Ultrasound will become a standard tool in these industries, he said.

In medicine, ultrasound has two uses — treatment and imaging. Ultrasound-based treatments include heating tumors to kill them and using the waves to help heal sports injuries.

Over the past seven years, MIT's Dr. Langer and his colleagues have expanded therapeutic uses to drug delivery systems. They've already found that ultrasound can dramatically accelerate the release of drugs from implants and the absorption of drugs from skin patches, according to their articles last year in *The Journal of Clinical Investigation* and *Proceedings of the National Academy of Sciences*.

Drug implants allow steady, uninterrupted release of hormones, drugs or other substances. Because the drug trickles out at a constant rate, patients don't experience the roller-coaster ride of waxing and waning blood concentrations of medicine.

But there are times when a patient might want a higher dose of the drug.

"There's many hormones that are produced quickly," Dr. Langer said. "(A diabetic) might want to turn on more insulin after a meal."

Working with rats and other experimental systems, the researchers studied the effects of intense ultrasound on different implants. They found that ultrasound stimulation caused biodegradable implants to release their contents as much as 20 times faster than normally — and to degrade five times faster.

Dr. Langer also has examined the effect of ultrasound on skin patches. Currently, only about four drugs are available in this form.

"Few drugs can get through the skin," he said. "When they do . . . they get through by being almost able to dissolve in the skin."

Ultrasound seems to change the skin's permeability. Dr. Langer's group placed skin patches on shaved rats. Three to five minutes of ultrasound exposure increased the permeation of two drugs five to 20 fold.

Ultrasound could "allow a wider variety of drugs through the skin," Dr. Langer said.

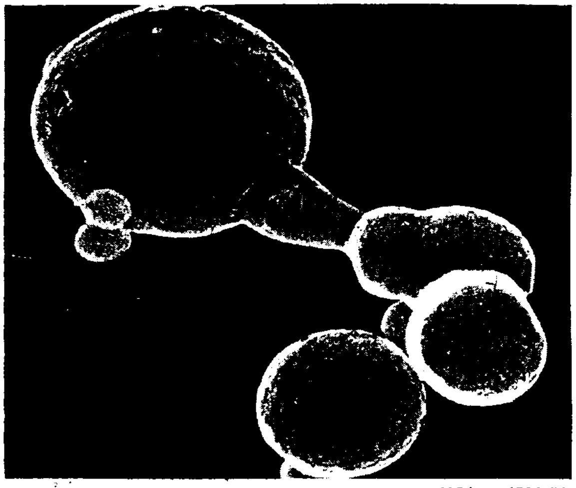
Human tests of ultrasound-activated skin patches may start this year, he said. Ultimately, patients might wear wristwatch-style ultrasound generators to turn on implants or skin patches, he said.

While researchers await development of wristwatch-sized ultrasound generators, improvements in ultrasound imaging equipment already are producing detailed glimpses of the inside of a living body.

Steven Nissen of the University of Kentucky is experimenting with a device that sees the inside of patients' arteries. The miniature ultrasound probe — a little fatter than cooked spaghetti — is embedded in a catheter, or slender flexible tube, and threaded through the patients' arteries.

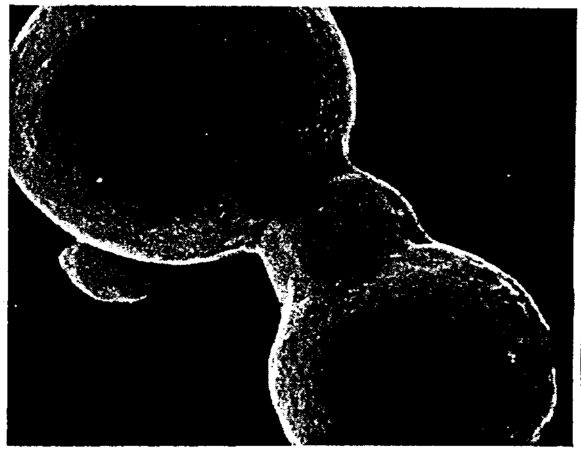
"We're seeing for the first time atherosclerosis in a living person," said Dr. Nissen, an associate professor of medicine. "We're going to be able to look at plaques and see which plaques are likely to regress."

That would help doctors decide on the most appropriate treatment for each patient and each artery in the patient, he said.



S.J. Doktycz and K.S. Suslick

Images from a scanning electron microscope (above and below) show how intense heat generated by ultrasonic vibrations causes particles of metallic zinc powder to melt and fuse together.



Searching for tumors is another common medical use of ultrasound. But like all other techniques, even the most sophisticated ultrasound scans occasionally miss some tumors. New York researchers are trying to improve tumor searches with a combination of low — audible — and extremely high frequencies.

"The research started because I was having trouble seeing prostate tumors," said the University of Rochester's Dr. Lerner.

Dr. Lerner and his colleague Kevin Parker, an electrical engineer, knew that tumors tend to be harder than surrounding tissue. Conventional ultrasound, X-rays and other techniques don't detect that difference in texture. But that difference should make the tumors vibrate differently, they reasoned.

The researchers modified an ultrasound machine that normally images blood flow to image different vibrational patterns instead. They coupled it with a device that produces low-frequency sound waves. The low-frequency waves make the tissues vibrate, and the ultrasound shows the differences in vibration.

The researchers tested their equipment on model tumors of agar and polymers and on rabbits and tissues removed from cancer patients. The device detected several tumors that remained invisible with other imaging techniques. They've started informally checking living humans.

"We've looked at my liver and other people's livers, but we had no tumors, thank goodness," Dr. Lerner said.

"We think we see quite well with it," he said. "If all goes well, it might be on the market in two to three years."