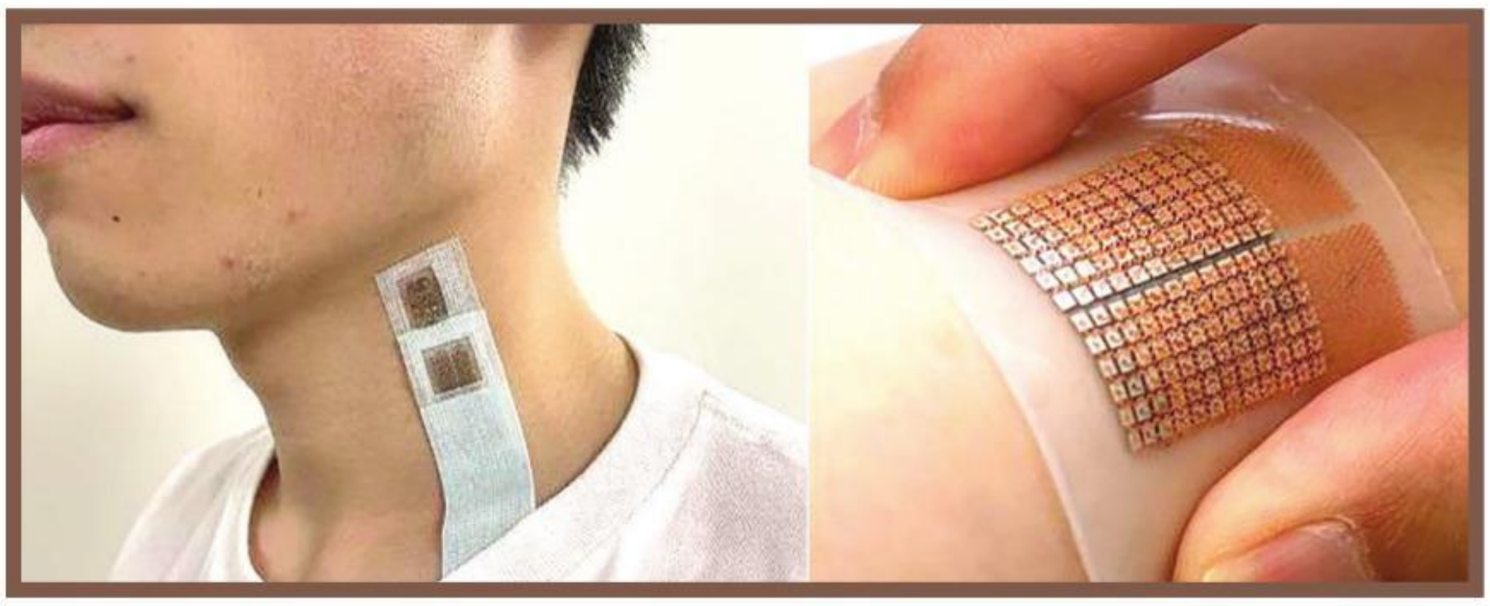
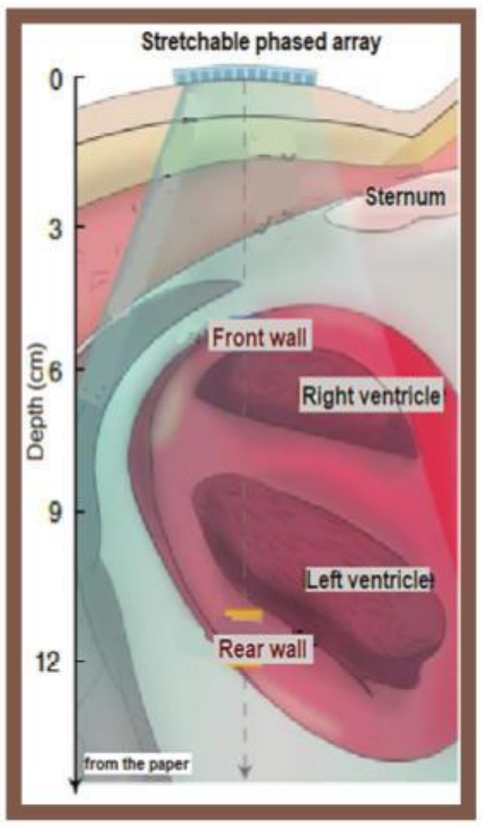
The physician cocks an ear

A prototype wearable skin patch uses sound waves to provide good quality, real-time images of internal organs





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The organs of the body, which a doctor treats, are invisible. Till not so long ago, diagnoses were based only on signs that could be made out on the surface. But now, a doctor has lab reports, x-ray pictures and scan reports to help her.

The x-ray was the first probe that provided physicians a picture, without the need for surgery, of the state of tissues within the body. X-rays are a form of light, but of short wavelength, which enables them to pass through soft tissue.

Many decades later, sound waves, which were used to detect flaws in things made of metal, found an application in medicine. The wavelength, again, was shorter than of audible sound, to be of dimensions close to those of the things to be imaged.

Then entered electronics and computers. The computed tomography, or CT scan, was a series of X-ray pictures that were taken in slices through parts of the body and put together to create 3-D images. And ultrasound scans, with a probe that directed ultrasound into the body and displayed images on a computer screen, with the facility for measurements and recording the images — this was the ultrasound sonograph, or USG.

Further tools that became available were magnetic resonance imaging, or MRI, which scanned the response of substances in cells to wireless radiation and strong magnetic fields, and positron emission tomography scan or PET, which works with radioactive tracers.

Such advances have extended the range of information that medical persons have to diagnose, plan treatment and monitor results. The drawback, however, is that the scans need large pieces of equipment, take some time, and are expensive.

A paper in the journal, *Nature, Biomedical Engineering*, now reports a development in stark contrast — a wearable skin patch, just a few centimetres across, which uses sound waves to provide good quality, real-time images of internal organs, and for as long as the wearer carries the patch. Chonghe Wang, Baiyan Qi, Muyang Lin, Zhuorui Zhang, Mitsutoshi Makihata, Boyu Liu, Sai Zhou, Yi-hsi Huang, Hongjie Hu, Yue Gu, Yimu Chen, Yusheng Lei, Taeyoon Lee, Shu Chien, Kyung-In Jang, Erik B Kistler and Sheng Xu , from the University of California, San Diego, Harvard University, Yonsei University, Korea Institute of Science and Technology, Seoul, Daegu Dyeongbuk Institute of Science and Technology, Daegu, Republic of Korea, describe a prototype of the skin patch, which can focus upon and monitor the dynamics of blood flow from as deep as 14 cm inside the body.

"Most chronic diseases directly manifest on one or more deep tissues. Thus, continuous and non-invasive monitoring of physiological signals in deep tissues to interrogate disease initiation and progression is paramount to support clinical decisions for diagnosing and treating chronic diseases," the paper says. Now, what it calls for is something that can penetrate the tissue surrounding the organ of interest and carry back useful information without being cumbersome.

Advances in communications and electronics have created possibilities of miniaturisation and portability. The information from a hand-held USG probe can connect to a cell phone, dispensing with the need of larger equipment, or permit the scan to be performed over a telecom link. The drawback, however, is that it cannot be continuous or done without a technician.

The answer, the paper says, appears to lie in stretchable electronics — devices that could be attached to a patient's body, monitoring her medical condition continuously, while she goes about her work, and not only at a specialised clinic. The devices would include electronic circuits to drive generators and detectors of different kinds of waves, devices to convert the reflection into electrical records, arrangements to record and transmit the information, the power supply, etc.

The devices need to be embedded in a flexible substrate, like silicone or polyurethane. And the interconnections must have the slack that allows the substrate to bend or use conductors that are stretchable. These conditions have been approximated, but optical or other electromagnetic waves, even chemical or heat signals, in the probe, do not have the ability, either to reach the target organs, or if it were possible, to usefully resolve an image, the paper says.

High frequency sound waves, however, do have the capacity to penetrate human tissue and with electronics, we can arrange for a panel of sources, which create a focused and directed beam of sound waves to select tissue masses of interest.

A single source of waves would spread out, like the ripples on a pond and grow rapidly weaker. If there were a pair of sources, however, there would be a plane, between the sources, where the waves would add, and become stronger. And with more sources, the region where the waves from all the sources add could be arranged to be a narrow beam, or a small volume, and the waves in the region would be powerful. With the control of the timing from different sources, called the "phased array technique", the region of concentrated waves could be moved and adjusted.

"An unfocused single element has a penetration depth of three to four cm and can sense a region directly beneath it. Considering the complexity of human anatomy, it is very challenging to target specific regions with a single element. The phased array technique, which synchronises an array of transducers to enhance the energy density and enable beam steering, is ideal for overcoming this challenge," the paper says.

The team has hence developed a panel of 12 millimetre-sized ultrasound generators, a number that can be increased to 128, embedded in a flexible, polymer medium. The interconnections are with "serpentine" wires, so that the device can be bent or stretched. And each device is separately controlled by a computer, which, conceivably, could be in a microchip, embedded in the device.

The flexible strip containing the device could be attached to the body, say the chest or neck, and it would follow the contours of the body if the wearer stretches or bends. As ultrasound is absorbed by air, it is important to avoid air gaps between the source and skin of the wearer. That is the reason for the special gel when a hand-held device is used to probe the body for the usual USG scan. With the flexible strip, however, close contact with body contours eliminates the need for a gel, and the strip can be in place for extended periods.

"The device allows for active focusing and steering of ultrasound beams over a range of incident angles so as to target regions of interest," the paper says. For the best convergence of the ultrasound beam, the wavelength needs to be near the spacing of the elements in the phased array. And then, a longer wavelength is good for deep penetration, but not for image resolution. The authors therefore selected a wavelength that best satisfied the conflicting requirements.

In a proof of concept, the authors probe the left and right ventricles of the human heart and record the blood flow, by measuring the "Doppler effect" — the effect that the movement of blood has on the frequency of the reflected sound waves. "The ultrasonic beam could be steered to intercept blood flow at an appropriate Doppler angle, allowing accurate recordings of blood flow spectra in major arteries and veins. Combining the blood flow and vessel dimension measurements, we were able to estimate cerebral blood flow in real time," they say.

The device could be coupled with an intelligent unit the wearer could carry, one that would record relevant body parameters over hours or days, possibly communicate with a medical team and even raise an alarm when specific features are seen.

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PLUS POINTS

mRNA for cancer

A cancer treatment that uses messenger ribonucleic acid, or mRNA, to attack cancer cells is being tested on humans after a new study found the therapy was able to completely shrink tumours in mice.

BioNTech, the German company that developed Pfizer's breakthrough mRNA vaccine, is beginning testing of the treatment to examine whether it can be effective in fighting cancerous cells in humans by producing tumour-fighting proteins.

mRNA are molecules that instruct cells in the body to make proteins. In the study, which was published in the medical journal, *Science Translational Medicine*, researchers developed a mixture of mRNA that would make cytokines — a protein naturally produced by immune cells to fight cancer cells.

Similar to the Pfizer coronavirus vaccine, the new therapy teaches the body to produce the desired protein. In this case, anti-tumour proteins that help the body fight cancerous cells.

The results of the study showed that when the mRNA mixture was injected into mice with two different types of cancer (skin and lung cancer), an immune response was triggered producing cytokines to an amount able to diminish the tumours in 17 out of 20 mice in fewer than 40 days.

In addition, some of the animals showed that the therapy travelled off site from the targeted skin cancer, to lung cancer cells where advanced anti-tumour responses were registered, further improving survival and tumour reduction.

The scientists also explained in their study that whilst the therapy could be a viable approach, it can also trigger unwanted side effects.

As a result of the successful study, clinical testing of the treatment is underway. A phase one/two trial has been ongoing since 2019 involving 231 participants. Preliminary results released in November 2020 found no adverse side effects to the trial treatment, currently known as "SAR441000".

The BioNTech-developed Pfizer vaccine has been at the forefront of global immunisation against coronavirus with over 90 per cent efficacy against Covid-19 after the second dose of its vaccine.

—The independent

New fly species

Two new species of flies with quirky characteristics were discovered in the mangroves of Singapore's Pulau Ubin in 2018 and 2019.

While one's offspring dwells in dung, the other feeds on sandflies — a known pest and bane of many beachgoers. The insect-gobbling fly, found in May 2018, is called the long-legged fly (*in photo left*), and its scientific name — *Trigonocera ubinensis* — was inspired by the island.

For the April 2019 discovery of the new sepsid fly, or black scavenger fly, that has a faecal connection (*in photo right*), it was a double victory. Not only is the insect a new species, its discovery also saw the creation of an insect category, or genus, new to science. This is notable because a genus ranks above a species in the hierarchy of biological classification, said the National Parks Board, Government of Singapore, or NParks.

The agency announced the twin discoveries on Ubin Day, which fell on 11 September. First held in 2002, Ubin Day celebrates the natural and cultural heritage of the northern island. The flies were discovered during a survey of insects, where traps were placed at parts of the mangroves on the island.

Both flies were found by Patrick Grootaert — an NParks research fellow and head of entomology at the Royal Belgian Institute of Natural Science — while he was doing fieldwork on Pulau Ubin. The findings underscore the rich biodiversity in Pulau Ubin, which has more than 530 known species of birds, butterflies, mammals and reptiles.

Further surveys, however, are needed to get a complete picture of the fly's population.

—The straits times/ann

LINGERING EFFECTS

Here's a lowdown on leprosy and its allied complications

TAPAN KUMAR MAITRA

The organism responsible for leprosy, *Mycobacterium leprae*, was discovered in 1874 by the Norwegian investigator Gerhard Hansen.

Leprosy, however, was well known even in Ancient Egypt. In the Middle Ages and during the Crusades, it spread as an epidemic, since that period was characterised by continuous wars that caused bad sanitary conditions. There were 2,000 leper colonies in France in 1429 but the disease disappeared from Europe at the end of the 17th century. In France, all leper colonies were closed on 24 August 1693. An increase in disease incidence occurred again from 1867, followed by a marked decline at the beginning of the 20th century. Disease prevalence, however, is still high in these times.

Infection source and route

The source of infection is a sick person and the causative agent is transmitted by the air droplet route through the nasopharynx and injured skin. The infection may also be spread by various objects. Intimate and prolonged contact between healthy individuals and leprosy patients is, however, the main mode of infection.

After entering the body through the skin and mucous membranes, the organisms penetrate the nerve endings, lymphatic and blood vessels, and disseminate gradually without causing any changes at the site of entry. In the presence of high body resistance, the majority of *M. leprae* perish. In some cases, infection leads to the development of latent forms of leprosy.

The duration of such latent forms depends on body resistance, and may persist for a lifetime and, as a rule, terminates with the death of the causative agent. The latent form may change to the active form with development of the disease, if living and working conditions become unfavourable. The incubation period may last for years, may be from a period of three to five or 20-35 years.

Types of leprosy

Three types of leprosy are distinguished based on clinical manifestations — lepromatous, tuberculoid and undifferentiated. The lepromatous type is characterised by minimum body resistance to the presence, multiplication and spread of the causative agent. *M. leprae* are constantly present at the sites of the lesions and the lepromin skin test is negative.

On the other hand, the tuberculoid type is distinguished by high body resistance to the multiplication and spread of *M. leprae*. Either no organism is found at the site of lesions, or only a small number of them may be present during the reactive state. The allergic test is usually positive.

Finally, the undifferentiated type (non-specific group) is characterised by varying body resistance. Microscopic examination does not always reveal the presence of *M. leprue* and allergic tests are negative or yield a slightly positive reaction.

Immunity

Little is known about immunity in connection with leprosy, but an allergic condition develops during the disease. The mechanism of immunity in leprosy is like that in tuberculosis.

In individuals with high body resistance, organisms are phagocytosed by histiocytes in which they are destroyed quite rapidly. In such cases leprosy assumes a benign tuberculoid type. In individuals with low resistance, *M. leprae* multiply in great numbers even within the phagocytes (incomplete phagocytosis), and the organisms disseminate throughout the body. A severe lepromatous type of the disease develops in such individuals.

Resistance may vary from high to low in undifferentiated types of leprosy. Relatively benign lesions persist for years, but if body resistance lowers, the disease assumes a lepromatous form with numbers of mycobacteria present in the tissues and organs. The clinical picture changes to the tuberculoid type when immunity intensifies.

Immunity in leprosy is associated with the general condition of the host body. In most cases, the disease occurs among people living in unhygienic conditions and children are most susceptible. In five per cent cases, the disease is acquired through contact with sick parents.

Laboratory diagnosis

Specimens for examination are obtained from nasal mucosa scrapings (on both sides), skin lepromas, sputum and ulcer excretions. Blood is examined during the fever period and microscopic examination is the principal method of leprosy diagnosis.

The biopsy of leprotic lesions and puncture of lymph nodes are employed in some cases. *M. leprae* can be seen as clusters resembling packets of cigars; in preparations from nasal mucus they appear as red balls. The allergic Mitsuda test is considered positive when an erythema and a small papule (early reaction) are produced at the site of an 0.1 millimetre lepromin (a suspension prepared from a leproma after trituration and prolonged boiling) injection in 48 to 72 hours.

This reaction either disappears completely at the end of the first week or changes to the late reaction. The latter is manifested by a nodule, which appears at the site of injection in 10-14 days and grows to a diameter of one to two cm with necrosis at the centre. This test, however, is of no diagnostic value and is used to distinguish the clinical type of leprosy. The complement-fixation reaction and the Middlebrook-Dubos Haemagglutination test are employed for leprosy diagnosis.

Treatment

Leprosy is treated with sulphone drugs (dapson), and diaminodiphenylsulphone and its derivatives (sulphetrone, promin, diazone and promacetin). In addition to that, conteben, desensitising agents, and corticosteroid preparations (cortisone, prednisolone, etc) are employed.

For a long period of time, leprosy patients were treated with chaulmoogra oil. At present it is administered intramuscularly or intracutaneously. Chaulmoogra preparations promote the resolution of lesions and, sometimes, eliminate visible leprosy manifestations. They, however, give no protection from relapses and have no specific effect.

According to the World Health Organisation, more than 10 million people suffering from leprosy are registered throughout the world — 6.4 million in Asia, 3.8 million in Africa, 385,000 in America, 52,000 in Europe and 33,000 in Oceania. The high prevalence of leprosy makes research into the methods of its specific prophylaxis necessary.

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