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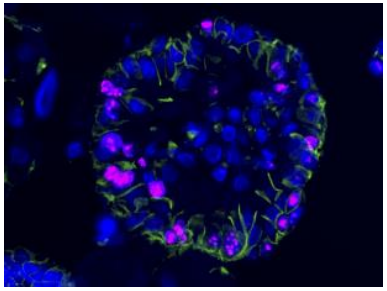
Cutting off kidney cancer at its roots

Scientists at the MDC have discovered stem cells responsible for the most common form of kidney cancer.

Scientists at the MDC have discovered stem cells responsible for the most common form of kidney cancer. The team of Walter Birchmeier has found a way to block the growth of these tumors in three models of the disease.

Not all cancer cells are equal. Tumors contain potent cancer stem cells which produce metastases and can regenerate the disease if they escape a treatment. This makes them vital targets for therapies - if scientists can isolate them and probe their weaknesses. But the cells are often so rare that for many types of cancer, they have yet to be found.



***Human ccRCC organoids under the microscope, labeled with fluorescent markers. The scientists extracted cancer stem cells from patients and used them to grow these miniature versions of kidney tumors in the lab. The structure of the organoids resembles patients' tumors and contains the same types of cells*. Birchmeier Lab, MDC**

Professor Walter Birchmeier's lab at the Max Delbrueck Centrum for Molecular Medicine in the Helmholtz Association (MDC), in a collaboration with the Urology Department of the Charite, has now discovered cancer stem cells responsible for the most common form of kidney cancer: clear cell renal cell carcinoma, or ccRCC. In a Berlin-wide collaboration, the scientists found a weakness. The cells depend on two critical biochemical signals. Blocking them both hinders the growth of tumors in several laboratory models of the disease, suggesting a promising new approach to treating human patients. The work also emphasizes the continued importance of mice in medical research. The study appears in the current issue of Nature Communications and includes authors from the MDC, the Urology Department of the Charite Berlin, the Berlin Institute of Health (BIH), the Screening Unit of the Leibniz Institute FMP, the company EPO, and other partners.

Two biochemical weaknesses

Identifying ccRCC cancer stem cells was crucial to the project. Dr. Annika Fendler, a postdoc in the Birchmeier group and a member of the Charite Urology Department, was first author on the paper. She identified three proteins on the surfaces of the cells that enabled them to be tagged and then isolated. This permitted Dr. Hans-Peter Rahn to isolate the cells using fluorescence-activated cell sorting (FACS). The scientists found that cancer stem cells accounted for only about two percent of the total found in the human tumors.

"Our analysis of these cells shows that they depend on signals passed along two biochemical networks called WNT and NOTCH," Fendler says. Because these networks were known to play roles in other types of cancer, the lab has learned to disrupt them. They had already developed a potent inhibitor of WNT signals with the FMP, their partner institute on campus.

Previously a role for WNT and NOTCH had not been suspected in kidney tumors; mutations in these networks are rarely found in the disease. Both signals are, however, linked to a tumor suppressor gene called VHL, which is strongly associated with ccRCC. The new findings suggested that blocking WNT, NOTCH or both signals might target the cancer stem cells and interfere with the most aggressive components of the tumors.

In the clinic, inhibitors against various biochemical pathways are increasingly replacing chemotherapy in treatments for cancer patients. "But you have to know what pathways to target," Fendler says, "and not enough was known about the biology of ccRCC."

The promise of multiple model systems

Initial tests of the new inhibitors were promising. "Remarkably, three quarters of cell cultures derived from the patients responded to at least one type of inhibitor, and 50 percent of the rest were inhibited in the presence of the two inhibitors," Birchmeier says.

But here the lab confronted one of the main challenges of cancer research. "What we learn in the lab is usually very difficult to translate into the real context of a patient," Birchmeier says. "Regular cell line cultures and animal models obtained from other labs don't reflect the complexity of a disease in a person's body." A solution is to develop more types of models which are closer to the human disease.

Birchmeier and his colleagues were already proficient at extracting cancer stem cells from patients, growing them in cultures and challenging them with a huge palette of drugs. In collaborations with the company EPO on the Berlin-Buch campus, they have also transplanted patients' cancer stem cells into mice, which develop tumors virtually identical to those of their human counterparts. These animals are essential in the search for therapies: what cures a human tumor in mice might also work in a patient. In the current project, EPO injected WNT and NOTCH inhibitors, singly and and combinations, into tumor-bearing mice and observed what happened. Blocking both signals turned out to be the most effective strategy. But would it work equally well in humans?

A new type of model

Very recently scientists have learned to use patient cells to generate organoids: miniature versions of organs, containing many types of cells. They are composed of human tissue, but can be used without the ethical problems of testing drugs on human patients. Organoids had already been created for healthy kidneys, various organs, and tumors such as colon cancer.

"Other groups had tried with ccRCC, but had been less successful," Fendler says. "The tissue didn't grow very well or did not produce organoids. Both of these factors are important in developing models for drug testing and treatments. A patient with the disease needs fast and reliable models on which treatment responses can be tested."

Different models, similar results

"The most crucial finding from the study," Birchmeier says, "is to have identified the essential roles of WNT and NOTCH signaling systems in ccRCC, and to show that inhibiting them has an impact on the tumors." There remain subtle differences between the model systems that still need to be explored; at the moment, studies of mice are still needed.

In the meantime, the work provides important new experimental systems for scientists working on the disease. Annika Fendler has moved on to the Francis Crick Institute in London, where she continues to work on models of kidney cancer. Ultimately, the scientists hope, the strategy developed in the models will make the jump to the clinic, in custom-designed therapies that target the most dangerous cells in the tumors.

Literature

Fendler, Annika et al. (2020): "Inhibiting WNT and NOTCH in renal cancer stem cells and the implications for human patients", Nature Communications, DOI: 10.1038/s41467-020-14700-7.

http://bit.ly/2P7fqTx

65,000-year-old plant remains show the earliest Australians spent plenty of time cooking

Many foods would have taken considerable time and knowledge to prepare, according to analysis of charred plant remains from a 65,000-year-old site.

S. Anna Florin[*] Andrew Fairbairn[**] Chris Clarkson[***]

Australia’s first people ate a wide variety of fruits, vegetables, nuts and other plant foods, many of which would have taken considerable time and knowledge to prepare, according to our

analysis of charred plant remains from a site dating back to 65,000 years ago.

We already know the earliest Aboriginal Australians arrived at least 65,000 years ago, after voyaging across Island Southeast Asia into the prehistoric supercontinent of Sahul, covering modern mainland Australia, Tasmania and New Guinea. But while the timing of this journey is becoming relatively clear, we know comparatively little about the people who made it, including their culture, technology, diet, and how they managed to thrive in these new landscapes.

Our research, published today in Nature Communications, describes charred plant remains found at the archaeological site of Madjedbebe, a sandstone rock shelter on Mirarr country in western Arnhem Land. It provides the earliest evidence for plant foods consumed by humans outside of Africa and the Middle East and tells an important story about the diet of the earliest known Aboriginal people in Australia.

What is the evidence?

While animal bones do not survive in the earliest levels of Madjedbebe, remarkably, plant remains do survive as a result of charring in ancient cooking hearths. We recovered these remains using a simple yet effective method. By immersing the samples in water, the light charcoal pieces float and separate easily from the heavier sandy sediment in which they are buried.

Among the charred plant remains are fruit pips, nutshells, peelings and fibrous parts from tubers, and fragments of palm stem. These are the discarded leftovers of meals cooked and shared at the rockshelter tens of thousands of years ago.

Today, the Madjedbebe rockshelter and the environments around it are just as culturally and economically significant to the Mirarr people as they were in the deep past. Our research is the result of a partnership with the Mirarr, bringing together Indigenous and scientific knowledge.

With the help of traditional owners and research colleagues, May Nango and Djaykuk Djandjomerr, we identified the modern-day plants that would have been eaten at Madjedbebe, and the cooking techniques needed to make them edible. Some foods, such as fruits, required minimal processing. But others, such as the *man-kindjek* or cheeky yam, needed to be cooked, leached and/or pounded before being eaten. Some of these preparation techniques can take up to several days.

We studied the charred plant remains under the microscope, identifying them by matching their features with the modern-day plant specimens. Using this technique we identified several fruits and nuts, including “plums” (*Buchanania* sp., *Persoonia falcata*, *Terminalia* sp.), and canarium (*Canarium australianum*) and pandanus nuts (*Pandanus spiralis*); three types of roots and tubers, including an aquatic-growing species; and two types of palm stem.

What does this tell us about early Aboriginal lifestyles?

Several of these plant foods would have required processing. This included the peeling and cooking of roots, tubers and palm stems; the pounding of palm pith to separate its edible starch from less-digestible fibres; and the laborious extraction of pandanus kernels from their hard drupes. We could only accomplish the latter feat with the help of an electric power saw, although they were traditionally opened by pounding with a mortar and pestle.

There is also evidence for the further processing of plants, including seed-grinding, left as microscopic traces on the grinding stones found in the same archaeological layer at the site. This represents the first evidence of seed-grinding outside Africa.

Along with other technology found at the site, such as the oldest known edge-ground axes in the world, it demonstrates the technological innovation of the first Australians. They were investing knowledge and labour into the acquisition of plant starches, fats and proteins, as well as into the production of the

technologies required to procure and process them (axes and grinding stones).

These findings predate any other evidence for human diet in this region, including Island Southeast Asia and New Guinea.

It calls into question the theory that humans migrating through Southeast Asia fed themselves with as little effort as possible, moving quickly along coastal pathways eating shellfish and other easy-to-catch foods.

Contrary to this, the plant remains found at Madjedbebe suggest that the first Aboriginal people were skilled foragers, using a range of techniques to eat a diverse range of plant foods, some of which were time-consuming and labour-intensive to eat.

Their ability to adapt to this new Australian setting had little to do with a “least effort” way of life, and everything to do with behavioural flexibility and innovation, drawing on the skills and knowledge that allowed successful migration across Island Southeast Asia and into Sahul.

This required the first Australians to pass their knowledge of plants and cooking techniques down through the generations and apply them to new Australian plant species. Along with the innovation of new technology, this allowed them to get the most out of the Australian environment.

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http://bit.ly/325TTQi

Scientists Built a Genius Device That Generates Electricity 'Out of Thin Air'

Strange "sediment organism" can do things not t ever seen before in bacteria.

Peter Dockrill

They found it buried in the muddy shores of the Potomac River more than three decades ago: a strange "sediment organism" that could do things nobody had ever seen before in bacteria.

This unusual microbe, belonging to the *Geobacter* genus, was first noted for its ability to produce magnetite in the absence of oxygen, but with time scientists found it could make other things too, like bacterial nanowires that conduct electricity.

For years, researchers have been trying to figure out ways to usefully exploit that natural gift, and they might have just hit pay-dirt with a device they're calling the Air-gen. According to the team, their device can create electricity out of… well, almost nothing.

"We are literally making electricity out of thin air," says electrical engineer Jun Yao from the University of Massachusetts Amherst. "The Air-gen generates clean energy 24/7."

The claim may sound like an overstatement, but a new study by Yao and his team describes how the air-powered generator can indeed create electricity with nothing but the presence of air around it. It's all thanks to the electrically conductive protein nanowires produced by *Geobacter* (*G. sulfurreducens*, in this instance).

The Air-gen consists of a thin film of the protein nanowires measuring just 7 micrometres thick, positioned between two electrodes, but also exposed to the air.

Because of that exposure, the nanowire film is able to adsorb water vapour that exists in the atmosphere, enabling the device to generate a continuous electrical current conducted between the two electrodes.

The team says the charge is likely created by a moisture gradient that creates a diffusion of protons in the nanowire material.

"This charge diffusion is expected to induce a counterbalancing electrical field or potential analogous to the resting membrane potential in biological systems," the authors explain in their study.

"A maintained moisture gradient, which is fundamentally different to anything seen in previous systems, explains the continuous voltage output from our nanowire device."

The discovery was made almost by accident, when Yao noticed devices he was experimenting with were conducting electricity seemingly all by themselves. "I saw that when the nanowires were contacted with electrodes in a specific way the devices generated a current," Yao says. "I found that exposure to atmospheric humidity was essential and that protein nanowires adsorbed water, producing a voltage gradient across the device."

Previous research has demonstrated hydrovoltaic power generation using other kinds of nanomaterials – such as graphene – but those attempts have largely produced only short bursts of electricity, lasting perhaps only seconds.

By contrast, the Air-gen produces a sustained voltage of around 0.5 volts, with a current density of about 17 microamperes per square centimetre. That's not much energy, but the team says that connecting multiple devices could generate enough power to charge small devices like smartphones and other personal electronics – all with no waste, and using nothing but ambient humidity (even in regions as dry as the Sahara Desert).

"The ultimate goal is to make large-scale systems," Yao says, explaining that future efforts could use the technology to power homes via nanowire incorporated into wall paint.

"Once we get to an industrial scale for wire production, I fully expect that we can make large systems that will make a major contribution to sustainable energy production."

If there is a hold-up to realising this seemingly incredible potential, it's the limited amount of nanowire *G. sulfurreducens* produces.

Related research by one of the team – microbiologist Derek Lovley, who first identified *Geobacter* microbes back in the 1980s – could have a fix for that: genetically engineering other bugs, like *E. coli*, to perform the same trick in massive supplies.

"We turned *E. coli* into a protein nanowire factory," Lovley says. "With this new scalable process, protein nanowire supply will no longer be a bottleneck to developing these applications."

The findings are reported in *Nature*.

http://bit.ly/37LBqTe

Researchers challenge new guidelines on aspirin in primary prevention

There has been considerable confusion from recently reported results of three large-scale randomized trials of aspirin in high risk primary prevention subjects

The most recent guidelines for primary prevention recommend aspirin use for individuals ages 40 to 70 years who are at higher risk of a first cardiovascular event, but not for those over 70. Yet, people over 70 are at increasingly higher risks of cardiovascular events than those under 70. There has been considerable confusion from recently reported results of three large-scale randomized trials of aspirin in high risk primary prevention subjects, one of which showed a significant result, but the other two, based possibly on poor adherence and follow up, did not. As a result, health care providers are understandably confused about whether or not to prescribe aspirin for primary prevention of heart attacks or strokes, and if so, to whom.

In a commentary published online ahead of print in the American Journal of Medicine, researchers from Florida Atlantic University's Schmidt College of Medicine and collaborators from the University of Wisconsin School of Medicine and Public Health, and the

Harvard Medical School and Brigham and Women's Hospital, provide guidance to health care providers and their patients. They urge that to do the most good for the most patients in primary care, health care providers should make individual clinical judgements about prescribing aspirin on a case-by-case basis.

"All patients suffering from an acute heart attack should receive 325 mg of regular aspirin promptly, and daily thereafter, to reduce their death rate as well as subsequent risks of heart attacks and strokes," said Charles H. Hennekens, M.D., Dr.P.H., senior author, the first Sir Richard Doll Professor, and senior academic advisor in FAU's Schmidt College of Medicine. "In addition, among long-term survivors of prior heart attacks or occlusive strokes, aspirin should be prescribed long-term unless there is a specific contraindication. In primary prevention, however, the balance of absolute benefits, which are lower than in secondary prevention patients, and risks of aspirin, which are the same as in secondary prevention, is far less clear."

The researchers emphasize that, based on the current totality of evidence, any judgments about prescribing long-term aspirin therapy for apparently healthy individuals should be based on individual clinical judgments between the health care provider and each of his or her patients that weighs the absolute benefit on clotting against the absolute risk of bleeding.

The increasing burden of cardiovascular disease in developed and developing countries underscores the need for more widespread therapeutic lifestyle changes as well as the adjunctive use of drug therapies of proven net benefit in the primary prevention of heart attacks and strokes. The therapeutic lifestyle changes should include avoidance or cessation of smoking, weight loss and increased daily physical activity, and the drugs should include statins for lipid modification, and multiple classes of drugs likely to be necessary to achieve control of high blood pressure.

"When the magnitudes of the absolute benefits and risks are similar, patient preference assumes increasing importance," said Hennekens. "This may include consideration of whether the prevention of a first heart attack or stroke is a more important consideration to a patient than their risk of a gastrointestinal bleed."

Individual clinical judgements by health care providers about prescribing aspirin in primary prevention may affect a relatively large proportion of their patients. For example, primary prevention patients with metabolic syndrome, a constellation of overweight and obesity, hypertension, high cholesterol, and insulin resistance, a precursor to diabetes mellitus, affects about 40 percent of Americans over age 40. Their high risks of a first heart attack and stroke may approach those in survivors of a prior event.

"General guidelines for aspirin in primary prevention do not seem to be justified," said Hennekens. "As is generally the case, the primary care provider has the most complete information about the benefits and risks for each of his or her patients."

According to the United States Centers for Disease Control and Prevention, more than 859,000 Americans die of heart attacks or stroke every year, which account for more than 1 in 3 of all U.S. deaths. These common and serious diseases take a very large economic toll, costing $213.8 billion a year to the health care system and $137.4 billion in lost productivity from premature death alone.

Collaborators in this commentary are Alexander Gitin, B.S., first author, an honors graduate of FAU and a first-year medical student at the University of Florida College of Medicine; David L. DeMets, Ph.D., the first Max Halperin Professor and chair emeritus of biostatistics and informatics at the University of Wisconsin School of Medicine and Public Health; and Marc A. Pfeffer, M.D., Ph.D., the first Dzau Professor of Medicine at Harvard Medical School.

Hennekens was the first to discover that aspirin prevents a first heart attack in men and stroke in women and has lifesaving benefits when given during a heart attack as well as among long-term survivors' prior events. Science Watch ranked him as the third most widely cited medical researcher in the world from 1995 to 2005, and five of the top 20 were his former trainees and/or fellows. Science Heroes also ranked Hennekens No. 81 in

the history of the world for having saved more than 1.1 million lives, and the Via Academy lists him as the No. 14 top living medical researcher in the world.
He has accepted an invitation to present these findings at the International Academy of Cardiology meeting in July in Boston.

http://bit.ly/37HURDv

Newly Named Chibanian Age Demarcates Earth's Last Magnetic Flip

The time period, which spans 770,000 to 126,000 years ago, started with a reversal of the planet's magnetic field.

Kerry Grens

The International Union of Geological Sciences has designated the time in Earth's history from 770,000 to 126,000 years ago as the Chibanian, notable for being the most recent reversal of the planet's magnetic poles, *The Japan Times* reported January 17.

It's named for the Chiba Prefecture in Japan, where a deposition of minerals and marine fossils reveals the flip in polarity that occurred at the start of the Chibanian.

The Yoro River in Chiba Prefecture, Japan, has mineral deposits that document a reversal in the Earth's magnetic field, which marked the start of the Chibanian. **© ISTOCK.COM, VOYATA**

According to *The Washington Post*, iron within minerals of the deposition aligned with Earth's magnetic field at the time the rocks cooled from a molten form, logging the field's change in polarity. "This sedimentary sequence, called the Kazusa Group, has a total thickness of 3 kilometers with an anomalously high deposition rate reaching 2 meters per thousand years on average," Makoto Okada, a professor of paleomagnetic studies at Ibaraki University in Mito, Japan, tells *Eos*. "[T]his sequence provides us reliable geomagnetic polarity signals and abundant marine microfossils."

The Chibanian designates the first geological age named for Japan, *The Japan Times* reports. "As a Japanese geologist, I am happy [the International Union of Geological Sciences] made a good decision," Hiroshi Kitazato, a professor at Tokyo University of Marine Science and Technology and an executive member of the International Union of Geological Sciences (IUGS) who participated in the discussions for naming the Chibanian, tells *Eos*. "The Chibanian section is certainly the most well preserved paleomagnetic reversal transition from Reversal (Matuyama) to Normal (Brunhes)."

The Japan Times notes that when geologists had requested to register the name Chibanian with IUGS in 2017, another group accused them of fabricating data. This delayed the decision by the IUGS to choose Chibanian, *The Mainichi* reported in 2018, but, ultimately, the allegations were determined to be unfounded.

http://bit.ly/2vOaBrr

Exposure to cleaning products in first 3 months of life increases risk of childhood asthma

New research from the CHILD Cohort Study shows that frequent exposure to common household cleaning products can increase a child's risk of developing asthma.

Asthma is the most common chronic childhood disease and is the primary reason why children miss school or end up in hospital.

The study was published today in the Canadian Medical Association Journal. It found that young infants (birth to three months) living in homes where household cleaning products were used frequently were more likely to develop childhood wheeze and asthma by three years of age.

"Most of the available evidence linking asthma to the use of cleaning products comes from research in adults," said the study's

lead researcher, Dr. Tim Takaro, a professor and clinician- scientist in the Faculty of Health Sciences at Simon Fraser University (SFU). "Our study looked at infants, who typically spend 80-90% of their time indoors and are especially vulnerable to chemical exposures through the lungs and skin due to their higher respiration rates and regular contact with household surfaces."

In the study, at three years of age, children living in homes where cleaning products were used with high frequency during their infancy were more likely to have:

Recurrent wheeze (10.8 percent, compared to 7.7 percent of infants in homes with low use of these products)

Recurrent wheeze with atopy, a heightened immune response to common allergens (3.0 percent, compared to 1.5 percent of infants in homes with low use of these products)

Asthma (7.9 percent, compared to 4.8 percent of infants in homes with low use of these products)

Other factors known to affect the onset of asthma, such as family history and early life exposure to tobacco smoke, were accounted for in the analysis.

"Interestingly, we did not find an association between the use of cleaning products and a risk of atopy alone," noted Dr. Takaro. "Therefore, a proposed mechanism underlying these findings is that chemicals in cleaning products damage the cells that line the respiratory tract through innate inflammatory pathways rather than acquired allergic pathways."

"We also found that at age three, the relationship between product exposure and respiratory problems was much stronger in girls than boys," he added. "This is an interesting finding that requires more research to better understand male versus female biological responses to inflammatory exposures in early life."

The study used data from 2,022 children participating in the CHILD Cohort Study and examined their daily, weekly and monthly exposure to 26 types of household cleaners, including dishwashing and laundry detergents, cleaners, disinfectants, polishes, and air fresheners.

"The risks of recurrent wheeze and asthma were notably higher in homes with frequent use of certain products, such as liquid or solid air fresheners, plug-in deodorizers, dusting sprays, antimicrobial hand sanitizers and oven cleaners," commented the paper's lead author, Jaclyn Parks, a graduate student in the Faculty of Health Sciences at SFU. "It may be important for people to consider removing scented spray cleaning products from their cleaning routine. We believe that the smell of a healthy home is no smell at all."

"The big takeaway from this study is that the first few months of life are critical for the development of a baby's immune and respiratory systems," concluded Parks. "By identifying hazardous exposures during infancy, preventive measures can be taken to potentially reduce childhood asthma and subsequent allergy risk."

About the CHILD Cohort Study:

Launched in 2008 by CIHR and AllerGen NCE, the CHILD Cohort Study (CHILD) is tracking nearly 3,500 Canadian infants and their families to help determine the root causes of chronic diseases such as asthma, allergies and obesity. CHILD spans four provinces, involving over 140 multidisciplinary researchers, students and research staff. Watch the CHILD Cohort Study videos.

https://wb.md/3c62XJM

Even Very Old People Deserve Aggressive Medical Care

There has been some discussion over the past few years about whether age should be taken into account when giving people access to aggressive healthcare for serious problems.

Arthur L. Caplan, PhD

This transcript has been edited for clarity.

Hi. I'm Art Caplan. I'm at the NYU Grossman School of Medicine, where I'm the head of the Division of Medical Ethics.

Some of you may have heard some discussion over the past few years about whether age should be taken into account when giving people access to aggressive healthcare for serious problems. Some people—Ezekiel Emanuel, for example, at the University of Pennsylvania—have suggested that we need a cut-off of 75 years, beyond which we start to cut back on the kinds of medical interventions that individuals can access.

That position has been echoed by earlier writers. Daniel Callahan suggested that society should agree that pursuing healthcare for everyone forever was unaffordable; therefore, we should have an age cut-off. I think he had posited a cut-off of age 65 years.

Well, an interesting paper was recently published by surgeons at Stanford University who deal with lung cancer. They showed that among patients with early-stage lung cancer, those who were relatively healthy at age 90 years experienced significant benefit from surgery. Of these, 33% lived much longer, with a good quality of life. In addition, about 20% of patients benefited from drug treatment, as opposed to those who didn't do anything and who died quickly.

It seems to me that we want to guide our decisions about access to healthcare not by biases about being too old or treatments being too expensive, but first and foremost, we want to ask whether there is benefit. Does it work? Is it going to help the individual? This paper seems to indicate that even at age 90, for early-stage lung cancer, there are people who could benefit from aggressive care.

Admittedly, not every 90-year-old is going to want it. Some 90-year-olds may say, "I'm going to forgo that. My time has come. I don't want any more treatment. I don't want to go through any more surgeries."

But as we also know, more and more anticancer treatments are drug-based, not surgically based. They're not cheap, but many of them are going to prove efficacious for some of those elderly people.

It's wrong to set an age limit based only on the notion of a fulfilled life or someone having had the chance to live a complete life. If you can make it to age 90 and you still love your family, have your hobbies, or are still working, you should have the choice about whether to take more treatment for life-threatening diseases that you face.

I understand that you may also say, "I'm done, and I don't want to do anymore." I have no objection to that, as long as it's a choice informed by data—not by bias, by bigotry, or by ageism.

The data ought to drive the things that are offered and then we should dispute whether or not we can afford everything that might be available to the very old. However, we should not decline, disguise, or fail to disclose the opportunities that might be out there when the data show that real benefit is possible.

I'm Art Caplan at the Division of Medical Ethics at NYU. Thanks for watching.

http://bit.ly/2SMejeb

FDA clears ‘world’s first’ portable, low-cost MRI following positive clinical research

Bedside device can accurately and safely image patient’s brains for stroke.

Matt O'Connor

Magnetic resonance imaging is no longer confined to radiology departments. The U.S. Food and Drug Administration announced Wednesday that it has provided clearance to the “world’s first” bedside MRI system, according to an announcement.

Hyperfine said it will begin shipping its portable, low-field modalities this summer. It’s 510(k) clearance falls on the same day that Yale researchers reported the device can accurately and safely image patient’s brains for stroke. Those preliminary results are set

to be presented next week at the American Stroke Association's International conference in Los Angeles, the group announced.

Courtesy of Hyperfine Research.

"We've flipped the concept from having to get patients to the MRI to bringing the MRI to the patients," said Kevin Sheth, MD, senior author and a chief physician at Yale School of Medicine. "This early work suggests our approach is safe and viable in a complex clinical care environment."

The study included 85 stroke patients who underwent bedside MRI within seven days of experiencing symptoms. A majority of individuals completed the exam, which took an average of 30 minutes. Six experienced claustrophobia and a few couldn't fit into the machine, but there were no adverse events.

According to Connecticut-based Hyperfine, their machine will cost $50,000, which is 20-times cheaper than traditional systems, runs on 35-times less power and weights 10 times less than normal 1.5T MRI machines.

The FDA clearance includes head imaging for patients 2 years and older, and could help bring the modality to underserved areas such as rural settings and remote villages, said Sheth, who added they've "cracked the door open" on bringing this tech to any region.

Sheth also noted that his team will perform further research using this device—built around a 0.064 Tesla magnet—to scan more patients, improve image quality and even employ machine learning to extract vast amounts of its novel imaging data.

For Jonathan Rothberg, PhD, who founded Hyperfine in 2014 and now chairs the company, the goal of revolutionizing how doctors think about MRI is now a reality.

"Nearly six years ago, a dream to create a portable, affordable MRI system was born," he said in a statement. "We assembled an astounding team, and they took the 10 million-fold improvement in computing power since MRI was invented, the best of the billions invested in green electronics and they built something astonishing, something disruptive."

http://bit.ly/37L74rk

When the best treatment for hypertension is to wait

A study of 'therapeutic inertia' and home blood pressure follow-up

A new study from the University of Missouri concluded that a physician's decision not to intensify hypertension treatment is often a contextually appropriate choice. In two-thirds of cases where physicians did not change treatment for patients with hypertension, patients' blood pressure returned to normal in follow-up readings taken at home. This pre- and post-study tracked 90 patients with hypertension to understand the role that follow-up home blood pressure measures could play in understanding cases of "therapeutic inertia." Sixty-six percent of patients who had a blood pressure reading of 140/90 or higher when they were in the clinic and whose doctors did not change their treatment, had average readings under 140/90 when patients took their blood pressure at home.

According to the authors, there are implications for health care quality metrics. Doctors' success rates in controlling hypertension are based solely on clinic blood pressure rates. The authors extrapolated the home blood pressure metrics to show that when home metrics replaced clinical ones, the department's hypertension control success rates rose from 58% to 86%. They conclude, "Most validated home blood pressure should be accepted and preferred for physician hypertension performance measures."

Additionally, when surveyed after the home blood pressure reading intervention, participants shared that home blood pressure

monitoring enhanced their understanding of blood pressure control. Eighty-three percent of participants agreed that they would consider buying a home blood pressure monitor if it was covered by insurance.

Home Blood Pressure Monitoring in Cases of Clinical Uncertainty to Differentiate Appropriate Inaction From Therapeutic Inertia Sonal J. Patil, MD, MSPH, et al
http://www.annfammed.org/content/18/1/50

http://bit.ly/2SMS7k8

New Discoveries in Human Anatomy

Using advanced microscopy and imaging techniques, scientists have revealed new parts of the human body and overturned previous misconceptions.

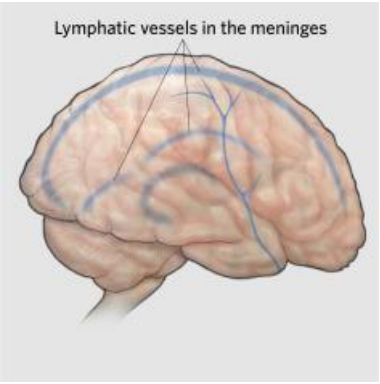
Diana Kwon

In the 16th century, when the study of human anatomy was still in its infancy, curious onlookers would gather in anatomical theaters to catch of a glimpse of public dissections of the dead. In the years since, scientists have carefully mapped the viscera, bones, muscles, nerves, and many other components of our bodies, such that a human corpse no longer holds that same sense of mystery that used to draw crowds.

New discoveries in gross anatomy—the study of bodily structures at the macroscopic level—are now rare, and their significance is often overblown, says Paul Neumann, a professor who specializes in the history of medicine and anatomical nomenclature at Dalhousie University. "The important discoveries about anatomy, I think, are now coming from studies of tissues and cells."

Over the last decade, there have been a handful of discoveries that have helped overturn previous assumptions and revealed new insights into our anatomy. "What's really interesting and exciting about almost all of the new studies is the illustration of the power of new [microscopy and imaging] technologies to give deeper insight," says Tom Gillingwater, a professor of anatomy at the University of Edinburgh in the UK. "I would guess that many of these discoveries are the start, rather than the end, of a developing view of the human body." Here is a sampling of some of those discoveries.

The brain's drain

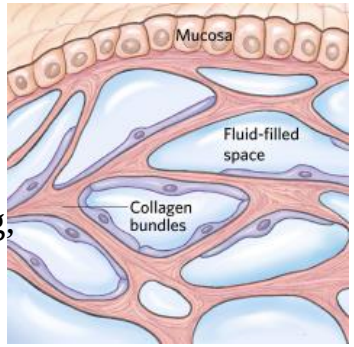


The lymphatic system, a body-wide network of vessels that drains fluids and removes waste from tissues and organs, was long-believed to be absent from the brain. Early reports of lymphatic vessels in the meninges, the membrane coating the brain, date as far back as the 18th century—but these findings were met with skepticism.

Laurie O'Keefe

Only recently has this view been overturned, after a 2015 report of lymphatic vessels in mouse meninges and the 2012 discovery of the so-called glymphatic system, an interconnected network of glial cells that facilitates the circulation of fluid throughout mouse brains. In 2017, neuroimaging work revealed evidence for such lymphatic vessels in human meninges.

Fluid-filled spaces

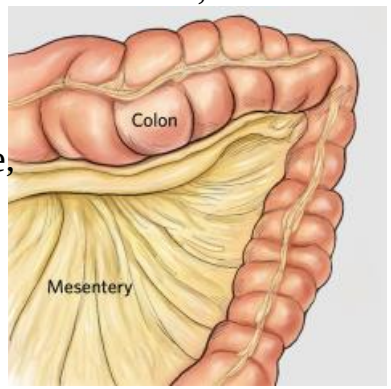


In 2018, researchers reported that the space between cells was a collagen-lined, fluid-filled network, which they dubbed the interstitium. They proposed that this finding, which emerged from close examinations of tissue from patients' bile ducts, bladders, digestive tracts, and skin, may help scientists better understand how tumors spread through the body.

Laurie O'Keefe

The team also called the interstitium a newly-discovered organ, but many dismissed this claim. "Most biologists would be reticent to

put the moniker of an ‘organ’ on microscopic uneven spaces between tissues that contain fluid,” Anirban Maitra, a pathologist at the University of Texas MD Anderson Center, told *The Scientist* last year.

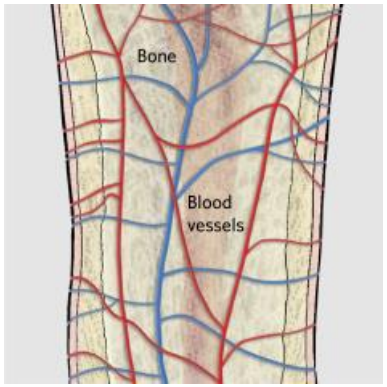


The mesentery: An organ?

Until recently, the prevailing view among scientists was that the mesentery, the large, fan-like sheet of tissue that holds our intestines in place, consisted of multiple fragments. In 2016, after examining the mesentery of both cadavers and patients undergoing surgery, a team of researchers concluded that the mesentery was actually a single unit.

Laurie O’Keefe

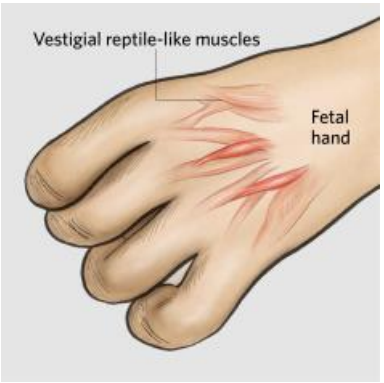
This wasn’t the first time the mesentery was described as continuous—in one of the first depictions of the structure, Leonardo da Vinci also portrayed it in this way. But in the 2016 paper, the scientists argued that its continuity should qualify the mesentery as an organ. As with the interstitium, however, other experts have objected to this claim. In both of these cases, “there seems to have been a misunderstanding of what the term organ means,” Neumann says.



Laurie O’Keefe

Blood vessel networks in bone

In January 2019, scientists described a previously unknown web of capillaries that pass through the bones of mice. Textbooks describe large veins and arteries jutting out the ends of bones, but this newly-described network of tunnels provide a faster route for blood cells produced in the bone marrow to enter the circulation. The research team also looked at human bones using a variety of methods: taking photos from patients undergoing surgery, conducting MRI scans of a healthy leg, and investigating extracted samples under a microscope—and revealed a similar, albeit less extensive, system of capillaries.



Reptile-like muscles in fetuses

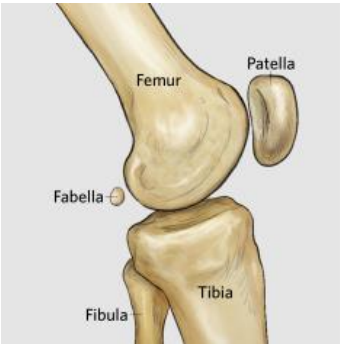
Last October, researchers reported that muscles typically seen in reptiles and other animals—but not people—were present in the limbs of human embryos. Using a combination of immunostaining, tissue clearing, and microscopy, the team generated high-resolution 3-D images of upper and lower limb muscles in tissue samples from preserved 8- to 14-week-old embryos and fetuses.

Laurie O’Keefe

These structures, which disappear before birth, may be anatomical remnants of our evolutionary ancestors that disappear during the early stages of development, the authors suggest. They only examined 13 images, however, so experts caution that it’s a preliminary finding that needs to be replicated in a larger sample.

The fabella makes a comeback

The fabella, a tiny bone located in a tendon behind the knee, is becoming more common in humans, according to a study published last spring. After reviewing 58 studies on fabella prevalence in 27 different countries, researchers reported that people were approximately 3.5 times more likely to have the little bone in 2018 than 1918.



Laurie O’Keefe

The cause of this trend remains an open question, but the authors suggest that changes in muscle mass and bone length—driven by increased diet quality in many parts of the world—could be one explanation.

https://bbc.in/32cpPTk

'My horse knew I had brain cancer before I did'

A woman has told how she truly believes her pet horse was trying to tell her she had cancer.

Kelly Ann Alexander, from Blackburn in West Lothian, said she was puzzled why Aliyana paid so much attention to the right-hand side of her head. Following several seizures, the 43-year-old was eventually diagnosed with two brain tumours in 2015. She has since recovered after having had an operation, radiotherapy and chemotherapy. Mrs Alexander, who still has a weak left side, said she would never give up her horse, which was a wedding present.

'Special bond'

She told BBC Scotland's Mornings with Kaye Adams programme: "I couldn't work out why she was trying to sniff my head.

"I was trying to think did I have different shampoo? But I always had the same shampoo and she kept sniffing the right hand side of my head. "I've got a special bond with Aliyana and I will never give her up as she is part of the family now."

Mrs Alexander said she had previously suffered seizures but her brain tumour was not diagnosed until later.

She said: "When I was taken to hospital after collapsing with a seizure the doctors more or less said it was an alcohol problem and they told me to go to my GP when I had sobered up. "I had never had a drink for weeks though. "At worst I thought I had epilepsy, never did I think I had two brain tumours."

Hugh Adams, Brain Tumour Research's charity spokesman, said he had heard of similar stories where animals appear to detect cancers.

He added: "What was really interesting with what Kelly Ann has been saying was the problems of her own route to diagnosis through her doctors. "That is truly shocking to be told to go home and sober up.

"It is something we hear about all too frequently because brain tumours are comparatively rare and the route to diagnosis can be problematic because GPs don't know enough about the symptoms."

Symptoms of brain tumours include headaches, vision problems, nausea, seizures, personality changes or changes to the senses.

http://bit.ly/37POyOi

We've Vastly Underestimated How Much Methane Humans Are Spewing Into The Atmosphere

Tiny bubbles of ancient air trapped in ice cores from Greenland suggest we've been seriously overestimating the natural cycle of methane, while vastly undervaluing our own terrible impact.

Carly Cassella

Methane is an 'invisible climate menace' - roughly 30 times more potent as a heat-trapper than carbon dioxide - and while some of this atmospheric gas is produced naturally, new research indicates humans are responsible for far more of it than we thought until now.

Before the industrial revolution, when humans began to extract and burn fossil fuels on the regular, natural methane emissions were an order of magnitude smaller than current estimates, the study suggests.

Today, this means our own methane emissions might be up to 40 percent higher than suspected.

"Our results imply that anthropogenic methane emissions now account for about 30 percent of the global methane source and for nearly half of [all] anthropogenic emissions… " the authors write.

Over the past three centuries, methane emissions have shot up by roughly 150 percent, but because this atmospheric gas is also

produced naturally, it's been difficult to tell exactly where the emissions are coming from.

To figure out the scope of our own impact from coal, oil and natural gas, it's therefore necessary to know how much methane comes from wetlands and other natural sinks.

"As a scientific community we've been struggling to understand exactly how much methane we as humans are emitting into the atmosphere," says Vasilii Petrenko, a geochemist from the University of Rochester.

"We know that the fossil fuel component is one of our biggest component emissions, but it has been challenging to pin that down because in today's atmosphere, the natural and anthropogenic components of the fossil emissions look the same, isotopically."

There is one rare radioactive isotope however, known as carbon-14, which is contained in biological methane and not in fossil fuel methane.

By drilling and collecting ice cores in Greenland, Petrenko and his colleagues were able to use this isotope as a sort of time capsule for past atmospheres, ranging from roughly 1750 to 2013.

Until about 1870, the findings suggest very low levels of methane were emitted into the atmosphere and almost all of it was biological in nature. Only after this date was there a sharp increase in methane, coinciding with an increase in fossil fuel use.

In practice this means that each year, the scientific community has been underestimating methane emissions from humans by as little as 25 percent and as high as 40 percent. And while that might sound entirely grim, the authors see a silver lining on the edge of this dark cloud.

"I don't want to get too hopeless on this because my data does have a positive implication: most of the methane emissions are anthropogenic, so we have more control," says University of Rochester geochemist Benjamin Hmiel.

"If we can reduce our emissions, it's going to have more of an impact."

Compared to carbon dioxide, methane is short-lived in the atmosphere, so stricter regulations could have a sizeable impact on future greenhouse gas emissions.

And, at least in the United States, there's plenty of room for improvement in that respect. A study in 2018, for example, found methane emissions from oil and natural gas were 60 percent higher than those reported by the US Environmental Protection Agency.

This missing chunk could be part of the reason why we are currently underestimating methane emissions so much. It seems that what we are reporting on the ground is not matching up with what's going on in the sky. The study was published in *Nature*.

http://bit.ly/2SLh9ju

Some antibiotics prescribed during pregnancy linked with birth defects

They should be used with caution during pregnancy, say researchers

Children of mothers prescribed macrolide antibiotics during early pregnancy are at an increased risk of major birth defects, particularly heart defects, compared with children of mothers prescribed penicillin, finds a study published by The BMJ today.

The researchers say these findings show that macrolides should be used with caution during pregnancy and if feasible alternative antibiotics should be prescribed until further research is available.

Macrolide antibiotics (including erythromycin, clarithromycin, and azithromycin) are - widely used to treat common bacterial infections. They are often used as alternatives for patients with penicillin allergy.

Previous studies suggest evidence of rare but serious adverse outcomes of macrolide use, especially for unborn babies. The adverse outcomes might be associated with the pro-arrhythmic

(heart rhythm problems) potential of macrolides. Policy advice about macrolide use in pregnancy varies.

To address these uncertainties, a team of researchers based at UCL set out to assess the association between macrolide antibiotics prescribed during pregnancy and major malformations as well as four neurodevelopmental disorders (cerebral palsy, epilepsy, ADHD, and autism spectrum disorder) in children.

Researchers analysed data from 104,605 children born in the UK from 1990 to 2016 with a median follow up of 5.8 years after birth. A further 82,314 children whose mothers were prescribed macrolides or penicillins before pregnancy, and 53,735 children who were siblings of children in the study group acted as negative control cohorts.

Major malformations were recorded in 186 of 8,632 children whose mothers were prescribed macrolides at any point during pregnancy and 1,666 of 95,973 children whose mothers were prescribed penicillins during pregnancy.

After taking account of potentially influential factors, the researchers found macrolide prescribing during the first three months (the first trimester) of pregnancy was associated with an increased risk of any major malformation compared with penicillin (28 v 18 per 1000) and specifically cardiovascular malformations (11 v 7 per 1000).

The increased risks were not observed in children of mothers whose macrolides were prescribed in later pregnancy (during the second to third trimester).

Macrolide prescribing in any trimester was also associated with a slightly increased risk of genital malformations (5 v 3 per 1000). No statistically significant associations were found for other system specific malformations or for any of the four neurodevelopmental disorders.

This is an observational study, so can't establish cause, and the researchers point to some limitations, such as being unable to examine treatment exposure during known critical periods for specific malformations and neurodevelopmental disorders.

However, results were largely unchanged after further analyses, suggesting that the findings withstand scrutiny.

If the associations are shown to be causal, the researchers estimate that an additional 4 children with cardiovascular malformations would occur for every 1000 children exposed to macrolides instead of penicillins in the first trimester.

"These findings show that macrolides should be used with caution during pregnancy and if feasible alternative antibiotics should be prescribed until further research is available," they conclude.

Peer-reviewed? Yes
Evidence type: Observational
Subjects: Mothers and their children

http://bit.ly/2PbdHMQ

Weed-derived compounds in Serbian groundwater could contribute to endemic kidney disease

People in Balkan farming villages have long suffered from a unique kidney disease known as Balkan endemic nephropathy.

People living in Balkan farming villages along the Danube River have long suffered from a unique type of kidney disease known as Balkan endemic nephropathy. Recently, scientists linked the disorder to compounds from a local weed that could be taken up into food crops from the soil. Now, researchers reporting in ACS' journal *Environmental Science & Technology* have discovered that contaminated groundwater could be another important source of human exposure.

Aristolochic acids (AAs) were recognized as potent kidney toxins after people taking herbal medicines containing the compounds developed kidney disease. A weed that is widespread in the Balkan

regions, *Aristolochia clematitis L.*, produces AAs, and when the plant decays, it releases the toxic compounds into the soil. As a result, scientists have detected AAs in Balkan food products. Nikola Pavlovic, Wan Chan and colleagues wondered if the weed-derived compounds could also leach into groundwater, polluting the drinking water of local residents.

To measure AAs in water, the researchers used a positively charged silica-based sorbent to collect AAs, which are negatively charged, from water samples. They released the AAs from the sorbent and then converted the substances to aristolactams for detection by mass spectrometry. The team applied this new method to the analysis of 123 water samples collected from wells in rural Serbia. They found that the groundwater was extensively contaminated with one form of AA at nanogram/liter levels. These results suggest that drinking, cooking and irrigating with the contaminated water is a highly important, but previously unrecognized, source of AA exposure. Weed control of *A. clematitis* is urgently needed to reduce the incidence of Balkan endemic nephropathy, the researchers say.

More information: *Ka-Ki Tung et al. Occurrence and Environmental Stability of Aristolochic Acids in Groundwater Collected from Serbia: Links to Human Exposure and Balkan Endemic Nephropathy, Environmental Science & Technology (2019).* [*DOI: 10.1021/acs.est.9b05337*]

http://bit.ly/2HOWEMI

New study indicates amino acid may be useful in treating ALS

Study published in Journal of Neuropathology & Experimental Neurology provides new model for ALS and its treatment

JACKSON, Wyo.- A naturally occurring amino acid is gaining increased attention from scientists as a possible treatment for ALS following a new study published today in the *Journal of Neuropathology & Experimental Neurology*. The study showed that the amino acid, L-serine, successfully reduced ALS-like changes in an animal model of ALS.

The scientists conducted the vervet study at the Behavioural Science Foundation, a specialized research facility on the Caribbean island of St. Kitts. After being exposed to a cyanobacterial neurotoxin called BMAA, the vervets developed aggregations of misfolded proteins similar to those seen in human ALS patients, and activated microglia, a type of immune cells, in their spinal cord and brain, similar to those that occur in the early stages of ALS. In contrast, vervets that also received the amino acid L-serine had significantly reduced ALS pathology.

Dr. David Davis at the Department of Neurology, University of Miami Miller School of Medicine who served as first author on the paper, said that the differences were profound.

"Without L-serine co-administration, the BMAA-exposed vervets developed motor neuron degeneration, pro-inflammatory microglia and dense inclusions of TDP-43 and other misfolded proteins known to be associated with ALS," Dr. Davis explained. "In animals dosed with L-serine, the progression of these ALS-like changes was considerably reduced."

ALS is a devastating disease that hits people in the prime of life, causing increasing paralysis and often results in death within two to three years after diagnosis. At present, only two drugs are available that slow the disease modestly. This study offers the possibility that L-serine may slow the progression of the disease even more.

Potential Implications for L-Serine as a Treatment

Neurobiologist Dr. Deborah Mash of Nova Southeastern University, who was also an author on the study, said that the results "holds promise for identifying a cause of sporadic ALS, which accounts for 90 percent of all ALS cases."

Dr. Elijah Stommel, a Professor of Neurology at Dartmouth Medical School, who was not associated with the study, said that

these experimental results are encouraging. Stommel is conducting a Phase II trial of L-serine in 50 ALS patients. "We are attempting to replicate a previous positive trial of L-serine for ALS patients, but won't know the results until the trial is finished," he said.

L-serine is one of the twenty amino acids that make up human proteins. L-serine molecules in proteins are often the site where proteins are phosphorylated, or charged, so they can be properly folded.

"Think of a charging port for an electric car," explained Dr. Paul Alan Cox, Executive Director of the Brain Chemistry Labs in Jackson Hole, "If the cable can't be connected there, the car can't be charged." Scientists at the Brain Chemistry Labs have also discovered that L-serine modulates the unfolded protein response which helps protect neurons from the damage produced by misfolded proteins.

"While these data provide valuable insights, we do not yet know if L-serine will improve outcomes for human patients with ALS," cautioned internationally renowned ALS expert, Dr. Walter Bradley, who was also an author on the study. "We need to carefully continue FDA-approved clinical trials before we can recommend that L-serine be added to the neurologists' toolbox for the treatment of ALS. However, this vervet BMAA model will be an important new tool in the quest for new drugs to treat ALS."

Dr. Larry Brand, a prominent oceanographer unassociated with the study, said that there are even broader implications of the study for human health.

"These vervets were exposed to the same cyanobacterial toxin that was found in the brains of beached dolphins with Alzheimer's neuropathology," he said. "This is one more indication that we need to carefully monitor the health effects of exposure to cyanobacterial blooms."

http://bit.ly/2PhXaXP

Scientists Find a Wild Salamander That Hasn't Moved From Its Spot For 7 Years

In the depths of a European cave, dwells what must be the laziest and most underwhelming of all creatures to have ever been called a dragon.

Tessa Koumoundouros

With disturbingly fleshy-coloured skin, it has also earned the label of "human fish". But the olm (*Proteus anguinus*), with its cute stubby limbs, is actually an amphibian - a type of salamander that has adapted to life in the eternal darkness of a skyless existence.

This troglobite lifestyle has resulted in under-developed eyes covered by layers of skin, which led Charles Darwin to refer to the species as "wrecks of ancient life".

(IvanaOK/iStock)

Olm eyes can only detect the presence of light, but not much else. Thus, these little gill-adorned weirdos are essentially blind, but they make up for this with a keen sense of smell, underwater hearing, and the ability to detect movements in their watery home.

Between 2010 and 2018, researchers captured, tagged, and recaptured a number of olms in the caves of eastern Bosnia-Herzegovina. Based on the frequency of their encounters, they estimated there were 26 adult olms making themselves at home there; across these eight years, checking in on their research subjects revealed the animals had a rather limited movement range.

"The majority of recaptured individuals moved less than 10 metres (33 feet) during several years," wrote zoologist Gergely Balázs from Eötvös Loránd University and colleagues in their paper.

One of these individuals was even lazier than the rest. It was found in the exact same spot a crazy 2,569 days after it was first recorded.

That's over seven years! But there are clues in olm biology that might explain this seemingly unbelievable feat.

These little slackers have a lifespan of up to a century. For such slight creatures, up to 20 grams (0.7 ounces) and 30 centimetres long (12 inches), that's an impressive feat, so clearly they're doing something right. "They are hanging around, doing almost nothing," Balázs told *New Scientist*.

This may be key to their longevity - the olms' strategy of primarily doing diddly-squat has been working well for them since they colonised caves around 20 million years ago.

Olms are able to achieve these epic heights of laziness thanks to a very low metabolism. They eat snails and crustaceans (which aren't exactly plentiful in the caves), but can survive for years without food.

The lack of predators within their cave systems would also encourage their couch potato ways, allowing olms to be perfectly safe just plonking themselves wherever. Additionally, they only bother to breed about every 12 years. But when they do, they produce a clutch of around 35 of these spectacular looking eggs.

And it's not like they can't move - some olms have easily fled from nosy scientists, by wiggling their way through tens of metres of water. Nor can the scientists say for sure that their tagged subjects *didn't* go for a wonder while they weren't looking, before sneaking back to their favourite position.

But Balázs and colleagues found this group of olms has very low genetic diversity, suggesting the population recently shrunk, or has a high level of inbreeding, which again hints at a very sedentary life. A previous study suggested only their young might be dispersing.

(Arne Hodalič/Wikimedia Commons/CC BY-SA 3.0)

This lack of genetic diversity was not found in Slovenian olm populations, so further research is required to see if the incredibly slow-paced lifestyle of the recently studied population is shared by the rest of the species.

"We can only speculate that animals feeding on a very low food supply, reproducing sporadically and living for a century are very energy cautious and limit their movements to the minimum," the researchers wrote.

Biologist Matthew Niemiller of the University of Alabama, who was not involved in the study, agrees. He told Science News:

"If you're a salamander trying to survive in this … food-poor environment and you find a nice area to establish a home or territory - why would you leave?"

In this fast-paced, stressed-out world, perhaps we should all aspire to be a bit more like these olms.

This research was published in the *Journal of Zoology*.

http://bit.ly/2v8uvqQ

Mysterious 'ghost' populations had multiple trysts with human ancestors

The ancestors of all three groups mixed at least twice with even older "ghost" lineages of unknown extinct hominins.

By Ann Gibbons

The story of human evolution is full of ancient trysts. Genes from fossils have shown that the ancestors of many living people mated with Neanderthals and with Denisovans, a mysterious group of extinct humans who lived in Asia.

Human ancestors mated with "super-archaics," perhaps like this 700,000-year-old* Homo erectus *from Java. Natural History Museum, London/Science Source

Now, a flurry of papers suggests the ancestors of all three groups mixed at least twice with even older "ghost" lineages of unknown extinct hominins. One candidate partner: *Homo erectus*, an early human who left Africa by 1.8 million years ago, spread around the world, and could have mated with later waves of human ancestors.

The new genomic studies rely on complex models of inheritance and population mixing, and they have many uncertainties, not least the precise identities of our ancestors' strange bedfellows and when and where the encounters took place. But, taken together, they build a strong case that even before modern humans left Africa, it was not uncommon for different human ancestors to meet and mate. "It's now clear that interbreeding between different groups of humans goes all the way back," says computational biologist Murray Cox of Massey University of New Zealand, Turitea, who was not involved in the new studies.

The gold standard for detecting interbreeding with archaic humans is to sequence ancient DNA from fossils of the archaic group, then look for traces of it in modern genomes. Researchers have done just that with Neanderthal and Denisovan genomes up to 200,000 years old from Eurasia. But no one has been able to extract full genomes from more ancient human ancestors. So population geneticists have developed statistical tools to find unusually ancient DNA in genomes of living people. After almost a decade of tantalizing but unproven sightings, several teams now seem to be converging on at least two distinct episodes of very ancient interbreeding.

In *Science Advances* today, Alan Rogers, a population geneticist at the University of Utah, Salt Lake City, and his team identified variations at matching sites in the genomes of different human populations, including Europeans, Asians, Neanderthals, and Denisovans. The team tested eight scenarios of how genes are distributed before and after mixing with another group, to see which scenario best simulated the observed patterns. They conclude that the ancestors of Neanderthals and Denisovans—whom they call Neandersovans—interbred with a "super-archaic" population that separated from other humans about 2 million years ago. Likely candidates include early members of our genus, such as *H. erectus* or one of its contemporaries. The mixing likely happened outside of Africa, because that's where both Neanderthals and Denisovans emerged, and it could have taken place at least 600,000 years ago.

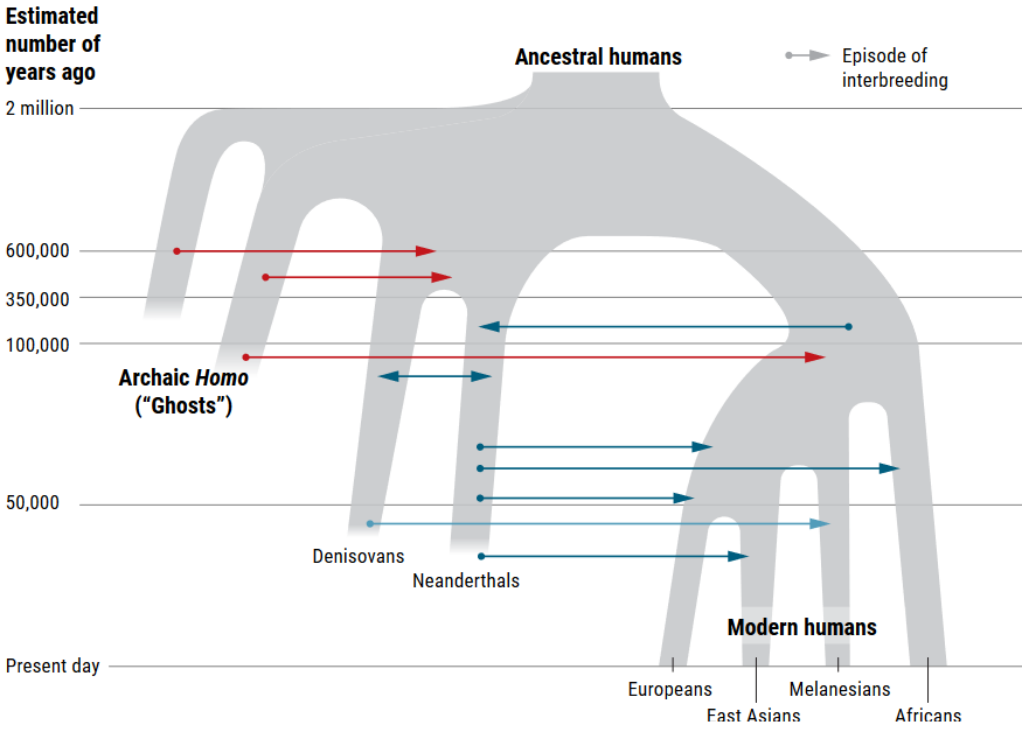
"I think the super-archaics were in the first wave of hominids who left Africa," Rogers says. "They stayed in Eurasia, largely isolated from Africans, until 700,000 years ago when Neandersovans left Africa and interbred with them.

Occurring much earlier than encounters of modern humans with Neanderthals and Denisovans, the episode was "the earliest known interbreeding between ancient human populations and an expansion out of Africa," Rogers says. Other studies have hinted at such ancient mixing, Cox says, but Rogers's analysis is "particularly convincing."

Others, though, say Rogers's bold claim needs testing. One challenge is reconciling it with new results from other researchers that show modern human ancestors mixed with super-archaic groups more recently, in Africa. Just last week, for example, population geneticist Sriram Sankararaman and his student Arun Durvasula at the University of California (UC), Los Angeles, identified signs of a separate, more recent episode of mixing. The researchers analyzed the genomes of 405 people from four subpopulations in West Africa that were included in the 1000 Genomes Project, a catalog of genomes from around the world. They found numerous gene variants not seen in Neanderthals or Denisovans and concluded that the best explanation was that the variants came from an archaic, extinct human.

Ghosts in the family tree

At least two super-archaic "ghost" hominins interbred with the ancestors of Neanderthals, Denisovans, and modern humans (red lines). Later, those three groups also met and mingled (blue lines), leaving complex traces in each other's genomes. (Split times are rough estimates; timeline is not drawn to scale).



Graphic: Vernot *Et Al.*/*Science*, Adapted By V. Altounin/*Science*; Data: A. Rogers And S. Sankararaman

This ghost species may have been late *H. erectus*, *H. heidelbergensis*, or a close relative. One or more late-surviving members of this ancient group met and mated with the ancestors of living Africans sometime in the past 124,000 years, the modern genomes suggest.

Another paper last month reported Neanderthal DNA in living Africans, likely from migrations back to Africa by early Europeans who bore Neanderthal DNA. Sankararaman thinks some of the archaic DNA he detects in Africans may be from Neanderthals, but most is from the older ghost species. "I think the true picture is a combination of both an archaic population unrelated to Neanderthals as well as Neanderthal-related ancestry," he says.

In December 2019, yet another study found hints of an extinct ghost population in living Africans, although it was silent on the identity of the ghosts and when they bred with our ancestors. Population geneticist Jeff Wall at UC San Francisco and colleagues analyzed 1667 genomes from diverse populations in the GenomeAsia 100K consortium. They reported the strongest ghost signal in the Khoisan people and in Central African hunter-gatherers formerly known as pygmies.

But Wall and others warn their methods cannot rule out that the "ghosts" could be one or several groups of modern humans in Africa that were separated from other moderns for so long that their genes looked "archaic" when the groups finally came together again and mixed. "Our understanding of African population history, in particular, is so far behind," says Joshua Akey of Princeton University.

Even if they differ on particulars, the studies emphasize that long after new lineages of humans emerge, they still can mix with others quite different from themselves. Other species, such as cave bears and mammoths, show the same pattern of divergence and later mixing, says population geneticist Pontus Skoglund of the Francis Crick Institute in London. "We are losing the idea that separation between populations is simple with instant isolation." Such mating between long isolated groups may quickly introduce valuable new genes (*Science*, 18 November 2016, p. 818). For example, some of the archaic alleles Sankararaman spotted in Africans were in genes that suppress tumors and regulate hormones.

Today, *H. sapiens* doesn't have the possibility of quickly grabbing a load of diversity by mating with another group: For perhaps the first time in our history, we're the only humans on the planet. It's

another reason to miss our extinct cousins, says population geneticist Carina Schlebusch of Uppsala University. “To have such a large densely spread species with … so little genetic diversity … is a dangerous situation,” she says.

https://nyti.ms/2SRMyRn

How Common Mental Shortcuts Can Cause Major Physician Errors

Tendencies like left-digit bias can have life-altering consequences for patients.

By Anupam B. Jena and Andrew R. Olenski

It’s tempting to believe that physicians are logical, meticulous thinkers who perfectly weigh the pros and cons of treatment options, acting as unbiased surrogates for their patients.

In reality, this is often far from the case. Bias, which takes many forms, affects how doctors think and the treatment decisions they make.

Racial biases in treatment decisions by physicians are well documented. One study found that black patients were significantly less likely than white patients to receive pain medication in the emergency department, despite reporting similar levels of pain. Other research suggests that longstanding racial biases among providers might have contributed to racial differences in patient trust in the health system.

But a growing body of scientific research on physician decision-making shows that doctors exhibit other biases as well — cognitive ones — that influence the way they think and treat patients. These biases lead doctors to make the same mistakes as the rest of us, but usually at a greater cost.

Cognitive biases refer to a range of systematic errors in human decision-making stemming from the tendency to use mental shortcuts.

Prominent examples include confirmation bias, the tendency to interpret new information in a way favorable to one’s preconceptions; and anchoring, the tendency to overly weight an initial piece of information, even when order does not matter. Anchoring helps explain why if you see a car priced at $20,000 and a second car priced at $8,000, you might conclude the second car is cheap, whereas if the first car cost $3,000 you might conclude that the second car is expensive.

In health care, such unconscious biases can lead to disparate treatment of patients and can affect whether similar patients live or die.

Sometimes these cognitive biases are simple overreactions to recent events, what psychologists term availability bias. One study found that when patients experienced an unlikely adverse side effect of a drug, their doctor was less likely to order that same drug for the next patient whose condition might call for it, even though the efficacy and appropriateness of the drug had not changed.

A similar study found that when mothers giving birth experienced an adverse event, their obstetrician was more likely to switch delivery modes for the next patient (C-section vs. vaginal delivery), regardless of the appropriateness for that next patient. This cognitive bias resulted in both higher spending and worse outcomes.

Doctor biases don’t affect treatment decisions alone; they can shape the profession as a whole. A recent study analyzed gender bias in surgeon referrals and found that when the patient of a female surgeon dies, the physician who made the referral to that surgeon sends fewer patients to *all* female surgeons in the future. The study found no such decline in referrals for male surgeons after a patient death.

This list of biases is far from exhaustive, and though they may be disconcerting, uncovering new systematic mistakes is critical for improving clinical practice.

In a new study of physician treatment decisions, published on Thursday in The New England Journal of Medicine, we document signs of left-digit bias. This is the bias that explains why many goods are priced at $4.99 instead of $5, as consumers' minds round down to the left-most digit of $4.

We hypothesized that doctors may be overly sensitive to the left-most digit of a patient's age when recommending treatment, and indeed, in cardiac surgery they appear to be. When comparing patients who had a heart attack in the weeks leading up to their 80th birthdays with those who'd recently had an 80th birthday, we found that physicians were significantly less likely to perform a coronary artery bypass surgery for the "older" patients. The doctors might have perceived them to be "in their 80s" rather than "in their 70s." This behavior seems to have translated into meaningful differences for patients. The slightly younger patients, more likely to undergo surgery, were less likely to die within 30 days.

Our study confirms previous work that found doctors are overly responsive to patient age when diagnosing illness, and that showed how seemingly irrelevant factors, such as the difference of a few weeks of age, could govern physicians' decisions about treatment, with potentially life-altering consequences for patients.

Left-digit bias could affect many clinical decisions. For example, patients with hemoglobin levels of 9.9 grams per deciliter may be perceived as being substantially more anemic than patients with hemoglobin levels of 10.0 grams per deciliter (the difference in the two values has no clinical significance).

Awareness of these cognitive biases has prompted efforts to reduce them in clinical decision-making. One trial studied the effect on general practitioner diagnostic accuracy of a computer program that provided "nudges" in the right direction and highlighted particularly relevant information. The trial of these so-called decision support systems, while small, found that they improved diagnosis at a relatively low cost. Another, larger study found that changing an electronic medical record's default options for opioid prescribing — an example of so-called choice architecture — nudged physicians to prescribe fewer of the drugs.

Tools such as these have the potential to overcome some, but not all, of the cognitive biases that commonly plague clinical decision-making. Given our growing understanding of the errors that doctors can make, these biases are too costly to ignore.

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http://bit.ly/37QbqNJ

New drug combination restores beta cell function in animal model

Potential for diabetes remission

The loss of the identity of insulin-secreting beta cells in the islet of Langerhans, a process also called beta cell dedifferentiation, has been proposed to be a main reason for the development of diabetes. If and how dedifferentiated beta cells can be targeted by pharmacological intervention for beta cell regeneration is unknown. In a new study in mice, Helmholtz Zentrum München in collaboration with Novo Nordisk, demonstrated for the first time that a targeted combinatorial drug treatment is able to restore beta cell function, achieve beta cell redifferentiation and therefore potentially open new ways for diabetes remission.

Under certain conditions, beta cells can lose their identity and regress to a less differentiated state in which they lose most of their prior functions. It has been proposed that this dedifferentiation contributes to an ongoing degenerative process of beta cell dysfunction.

Current pharmacological diabetes treatments are not able to stop the decline of functional beta cell mass loss. The earlier this decline can

be prevented, ideally already when first diabetic symptoms appear, the higher the amount and the level of beta cell function that will be preserved.

New target: Dedifferentiated beta cells

To investigate whether dedifferentiated beta cells can be targeted pharmacologically to restore beta cell function, the researchers used streptozotocin-induced diabetes in mice. Streptozotocin kills insulin-producing beta cells and causes severe diabetes. When injected in multiple low doses, however, some beta cells survive which replicates the decline in function the researchers wanted to establish for their experiment.

Using single cell RNA sequencing the researchers could show that after streptozotocin treatment, the surviving beta cells dedifferentiate into a dysfunctional state. The simplicity of the model used (no genetic lesions nor autoimmunity) would help them better monitor the effect of the pharmacological treatment.

A good match: GLP-1/estrogen and insulin have additive effects in preclinical models

The team then tested treatments for their potential to restore beta cell function. To this end, they stratified seven cohorts of severely diabetic mice and treated them daily for 100 days with single and combinatorial pharmacology.

The researchers showed that a stable Glucagon-like peptide-1 (GLP-1)/estrogen conjugate (provided by Novo Nordisk) enables targeted and selective delivery of the nuclear hormone cargo to beta cells.

The combination of GLP-1/estrogen and a long acting insulin was superior to mono-treatments to both normalize glycemia, glucose tolerance, to increase pancreatic insulin content and to increase the number of beta cells. Importantly, administration of high doses of GLP-1/estrogen did not show signs of systemic toxicity in rats, a pre-requisite for any future clinical testing.

In a collaboration with the biotech company InSphero, the researchers could also show that GLP-1/estrogen, but not GLP-1 or estrogen alone, increases human beta cell function when human pancreatic islets are exposed to cytokine stress, which is known to impair human beta cell function.

"Not only does our study describe paths and processes of beta cell dedifferentiation, it also demonstrates the potential of single and combinatorial drug treatments to achieve diabetes remission by targeting dedifferentiated beta cells" explains Prof. Dr. Heiko Lickert, director of the Institute for Diabetes and Regeneration Research at Helmholtz Zentrum München and Professor of Beta Cell Biology at TUM School of Medicine.

"This is the first study that shows beta cell redifferentiation with targeted pharmacology performed by an interdisciplinary team that used cutting edge single cell technology, computational biology, pharmacology and regeneration biology" says Lickert who, together with Susanna M. Hofmann, Fabian Theis and Timo D. Müller at Helmholtz Zentrum München, lead this research project.

Future clinical studies?

This study brought together scientists from Helmholtz Zentrum München (Helmholtz Diabetes Center and Institute for Computational Biology), the German Center for Diabetes Research (DZD), Technical University of Munich (TUM) as well as InSphero AG and Novo Nordisk with the aim to explore the potential therapeutic benefits of GLP1/estrogen treatment in an animal models and in human cells in vitro.

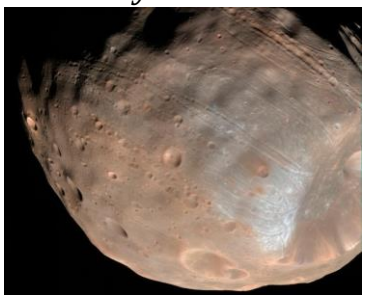
The results from this study as well as future studies to support translation to humans and safety of the compound may pave the way for clinical studies that use GLP-1 as a carrier peptide for estrogen but potentially also other, novel cargos to directly target beta cells for regenerative therapy and diabetes remission.

http://bit.ly/32lwB9l

Japan's space agency moving ahead with Phobos lander mission

Is Phobos a captured asteroid? Or was it created by some ancient cataclysm?

Eric Berger



An image of Phobos captured by NASA's Mars Reconnaissance Orbiter.
NASA/JPL-Caltech/University of Arizona

Japan's space agency has finalized a plan to send a probe to the Martian moons of Phobos and Deimos, and it includes an ambitious lander to collect samples from Phobos to return to Earth.

The agency, JAXA, submitted the plan to the country's science ministry on Wednesday, the *Asahi Shimbun* newspaper reported. On Twitter, the Martian Moons Exploration (MMX) official account also announced that it had formally moved from design into the "development" phase of operations. The space agency estimated that the total cost for the mission would come to $417 million.

The current plan calls for a 2024 launch of the probe on an H-3 rocket, a new booster built by Mitsubishi Heavy Industries and expected to debut late this year or in 2021. The MMX spacecraft would enter into orbit around Mars in 2025 and return to Earth in 2029.

Japan has experience with similar kinds of missions to small bodies in the Solar System. Its Hayabusa-2 probe successfully grabbed material from surface of the asteroid Ryugu and is scheduled to return the asteroid samples to Earth late this year. With a diameter of just 23km, Phobos has a surface gravity that is about one-thousandth that of Earth.

The MMX team has already said it plans to work on a similar small lander to Hayabusa-2 for the Mars mission, collaborating with the German and French space agencies.

No spacecraft have yet flown to Mars with the designated purpose of studying its small moons, nor has material ever been collected from them. Scientists would be keen to study the surface of a moon other than that of Earth's companion, which should help them better understand the formation of terrestrial planets. For Phobos and Deimos, it is also important to understand whether they are captured asteroids or fragments of the red planet ejected during some ancient impact.

Detailing the surface of Phobos is also important because it's possible that the first human missions to Mars will land there rather than on the surface of Mars. With its much smaller gravity well, it would be much easier for astronauts to leave Phobos for the return journey to Earth than the surface of Mars itself.

http://bit.ly/32hjOor

The fat around your arteries may actually keep them healthy

Finding could affect how researchers test for treatments related to plaque buildup in our arteries, or atherosclerosis

EAST LANSING, Mich. - A Michigan State University researcher is adding new evidence to the argument that the fat around our arteries may play an important role in keeping those blood vessels healthy.

The finding could affect how researchers test for treatments related to plaque buildup in our arteries, or atherosclerosis, an issue that can often lead to a heart attack, which is currently a leading cause of death in the United States.

The fat, known as perivascular adipose tissue, or PVAT, helps arteries do what scientists call "stress relax," or let go of muscular tension while under constant strain. This is similar to the bladder,

which expands to accommodate more liquid while at the same time keeping it from spilling out.

"In our study, PVAT reduced the tension that blood vessels experience when stretched," said Stephanie Watts, MSU professor of pharmacology and toxicology in the College of Osteopathic Medicine. "And that's a good thing, because the vessel then expends less energy. It's not under as much stress."

What made the finding so exciting, Watts said, whose study was recently published in the journal *Scientific Reports*, is that PVAT has largely been ignored by researchers who have thought its main job was to store lipids and do little more. Now her findings, built on previous results, could help redefine the way scientists view blood vessels.

Right now, scientists only divide blood vessels into three parts, the innermost layer called the tunica intima, the middle layer called the tunica media and the outermost layer called the tunica adventitia.

Watts would like scientists to recognize PVAT as the fourth layer, which others have called tunica adiposa - tunica means a membranous sheath enveloping or lining an organ and adiposa is a synonym for fat.

"For years, we ignored this layer - in the lab it was thrown out; in the clinic it wasn't imaged. But now we're discovering it may be integral to our blood vessels," Watts said. "Our finding redefines what the functional blood vessels are and is part of what can be dysfunctional in diseases that afflict us, including hypertension. We need to pay attention to this layer of a blood vessel because it does far more than we originally thought."

Other investigators have shown that PVAT plays a role in the functioning of blood vessels, finding that it secretes substances that can cause blood vessels to relax as well as substances that can cause it to contract.

But Watts and her colleagues wanted to test whether PVAT itself, rather than the substances it secretes, might play a role in how blood vessels perform. So, they decided to test whether PVAT provides a structural benefit to arteries by assisting the function of stress relaxation.

To do that, they tested the thoracic aorta in rats and found those with intact PVAT had more stress relaxation than those without.

"My mind was blown," Watts said when she saw that the pieces with surrounding fat had measurably relaxed more than those without. "I made every single person in my lab come and look and I asked, 'Tell me if I'm hallucinating...do you think this is real?'"

Watts and her colleagues also tested other arteries and were able to duplicate the same response. "So, this tells us, it's not just a one off," Watts said. "It's not something you see only in this particular vessel or this particular species or this particular strain. But that maybe it's a general phenomenon."

Note for media: Please include a link to the original paper in online coverage: https://www.nature.com/articles/s41598-020-58368-x

http://bit.ly/2v1WNK2

3D Printing of Body Parts Is Coming Fast—but Regulations Are Not Ready

It's far from clear how bioprinting and its products will be regulated.

By Dinusha Mendis and Ana Santos Rutschman

In the last few years, the use of 3D printing has exploded in medicine. Engineers and medical professionals now routinely 3D print prosthetic hands and surgical tools. But 3D printing has only just begun to transform the field.

Today, a quickly emerging set of technologies known as bioprinting is poised to push the boundaries further. Bioprinting uses 3D printers and techniques to fabricate the three-dimensional structures of biological materials, from cells to biochemicals, through precise

layer-by-layer positioning. The ultimate goal is to replicate functioning tissue and material, such as organs, which can then be transplanted into human beings.

We have been mapping the adoption of 3D printing technologies in the field of health care, and particularly bioprinting, in a collaboration between the law schools of Bournemouth University in the United Kingdom and Saint Louis University in the United States. While the future looks promising from a technical and scientific perspective, it's far from clear how bioprinting and its products will be regulated. Such uncertainty can be problematic for manufacturers and patients alike, and could prevent bioprinting from living up to its promise.

From 3D Printing to Bioprinting

Bioprinting has its origins in 3D printing. Generally, 3D printing refers to all technologies that use a process of joining materials, usually layer upon layer, to make objects from data described in a digital 3D model. Though the technology initially had limited applications, it is now a widely recognized manufacturing system that is used across a broad range of industrial sectors. Companies are now 3D printing car parts, education tools like frog dissection kits and even 3D-printed houses. Both the United States Air Force and British Airways are developing ways of 3D printing airplane parts.

In medicine, doctors and researchers use 3D printing for several purposes. It can be used to generate accurate replicas of a patient's body part. In reconstructive and plastic surgeries, implants can be specifically customized for patients using "biomodels" made possible by special software tools. Human heart valves, for instance, are now being 3D printed through several different processes although none have been transplanted into people yet. And there have been significant advances in 3D print methods in areas like dentistry over the past few years.

Bioprinting's rapid emergence is built on recent advances in 3D printing techniques to engineer different types of products involving biological components, including human tissue and, more recently, vaccines.

While bioprinting is not entirely a new field because it is derived from general 3D printing principles, it is a novel concept for legal and regulatory purposes. And that is where the field could get tripped up if regulators cannot decide how to approach it.

State of the Art in Bioprinting

Scientists are still far from accomplishing 3D-printed organs because it's incredibly difficult to connect printed structures to the vascular systems that carry life-sustaining blood and lymph throughout our bodies. But they have been successful in printing nonvascularized tissue like certain types of cartilage. They have also been able to produce ceramic and metal scaffolds that support bone tissue by using different types of bioprintable materials, such as gels and certain nanomaterials. A number of promising animal studies, some involving cardiac tissue, blood vessels and skin, suggest that the field is getting closer to its ultimate goal of transplantable organs.

We expect that advancements in bioprinting will increase at a steady pace, even with current technological limitations, potentially improving the lives of many patients. In 2019 alone, several research teams reported a number of breakthroughs. Bioengineers at Rice and Washington Universities, for example, used hydrogels to successfully print the first series of complex vascular networks. Scientists at Tel Aviv University managed to produce the first 3D-printed heart. It included "cells, blood vessels, ventricles and chambers" and used cells and biological materials from a human patient. In the United Kingdom, a team from Swansea University developed a bioprinting process to create an artificial bone matrix, using durable, regenerative biomaterial.

‘Cloneprinting’

Though the future looks promising from a technical and scientific perspective, current regulations around bioprinting pose some hurdles. From a conceptual point of view, it is hard to determine what bioprinting effectively is. Consider the case of a 3D-printed heart: Is it best described as an organ or a product? Or should regulators look at it more like a medical device?

Regulators have a number of questions to answer. To begin with, they need to decide whether bioprinting should be regulated under new or existing frameworks, and if the latter, which ones. For instance, should they apply regulations for biologics, a class of complex pharmaceuticals that includes treatments for cancer and rheumatoid arthritis, because biologic materials are involved, as is the case with 3D-printed vaccines? Or should there be a regulatory framework for medical devices better suited to the task of customizing 3D-printed products like splints for newborns suffering from life-threatening medical conditions?

In Europe and the U.S., scholars and commentators have questioned whether bioprinted materials should enjoy patent protection because of the moral issues they raise. An analogy can be drawn from the famed Dolly the sheep over 20 years ago. In this case, it was held by the U.S. Court of Appeals for the Federal Circuit that cloned sheep cannot be patented because they were identical copies of naturally occurring sheep. This is a clear example of the parallels that exist between cloning and bioprinting. Some people speculate in the future there will be ‘cloneprinting,’ which has the potential for reviving extinct species or solving the organ transplant shortage. Dolly the sheep’s example illustrates the court’s reluctance to traverse this path. Therefore, if, at some point in the future, bioprinters or indeed cloneprinters can be used to replicate not simply organs but also human beings using cloning technologies, a patent application of this nature could potentially fail, based on the current law. A study funded by the European Commission, led by Bournemouth University and due for completion in early 2020 aims to provide legal guidance on the various intellectual property and regulatory issues surrounding such issues, among others.

On the other hand, if European regulators classify the product of bioprinting as a medical device, there will be at least some degree of legal clarity, as a regulatory regime for medical devices has long been in place. In the United States, the FDA has issued guidance on 3D-printed medical devices, but not on the specifics of bioprinting. More important, such guidance is not binding and only represents the thinking of a particular agency at a point in time.

Cloudy Regulatory Outlook

Those are not the only uncertainties that are racking the field. Consider the recent progress surrounding 3D-printed organs, particularly the example of a 3D-printed heart. If a functioning 3D-printed heart becomes available, which body of law should apply beyond the realm of FDA regulations? In the United States, should the National Organ Transplant Act, which was written with human organs in mind, apply? Or do we need to amend the law, or even create a separate set of rules for 3D-printed organs?

We have no doubt that 3D printing in general, and bioprinting specifically, will advance rapidly in the coming years. Policymakers should be paying closer attention to the field to ensure that its progress does not outstrip their capacity to safely and effectively regulate it. If they succeed, it could usher in a new era in medicine that could improve the lives of countless patients.

Dinusha Mendis Professor Dinusha Mendis is a leading expert in the field of intellectual property (IP) law, particularly copyright law and its interaction with new and emerging technologies such as 3D printing, AI and blockchain.

Ana Santos Rutschman Ana Santos Rutschman is an assistant professor of law at Saint Louis University School of Law, where she teaches courses in health law, intellectual property, and regulation in the life sciences.

https://bbc.in/3a03T0o

Have archaeologists found the burial place of Rome's founder? Tomb found under the city's Forum may be the final resting place of Romulus

Tomb discovered under the Roman Forum could be the resting place of Romulus. Archaeologists uncovered an area devoted to Romulus dating to 6th century BC.

By Emily Webber For Mailonline

A tomb discovered under the Roman Forum could be the resting place of the city's legendary founder Romulus. Archaeologists are believed to have uncovered an area devoted to the first King of Rome and a rock sarcophagus, measuring 4.6ft, which are believed to date back to the 6th century BC.

Director of the Colosseum Archaeological Park Alfonsina Russo told **The Times**: 'This is an extraordinary discovery. The forum never ceases to yield amazing fresh treasures.'

Tomb discovered under the Roman Forum (pictured) could be the resting place of the city's legendary founder Romulus

What is the Roman Forum?

The Roman Forum, known as the Forum Romanum in Latin, was the heartbeat of both Ancient Rome and its continent-straddling empire. Historians believe people first began meeting in the Forum in 500BC when the Roman Republic was founded.

The area is situated between Palatine Hill and Capitoline Hill.

The Temple of Julius Caesar is the most striking monument and was built a couple of years after Ancient Rome's most famous leader was murdered in 44BC. The underground temple is buried beneath the entrance stairway to the Curia and was the place where Roman senators voted with every presumed to belong to one.

Scholars believed, according to Ms Russo, that the temple's altar has been positioned where ancient Romans believed Romulus was buried. Yet no bones were found in the coffin.

The finding had taken place near the Lapis Niger, an ancient black shrine in the Roman Forum, according to Andreas Steiner, editor of the magazine Archeo.

The shrine, discovered in 1899, has a Greek inscription referring to how the sacred ground must not be disturbed.

In Roman mythology, Romulus and his twin brother Remus were left in a basket on the River Tiber.

The pair survived and were discovered under a fig tree and a she-wolf suckled them.

Romulus later killed his brother Remus in a fight on what became Palatine Hill in 753BC.

The pair survived and were discovered under a fig tree and a she-wolf suckled them Pictured: The Capitoline Wolf statue in Rome

WHO WAS ROMULUS?

In Roman mythology, Romulus and his twin brother Remus were left in a basket on the River Tiber.

In legend, they were the sons of Rhea Silvia, the daughter of Numitor, the former king of Alba Longa. Through this lineage, the twins were descended from the Trojan hero Aeneas and Latinus.

A she-wolf found the twins at the the base of a fig tree after their mother was forced to abandon them. The wolf cared for the boys and raised them. letting them suckle on her.

They learned of their true ancestry as they grew up and overthrew Amulius, the man who forced them to be abandoned.

The two brothers set out to build their own city but cold not agree on where. An ensuing melee resulted in the death of his brother Remus.

http://bit.ly/2Td1wAF

Ethnobotanical medicine is effective against the bacterium causing Lyme disease

A preclinical study in test tubes showed that selected plant-based herbal medicines, especially Ghanaian quinine and Japanese knotweed, work better than antibiotics

Lyme disease, also called borreliosis, is the most common vector-borne disease in the Northern hemisphere. It is caused by the spirochete (corkscrew-shaped) bacterium Borrelia burgdorferi and close relatives and mainly spread through the bite of infected ticks.

Currently, more than 300,000 new cases are reported in the USA each year, compared to 65,000 in Europe, and these numbers are rising due to climate change and urban sprawl. The standard of care for Lyme disease, a course of antibiotics over 2-4 weeks, is not always effective: at least 10-20% of treated patients continue to experience symptoms after treatment. Late-stage Lyme patients may experience many different symptoms, including fatigue, joint pains, memory problems, facial paralysis, aches, stiffness in the neck, heart palpitations, and severe headaches. The discovery of novel treatments against Lyme disease is therefore of great interest.

In a new study published in *Frontiers in Medicine*, researchers from the Johns Hopkins Bloomberg School of Public Health, with colleagues at the California Center for Functional Medicine and Focus Health, surveyed the power of 14 plant-based extracts to kill Borrelia burgdorferi, compared to the currently used Lyme antibiotics doxycycline and cefuroxime.

The researchers tested these extracts' effectiveness in vitro (outside of a living organism) against the free-swimming "planktonic" form of the bacterium as well as against microcolonies. Microcolonies are aggregates of bacteria, the first stage in the development of biofilms - structured bacterial communities that stick to a surface and are embedded in a slimy extracellular matrix.

The researchers show that plant extracts from black walnut, cat's claw, sweet wormwood, Mediterranean rockrose, and Chinese skullcap had strong activity against B. burgdorferi, outperforming both tested antibiotics.

But by far the strongest performers were Ghanaian quinine (Cryptolepis sanguinolenta; also known as yellow-dye root, nibima, or kadze) and Japanese knotweed (Polygonum cuspidatum).

Ghanaian quinine is a shrub from West Africa containing the antimicrobial alkaloid cryptolepine, and is used in ethnomedicine to treat malaria, hepatitis, septicemia, and tuberculosis. Japanese knotweed is a traditional medicine in India and China that contains the polyphenol resveratrol. In other preclinical studies it has been found to have anti-tumor and anti-inflammatory effects and protect the nervous system and heart. Extracts from both plants were found to kill microcolonies of Borrelia burgdorferi and inhibit division of the planktonic form, even at low concentrations (0.03-0.5%). Remarkably, a single 7-day treatment with 1% Ghanaian quinine could completely eradicate the bacterium - it did not regrow, even under optimal conditions in the drug's absence.

"This study provides the first convincing evidence that some of the herbs used by patients such as Cryptolepis, black walnut, sweet wormwood, cat's claw, and Japanese knotweed have potent activity against Lyme disease bacteria, especially the dormant persister forms, which are not killed by the current Lyme antibiotics," says Dr Ying Zhang from the Johns Hopkins Bloomberg School of Public Health.

"These findings are exciting as they offer opportunities for improved treatment of persistent Lyme disease, which is not helped by the current standard treatment. We are interested in further evaluating these potent herbal medicines through animal studies as well as clinical trials."

However, not all tested compounds or herbs yielded positive results against the bacterium. Extracts of grapefruit seeds, green chiretta, ashwagandha, candy leaf (also known as stevia), fuller's teasel, and Japanese teasel had little or no effect, and neither did the chemicals colloidal silver, monoglyceride monolaurin, or antimicrobial peptide LL37 from human immune cells. This was surprising, as anecdotal and preclinical studies suggested that they might be effective, and they are often used in the community of Lyme disease practitioners and patients.

"Many thousands of Lyme patients today, especially those with later-stage symptoms who have not been effectively treated, are in great need of efficacious, accessible treatment options," says Dr Sunjya K. Schweig, CEO and co-Director of the California Center for Functional Medicine and Scientific Advisory Board Member of the Bay Area Lyme Foundation.

Coauthor Jacob Leone of the FOCUS Health Group stresses: "Patients and their clinicians are increasingly turning to herbal remedies as additional treatment options, and we hope that these findings will help point the way toward a greater understanding of these therapies. But further preclinical studies and clinical trials will be required to establish evidence for effective treatment of Lyme disease patients."

This research was supported by the Bay Area Lyme Foundation and the Steven & Alexandra Cohen Foundation.

http://bit.ly/2HLv2YK

This Tree Is So Toxic, You Can't Even Stand Under It When It Rains

The manchineel tree is in fact the most dangerous tree in the world.

Signe Dean

In 1999, radiologist Nicola Strickland went on a holiday to the Caribbean island of Tobago, a tropical paradise complete with idyllic, deserted beaches.

On her first morning there, she went foraging for shells and corals in the white sand, but the holiday quickly took a turn for the worse.

Scattered amongst the coconuts and mangoes on the beach, Strickland and her friend found some sweet-smelling green fruit that looked much like small crabapples.

Both foolishly decided to take a bite. Within moments the pleasantly sweet flavour was overwhelmed by a peppery, burning feeling and an excruciating tightness in the throat that gradually got so bad, the women could barely swallow.

The fruit in question belonged to the manchineel tree (*Hippomane mancinella*), sometimes referred to as 'beach apple' or 'poison guava'. It's native to the tropical parts of southern North America, as well as Central America, the Caribbean, and parts of northern South America.

The plant bears another name in Spanish, *arbol de la muerte*, which literally means "tree of death". According to the Guinness World Records, the manchineel tree is in fact the most dangerous tree in the world. As explained by the Florida Institute of Food and Agricultural Sciences, all parts of manchineel are extremely poisonous, and "interaction with and ingestion of any part of this tree may be lethal".

Manchineel belongs to the large and diverse *Euphorbia* genus, which also contains the decorative Christmas poinsettia. The tree produces a thick, milky sap, which oozes out of everything - the bark, the leaves and even the fruit - and can cause severe, burn-like blisters if it comes into contact with skin. That's because the sap contains a range of toxins; it's thought that the most serious reactions come from phorbol, an organic compound that belongs to the diterpene family of esters.

Because phorbol is highly water-soluble, you don't even want to be standing under a manchineel when it's raining - the raindrops carrying the diluted sap can still severely burn your skin. Because of these horrifying properties, in some parts of the tree's natural

range they are painted with a red cross, a red ring of paint, or even paired with explicit warning signs.

You'd think humans could just remove the trees, but they actually play a valuable role in their local ecosystems - as a large shrub, the manchineel grows into dense thickets that provide excellent windbreaking, and a protection against coastal erosion on Central American beaches.

There have been reports of severe cases of eye inflammation and even temporary blindness caused by the smoke of burning manchineel wood - not to mention the effects of inhaling the stuff.

However, Caribbean carpenters have been using manchineel wood in furniture for centuries, after carefully cutting it and drying in the sun to neutralise the poisonous sap.

"The real death threat comes from eating its small round fruit," Ella Davies writes for the BBC. "Ingesting the fruit can prove fatal when severe vomiting and diarrhoea dehydrate the body to the point of no return." Fortunately, Strickland and her friend lived to tell the tale, because they only ate a tiny amount of death apple. In 2000, Strickland published a letter in *The British Medical Journal*, describing her symptoms in detail.

It took over eight hours for their pain to slowly subside, as they carefully sipped pina coladas and milk. The toxin went on to drain into the lymph nodes on their necks, providing further agony.

"Recounting our experience to the locals elicited frank horror and incredulity, such was the fruit's poisonous reputation," Strickland wrote. "We found our experience frightening."

http://bit.ly/2SS4paN

AI tool screens 107 million molecules, discovers potent new antibiotics

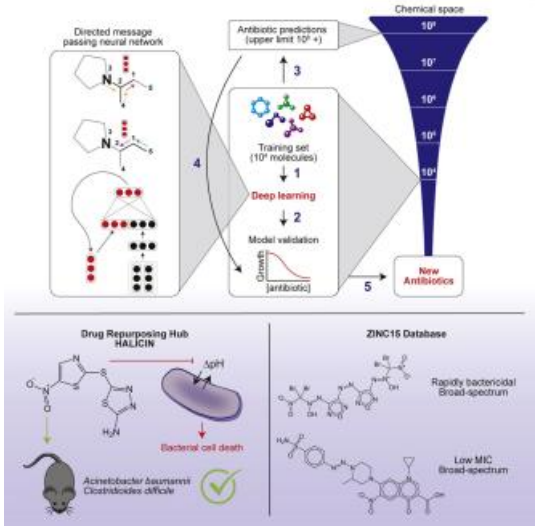
Found nine potential antibiotics, one in particular showing potency against 97% of drug-resistant bacteria tested against.

By Jamie Durrani

A machine learning platform has been used to discover new antibacterial compounds. The system screened more than 107 million chemical structures and found nine potential antibiotics, with one in particular showing potency against 97% of the drug-resistant bacteria it was tested against.

Aiming to tackle the growing antibiotic resistance crisis, a collaboration of synthetic biologists and computer scientists developed a deep learning platform to predict antibiotic activity. In particular, the group wanted to discover compounds with structures distinct from known antibiotics, to boost their chances of success against drug-resistant bacteria.

'We wanted to demonstrate that these techniques are sufficiently strong to be used to identify therapeutic molecules,' says Massachusetts Institute of Technology (MIT) computer scientist, Regina Barzilay, whose team developed the machine learning tool. Barzilay and her colleagues teamed up with researchers from synthetic biologist James Collins' lab, who hoped to see if AI could help address the threat of antibiotic resistance.



The machine learning software was able to pick out just a few promising antibiotic candidates from a library of millions of molecules

Collins explains that the machine learning model was trained using a library of 2500 molecules, comprising 1500 Food and Drug

Administration approved drugs and another 800 natural compounds, which had been tested for activity against *Escherichia coli*.

'The model that we developed learns to translate molecules into a continuous vector. It starts by having every atom represented with a vector of simple properties like the type of atom and whether it is in a ring and so on,' says Barzilay. This is used to build up a fingerprint of the molecule's structure, which coupled with the results of the *E. coli* tests, helps the neural network 'learn' molecular features that are associated with antibacterial activity.

Antibiotic hit

The model was then applied to the Broad Institute's drug repurposing hub – an open access library of more than 6000 molecules with known biological activity. 'It contains compounds at various positions in the drug development pipeline,' explains Jonathan Stokes, who worked on the project at MIT. 'So, it contains more or less the human pharmacopoeia of drugs, as well as molecules in late preclinical, and then phase one, phase two and phase three clinical trials.' From this they discovered a compound, halicin, which has impressive antibiotic activity, despite having a chemical structure unlike conventional antibiotics.

Halicin was one compound identified by the machine learning software and it is proving to be an excellent antibiotic, despite its unusual structure for this class of drug

'Halicin turns out to be a remarkably potent novel antibiotic, with broad activity against a range of antibiotic-resistant pathogens,' says Collins. 'We applied it to 36 different panels of multidrug-resistant bacterial pathogens from the [US Centers for Disease Control]. And halicin was effective against 35 of those 36.'

The team then tested halicin in two different mouse models. 'The first mouse model was an *Acinetobacter baumannii* skin infection model,' explains Stokes. *A. baumannii* is a key target for medical researchers, as it acts as a reservoir for antibiotic-resistance genes and survives for prolonged periods on surfaces. 'So, we establish an infection on the back of mice and then topically treat it with halicin,' says Stokes. 'And in 24 hours, we were able to eradicate the infection.'

The second mouse model demonstrated that halicin could clear a *Clostridium difficile* gut infection within four days.

Needle in a haystack

Following this success, the team applied their AI technique to a database known as ZINC15. The database contains more than 1.5 billion compounds and of these, 107 million were selected for screening based on physical properties known to affect biological uptake.

Based on the deep learning tool's predictions, 23 compounds were chosen for further investigation, with eight displaying antibacterial activity against a range of pathogens. Two of these compounds showed promise against a range of drug-resistant *E. coli*.

'It is great to see the application of machine learning to the search for new antibiotics whilst taking into account [adsorption, distribution, metabolism, excretion],' says University of Birmingham microbiologist Laura Piddock, who directs scientific affairs at the Global Antibiotic Research and Development Partnership. Piddock is impressed with the proof of principal data for halicin, and highlights its low predicted toxicity in humans.

Katie Simmons, an expert in virtual high-throughput screening based at the University of Leeds, UK, describes the halicin results as 'stunning'. 'What is even more amazing is the ability of deep learning to select antibacterial compounds from such a large subset of the ZINC15 database,' she adds.

'It is unfortunate that research into new antibacterials has largely fallen out of favour with "big pharma" but the approaches described here could go some way to helping address our need for new therapies,' says Simmons.

While the predictive power of the deep learning tool is impressive, Barzilay notes that it still requires scientists' knowledge and experience. 'These methods are becoming stronger and stronger, but they're still not at the point when we can say that in silico screening can fully substitute experimental high-throughput screening,' notes Barzilay. 'Even if you have an imperfect predictor, it's still useful for identifying interesting patterns and correlations that you can take advantage of. But for that you need the knowledge of medicinal chemists and biologists,' she says.

Barzilay adds that further work is underway to improve the accuracy of the deep learning tool's predictions. Her team are also developing AI methods that can be used beyond an initial screen – so that after identifying a lead molecule, the model will then suggest modifications that could improve its biological activity. Meanwhile, Collins' lab aims to complete preclinical work on halicin and then potentially partner with industry to get it into clinical trials.

References *J M Stokes* et al, Cell, *2020, DOI: **10.1016/j.cell.2020.01.02***

http://bit.ly/37RsOSf

Surgeons successfully treat brain aneurysms using a robot

American Stroke Association International Stroke Conference - Late breaking science news release

Los Angeles - Using a robot to treat brain aneurysms is feasible and could allow for improved precision when placing stents, coils and other devices, according to late breaking science presented today at the American Stroke Association's International Stroke Conference 2020 . The conference, Feb. 19-21 in Los Angeles, is a world premier meeting for researchers and clinicians dedicated to the science of stroke and brain health.

Robotic technology is used in surgery and cardiology, but not for brain vascular procedures. In this study, Canadian researchers report the results of the first robotic brain vascular procedures. They used a robotic system specifically adapted for neurovascular procedures. Software and hardware adaptations enable it to accommodate microcatheters, guidewires and the other devices used for endovascular procedures in the brain. These modifications also provide the operator additional precise fine-motor control compared to previous system models.

"This experience is the first step towards achieving our vision of remote neurovascular procedures," said lead researcher Vitor Mendes Pereira, M.D., M.Sc., a neurosurgeon and neuroradiologist at the Toronto Western Hospital, and professor of medical imaging and surgery at the University of Toronto in Canada. "The ability to robotically perform intracranial aneurysm treatment is a major step forward in neuro-endovascular intervention."

In the first case, a 64-year-old female patient presented with an unruptured aneurysm at the base of her skull. The surgical team successfully used the robot to place a stent and then, using the same microcatheter, entered the aneurysm sac and secured the aneurysm by placing various coils. All intracranial steps were performed with the robotic arm. Since this first case, the team has successfully performed five additional aneurysm treatments using the robot, which included deploying various devices such as flow-diverting stents.

"The expectation is that future robotic systems will be able to be controlled remotely. For example, I could be at my hospital and deliver therapy to a patient hundreds or even thousands of kilometers away," Mendes Pereira said. "The ability to deliver rapid care through remote robotics for time-critical procedures such as stroke could have a huge impact on improving patient outcomes and allow us to deliver cutting-edge care to patients everywhere, regardless of geography."

"Our experience, and that of future operators of this technology, will help develop the workflows and processes necessary to implement successful robotic programs, which will ultimately help establish remote care networks in the future," Mendes Pereira said.

The list of study authors and disclosures are available in the abstract. The work reported was funded by institutional sources. Single patient-use cassettes were provided by Corindus, a Siemens Healthineers Company.

http://bit.ly/2Vh85EF

Study of 418,000 Europeans finds different foods linked to different types of stroke

Different types of food are linked to risks of different types of stroke, according to the largest study to investigate this, published in the European Heart Journal [1] today (Monday).

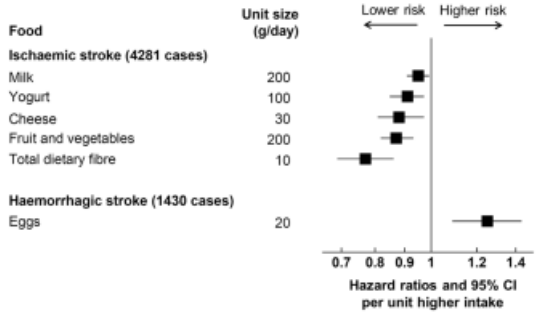
Until now, most studies have looked at the association between food and total stroke (all types of stroke combined), or focused on ischaemic stroke only. However, the current study of more than 418,000 people in nine European countries investigated ischaemic stroke and haemorrhagic stroke separately.

The study found that while higher intakes of fruit, vegetables, fibre, milk, cheese or yoghurt were each linked to a lower risk of ischaemic stroke, there was no significant association with a lower risk of haemorrhagic stroke. However, greater consumption of eggs was associated with a higher risk of haemorrhagic stroke, but not with ischaemic stroke.

Ischaemic stroke occurs when a blood clot blocks an artery supplying blood to the brain or forms somewhere else in the body and travels to the brain where it blocks blood flow. Haemorrhagic stroke occurs when there is bleeding in the brain that damages nearby cells. About 85% of strokes are ischaemic and 15% are haemorrhagic. Stroke is the second leading cause of deaths worldwide.

Dr Tammy Tong, the first author of the paper and a nutritional epidemiologist at the Nuffield Department of Population Health, University of Oxford (UK), said: "The most important finding is that higher consumption of both dietary fibre and fruit and vegetables was strongly associated with lower risks of ischaemic stroke, which supports current European guidelines. The general public should be recommended to increase their fibre and fruit and vegetable consumption, if they are not already meeting these guidelines.

"Our study also highlights the importance of examining stroke subtypes separately, as the dietary associations differ for ischaemic and haemorrhagic stroke, and is consistent with other evidence, which shows that other risk factors, such as cholesterol levels or obesity, also influence the two stroke subtypes differently."



TAKE HOME FIGURE

This is the largest study on multiple dietary factors and subtypes of stroke. Ischaemic and haemorrhagic stroke have markedly different patterns of dietary associations. For ischaemic stroke, lower risks were associated with higher consumption of dietary fibre, fruit and vegetables, and dairy foods. For haemorrhagic stroke, higher risk was associated with higher egg consumption. The results highlight the importance of examining stroke subtypes separately. **European Heart Journal**

The total amount of fibre (including fibre from fruit, vegetables, cereal, legumes, nuts and seeds) that people ate was associated with the greatest potential reduction in the risk of ischaemic stroke. Every 10g more intake of fibre a day was associated with a 23% lower risk, which is equivalent to around two fewer cases per 1000 of the population over ten years.

Fruit and vegetables alone were associated with a 13% lower risk for every 200g eaten a day, which is equivalent to one less case per 1000 of the population over ten years. No foods were linked to a statistically significant higher risk of ischaemic stroke.

Based on UK estimates, two thick slices of wholemeal toast provide 6.6g of fibre, a portion of broccoli (around eight florets) provides about 3g, and a medium raw, unpeeled apple provides about 1.2g of fibre. The European Society of Cardiology (ESC) and the World Health Organization Regional Office for Europe recommend consuming at least 400g of fruit and vegetables a day; the ESC also suggests people should consume 30-45g of fibre a day.

The researchers found that for every extra 20g of eggs consumed a day there was a 25% higher risk of haemorrhagic stroke, equivalent to 0.66 extra cases per 1000 (or around two cases per 3000) of the population over ten years. An average large-sized egg weighs approximately 60g. Egg consumption in the EPIC study was low overall, with an average of less than 20g eaten a day.

The researchers say the associations they found between different foods and ischaemic and haemorrhagic stroke might be explained partly by the effects on blood pressure and cholesterol.

Dr Tong and her colleagues analysed data from 418,329 men and women in nine countries (Denmark, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom) who were recruited to the European Prospective Investigation into Cancer and Nutrition (EPIC) study between 1992 and 2000. The participants completed questionnaires asking about diet, lifestyle, medical history and socio-demographic factors, and were followed up for an average of 12.7 years. During this time, there were 4281 cases of ischaemic stroke and 1430 cases of haemorrhagic stroke.

Food groups studied included meat and meat products (red meat, processed meat and poultry), fish and fish products (white fish and fatty fish), dairy products (including milk, yogurt, cheese), eggs, cereals and cereal products, fruit and vegetables (combined and separately), legumes, nuts and seeds, and dietary fibre (total fibre and cereal, fruit and vegetable fibre).

Major strengths of the study include the large numbers of people studied in several different countries and long follow-up period. Most types of food were included in the study, although information on diet was collected at only one point in time, when the participants joined the study. As the study is observational it cannot show that the foods studied cause an increase or decrease in risk of ischaemic or haemorrhagic stroke, only that they are associated with different risks. Information on medication use (including statins) was not available.

[1] *"The associations of major foods and fibre with risks of ischaemic and haemorrhagic stroke: a prospective study of 418,329 participants in the EPIC cohort across nine European countries", by Tammy Tong et al. European Heart Journal. doi:10.1093/eurheartj/ehaa007*

http://bit.ly/3a3UTHD

Textbook structure rules formulated by Linus Pauling 90 years ago prove unreliable

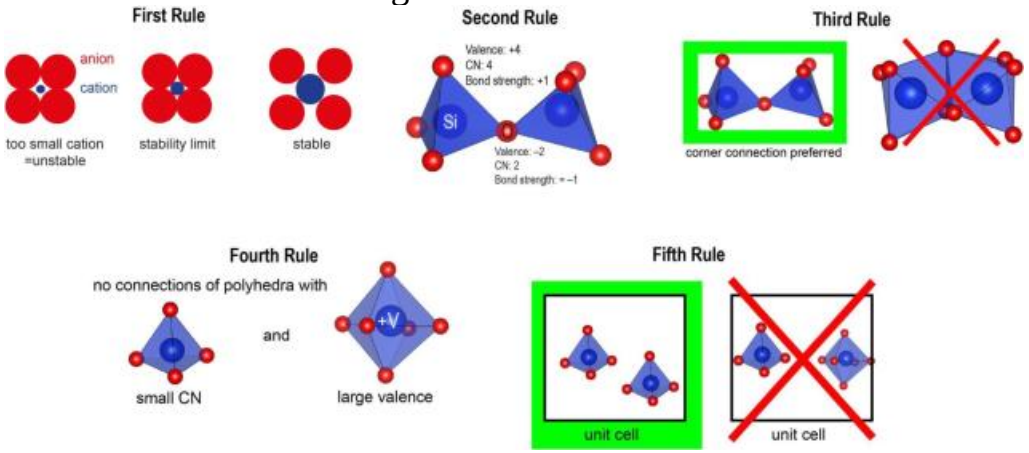
After testing the five rules against 5000 oxide structures found that just 13% satisfied four of the five rules

By Andy Extance

Rules devised by double Nobel prize winner Linus Pauling describing the preferred crystal structures ionic compounds adopt are more like loose guidelines, chemists in Belgium have discovered. Janine George, Geoffroy Hautier and colleagues at the Catholic University of Louvain tested the five rules against 5000 oxide structures. They found that just 13% satisfied four of the five rules, a fact Hautier describes as ‘shocking’. ‘These rules, despite being taught in every chemistry textbook, have a much lower predictive power than one would think,’ he says.

Pauling developed the rules in 1929 by connecting his unrivalled knowledge of both inorganic crystal structures and the underlying

bonding theories. Hautier notes that some exceptions had already been found, and the rules improved on that basis, although they're often still used in their original form.



Pauling's five rules have been used for decades to rationalise the crystal structures of ionic compounds. zoom inzoom out

Source: *© 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim*

Hautier and colleagues work on methods for predicting new materials, and had sought to build on Pauling's rules. 'We started realising that they had many exceptions and that no real statistical assessment of these rules had ever been made,' he explains. The researchers have developed software that automatically detects the coordination geometry of shapes that atoms form around each other in crystals, and the connections between them. 'Combined with the easy access to a database of crystal structures, this enabled us to scale up the assessment of the Pauling rules to an unprecedented level and to perform a truly statistical benchmark of these rules,' Hautier says.

Five rules to rule them all?

Radius Ratio Rule: 'The coordination number of the cation is determined by the radius ratio of cation and anion.'

Electrostatic Valence Rule: 'In a stable coordination structure the electric charge of each anion tends to compensate the strength of the electrostatic valence bonds reaching to it from the cations at the centres of the polyhedra of which it forms a corner.'

The Sharing of Edges and Faces: 'The presence of shared edges, and particularly of shared faces, in a coordinated structure decreases its stability.'

The Nature of Contiguous Polyhedra: 'In a crystal containing different cations those with large valence and small coordination number tend not to share polyhedron elements with each other.'

The Rule of Parsimony: 'The number of essentially different kinds of constituents in a crystal tends to be small.'

Of the five rules, 'by far the worst performing' is the first, which relates the coordination number of atoms neighbouring a cation to the cation's radius, says George. The second, which relates the charge of an anion to the charge of the connected cations, also performs 'quite badly'. The third and fourth rules, which deal with the connections of coordination environments, 'have an intermediate level of performance', George adds. 'The rule that works the best is the fifth – the rule of parsimony – stating that simpler structures are preferred.'

Anubhav Jain from Lawrence Berkeley National Laboratory in Berkeley, California, says that perhaps Pauling should have listed his rules backwards. 'In particular, rules that try to minimise the overall electrostatic energy, as opposed to local electroneutrality or hard sphere interactions, seem to get an overall pass as they have a clear correlation to the overall crystal energy,' he says.

The Louvain team will now try to update the rules using machine learning, George says. 'This work might also ultimately show if Pauling's intuition was correct that coordination environments and their connections are the adequate descriptors, or features, to predict the crystal structure of a material,' she observes.

References J George at al, *Angew. Chem., Int. Ed.*, 2020, DOI: 10.1002/anie.202000829

COVID-19 SPECIAL

https://nyti.ms/2v1KDRq

Why the Coronavirus Seems to Hit Men Harder Than Women

Women mount stronger immune responses to infection, scientists say. And in China, men smoke in much greater numbers.

By Roni Caryn Rabin

The coronavirus that originated in China has spread fear and anxiety around the world. But while the novel virus has largely spared one vulnerable group — children — it appears to pose a particular threat to middle-aged and older adults, particularly men.

This week, the Chinese Center for Disease Control and Prevention published the largest analysis of coronavirus cases to date. Although men and women have been infected in roughly equal numbers, researchers found, the death rate among men was 2.8 percent, compared with 1.7 percent among women.

Men also were disproportionately affected during the SARS and MERS outbreaks, which were caused by coronaviruses. More women than men were infected by SARS in Hong Kong in 2003, but the death rate among men was 50 percent higher, according to a study published in the Annals of Internal Medicine.

Some 32 percent of men infected with Middle East Respiratory Syndrome died, compared with 25.8 percent of women. Young adult men also died at higher rates than female peers during the influenza epidemic of 1918.

A number of factors may be working against men in the current epidemic, scientists say, including some that are biological, and some that are rooted in lifestyle. When it comes to mounting an immune response against infections, men are the weaker sex.

“This is a pattern we’ve seen with many viral infections of the respiratory tract — men can have worse outcomes,” said Sabra Klein, a scientist who studies sex differences in viral infections and vaccination responses at the Johns Hopkins Bloomberg School of Public Health. “We’ve seen this with other viruses. Women fight them off better,” she added.

Women also produce stronger immune responses after vaccinations, and have enhanced memory immune responses, which protect adults from pathogens they were exposed to as children.

“There’s something about the immune system in females that is more exuberant,” said Dr. Janine Clayton, director of the Office of Research on Women’s Health at the National Institutes of Health.

But there’s a high price, she added: Women are far more susceptible to autoimmune diseases, like rheumatoid arthritis and lupus, in which the immune system shifts into overdrive and attacks the body’s own organs and tissues. Nearly 80 percent of those with autoimmune diseases are women, Dr. Clayton noted.

The reasons women have stronger immune responses aren’t entirely clear, and the research is still at an early stage, experts caution.

One hypothesis is that women’s stronger immune systems confer a survival advantage to their offspring, who imbibe antibodies from mothers’ breast milk that help ward off disease while the infants’ immune systems are still developing.

A stew of biological factors may be responsible, including the female sex hormone estrogen, which appears to play a role in immunity, and the fact that women carry two X chromosomes, which contain immune-related genes. Men, of course, carry only one.

Experiments in which mice were exposed to the SARS coronavirus found that the males were more susceptible to infection than the females, a disparity that increased with age.

The male mice developed SARS at lower viral exposures, had a lower immune response and were slower to clear the virus from their bodies. They suffered more lung damage, and died at higher

rates, said Dr. Stanley Perlman, a professor of microbiology at the University of Iowa who was the senior author of the study.

When researchers blocked estrogen in the infected females or removed their ovaries, they were more likely to die, but blocking testosterone in male mice made no difference, indicating that estrogen may play a protective role. “It’s an exaggerated model of what happens in humans,” Dr. Perlman said. “The differences between men and women are subtle — in mice, it’s not so subtle.”

Health behaviors that differ by sex in some societies may also play a role in disparate responses to infections.

China has the largest population of smokers in the world — 316 million people — accounting for nearly one-third of the world’s smokers and 40 percent of tobacco consumption worldwide. But just over 2 percent of Chinese women smoke, compared with more than half of all men.

Chinese men also have higher rates of Type 2 diabetes and high blood pressure than women, both of which increase the risk of complications following infection with the coronavirus. Rates of chronic obstructive pulmonary disease are almost twice as high among Chinese men as among women.

In the United States, women are more proactive about seeking health care than men, and some small studies have found the generalization applies to Chinese students at universities in the United States, as well.

In unpublished studies, Chinese researchers have emphasized that patients whose diagnoses were delayed, or who had severe pneumonia when they were first diagnosed, were at greatest risk of dying. One study of 4,021 patients with the coronavirus emphasized the importance of early detection, particularly in older men. And men have been turning up in hospitals with more advanced disease.

But in areas of China outside Hubei Province, the disease's epicenter and where the majority of those affected are concentrated, the patterns are different: The disease appears to have dramatically lower mortality rates, and men are being infected at much higher rates than women, according to the Chinese C.D.C. analysis.

Men may have a “false sense of security” when it comes to the coronavirus, said Akiko Iwasaki, a professor of immunology at Yale University who studies why some viruses affect women more severely. Gathering and analyzing data about the new virus by sex is important both for the scientists studying it and for the general public, experts said.

Since the start of the outbreak, for example, public health officials have emphasized the importance of washing hands well and often, to prevent infection. But several studies have found that men — even health care workers — are less likely to wash their hands or to use soap than women, Dr. Klein said.

“We make these broad sweeping assumptions that men and women are the same behaviorally, in terms of comorbidities, biology and our immune system, and we just are not,” Dr. Klein said.

https://nyti.ms/32lYPAI

What a Party in Japan May Tell Us About the Coronavirus’s Spread

Will the virus spiral beyond China? Public health experts are closely studying cluster cases in other Asian countries.

By Sui-Lee Wee and Makiko Inoue

Rain was falling on the night of Jan. 18, so the windows of the Tokyo party boat were shut. Inside were about 90 guests of a local taxi association who were celebrating the new year as the vessel floated down the Sumida River. Also on board, unbeknown to them, was a coronavirus capable of spreading ferociously.

It did just that. A driver in his 70s soon fell ill with fever; he later tested positive. The same day as his diagnosis, his mother-in-law died; she also was infected. Officials then discovered that 10 others from the boat were, too, including an employee who had served

passengers from Wuhan, China. Still more who did not attend the party caught the virus after coming into contact with those who did.

As public health officials look for clues to one of the biggest uncertainties about the new coronavirus epidemic — whether it will eventually expand rapidly beyond its center in China — they are closely studying clusters of cases that have emerged recently in Japan.

The issue has taken on more urgency as passengers have begun walking off a contaminated cruise ship in Yokohama where 634 people have tested positive for the virus and two later died. Experts fear that some who were cleared to leave an onboard quarantine could later test positive, spreading infections on land in the same way that the party boat has done.

Alarmed officials are rushing to learn more about how the virus is transmitted, including how many of those infected experience mild symptoms or none at all, and whether it can be spread by people who are symptom-free.

Katsunobu Kato, Japan's health minister, said the country had entered "another phase" in its fight against the coronavirus.

"Doctors at the medical institutes share the recognition that the numbers of infection cases will increase in the future and that it's necessary to take firm measures," he said at a news conference on Sunday. The government announced a $139 million package of urgent measures to contain the outbreak, including strengthening its testing and quarantining capacity.

Concern about the transmission of the virus has grown with cluster cases in Japan, which has reported 94 infections outside the cruise ship, as well as in Singapore, where 84 infections have been confirmed, and in South Korea, which has had 156. China has reported more than 75,000 cases and more than 2,200 deaths.

The figure in South Korea has nearly tripled over the course of three days, and officials tied 77 cases to a church in the city of Daegu. In Singapore, the government has identified five clusters and is investigating the connections within them. The virus has been detected in at least 25 other countries, with most infections involving people who had traveled from China.

"What we are worried about is sustained transmission in the community in countries outside China," said Raina MacIntyre, head of the biosecurity program at the Kirby Institute of the University of New South Wales in Sydney.

"Because once it becomes widespread and there's transmission happening in two continents, that means it's a pandemic."

Public health experts say most viral clusters are hard to investigate, and that is especially true with the current coronavirus outbreak, in which many infected people say they have no symptoms. If asymptomatic people can spread the virus, it will be much harder to slow its spread, as carriers transmit it unwittingly.

"There are ongoing silent transmissions" because of the very nature of the virus, Shigeru Omi, regional director emeritus of the World Health Organization's Western Pacific region, said in a news conference on Monday.

David Heymann, an epidemiologist at the London School of Hygiene and Tropical Medicine, said there was no definitive evidence yet that people who are asymptomatic can pass on infections. He said experts who are trying to understand the virus are waiting for information from countries outside China that are closely documenting cases.

"China has such an overwhelming number of patients that they are not able to do it meticulously," said Dr. Heymann, a former chief of communicable diseases at the World Health Organization.

"How easily does it transmit from person to person?" he said. "We don't know that yet."

Virologists see two likely explanations for the spread of clusters. In one, a "superspreader" — a person who has the propensity to spew

more germs than others — transmits the virus to a large group of people. Some of these superspreaders have no symptoms and feel well enough to go out, or they encounter a group of people with low resistance.

During the outbreak of SARS in 2002-03, the biggest reported superspreader was a 26-year-old airport worker admitted to Prince of Wales Hospital in Hong Kong. He infected 112 people, including every doctor and nurse who treated him.

Alternatively, people can independently catch a virus from contaminated surfaces. It is unclear how long the new coronavirus can survive on surfaces, but studies of other such viruses have found they can stay active for a week or more.

Outside the Diamond Princess cruise ship, the largest human-to-human cluster in Japan involves the Tokyo party boat.

Four days after the river cruise, on Jan. 22, the mother-in-law of the taxi driver in his 70s said she felt fatigued. Six days later, the woman, who was in her 80s, sought medical help but was told to monitor her condition. On Feb. 1, she was hospitalized after being given a diagnosis of pneumonia.

Her respiratory condition worsened, and she was moved to another hospital on Feb. 6. She was given the coronavirus test on Feb. 12. A day later, she died, and the results of her test soon came back positive. Her death was the first from the virus in Japan.

After health officials in Tokyo discovered that the infected taxi driver was the son-in-law of the woman who had died, they started tracing his contacts. They discovered that he had attended the boat party, and tested everyone who had been there. Seven others who were confirmed infected said they had no symptoms.

Others, like a female employee of the taxi drivers association who did not attend the party, contracted the virus after having casual interactions with those who did. In yet another case, a doctor in his 60s tested positive after dining with a nurse — the wife of a taxi driver — who had been at the party. He, too, did not have symptoms.

Another cluster of cases in Japan has occurred in Wakayama Prefecture, where a surgeon in a hospital, a colleague of his, the colleague's wife and their child tested positive for the virus, as well as two patients who visited the hospital. One of them was a farmer in his 70s who went to the hospital after the first doctor had stopped working.

The mother, wife and younger brother of a patient in his 60s from the same hospital also came down with the coronavirus, as did a nurse in his 30s who had temporarily worked on the Diamond Princess as part of the disaster response.

Yoshinobu Nisaka, the prefecture's governor, said he could not rule out the possibility that infections had occurred within the hospital. "We're having trouble tracking down how these people were infected," he said at a news conference on Saturday.

In another cluster in Japan, four people from Aichi Prefecture were found to be infected: a couple who had traveled back from Hawaii and their friends.

Takaji Wakita, the head of Japan's National Institute of Infectious Diseases, said that while it would be difficult to stop the transmission of the virus, the outbreak could be contained. He urged people during a news conference to consider telecommuting and to refrain from having meetings that are not urgent.

Dominic Dwyer, a medical virologist at the University of Sydney in Australia, said it was reassuring that governments were identifying clusters, because that was a sign that their public health surveillance was working.

"I suppose what one is concerned about is, are there other clusters going on that they haven't recognized?" he said. "Identifying clusters is a sign of good laboratory investigation. But as for how good that is, time will tell."

http://bit.ly/2STr72x

Specialized respirators are key to stopping spread of coronavirus to medical staff

Specialized respirators appear to protect medical staff against COVID-19, but they must be worn to work.

By Nicoletta Lanese - Staff Writer 4 days ago

A certain type of respirator effectively protects medical workers from catching COVID-19, the viral disease that has sickened more than 75,000 people since December 2019.

(Image: © Shutterstock)

Caused by the newfound coronavirus SARS-CoV-2, COVID-19 can spread to new hosts when infected people expel bits of the virus through their sneezes and coughs. Those who come into close contact with infected people face the highest risk of infection; that means that the medical staff treating sick patients are among the most likely to catch the disease. As of Feb. 14, about 1,716 medical workers in China have contracted COVID-19, and six of these workers have died, according to The New York Times.

The high rate of infection may be blamed, in part, on inadequate hand disinfection and sparse use of N95 respirators, which are designed to filter out virus particles, according to a study posted Feb. 19 on the preprint server medRxiv. (The research has not yet been peer-reviewed or published in a scientific journal.)

The "N95" designation means that the respirators block out at least 95 percent of tiny particles that come into contact with them, on the scale of 0.0001 inches (0.3 microns) in diameter, according to the U.S. Food and Drug Administration.

That said, at the start of the outbreak, not all medical personnel treating patients with COVID-19 wore respirators, as little was known about the disease at the time, the study authors noted.

"The medical staff in our hospital has not realized that the 'flu' was caused by a novel coronavirus named SARS-CoV-2 (2019-nCoV) with high risk of transmission," senior author Dr. Xinghuan Wang, a director and professor in the Department of Urology at the Zhongnan Hospital of Wuhan University, told Live Science in an email. "Therefore, at that time, the medical staff (especially surgical doctors and nurses) [did] not wear any kind of mask when talking to patients without fever," and they only wore medical masks while delivering treatment or surgery, he said.

As Wang's study revealed, rates of infection differed between doctors and nurses with respirators and those without.

Specifically, the authors examined data collected from Jan. 2-22 at six departments within the Zhongnan Hospital. Within the 10-day period, the hospital treated 28 individuals with confirmed cases of COVID-19 and 58 "suspicious" cases. The medical staff in each department followed different safety protocols when treating the patients.

About 280 medical staff in the hospital's Respiratory, ICU and Infectious Diseases departments wore N95 respirators and washed their hands frequently, while about 215 in the departments of Hepatobiliary Pancreatic Surgery, Trauma and Microsurgery, and Urology wore no masks and disinfected their hands less frequently. Although the respirator group encountered confirmed cases more often than the unmasked group — more than 730% more often — no one in the respirator group became infected.

In comparison, 10 people in the unmasked group contracted the novel disease, despite treating fewer infected patients.

"It would appear that N95 respirators, no surprise, protect against health care acquisition of the virus," said Dr. William Schaffner, an infectious-diseases specialist at Vanderbilt University in Tennessee, who was not involved in the current study. The small study is "reassuring in that sense," although there was no reason to think

that N95 respirators wouldn't block out the novel coronavirus effectively, he added.

Wang and his co-authors went on to review infection data from the Huangmei People's Hospital and the Qichun People's Hospital, which each housed more than 10 infected patients during the time surveyed. As at the Zhongnan Hospital, no medical staff who wore N95 respirators and frequently washed their hands caught COVID-19.

"China is currently working to ramp up production of medical supplies and promote international purchasing to address a supply shortage as part of its broader drive to fight the novel coronavirus outbreak," Wang said. As of Feb. 4, production of N95 masks for medical protective purposes reached 600,000 a day, he added. Since learning about the high transmissibility of COVID-19, the medical staff at Zhongnan Hospital now all wear N95 respirators when treating suspected and confirmed cases and no further infections have been reported among doctors or nurses, he said.

Medical staff require training to properly fit N95 respirators around their noses, cheeks and chins to ensure that no air can sneak around the edges of the mask, Live Science previously reported. To breathe through the thick respirators, wearers work much harder than normal to inhale and exhale and must occasionally take breaks from wearing the equipment. Each time they take the respirator off, the wearer must double-check that it hasn't been soiled or damaged before donning it again.

Although people must be trained before wearing an N95 respirator, "one could conjure up circumstances" where civilians could be trained to use the respirators at home, say, if hospitals became overrun with patients and those with mild symptoms came to rely on home care instead, Schaffner said. Without adequate training, though, the measure would be no more effective at blocking the virus than an average surgical mask, he added.

https://wb.md/3c8sW3l

Novel Coronavirus: Study Suggests Multiple Shedding Routes

***The novel coronavirus (2019-nCoV) responsible for the COVID-19 global outbreak may have multiple infection routes, according to a study published online February 17 in* Emerging Microbes & Infection.**

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"We detected the virus in oral swabs, anal swabs, and blood," write Wei Zhang, from Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan, China, and colleagues.

"[T]hus, infected patients can potentially shed this pathogen through respiratory, fecal–oral, or body fluid routes," they write.

But one US infectious disease expert cautions that, overall, the epidemiologic data continue to point to airborne transmission being the driver of the COVID-19 outbreak. "It's almost a rewrite of the influenza playbook," said Michael T. Osterholm, PhD, MPH, Director of the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota in Minneapolis.

To date, oral swabs have been used to test for 2019-nCoV antigen to confirm a diagnosis of COVID-19. And patients who have two sequential negative oral swabs are thought to have cleared the virus and no longer be contagious.

However, according to the authors, many coronaviruses can also undergo fecal–oral transmission.

With this in mind, Zhang and colleagues conducted a study in a hospital in Wuhan to investigate the possibility of alternate routes of transmission of 2019-nCoV.

They collected oral swabs, anal swabs, and blood samples from a total of 178 patients infected with the virus.

In the first part of their study, the researchers examined samples from 39 of the patients who had tested positive for 2019-nCoV

based on oral swabs taken at the time of admission to the hospital. They performed molecular testing (quantitative polymerase chain reaction [qPCR]) for 2019-nCoV on blood, oral swabs, and anal swabs.

According to Zhang and colleagues, 15 of these 39 patients still tested positive for the virus even after several days of treatment. Of these, 8 (53.3%) tested positive on oral swabs, 4 (26.7%) on anal swabs, 6 (40%) on blood samples, and 3 (20%) on serum samples.

Notably, the researchers found instances when viral nucleotide was present in anal swabs or blood samples even when oral swabs tested negative.

In the second part of their study, the researchers examined samples from 139 of the 178 patients to investigate changes in the presence of virus in oral and anal swabs over time. In these samples, they tested for the presence of both viral antibody and viral nucleotide.

The authors report detailed characterization of samples from 16 patients. Among those, Zhang and colleagues found that antiviral immunoglobulin (Ig) M and IgG titers were relatively low or undetectable on the first day of sampling. However, by day 5, the titers of both antibodies had risen in most patients. The rate of detection rose from 50% (8/16) on day 0 to 81% (13/16) on day 5 for IgM, and from 81% (13/16) to 100% (16/16) for IgG.

In contrast, on day 0, 8 out of 16 (50%) oral swabs tested positive with qPCR as did 4 anal swabs (25%). By day 5, 25% of oral swabs and 37.5% of anal swabs tested positive for the viral nucleotide.

These findings suggest the potential for patients to transition from testing positive for the virus on oral swabs during early infection to testing positive on anal swabs during late infection.

In an email interview with *Medscape Medical News*, one of the study's lead authors, Peng Zhou, also from Wuhan Institute of Virology, noted that although the group has not yet tried to isolate the virus from fecal samples from infected patients, other groups have apparently had some success doing this.

"In summary, we provide a cautionary warning that 2019-nCoV may be transmitted through multiple routes," the authors write.

Although gastrointestinal symptoms have been reported in COVID-19, they are infrequent. For example, one case series showed that 8% of patients with 2019-nCoV infection presented with diarrhea at the onset of their illness.

And health officials in Hong Kong recently evacuated residents from one apartment block because they were concerned about transmission of 2019-nCoV via the building's bathroom pipes, according to several news sources. Two people living on different floors of the building had tested positive for the virus. After discovering an unsealed bathroom pipe in one of the patient's bathrooms, officials raised the possibility of stool-based transmission in these two cases.

Because the pipe that carried feces was connected to the ventilation pipe, officials suspected that the virus present in the feces may have been transmitted through the ventilation system into people's apartments.

However, in an interview with *Medscape Medical News*, Osterholm, CIDRAP's director, said "the question still remains wide open about what role fecal–oral transmission might play in this novel coronavirus disease."

He indicated the need to avoid overinterpreting the data from this latest study, especially because PCR was used to detect the virus in the different patient samples.

Although this confirms that the patients were infected with 2019-nCoV, Osterholm stressed that it does not necessarily mean that the samples contained infectious virus.

He explained that this is similar to the situation in patients with some other infectious diseases. For example, Osterholm described

one study in which researchers simultaneously performed PCR and virus isolation on stool samples from patients infected with a related coronavirus that causes Middle East respiratory syndrome (MERS). In that case, although the samples tested PCR-positive for the MERS virus, the researchers were unable to isolate the virus from them.

He clarified that when a sample tests positive with PCR, it indicates the presence of viral nucleotides, which could be a breakdown product from the infection. But it doesn't automatically reflect the presence of viable virus that is infectious and could put other people at risk.

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