BERNARD CHANTAL/ALAMY

People with type 1 diabetes, a known COVID-19 risk factor, can't produce the hormone insulin.

a pandemic just like the COVID-19 pandemic. The two pandemics could be clashing," he says.

Their hunch is based on a handful of people such as Gnadt, who have spontaneously developed diabetes[4] after being infected with SARS-CoV-2, and on evidence from dozens more people with COVID-19 who have arrived in hospital with extremely high levels of blood sugar and ketones[5], which are produced from fatty deposits in the liver. When the body doesn't make enough insulin to break down sugar, it uses ketones as an alternative source of fuel.

Researchers cite other evidence, too. Various viruses, including the one that causes severe acute respiratory syndrome (SARS), have been linked with autoimmune conditions such as type 1 diabetes[6]. And many organs involved in controlling blood sugar are rich in a protein called ACE2, which SARS-CoV-2 uses to infect cells[7].

The latest clue comes from an experimental study in miniature lab-grown pancreases. Published last month[8], the work suggests that the virus might trigger diabetes by damaging the cells that control blood sugar.

But other researchers are cautious about such suggestions. "We need to keep an eye on diabetes rates in those with prior COVID-19, and determine if rates go up over and above expected levels," says Naveed Sattar, a metabolic-disease researcher at the University of Glasgow, UK.

To establish a link, researchers need more robust evidence, says Abd Tahrani, a clinician–scientist at the University of Birmingham, UK.

One initiative is now under way. Earlier this month, an international group of scientists, including Zimmet, established a global database[3] to collect information from people with COVID-19 and high blood-sugar levels who do not have a history of diabetes or problems controlling their blood sugar.

Cases are beginning to trickle in, says Stefan Bornstein, a physician at the Technical University of Dresden, Germany, who also helped to establish the registry. The researchers hope to use the cases to understand whether SARS-CoV-2 can induce type 1 diabetes or a new form of the disease. And they want to investigate whether the sudden-onset diabetes becomes permanent in people who've had COVID-19. They also want to know whether the virus can tip people who were already on their way to developing type 2 diabetes into a diabetic state.

The organoid study shows how SARS-CoV-2 could be damaging the pancreas[8]. Shuibing Chen, a stem-cell biologist at Weill Cornell Medicine in New York City, and her colleagues showed that the virus can infect the organoid's α- and β-cells, some of which then die. Whereas β-cells produce insulin to decrease blood-sugar levels, α-cells produce the hormone glucagon, which increases blood sugar. The virus can also induce the production of proteins known as chemokines and cytokines, which can trigger an immune response that might also kill the cells, according to the study, which was published in *Cell Stem Cell* on 19 June.

Chen says the experiments suggest that the virus can disrupt the function of key cells involved in diabetes – by directly killing them or by triggering an immune response that attacks them.

The virus also attacked pancreatic organoids that had been transplanted into mice, and cells in liver organoids. The liver is important for storing and releasing sugar into the blood stream when it senses insulin.

The organoid study adds strength to the argument that SARS-CoV-2 might cause or worsen diabetes, but the paper itself is not enough to prove the link, says Tahrani.

There could be more going on than some scientists suggest, says Shane Grey, an immunologist at the Garvan Institute of Medical Research in Sydney, Australia. The virus could trigger an extreme inflammatory state, which would impair the ability of the pancreas to sense glucose and release insulin, and dampen the ability of the liver and muscles to detect the hormone, he says. This could trigger diabetes.

Only long-term studies will reveal what's really going on, says Sattar.

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CRISPR EDITING WREAKS CHROMOSOMAL MAYHEM IN HUMAN EMBRYOS

Studies showing large DNA deletions and reshuffling heighten concerns about heritable genome editing.

By Heidi Ledford

A suite of experiments that use the gene-editing tool CRISPR–Cas9 to modify human embryos have revealed that the process can make large, unwanted changes to the genome at or near the target site.

The studies were published last month on the preprint server bioRxiv, and have not yet been peer-reviewed[1–3]. But taken together, they give scientists a good look at what some say is an underappreciated risk of CRISPR–Cas9 editing. Previous experiments have revealed that the tool can make 'off target' gene mutations far from the target site, but the nearby changes identified in the latest studies can be missed by standard assessment methods.

"The on-target effects are more important

and would be much more difficult to eliminate," says Gaétan Burgio, a geneticist at the Australian National University in Canberra.

These safety concerns are likely to inform the ongoing debate over whether scientists should edit human embryos to prevent genetic diseases — a process that is controversial because it makes a permanent change to the genome that can be passed down for generations. The first laboratory experiments using CRISPR to edit human embryos took place in 2015. But such studies are still rare and are generally strictly regulated. When, in 2018, biophysicist He Jiankui — the only person known to have edited human embryos that were used for reproduction — revealed the birth in China of twin babies with edited genomes, the work was widely condemned as unethical. He has since been given a prison sentence for "illegal medical practice".

"If human embryo editing for reproductive purposes, or germline editing, were space flight, the new data are the equivalent of having the rocket explode at the launch pad before take-off," says Fyodor Urnov, who studies genome editing at the University of California, Berkeley, but was not involved the latest works.

Unwanted effects

The current research underscores how little is known about how human embryos repair DNA cut by the genome-editing tools — a key step in CRISPR–Cas9 editing — says reproductive biologist Mary Herbert at Newcastle University, UK. "We need a basic road map of what's going on in there before we start hitting it with DNA-cutting enzymes," she says.

The first preprint was posted online on 5 June by developmental biologist Kathy Niakan at the Francis Crick Institute in London and her colleagues. In that study[1], the researchers used CRISPR–Cas9 to create mutations in the *POU5F1* gene, which is important for embryonic development. Of 18 genome-edited embryos, about 22% contained unwanted changes affecting large swathes of the DNA surrounding *POU5F1*. These included DNA rearrangements and large deletions of several thousand DNA bases — much greater changes than are typically intended.

Another group, led by stem-cell biologist Dieter Egli at Columbia University in New York City, studied[2] embryos created with sperm carrying a blindness-causing mutation in a gene called *EYS*. The team used CRISPR–Cas9 to break the DNA in the *EYS* gene, and found that about half of the embryos lost large segments of the chromosome on which *EYS* is situated — and sometimes all of it.

> **"This is something that all of us in the scientific community will take more seriously."**

And a third group, led by reproductive biologist Shoukhrat Mitalipov at Oregon Health & Science University in Portland, studied embryos made using sperm with a mutation that causes a heart condition[3]. This team also found signs that editing affected large regions of the chromosome containing the mutated gene.

In all the studies, researchers used the embryos for scientific purposes only, and not to generate pregnancies. The lead authors of the three preprints declined to discuss the details of their work with *Nature*'s news team until the articles are published in peer-reviewed journals.

The changes are the result of DNA-repair processes harnessed by genome-editing tools. CRISPR–Cas9 uses a strand of RNA to direct the Cas9 enzyme to a site in the genome with a similar sequence. The enzyme then cuts both strands of DNA at that site, and the cell's repair systems heal the gap.

The edits occur during that repair process: most often, the cell seals up the cut using an error-prone mechanism that can insert or delete a small number of DNA letters. If researchers provide a DNA template, the cell might use that sequence to mend the cut, resulting in a true rewrite. But broken DNA can also cause shuffling or loss of a large region of the chromosome.

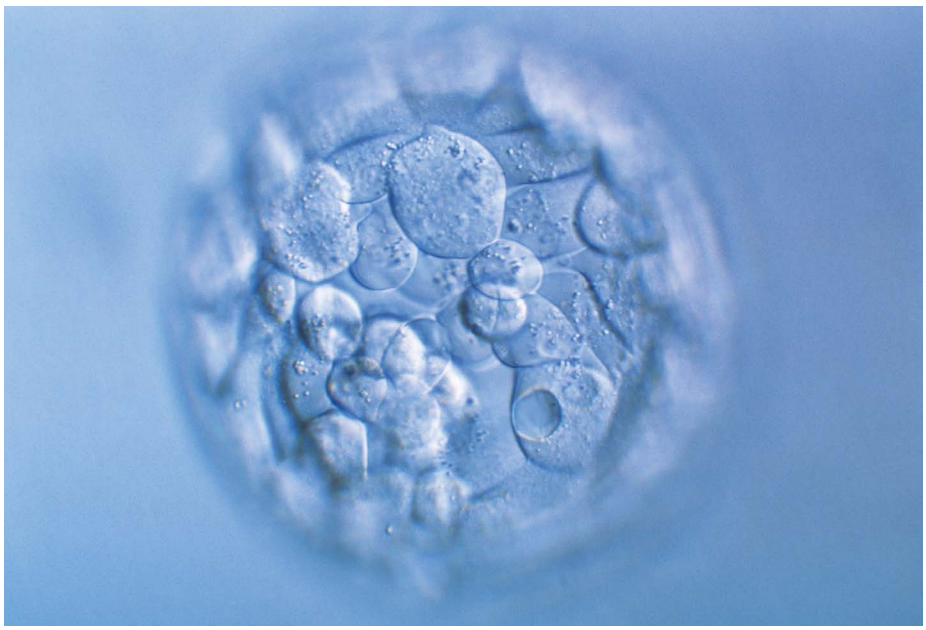
Previous work using CRISPR in mouse embryos and other kinds of human cell has demonstrated that editing genes can cause large, unwanted effects[4,5]. But it was important to demonstrate the work in human embryos, says Urnov, because various cell types might respond to genome editing differently.

Such rearrangements could easily be missed: many experiments look for other unwanted edits, such as single DNA-letter changes or insertions or deletions of only a few letters. But the latest studies looked specifically for large changes near the target. "This is something that all of us in the scientific community will, starting immediately, take more seriously than we already have," says Urnov. "This is not a one-time fluke."

Genetic changes

The three studies offered different explanations for how the DNA changes arose. Egli and Niakan's teams attributed the bulk of the changes observed in their embryos to large deletions and rearrangements. Mitalipov's group instead said that up to 40% of the changes it found were caused by a phenomenon called gene conversion, in which DNA-repair processes copy a sequence from one chromosome in a pair to heal the other.

Mitalipov and his colleagues reported[6] similar findings in 2017, but some researchers were sceptical that frequent gene conversions could occur in embryos. Egli and his colleagues tested for gene conversions in their latest work and didn't find them, and Burgio points out that the assays used in Mitalipov's study are similar to those the team used in 2017. One possibility is that DNA breaks heal differently at various positions along the chromosome, says Jin-Soo Kim, a geneticist at the Institute for Basic Science in Seoul and a co-author of the Mitalipov preprint.



PASCAL GOETGHELUCK/SPL

Editing human embryos is controversial because it makes heritable changes to the genome.

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