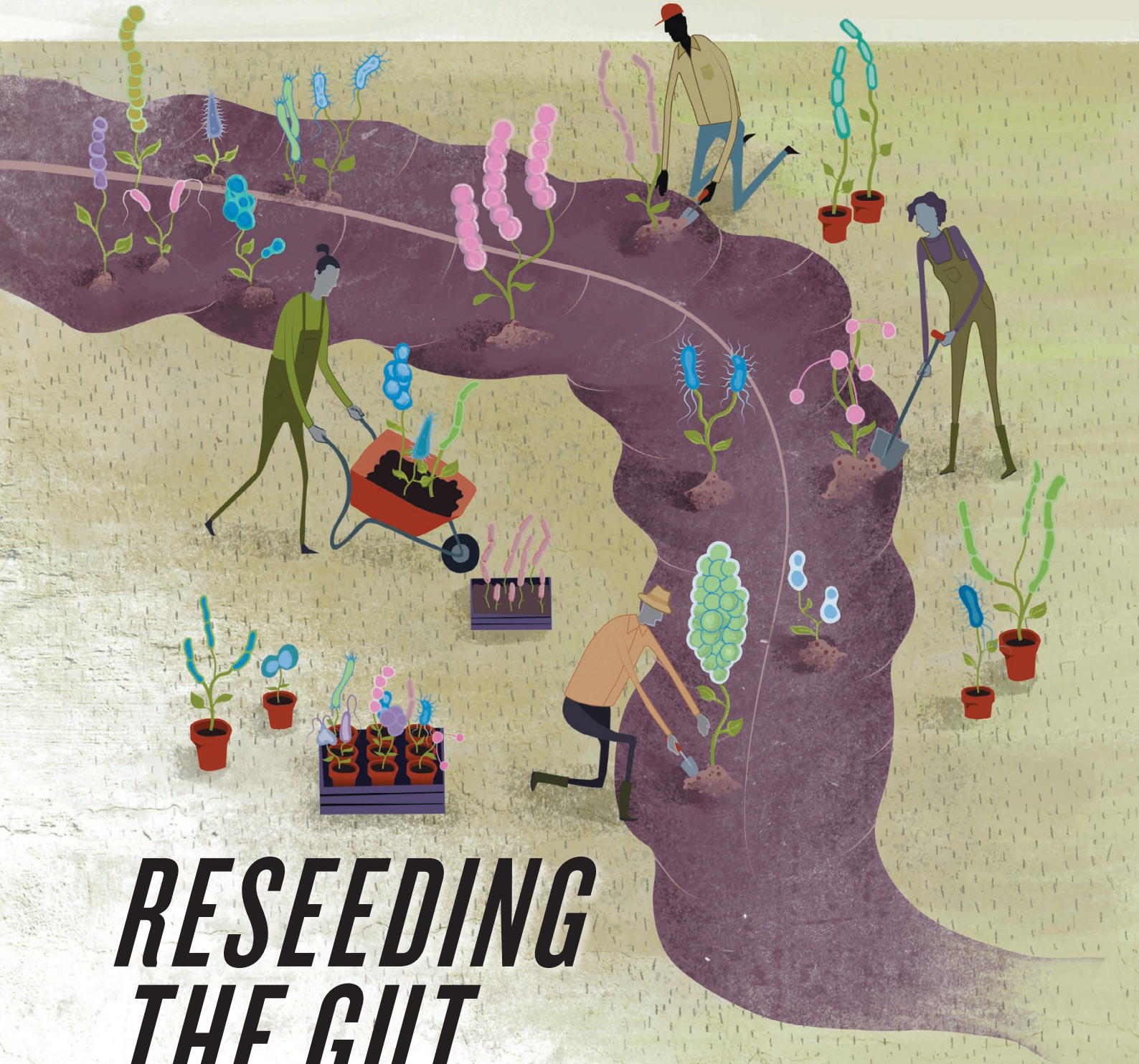


RESEEDING THE GUT

Transplants of faecal matter have done wonders for the treatment of certain gastrointestinal infections. Will they ever work for inflammatory bowel disease?

BY LIAM DREW

NIK SPENCER

Faced with an impending operation to remove his large intestine, Oli Adams started a desperate search for other options that might resolve his Crohn's disease and spare him surgery.

Then 29, Adams was diagnosed with Crohn's when he was 23. For a decade before that — as he forged a career as a professional surfer — his fluctuating health had mystified him. He was one of few British surfers to compete in the sport's world tour, but his performance was erratic: one tournament he'd ace it, the next, feeling weak and with shaky legs, he looked like a different surfer. He thought it might be nerves or possibly that his vegetarianism was to blame.

He hated the drugs he was prescribed when he was finally diagnosed — the side effects were horrendous. And for six years, Adams cycled through flare-ups and fleeting opportunities to ride waves, all the while trying to find a medication that he could tolerate and that managed his symptoms. One worked for a time, but the symptoms returned.

"There's no rhyme or reason to it," says Adams, of Crohn's. "How you're going to feel from one minute to the next, how your moods are going to be, whether you're going to be caught short … It's embarrassing, it's painful, and at worse you're so malnourished that you are in a place you can't even describe — it's like a zone of pain, but also your brain is so in crisis that you can't really think."

Crohn's and ulcerative colitis — the two main types of inflammatory bowel disease (IBD) — are caused by a hyperactive immune system attacking the walls of the gastrointestinal tract, causing inflammation and ulceration (see page S98). But no one knows why this happens. The drugs Adams was given included decades-old steroids that suppress immune function as a whole and newer drugs that block more specific aspects of the inflammatory cascade.

These drugs can be effective, but not for everybody — it's a common refrain in the IBD community that no two people's experiences are identical. When Adams's drugs stopped working and his intestine seemed to be in danger of rupturing, his doctors advised surgery. "It was like a race against time for me not to have the operation," says Adams. And of all the avenues he could explore, "Faecal transplant was the main thing on the list."

A faecal transplant — or the preferred term, faecal microbiota therapy (FMT) — comes at IBD from the opposite direction to most drugs. Instead of assuming that the immune system is inherently faulty, whether because of genetics or environment, proponents argue that the hyperactive immune system is being provoked by something in the lumen, or interior, of the gut. The most plausible candidates are a pathogenic microorganism, a combination of such microbes or perhaps a shortage of microorganisms that lower levels of inflammation. If this is the case, changing the contents of the gut by seeding a new healthy community of microorganisms might halt the disease.

Two years ago, when Adams thought FMT could be an alternative to surgery, there was nowhere in the United Kingdom that provided the treatment for those with IBD. Despite being gravely ill, Adams considered travelling to Australia to take part in a small study. But he ran out of time. When his condition deteriorated quickly, his doctors examined his intestines and feared they could burst at any moment. "I'd left it too long," he says. "They did the operation there and then."

Gastroenterologist Alexander Khoruts holds a bag of donated microbiota.

JEFF WHEELER

Adams will never know if FMT would have helped his IBD. But it has become an established procedure for people with recurrent infections of the bacterium *Clostridium difficile* (an increasing problem owing to antibiotic resistance), and a small number of patients and gastroenterologists make enthusiastic claims about its effectiveness for IBD. But many others point to the modest results of systematic trials and urge more measured expectations. "Is there something to it? Perhaps," says Alexander Khoruts, a gastroenterologist at the University of Minnesota in Minneapolis, who has used FMT extensively to treat *C. difficile* infections. "Are we anywhere close to it? No," he says. "Is it worth pursuing? Yes."

But pursuing it properly requires more than simply doing further transplants: it means knowing exactly how the procedure changes the recipient's microbiota. This information, alongside clinical observation, is necessary to truly evaluate the effects of FMT. And it may also shed light on the causes of IBD.

A NEW MEDICINE

Studies of the human microbiota — the myriad microorganisms that call our bodies home — have redefined how researchers view the contents of our gastrointestinal tracts. Scientists now know that humans co-evolved with a web of thousands of microbes: bacteria, viruses, fungi and unicellular organisms called archaea. The relationship we have with them is mutually beneficial — we provide warmth and nutrients, and they help us to digest our food, mop up toxins, make vitamins, hone our immune systems, communicate with our brains and crowd out malignant microbes such as *C. difficile*. To people in this field, poo ceased to be simply a repugnant by-product of human digestion years ago.

FMT is based on the idea that a healthy intestinal flora can be transferred from a donor to a recipient through, as the name suggests,

FAECAL ATTRACTION

The history of faecal microbiota therapy (FMT)

4TH CENTURY AD

Ge Hong, a Chinese physician, recommends faecal suspensions for food poisoning and severe diarrhoea. Influential Chinese physician Li Shizhen recommends a similar 'yellow soup' for abdominal complaints 1,200 years later.

1908

Russian zoologist and Nobel laureate Élie Metchnikoff speculates that certain gut bacteria, such as those gained by drinking soured milk, might ward off ageing in his book *The Prolongation of Life: Optimistic Studies*.

1958

US surgeon Ben Eiseman and colleagues treat four cases of pseudomembranous enterocolitis (now known to be caused by the bacterium *Clostridium difficile*) using faecal enemas. But the antibiotic vancomycin becomes the standard treatment.

JANUARY 1989

Justin Bennet and Mark Brinkman, then based in Kansas City, Missouri, write to *The Lancet* to report that Bennet's ulcerative colitis has been in remission for six months since a faecal enema. This is the first report of FMT being used to treat inflammatory bowel disease (IBD).

MAY 1989

Michael Tvede, then at the Statens Serum Institute in Denmark and Jorgen Rask-Madsen at the University of Copenhagen successfully treat six people with chronic *C. difficile* infections using FMT. Culturing intestinal bacteria shows the gut flora has changed.

faecal matter. The research behind it is increasingly sophisticated, but the procedure is not. The stool of a healthy donor is blitzed with saline, filtered and then delivered to the recipient's gastrointestinal tract. Various administration routes are used: an enema or colonoscopy coming up one way, or a nasogastric tube or capsules going down the other. The latter are popularly known as 'crapsules'. As one patient told *Nature*, these gastrointestinal diseases are serious enough by themselves, without anyone being uptight about toilet humour.

The first stool Khoruts ever transferred came from the husband of a 64-year-old woman with a recurrent *C. difficile* infection. When she came under his care in 2008, the patient was living in incontinence pads, passing diarrhoea every 15 minutes, night and day, and her weight had dropped by almost 30 kilograms. Fifteen months of antibiotics had got her nowhere.

Needing to try something new, Khoruts found a growing body of literature that included positive case reports and small studies that convinced him FMT was worth a try. The husband's stool was delivered by colonoscopy and the patient reported feeling better while still in recovery. Khoruts recalls that after more than a year of relentless diarrhoea, she said she felt something inside beginning to feel whole again. Within two days, she had a normal bowel movement.

Not only was this event transformative for the patient, but it was also a landmark for the field because Khoruts did something that those early case reports had not: with a group of microbial ecologists, he examined the DNA content of stool samples taken from the donor and the recipient before and after the transplant[1].

The analysis demonstrated that microorganisms from the husband's gut had colonized the patient's gut. "Suddenly," Khoruts says, "there was some science there." In the throes of her illness, the patient's gastrointestinal tract had been a desolate landscape, but seeded by her husband's intestinal flora, it now hosted a vigorous microbial ecosystem in which the bacteria causing the infection were unable to survive.

FMT's effectiveness at treating recurrent *C. difficile* infections was cemented in early 2013. As part of a randomized control trial, only 7 out of 26 people receiving a control (which included the antibiotic vancomycin) recovered, but 15 out of 16 patients receiving FMT were cured. The treatment was so successful that the trial was terminated early because withholding FMT from the control group was deemed unethical[2].

This remarkable 94% success rate seems to be holding up, and an increasing number of physicians now use FMT to combat *C. difficile*. "I've become completely addicted," Khoruts says. "I've helped 400 people like this in my own practice. We haven't charged them a penny, but I'm the richest man I know because of that feeling — saving somebody's life."

FLUSHED WITH SUCCESS

Buoyed by the effectiveness of FMT for treating *C. difficile*, the idea spread that any disease involving a malignant microbiota might be resolved by delivering a healthy one. IBD, in which inflammation and ulceration rage where the intestinal microbiota abuts human tissue, has long been thought to be next on the list of FMT-treatable conditions. But the reality showed that the procedure was anything but a straightforward fix and that understanding the exact role of the microbiota in disease is essential.

Reports of FMT's effectiveness for IBD began in a similar way to those for *C. difficile*. In 1989, a gastroenterologist described how he had been in remission from his ulcerative colitis for six months following an enema of healthy stool[3] (see 'Faecal attraction'). Since then, there has been a stream of anecdotal reports. No one doubts that at least some of these are valid, but whereas for *C. difficile* isolated accounts soon snowballed into larger studies and irrefutable clinical trials, for IBD they haven't.

In 2014, gastroenterologists David Rubin and Ruben Colman both then at the University of Chicago in Illinois, reviewed case studies, small open-label investigations and a randomized controlled trial on the use of FMT to treat IBD[4]. They found that the studies' methodologies varied considerably: patients had varying severities and duration of IBD, and had received different numbers of transplants that had been delivered by different routes. The studies had also used different criteria to judge success — from a decrease in symptoms to a verified healing of the mucosa. Rubin and Colman concluded that FMT for ulcerative colitis — with huge variability between reports — seemed to benefit 22% of people. For Crohn's, the figure was higher, but here the studies were too limited in both quality and quantity to draw firm conclusions. The bias towards studies of ulcerative colitis rather than Crohn's stems mainly from the fact that the former affects only the colon and rectum, whereas Crohn's can affect any region of the gastrointestinal tract, including the mouth.

> "SUDDENLY, THERE WAS SOME SCIENCE THERE."

Rubin says that their goal was to start a serious discussion about the procedure's use for IBD — and indeed, he says, "there was a signal" in the literature. The challenge now is for more controlled studies to decipher the nature of that signal.

Paul Moayyedi, a gastroenterologist at McMaster University in Hamilton, Canada, has taken up that mantle. He led a randomized controlled trial for FMT in ulcerative colitis, published in 2015, in which participants received either colonic FMT or a water enema once a week for six weeks. A week after the final enema, the patients were checked for signs of colon healing. In the control group, 2 out of 37 entered remission, compared with 9 out of 38 in the FMT group, a statistically significant effect[5].

2010

Using genetic sequencing to analyse microbe composition before and after transfer, Alexander Khoruts's team at the University of Minnesota, Minneapolis, shows that effective FMT for *C. difficile* is accompanied by recipient microbiota becoming more like the donor's.

JANUARY 2013

Els van Nood at the University of Amsterdam and colleagues report a randomized controlled trial that supports the effectiveness of FMT for the treatment of recurrent *C. difficile* infections.

MAY 2013

The US Food and Drug Administration classifies FMT as a drug rather than as transplanted human tissue. FMT is, therefore, subject to tighter government controls and any physician wanting to use it must file a lengthy application.

JULY 2013

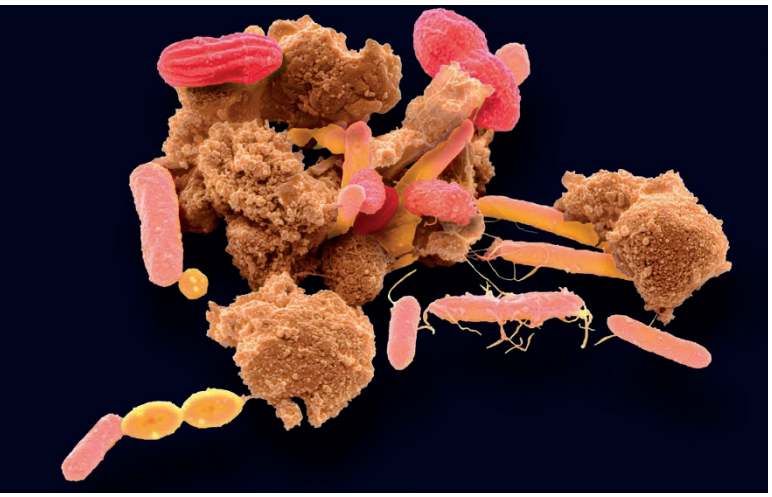
Following appeals from gastroenterologists, the FDA applies 'enforcement discretion' for FMT to treat *C. difficile* infections, essentially allowing the use of the therapy for just this condition.

2014

The United Kingdom's National Institute for Health and Care Excellence (NICE) recommends the use of FMT for recurrent *C. difficile* infections and calls for further research into optimal dose, method of administration and choice of donor.

2016

A pill containing synthetic stool — a purified cocktail of intestinal bacteria found in a healthy gut — unexpectedly fails a trial for the treatment of *C. difficile*. Systematic trials for FMT use in IBD are under way in the United States, United Kingdom, China and Australia.



STEVE GSCHMEISSNER/SPL

Scanning electron micrograph of various species of faecal bacteria.

The 24% success rate is similar to that described by Rubin and Colman. By Moayyedi's own admission, it "needs to be a lot better". But he also argues that this level of success is "the reality of treatments at the moment" and compares favourably with the remission rates seen with much-heralded immunosuppressant drugs.

Moayyedi is now in the early stages of a second trial for FMT in ulcerative colitis. It is one of a number of larger, better controlled trials that are under way for both this disorder and Crohn's to determine the future of FMT as a treatment for IBD.

FIRMING UP EVIDENCE

It is now clear that recurrent *C. difficile* infection was a low-hanging fruit: a condition that is essentially tailor-made for FMT. This bacterium wreaks havoc, mainly in the bowels of people whose native microbiota has been wiped out through heavy antibiotic use. *C. difficile* survives because of its drug-resistant spores. But once the antibiotics have cleared, a new microbiota can easily take hold and crowd the bacterium out. No other condition is likely to be so easily bested by FMT, but the expectation is that it must be used to treat conditions caused by a pathogenic microbiota. And that the microorganisms in a healthy donor's stool must be able to colonize the recipient's gastrointestinal tract.

"I WOULDN'T EXPECT ONE TRANSPLANT TO CHANGE THE MICROBIOTA THAT MUCH."

Various studies have attempted to identify causative microbial factors for IBD by using ever more sophisticated genetic tools to examine the full suite of patients' intestinal inhabitants. Most studies have found alterations — a common conclusion is that the IBD-associated microbiota is less diverse — but frustratingly there is no consensus about which specific microbial populations are altered.

More pressingly, however, these studies have been unable to determine whether these changes are pathogenic — provoking the immune system, and so causing the disease — or whether the pathological inflammation of IBD creates an intestinal environment that favours different microorganisms. Even studies showing that alterations in the microbiota correlate with disease severity, or that the microbiota normalizes with remission, fail to prove causation over correlation.

This creates uncertainty over the extent to which FMT might work for IBD. It also places the procedure in an interesting position: trials of FMT might be able to unpick the riddle of cause and effect.

Testing FMT is part clinical trial, part interventional clinical experiment. If installing a new microbiota works, it will be compelling evidence that the displaced microbiota had been central to generating IBD. Whereas, if symptoms persist after microbial transfer and the microbiota reverts, this will indicate that the problem lies with the immune system. A well-executed but failed trial of FMT, therefore, would offer the consolation of new insight into the mechanism of the disease.

But before any of this can happen, researchers need to know whether introduced microorganisms effectively colonize the recipient's gastrointestinal tract. Without this information, it is impossible to interpret a changing or unchanging disease course. For this reason, Khoruts argues that establishing a reliable methodology should be the first goal of IBD research. "I wouldn't expect that one administration of FMT would really change the microbial community structure that much," he says. Unlike the denuded bowels of people with a *C. difficile* infection, there are already microbes in the guts of people with IBD, leaving nowhere for the new arrivals to settle. "But if you do it repeatedly, there is a decent chance that you're going to have a substantial change in the microbial community," says Khoruts.

Moayyedi agrees. In his 2015 trial, DNA analysis of stool samples revealed that the microbial composition of FMT-treated participants shifted modestly towards the donor's profile after the six weekly transplants. In a second trial, set to begin next year, patients will first be given a two-week course of broad-spectrum antibiotics to make space in the gut, and then receive twice-weekly FMT for eight weeks.

Moayyedi is also tweaking other aspects of the methodology in the new trial to explore signals that he noticed in the 2015 trial. All participants will receive stool from a single donor, for instance. The original trial used two main donors, A and B. Intriguingly, A's donations cured nobody, whereas B's had a 39% success rate. Disease duration is another variable that they have their eye on this time around: 3 of the 4 participants who'd had ulcerative colitis for less than 1 year responded to FMT, compared with only 6 of 34 who'd had the disease for longer.

That is a lot of factors to explore, and every additional variable requires more participants and hence more funding. Rubin also wonders if there is a basic heterogeneity across IBD cases, such that a person whose disease began after a food-poisoning incident might benefit from FMT, whereas a more strongly genetic case might not. Funding large trials and sophisticated DNA analysis is challenging, especially for a treatment that, unlike a regular drug, has struggled to attract major financial investment.

But this seems to be changing, as recently funded clinical trials in the United States, Australia, China and the United Kingdom indicate. One of those trials is at the University of Birmingham, UK — much closer to Adams's home. But he has no need for it now: his surgery worked and he is back out surfing again. "I feel like a completely different person," he says. "I'm living a whole new life." His thoughts about the therapy he was never able to try are pragmatic: "I really hope it at least gets the length it needs to be trialled properly and for a proper outcome to be obvious." ■

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