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MAGAZINE

IS MEDICINE SEXIST?

**INSIDE THE FIGHT
TO CURE
CHRONIC UTI**

BY NATASHA ROBINSON

**“THEY ARE
LITERALLY SAYING
YOU ARE MAD.
THEY LOOK AT YOU
AS IF YOU ARE
MAKING IT ALL UP”**

BY NATASHA ROBINSON

It's a painful, debilitating condition that blights the lives of women and girls. Why are doctors only now waking up to the reality of chronic urinary tract infections?

On an ordinary day inside a children's hospital operating theatre, the last thing Ani Deshpande expected was to make a major scientific breakthrough. The paediatric urologist had taken a 10-year-old girl suffering from recurring urinary tract infections to theatre for a cystoscopy, a procedure to inspect the inside of the bladder.

As images of her bladder appeared on a screen, he felt his heart rate climb. "What I saw was unbelievable," the associate professor from Westmead Children's Hospital in Sydney says. "The inside of the bladder was like a battlefield. There was no normal lining left."

Deshpande was so stunned that he called colleagues into the theatre. They were concerned the girl may have a tumour, and suggested taking a tissue biopsy from the bladder wall. Later, when Deshpande inspected it under a microscope, he had no idea he was about to accidentally prove a theory of chronic bladder infection that is denied by a large proportion of Australia's medical profession.

Urinary tract infections – shortened to UTIs – are pervasive in the female population. One in three women contract a UTI in the course of their lifetime. It's the most common reason for the prescription of antibiotics.

Most women are familiar with the sting that marks the onset of cystitis, the most common type of UTI. Though extremely painful and uncomfortable, with the near-constant need to urinate, urinary tract infections are usually simple, acute, and easily treated with a single course of antibiotics. But there's always the risk of UTIs becoming complicated and intractable. One in four patients cannot get rid of them, and suffer recurrent infections. Some suffer chronic infections for decades. Recurrent UTIs also affect children, almost always girls. (Infections can affect men and boys, too, but it's much more rare.)

Whether it's the sexist stigma associated with "honeymoon cystitis", the culture of fear around antibiotic resistance or plain arrogance among doctors in an often patriarchal pro-

fession, lives and relationships have been destroyed by the failure to properly treat the condition. Now, at last, science is finally catching up with the experience of millions of women.

What Deshpande saw under the microscope when he examined the tissue biopsy from his patient were colonies of E.coli bacteria within the bladder's epithelium – its surface layer of cells. This was highly significant because

according to the medical textbooks, the epithelium is impermeable. Hence the widespread scepticism in the medical profession of the concept of chronic UTI as an embedded infection in which bacteria hide and replicate within the bladder wall where they cannot be neutralised by oral antibiotics.

"This patient had normal urine cultures at the end of every antibiotic treatment, and the infection seemed to be cleared at different points in time," Deshpande says. "For the bladder to be so inflamed, to the extent it was virtually destroyed, I was asking, 'What is going on? How can an infection do that?' I suspect there is something happening in the cells with these colonies of bacteria, which is ongoing."

It was an accidental discovery which is set to transform the diagnosis and treatment of UTIs.

"I honestly believe if I had been offered the right treatment at the very start, I wouldn't be in this mess," says Brisbane mother Lisa George, who wasn't offered antibiotics when she developed her first UTI 25 years ago. "I was told to drink Ural and cranberry juice. I was told it was all in my head and I needed better hygiene. I was told to take anti-depressants."

George is now 47 and a mother of four. For two decades, she suffered ongoing infections with symptoms so severe that she struggled to even leave the house for 10 minutes to take her children to school. "It was so bad I had to stop working, I needed to go to the toilet every five minutes," she says. "I lost friendships, I couldn't socialise. The pain in my urethra was so intense, it felt like I had a hot poker stabbing into me. I woke up every morning crying in pain, and it only got worse as the day went on."

Despite this raft of symptoms, bacteria were never detected in George's urine samples, leading doctors to conclude she did not have an active infection. She told them that when she looked in the toilet, her urine "looked like a snow cone", with floating bits visible. Doctors dismissed that as unrelated to her symptoms. "There was years and years of gaslighting, of

UTIs: THE FACTS



AFFLICTS 1 in 3 women

ONE IN FOUR women who get a UTI go on to develop chronic UTI

#1 REASON for prescribing antibiotics

SYMPTOMS OF CHRONIC UTI include bladder and pelvic pain, urgency and frequency of urination, incontinence

CAUSED by bacteria that burrow into the cells lining the urinary tract

TRIGGERS OF INFECTION are sexual intercourse, vigorous exercise, stress, alcohol

STANDARD URINE TESTING misses over 50% of infections

doctors telling me that it was nothing,” she says. “In the end you don’t want to go to the doctor at all. There’s no point.”

Finally, after performing an unnecessary and painful “bladder stretch” procedure and a cystoscopy that revealed a “red and angry” bladder, the urologist told her there were few options. “He said to me, ‘The only thing I can do now is remove your bladder,’” George recalls. “If you want, we can do that. Otherwise you’ll have to just learn to live with it.”

“I remember walking out of there bawling my eyes out. I was 28 years old. I wanted to have children. I didn’t want to live my life with a urine pouch. I told my husband, ‘I can’t live like this. This is not living.’”

Around the world, lobbying by patient groups – formed organically by women suffering severe symptoms but receiving inadequate medical care for chronic UTI – is slowly forcing change. In the UK, the National Health Service (NHS) and the National Institute for Health and Care Excellence, which makes evidence-based recommendations and guidelines for medical practice, formally recognised chronic UTI as a condition last year. (In Australia, the patient group Chronic UTI Australia is lobbying for the health system in this country to follow the UK’s example). Importantly, the NHS now acknowledges that interstitial cystitis – a diagnosis often given to women with chronic bladder symptoms and pelvic pain – may in fact be a chronic infection in some women. The NHS has also acknowledged the inadequacy of mid-stream urine testing, which is still used as a primary diagnostic tool by doctors.

“It’s largely the patients who have brought all of this to light, and they’re suffering,” says the female British urogynaecologist Rajvinder Khasriya, who as long ago as 2010 conducted research that established mid-stream urine testing missed around 50 per cent of UTIs. “We hope that chronic UTI is now firmly on the agenda. We consider that these patients need to be treated, and possibly treated in a different way. The first thing that has to happen is that there needs to be a recognition that these patients exist, that they have a problem.”

The Children’s Hospital at Westmead researchers are now at the forefront of seismic developments that have sprung out of Deshpande’s discovery that bacteria were embedded in the cells of the bladder wall in his child



“In the end you don’t want to go to the doctor at all. There’s no point”

Lisa George photographed by Lyndon Mechielsen

patient. A Westmead research lab is pioneering a new technique in urine testing, the results of which have further confirmed the theory of embedded infection. The technique utilises confocal microscopy, which allows pathologists to look deeply into cells from the bladder wall that are shed in the urine (these cells are routinely shed in urine – but much more so when infection is present). They have been able to detect the presence of bacterial communities inside these cells, indicating the presence of chronic UTI. It’s a potential game-changer in urine testing.

Deshpande has so far detected bacterial communities in the cells of 80 per cent of his paediatric patients. Sometimes, he says, there’s “a huge number of bacteria inside the cells that line the bladder”. Many of these kids have already had recurring infections; others have had only one, but are identified as being at high risk of chronic infection.

“Basically, this is a different way of looking at the urine,” Deshpande says. “Typically, what we do with the urine is use light microscopy. This particular technique, confocal microscopy, is an

established technique in microbiology but it has never been applied to urine in these little girls. What we’re now doing is trying to find out what the special properties of this bacteria are that are allowing them to penetrate the epithelium [the surface layer of cells in the bladder wall] and form these intracellular communities, which is known as urovirulence, or the ability of bacteria to create mischief. This microscopy also allows us to study how treatment is working.”

Deshpande’s advances in paediatric chronic UTI testing come more than a decade after UK researcher Harry Horsley, together with Professor James Malone-Lee from University College London, established in a scientific paper that recurrent UTIs usually occur in adult women in the presence of embedded infection by intracellular bacterial communities. But their discovery did little to change standard UTI treatment practice.

Urine testing remains outdated and inaccurate, with Malone-Lee – who died in 2022 – dismissed as a radical or even a quack by many doctors. Widespread ignorance of the science of embedded infection continues to pervade the

medical community. Patients are dismissed and told they have no infection even when they have raging symptoms; in paediatrics, parents are routinely told their kids will simply grow out of the problem. Thousands upon thousands of women and many children still now remain poorly treated or untreated; many live in abject misery and despair.

One of the reasons that understanding of chronic UTI remains so poor is that despite its prevalence in the community, UTI attracts a pitiful amount of research funding. One of the few researchers working in the space, Monash University's Dr Malcolm Starkey, is in no doubt that a major reason for this is that it's a "battler's disease" – that's to say, not acute or life-threatening – that predominantly affects women and girls. Although there are genuine reasons for concern about the impact of antibiotics on the gut microbiome, he describes as "insanity" the mass reluctance to prescribe the drugs long-term in the face of ongoing infection causing debilitating symptoms. "A lot of doctors are just so scared to go outside the guidelines," Starkey says. Pressure is being put on doctors to not prescribe the long courses of antibiotics that are needed to treat chronic, embedded infections, he explains. "But my gut feeling is we probably do need to at least consider targeting these bugs aggressively in the first instance with longer courses."

Antibiotic resistance is a genuine concern, with the prospect looming that a time will come in our lifetimes that people will increasingly experience infections that cannot be treated. Superbugs are endemic in the nation's hospitals, and overuse of antibiotics is a major cause of the problem. But it's unlikely that prescribing long courses of common antibiotics such as Keflex or Trimethoprim for the relatively small percentages of women who go on to experience chronic UTI after a first infection will be a driver of this trend. Not sufficiently treating chronic UTI, resulting in repeat short-term prescriptions, is more likely to cause harm.

Another concern is the impact of antibiotics on gut health. There's no doubt taking antibiotics negatively affects the gut flora, and that antibiotics should not be taken unless necessary. But for women suffering severe pain and disability from chronic UTI there is little alternative. A diverse diet high in fibre and prebiotics is recommended to rebuild intestinal health.

The maverick scientists



Rajvinder Khasriya leads the Lower Urinary Tract Symptoms Clinic at the NHS Whittington Hospital in North London, a clinic established by the late Professor James Malone-Lee (the pair are pictured above right). Malone-Lee became involved in studying chronic UTI after his clinical work saw him frequently visiting nursing homes. Chronic UTI is endemic in the elderly. "He described walking into geriatric wards or care homes, and just being hit with the smell of urine," Khasriya says.

"So he started looking at incontinence and the mechanisms of incontinence. He had lots of patients sent to him who were failing traditional treatments for bladder issues. When he spoke to those patients, and he wrote down freehand what they said, a lot of them would say things like, "I've been diagnosed with overactive bladder, and I've been given these pills" or "I've been diagnosed with bladder pain syndrome and I've been sent to you because nothing's working. But I think everything started when I had an infection." And he started to wonder, "Why are the tests sometimes positive? Why are they sometimes they negative?"

Standard diagnosis of UTIs relies on urine samples that contain pathological bacteria at a level able to be grown in a lab culture dish. Chronic sufferers experience more extensive symptoms including incontinence and severe pelvic pain. Doctors generally prescribe antibiotics in short courses, which usually clear simple infections quickly. But in cases of chronic infection, the infection keeps returning as new waves of bacteria are released from where they hide within the bladder wall. Malone-Lee and Khasriya noticed when they examined urine samples under the microscope that many patients who had symptoms but had been told they had no infection after standard testing actually had white blood cells in their urine. But this was often dismissed as sample contamination or an unrelated viral infection.

Malone-Lee and his team began treating women and children with chronic UTI at the Whittington Hospital clinic. Their pioneering approach was to prescribe long-term, narrow spectrum antibiotics at full dosage – radical, because it was a method that went against guidelines on antibiotic use and was criticised owing to a fear of antibiotic resistance and superbugs. It's a strange anomaly that doctors around the world routinely prescribe long-term antibiotics at prophylactic doses, or half dose, to prevent recurrent infection, yet balk at long-term prescribing in high doses. Khasriya says it's the low-dose prescription that is more likely to cause antibiotic resistance and result in intractable infections as the bugs become smarter and more adapted.

Deshpande is blunt about the prospects for his patients with chronic, embedded infection that is not appropriately treated. UTI in children is the main risk factor for the development of renal scarring, and can have rare consequences such as arterial hypertension or even renal failure. "I have not seen any self-resolution in my practice," he says. "So there's no reason to withhold treatment."

What that treatment should look like is a controversial matter. As Deshpande points out,

the colonies of bacteria in the epithelial cells lining the bladder wall do not by themselves usually cause a lot of symptoms; it's only when they're released that illness occurs. Over a decade ago, British researcher Malone-Lee concluded that since these cells were impenetrable to antibiotics, it was necessary to keep patients on antibiotics for the time it took for the entire bladder to shed its epithelial cells. In women that often took as long as two years. Such a course was so unpalatable to the

Whittington Health NHS Trust that in 2015 it moved to shut down Malone-Lee's clinic, and he was ordered to adhere to NHS guidelines.

But the controversy did not stop the flood of patients – some of them Australian – who sought help from Malone-Lee at his private Harley Street Clinic in London.

Melbourne mother Pippa Anderson was one of the women who'd been told by her doctor that her ongoing severe UTI symptoms would "just settle and kind of go away", she says. "I don't think if a man went in with the same symptoms, they'd be treated with such disregard for their pain and how much it affects their life. No way.

"I'd been told for years that what you've got is basically interstitial cystitis, this is your life now, get on with it. I've been told I'm incurable. I think it's disgraceful. And I think it's shameful

that something so relatively simple to treat with something that's low-cost and easily available is just ignored."

Deshpande is progressing with intensive research to try to identify the factors in the host response that cause the bladder to become more likely to be penetrable by bacteria after the first infection, and also the factors that may trigger the release of embedded bacteria if a child has intracellular colonies in their bladder wall. His team has so far identified two immune mechanisms that may be involved.

Another focus of research is the link between the bladder and the body's microbiomes. "There is an apparent interplay between the bladder and the vaginal and the gut microbiomes," Deshpande says. His team is looking at potential triggers for the release of embedded bacteria. "We're only scratching the surface so far, but it's becoming obvious that there are some triggers, which are largely local. For example, in adult women, harbouring abnormal

vaginal bacteria can cause release of these cells from the bladder lining. If you have good gut bacteria, then you're less likely to get bacteria in the bladder. So the link between the various microbiomes and the bladder is where the interest is now focused in terms of what causes the release of intracellular bacteria."

But in the meantime, with few other options, Deshpande has moved to institute treatment with long-term antibiotics for all of his patients that have been identified as having chronic UTI, when their parents consent. There is some research that supports this intervention. No doctor wants to prescribe long-term antibiotic treatment unless they absolutely have to, and it's far from an ideal approach. But the reality is it's currently the only option to relieve patients' suffering, which is enormous.

Deshpande is confident new therapies will arrive in coming years, but at this point in time, he doesn't believe there is any other way. "I've seen enough of these children who suffer a lot," he says. "The majority do clear their first infections effectively and do not develop a chronic infection. But what about those who don't? It's important to differentiate between the two at an early stage so that parents don't feel they are being ignored or being pushed under the carpet."

There are tentative signs in Australia that the approach to chronic and recurrent UTI is starting to shift at the highest levels. Patients are heartened that the respected Professor Helen O'Connell has taken the presidency of the Urological Society of Australia and New Zealand and makes frequent statements on social media challenging much of the dogma around urine testing and chronic infection.

O'Connell believes Australia should "absolutely" follow the UK in recognising chronic UTI and the inadequacy of midstream urine testing. "The idea that chronic infection is a furphy is obviously wrong," she says. "We know it's chronic UTI in some people. Not all patients who have recurrent infections have chronic infection, but probably a lot of them do. The infection is not actually cleared after treatment. And so we do need these long-term strategies.

"When I read James Malone-Lee's work, it dovetails beautifully with the teaching I had in the '90s and then having been in practice for a long time. When I went to a bladder science meeting at NIH [the National Institutes of



"I think it's shameful that something so simple to treat is just ignored"

Pippa Anderson photographed by Emma Brasier

Health] in the US in the early '90s, it was pretty clear that on electron microscopy you could see little colonies of bacteria in the cells. To me the idea of embedded infection is not news."

If chronic UTI as an embedded infection comes to be accepted as mainstream science it raises questions as to therapeutic guidelines on antibiotic use, given some people with chronic UTI will not be able to clear the infection without very long courses of antibiotics. And current guidelines for initial treatment of acute UTI – often patients are given only a three-day course – is likely raising the risks of simple infections ultimately becoming chronic.

"It is my belief that particular groups benefit from the Malone-Lee style treatment of very high doses of antibiotics," O'Connell says. "I don't think it's the majority, but I think some do. There are some people that are just not going to get better with standard treatments."

O'Connell describes the advent of pharmacists prescribing three-day courses of antibiotics to treat UTIs as a "deregulated situation which has the potential to be bad for patients".

"Malone-Lee presented some very interesting data on the rise of these chronic or recurrent infection situations in the era of short-course antibiotics," she says. "That has been part of the problem. And it's pretty clear with bad infections, people need at least 10 days to two weeks. All clinicians are conscious of minimising bacterial resistance by using the best available antibiotic strategy. If our antibiotic courses are failing a third of patients who are entering a chronic infection state, that is a significant problem.

"It is important then to prove that the cells in the urine or the inflammatory response cleared after treatment. If inflammation persists in the urine, patients are at risk of recurrent infections. Older treatments such as Hiprex [methenamine] have been shown in recent studies to be effective for preventing recurrent infections and helping to clear chronic infection."

O'Connell is hopeful that new national therapeutic guidelines, currently in development, may specifically address the issue of chronic UTI and the use of long-term antibiotics as well as other medications of proven efficacy. "I'm also hoping there will be clearer information about the interpretation and follow-up of urinary cultures, microscopy and sensitivity tests," she says.

The relief of hearing recognition of chronic

A child's story: "We were at a point of desperation"

Lili, now 13, contracted her first UTI at the age of two, and for the next eight years suffered pain and disability, with infections increasing in frequency and eventually occurring at the rate of about 10 a year. The family for years were told by doctors it was a hygiene issue – caused by an improper wiping technique on the toilet.

"It was heartbreaking," says Lili's father, Justin Drerup. "We were at a point of desperation. Nobody could tell us why this was happening. Lili was just in constant pain, I was sleeping in her room every night on a mattress on the floor to help her, she was wetting herself constantly. We'd have to change the sheets twice at night. To say I was exhausted is an understatement. We were desperate to find a solution."

Drerup eventually came across the treatment method of Malone-Lee and after attending a seminar on chronic UTI by a visiting London doctor, resolved to buy a scientific microscope and set up a home laboratory. He collected urine samples from his daughter every morning and began meticulously tracking her white blood cells, epithelial cells and bacteria, capturing the data in spreadsheets and photos that he then presented to his GP, who agreed that trying long-term antibiotics may be worth a shot. Every two months, Lili was taken off antibiotics and her father would track what occurred via her urine. Each time for months, the infection came raging back, with Lili's white blood cell count and bacterial colonies flourishing in a matter of hours. "What I learned was when there's an infection you need to hit it straight away," he says. "If you're waiting 24 or 48 hours for a urine sample to come back from lab or for symptoms to emerge, the chance of the infection taking hold again is huge."

It took a year for Lili (pictured above) to fully clear her chronic embedded infection. Now, she's 13 and a happy, active teenager who just obtained her surf life saving certificate. Drerup shudders to think what life would have been like for his daughter had he not taken matters into his own hands. "We were scared she was going to be incontinent for life," he says. "We couldn't have continued the way things were going. Every parent knows you will do anything for a sick child. If I could have tried to imagine what I have done before I did it, I wouldn't have thought it was possible.

"I think the more evidence that exists to demonstrate that this theory of embedded infection is actually true is welcome. I'm not a doctor, I don't have any medical training. I just followed a process because it seemed to make sense, and there was no other solution. I believe that people with actual clinical experience should continue to research this to further validate the theory so that people can be diagnosed and treated early so as to not go through what my child went through."





“The burning was so intense that you just couldn’t function”

Amber Sealey photographed by Philip Gostelow

UTI and the deficiencies of testing and treatment is enough to make 55-year Amber Sealey weep with relief. The Perth woman got her first UTI at the age of 14 and has experienced decades of pain and disability.

“I never thought this was going to go on all my life,” Sealey says. “I can’t tell you how distressing it is, to have been treated the way I have been treated for most of my life. You’re going to the toilet every ten minutes and screaming in pain. You would see all the flakes from your bladder in the bottom of the toilet. The burning was so intense that you just couldn’t function. I was unable to work for any employer for many, many, many years. I had to lay in bed three or four days a week. It’s nothing for me to have to lay in a bath all day long, just to get through that day.

“You don’t even want to go and see a doctor. You do not want to go to an emergency department, because you just get treated so badly. They’re telling you it’s all in your head. They are literally saying you are mad, and why are you taking that much pain relief? They look at you as if you are making it all up.

“I’ve sacrificed income, I’ve sacrificed my children, being able to take them places and do

things with them. I’ve sacrificed my own self-esteem, my own belief in myself. I could never exercise – I would go for a 20-minute walk and the next day I’d have a raging infection.

“These doctors should be in your corner, they are meant to be fixing this for you. You go to them and pay them money only to be told after 18 years of suffering that there’s absolutely nothing wrong with you. That’s not medical care in any way, shape or form. All of the opportunity to be a healthy, normal, functioning human being really was taken away from me all my life, because treatment was not given to me. And I personally know women that have taken their own lives because of this condition.”

Professor Steve Robson, President of the Australian Medical Association, is devastated when he hears the stories of patients like Sealey. He has seen many women in a similar position in his practice as an obstetrician and gynaecologist. “I’ve treated lots of what I thought was just interstitial cystitis,” Robson says. “It never occurred to me that it could be either a result or go hand-in-hand with chronic infection. But I have had my eyes opened to the new evidence over



“We’re only scratching the surface”

Ani Deshpande photographed by John Feder

the last couple of years. I would encourage all my colleagues who deal with this to take the same journey I did and have another look at the new evidence. Because if you don’t, you’re going to be misdiagnosing and not adequately treating lots and lots of women, leading to lots and lots of misery and debility.

“I think we’re at the point now where there’s sufficient evidence that there probably needs to be some national statement about this as a way of helping health practitioners around the country to understand the new paradigm. To avoid harm, either the harm of under-treating or the harm of over-treating, we really need to take this seriously, form a consensus and do it soon.”

Deshpande, who is seeing an increasing number of paediatric patients whose parents have not been able to find answers for why their children are getting infection after infection, agrees. “The paradigm shift is coming,” he says. “When you look at the evidence that is now emerging, I think we are finally breaking the shackles. But many specialists are still very sceptical in the paediatric world. I have a lot of colleagues who are not willing to believe that the infection never really clears. Our science is so far behind.” ●