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Aster Medical Journal

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Leadership
Why The Best Hospitals Are Managed by Doctors

Research
Effectiveness of Insulin -Pump Over Multiple Daily Injections

THE PEOPLE WHO HELP YOU DIE BETTER

A network of compassionate volunteers caring for their terminally ill neighbours is allowing more people in Kerala, India, to end their life at peace. This tiny Indian state known for its nature has just 3 percent of India's population but provides two-thirds of the country's palliative care services. Here's why a medico-social experiment started in 1993 is drawing attention from around the world and recommended by the WHO in end-of-life care.

Shaping the future of healthcare

SIEMENS Healthineers

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PHOTOGRAPH BY **LEIGH WEBBER**

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If there's anything I've learned this last three years, it's that the medication is not going to work by itself. If you do not work the muscles, you will not see progress.

- Cameron's mother, an employee of a bank's IT department.

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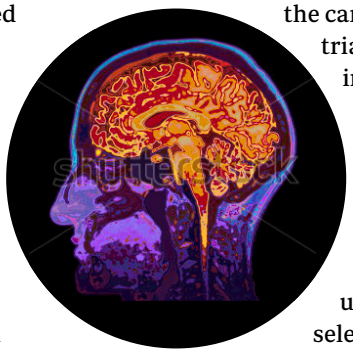
Neither Vitamin E Nor Selenium Prevents Dementia, Researchers Find

Evidence suggests that the virus may enter the pancreas through the ACE2 receptor and damage the pancreatic beta islet cells which produce insulin.

Taking vitamin E or selenium supplements did not prevent dementia in asymptomatic older men, research published in JAMA Neurology has found. Oxidative stress has been implicated in Alzheimer's disease, but it is unknown whether the use of antioxidant supplements can prevent dementia.

The Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADViSE) trial was piggybacked onto a larger randomised controlled trial looking at the antioxidant effects of selenium and vitamin E on the incidence of prostate cancer. The parent trial started in 2002 but was stopped in 2009 after a planned futility analysis showed no effects on prostate cancer incidence.



The trial recruited 7540 men with a mean age of 67.5 years who were randomly assigned to receive vitamin E, selenium, vitamin E and selenium, or placebo. They were given antioxidant supplements for an average of 5.4 years and assessed using a cognitive screen. When the parent trial ended, a subset of 3786 men received no additional supplements but continued to be observed for up to six more years.

There were 325 cases of dementia among 7338 men (4.4%) and the incidence rate was no different between the four study groups.

The study had a number of limitations, however. It had fewer participants than planned and a lower statistical power because of the cancellation of the parent trial. There was also a low incidence of dementia observed during follow-up, which may be partly because most of the men were in their 60s.

"The supplemental use of vitamin E and selenium did not forestall dementia and are not recommended as preventive agents. This conclusion is tempered by the underpowered study, inclusion of only men, a short supplement exposure time, dosage considerations, and methodologic limitations in relying on real world reporting of incident cases," the authors concluded.

Screen Time of Over Three Hours a Day is Linked to Diabetes Risk Factors in Children

Daily screen time of more than three hours is linked to several risk factors associated with the development of diabetes in children, including adiposity and insulin resistance, an observational study has found. Previous research had indicated that spending a lot of time in front of a screen is linked to a heightened risk of weight gain and type 2 diabetes in adults, but whether children were also at risk was unclear. Researchers from London and Glasgow assessed nearly 4500 9-10 year olds from 200 primary schools in London, Birmingham, and Leicester for a series of metabolic and cardiovascular

risk factors. The children were also asked about their daily screen time, to include TV, computers, and games consoles. The findings were reported in the Archives of Disease in Childhood.

Complete information was obtained for 4495 (2337 girls and 2158 boys) of the 5887 children who took part in the study between 2004 and 2007. Only 4% of the children said that screen time didn't take up any of their day, and just over a third (37%) said that they spent an hour or less looking at a screen. Of the remainder, 28% said they spent 1-2 hours looking at a screen, 13% said they spent 2-3 hours, and around one in five (18%) said that they spent more than three hours looking at a screen every day.

Children reporting screen time over 3 hours had a higher ponderal index (a measure of leanness; 1.9%, 95% confidence interval 0.5% to 3.4%), skinfold thickness (4.5%, 0.2% to 8.8%), fat mass index (3.3%, 0.0% to 6.7%), serum leptin concentration (9.2%, 1.1% to 18.0%), and homeostatic model assessment (a measure of insulin resistance; 10.5%, 4.9% to 16.4%) than those reporting an hour or less. Associations with insulin resistance remained after adjustment for adiposity, socioeconomic markers, and physical activity. Associations with glucose, HbA1c, physical activity, and cardiovascular risk markers were weak or absent.

The researchers emphasised that, although their findings were "of considerable potential public health interest," they could not draw definitive conclusions about causality because the study was observational. They pointed out that since the study was carried out the use of electronic devices has become more widespread with more options now available, such as tablets and smartphones.

Women Cancer Survivors Have Higher Risk of Preterm Births, Study Finds

Young women who have survived cancer have an increased risk of having a preterm birth and a low birthweight baby, a large case control study of cancer survivors has found.

Five year survival rates are now over 80% in patients who have had adolescent and young adult cancers. Studies show that around two thirds of young women who survive cancer want the possibility of having children, but information on their potential risk of adverse birth outcomes is limited.

Researchers used the North Carolina Central Cancer Registry to identify 2598 women who survived adolescent and young adult cancers diagnosed in 2000-13, linking their records to state birth certificate files to investigate birth outcomes in their offspring. They compared these with a control group of 12 990 women with no history of cancer who were matched on maternal age and the year of delivery.

The results, reported in JAMA Oncology,1 showed that cancer survivors had a significantly higher prevalence of preterm birth than in control participants without cancer (prevalence ratio 1.52 (95% confidence interval 1.34 to 1.71)). They were also more likely to have a low birthweight baby (1.59 (1.38 to 1.83)) and to undergo caesarean delivery (1.08 (1.01 to 1.14)).

The higher prevalence of adverse birth outcomes was concentrated among births to women whose cancer was diagnosed during pregnancy. But other factors associated with preterm birth and low birth weight included chemotherapy and having a diagnosis of breast cancer, non-Hodgkin's lymphoma, or a gynaecological cancer.

"Overall, our results suggest an increased risk of preterm birth and low birth weight among births to survivors of adolescent and young adult cancers," said the researchers, led by Chelsea Anderson, from the University of North Carolina at Chapel Hill, USA. "Our findings suggest the need for additional surveillance of pregnancies in this population."

They said that long term effects of cancer treatment may explain the study results. For example, chemotherapy may lead to cardiovascular or pulmonary effects that may affect blood volume regulation and adversely affect pregnancy outcomes.

Thrombosis rate is higher with bioresorbable scaffolds than metallic stents, study finds

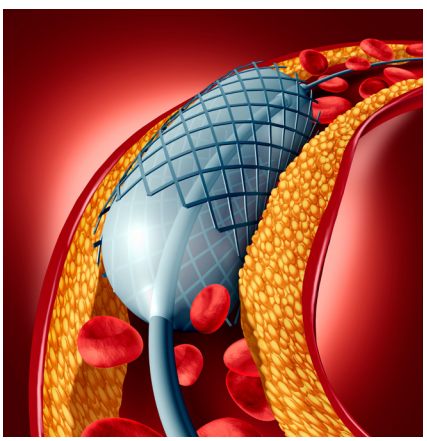
Bioresorbable stents were developed to remove the presence of a permanent implant and to allow normal blood vessel function.

Patients with coronary artery disease who undergo routine percutaneous coronary intervention (PCI) showed similar rates of target vessel failure but higher incidence of device thrombosis when a bioresorbable vascular scaffold was used instead of a metallic stent, in preliminary results from a randomised trial.

Drug eluting metallic stents are the standard of care for PCI, but their rigid structure can affect blood flow and lead to atherosclerosis and stent thrombosis. Bioresorbable stents were developed to remove the presence of a permanent implant and to allow normal blood vessel function.

Researchers at the Academic Medical Center at the University of Amsterdam, Netherlands, randomly assigned 1845 patients undergoing routine PCI to receive an everolimus eluting bioresorbable vascular scaffold or an everolimus eluting metallic stent. The participants were followed up for a median of two years (707 days).

The results, reported in the New England Journal of Medicine,1 showed no difference in the rate of target vessel failure between the two groups, with a two year cumulative event rate of 11.7% in patients given



with the scaffold device and 10.7% in those given stents (hazard ratio 1.12 (95% confidence interval 0.85 to 1.48); P=0.43).

But the study, which was funded by Abbott Vascular, showed a significantly higher incidence of device thrombosis in patients who received bioresorbable scaffolds than in those treated with stents (3.5% v 0.9%; hazard ratio 3.87 (1.78 to 8.42); P<0.001).

"We found that the rate of definite or probable device thrombosis in the scaffold group was approximately 3.5 times as high as that in the stent group over the course of two years," said the researchers, led by Joanna Wykrzykowska.

They noted that, because of the increased incidence of very late scaffold thrombosis, the data and safety monitoring board had recommended early reporting of the study findings, before follow-up was completed. The board also recommended that patients given bioresorbable scaffolds should be treated with extended dual antiplatelet therapy, which has been implemented.

In an accompanying editorial,2 Debabrata Mukherjee, of Texas Tech University Health Sciences Center in El Paso, USA, said that the findings were similar to those seen in previous trials.

"Given the lack of an advantage with respect to clinical efficacy . . . and the higher rate of device thrombosis, there is little justification for routine use of the everolimus-eluting bioresorbable scaffold over the everolimus-eluting metallic stent," he said.

Mukherjee added, "To overcome the safety issues associated with the currently available devices, device manufacturers need to focus their efforts on developing newer generations of bioresorbable scaffolds that use thinner or narrower struts and that are composed of a different material that would allow for higher radial strength and faster rates of resorption."

In focus

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A network of compassionate volunteers caring for their terminally ill neighbours is allowing more people in Kerala, India, to end their days at peace and at home.

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A white van coursed through narrow roads along the monsoonsoaked coastline of Kerala, a state in southwestern India.

26 **THE CURRENT STATUS OF PALLIATIVE CARE IN INDIA**
Less than 1% of India's 1.2 billion population has access to palliative care.

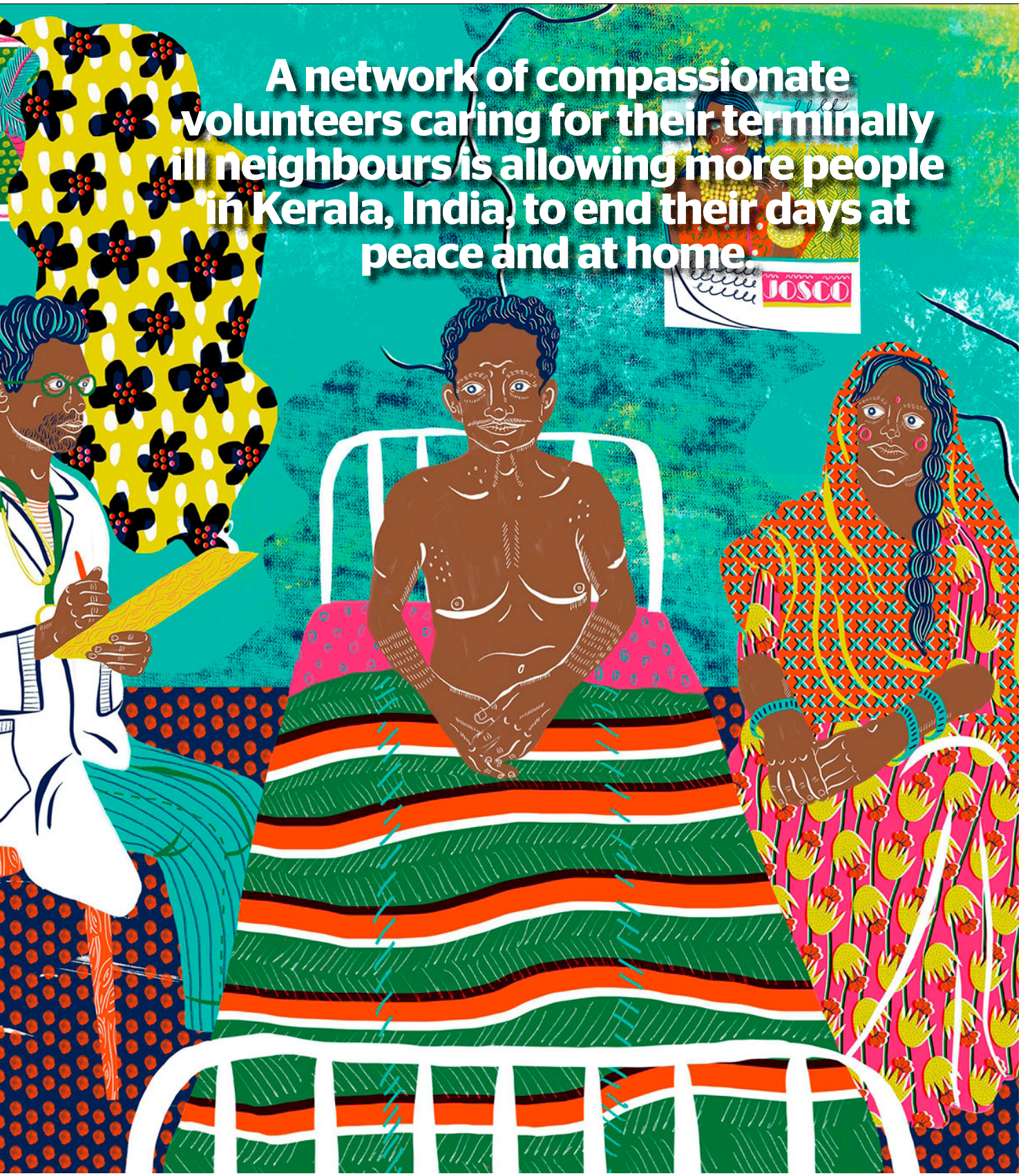
"What I've seen so far is that you cannot have a really good death unless you have lived a meaningful life."

Dr Suresh Kumar
Director of the World Health Organisation Collaborating Centre for Palliative Care

Palliative Care

Text by **Jeremy Laurance**
Illustration: **Camilla Perkins**

THE PEOPLE WHO HELP YOU DIE BETTER


A network of compassionate volunteers caring for their terminally ill neighbours is allowing more people in Kerala, India, to end their days at peace and at home.
JOSCO

Thirty years ago a young anaesthetist, newly appointed as head of department at Calicut Medical College Hospital in the Indian state of Kerala, encountered a case that would change his life. A college professor aged 42 with cancer of the tongue had been referred to him by an oncologist. The man was in severe pain and the anaesthetist, Dr M R Rajagopal, was asked if he could help. He injected the mandibular nerve in the jaw in a procedure known as a nerve block, and told the patient to return in 24 hours. Next day, the pain had almost completely gone and Dr Raj, as he is known, was pleased with his work.

"He asked me when he should come back. I told him there was no need to come back, unless the pain returned. I thought he would be happy I had cured the pain. Instead, he went home and killed himself that night."

It turned out that the oncologist had avoided explaining to the college professor that his cancer was terminal. Instead he had said he was referring him for further treatment.

"It was only when I told him there was no need to come back that he realised his cancer was incurable. He went home and told his family it was all over."

Dr Raj reaches for a glass of water. We are sitting in his simple home in Trivandrum, the leafy state capital, where he now lives with his wife, Chandrika, a pathologist. In front of us, a plate of yellow jackfruit gleams in the low afternoon light. A fan whirrs above.

That experience caused Dr Raj to examine his own practice. In addition to putting people to sleep for surgery, an anaesthetist's job is to tackle pain. So what was he missing, he wondered.

"In those days pain was all over the hospital. It was everywhere. We pretended not to see it, but it was there. Injections of morphine were used sparingly, after surgery and for patients injured in accidents. It was never used in cancer pain."

Medical staff coped with the suffering the same way they cope everywhere. "No one teaches you, but you learn to see only the disease, not the human being who has it. Maybe if there is nothing you can do it is easier to turn your back."

Dr Raj had had two earlier traumatic experiences involving the dying. Aged 18, in his first year in medical school, he had lived close to a man who had terminal cancer of the sweat glands. "I would hear him screaming in the night. He had nodules all over his scalp. The family knew I was a medical student and asked if I could do anything. I didn't know how – I was helpless. I am ashamed that I never visited him after that. I did not want to go there and feel helpless again."

Later, he was looking after a patient with a gangrenous toe who was in excruciating pain. "I asked my head of department if I could try a nerve block. He refused – it was not part of routine care and there was a shortage of anaesthetists. I had to tell the man there was nothing I could do. I still remember the look of hopelessness on his face."

When he became head of department at Calicut, there was no one to tell him what he could and couldn't do. That is how he came to treat the college professor. But his patient's suicide showed him that treating the pain was not enough.

"I realised that thinking about nerve blocks was too narrow. Pain is just the visible part of the iceberg of suffering. What is ignored is the part below the surface – feelings of hopelessness and despair, worries about money, about children. That is what palliative care is about. That man gave up his life to help me understand it."

We all wish for a pain-free, dignified death. Too few of us achieve it. Worldwide, the last year of life is marked by widespread unnecessary suffering. At least 40 million people need palliative care each year, but only around half that number receive it, according to the Worldwide Hospice Palliative Care Alliance.

India comes near the bottom of the global league in access to end-of-life care – ranked 67 out of 80 countries in 2015 – but Kerala is an exception. This small green and fertile state in the south-west has just 3 per cent of India's population but provides two-thirds of the country's palliative care services. These have developed over the last 20 years, driven by the

local community and supported by a unique system of volunteers.

Dr Raj, one of the drivers of the movement, disagrees. "Yes, of course the strength of the community is important. But is Kerala the only part of the world where there are compassionate people? Is Kerala the only place where people who may have gained material success then want to do something meaningful with their lives?"

Now a youthful 69, he recognised early on that tackling pain and supporting the dying could not be achieved by medical staff alone. The need was too great. It would depend on harnessing the commitment of volunteers.

In 1993, after he had attended a course run by an English nurse, Gilly Burn, he and his colleague Suresh Kumar established the Pain and Palliative Care Society in Calicut, a town in the north of Kerala, together with an activist friend, Ashok Kumar, who ran a printing business and provided a vital layman's perspective.

"Six of us put in 250 rupees each, worth about £10 then," says Dr Raj. "We found two volunteers, young women with children at school, to register patients and sit and talk to them. Then I would come after work to see them."

The project took off after Burn, who ran a trust, Cancer Relief India, donated 100,000 rupees (£4,000 in the mid-1990s), enabling them to appoint their first doctor. Calicut hospital provided two nurses.

"It very quickly got attention. In the hospital, we were working in a sea of suffering. But in the clinic, you could see people smiling, talking, finding comfort."

Within a year, it was being copied – by a medic whom Dr Raj met on a train and by a former student who wanted to open a clinic in his own town. The ball was rolling.

There was a limitation, however. It was exposed early on when a young man came begging for help for his mother, who was in severe pain. She lived in a remote spot where there was no road and could not be moved. When Kumar told the man that the doctors could not prescribe without seeing the patient, he broke down in tears. Kumar weakened and told the man someone would come. It was their first home visit. Gradually demand increased. Then someone donated a vehicle.

The doctors, working in their spare time, could not meet the demand alone. The organisation of the clinics and the home visits depended on volunteers. But the volunteers also provided the link between their communities and the service – they knew who was sick and where to get help. Over time, they became more and more involved. Some assisted with nursing tasks, following brief training, but most provided social care – advice, support, a shoulder to cry on.

By 2000, there were 30 palliative care groups in northern Kerala, run by volunteers and supported by mobile medical teams. Today, though there are no official figures, Dr Raj estimates there are 300 voluntary groups across the state, providing care to patients in their own homes, identifying those in need, and helping to direct limited medical resources to where they can do most good. Kerala is now a World Health Organization demonstration site for palliative care and plays host to a stream of international visitors wishing to learn how it was done.

The strength of the groups is that they have grown organically, rooted in their communities, by popular demand, and thus have strong local support. They are largely funded by local donations, some as little as 10 rupees (12 pence) a month.

They supplement the work of the 167 institutions licensed to dispense morphine and the 900 government–funded panchayats, or village councils, each of which employs a nurse who provides palliative care – though they may visit patients only once a month.

Thirty kilometres outside Trivandrum, in the dis-

"It was only when I told him there was no need to come back that he realised his cancer was incurable. He went home and told his family it was all over."

Summary

Challenge:
40 million people need palliative care each year, but half that number receive it, according to the Worldwide Hospice Palliative Care Alliance.

Solution:
What Kerala has recognised, though the rest of the world has been slow to do so, is that the scale of the need for palliative care cannot be met by professionals alone.

Result:
This tiny Indian state has 3 percent of India's population but provides two-thirds of the country's palliative care services.

trict of Uzhamalakkal, the white van carrying the community team turns off the road and bounces along a rutted track to a group of houses half-hidden in the rubber trees. The team of doctor, nurse and volunteers enter a house where Surendran, a former rubber tapper aged 50, is lying on a bed naked to the waist, his lower body covered by a striped cloth. His chest rattles, his stick-like arms are drawn up to his face and his breath comes in painful rasps. He is in the terminal stages of lung cancer, and for the last week has been unable to swallow – food, liquid or morphine tablets. A Josco Jewellers calendar hangs on the bare cement walls, under a strip light, and a blanket covers the window. Mini, his wife, stands at the foot of the bed.

Dr Raj lays a hand on Surendran's arm and gently explains that, as he can not swallow, to treat his pain the morphine will have to be administered rectally. The nurse will teach Mini how to do it. Dr Raj asks if he has any questions. "Can I get out of this?" Surendran says. Before Dr Raj can answer, Mini intervenes: **"Yes of course you can. You will get better."**

Dr Raj suspects she knows the truth, but decides against trying to broach it with her at that point, worried about the reaction it might provoke. Just as a wrong dose of a drug can harm, so can an ill-chosen word, he says later. A reflective man, with kind eyes and neat moustache, he comes ever ready to lay a soothing hand on a fevered brow. Wearing a blue open-necked shirt and sandals, his gentle demeanour and soft voice put patients at their ease while he probes for their stories before quietly instructing his team, who hang on his words.

"We help people live at home and die at home. Most want that," he says. But Surendran's condition is extreme, and his suffering severe, so Dr Raj urges Mini to bring him to the city, where there are a few hospice-style beds. She says she can not leave her 17-year-old daughter alone, so Dr Raj suggests bringing her too. While neighbours are often supportive, in this case they stopped visiting when they heard Surendran had cancer. Mini says she will consider it. The volunteers will help arrange transport.

The group that requested the home visit, called Sangamam (meaning "confluence"), was started four years ago by Dileep, 43, the manager of a paint shop, whose wife died of cancer. It is one of 11 that have sprung up in the Trivandrum area in the last decade. They are supported by Pallium India – the organisation Dr Raj founded in 2006 after he retired from the government medical service and moved to the city – which provided the mobile medical team.

Sangamam is one of the most successful groups, with 12 active volunteers and another 50 whose help can be drawn upon. It is funded by donations from the local community. In this case, friends have been generous enough to allow Dileep to hire a nurse and buy some land, where he hopes to construct a clinic. The local panchayat gives 50,000 rupees a year for drugs. "Because they are convinced we are doing good work," Dileep says.

Guided by the Sangamam volunteers, the Pallium India team sees two more cases this Tuesday morning in January. One, a woman of 55, who had her tongue removed a month previously because of cancer, has developed severe pains in her neck, which prevent her sleeping. Wearing a pink sari, she breaks down in tears as it emerges from Dr Raj's careful questioning that she has argued with her son in a dispute over land, and he has left. Sobha, a volunteer, has learned from neighbours that the son is planning to get married but has not told his mother. She undertakes to contact him to try to negotiate a reconciliation. Palliative care, in this conception, is about tackling emotional pain, as well as the physical kind.

What Kerala has recognised, though the rest of the world has been slow to do so, is that the scale of the need for palliative care cannot be met by professionals alone. In the UK, the hospice movement provides the gold standard for end-of-life care. Yet just 4 per cent of deaths occur in hospices. Most people – over three-quarters in some surveys – say they would prefer to die at home, but less than a quarter do so.

Julia Riley, consultant at the Royal Marsden Hospital, London, and visiting professor at the Institute of Global Health Innovation, Imperial College, says: "Hospices do terrific things – but there are not enough of them. We have got to get the service out into the community – it can be done at home. Only 10 per cent of people who are terminally ill need specialist palliative care. The rest need only generic care.

"Palliative care is so cheap. We can do so much, relative to other areas of medicine, for so little. Giving people a dignified death is so important – both for them and for their families."

In the UK, the number of deaths is rising as the post-war baby boomers age, says Max Watson, consultant in palliative care at the Northern Ireland Hospice and visiting professor at the University of Ulster. "To continue in the way we are – relying on hospices and specialist care – isn't an option," he says. "It is really important to democratise specialist knowledge. We need to engage carers, voluntary groups, nursing homes and patients themselves so they can be empowered to provide good-quality end-of-life care. Most of those helping are over 60 themselves. They are a fantastic resource we are not using properly."

In the US, hospice care is more widespread – 45 per cent of Americans at the end of their lives in 2010 received hospice care, more than half of them at home. These are among the highest rates in the world, according to Atul Gawande in his book Being Mortal. However, spending on the US health system is widely acknowledged to be out of control, substantially outstripping the costs of comparable systems in Europe.

The Kerala model is thus drawing attention from around the world. The estimated 300 voluntary groups are often described as a network. This suggests, wrongly, that there is some overarching organisation that links them all. In truth they are a series of networks that have grown organically, from the ground up, wherever the community has decided there is a need. One of the biggest is the Neighbourhood Network in Palliative Care in northern Kerala, led by Suresh Kumar, Dr Raj's former colleague.

In Trivandrum, Pallium India, staffed by six doctors, five social workers and 20 nurses, provides five mobile medical teams to support the 11 local groups. It also runs an outpatient clinic and an inpatient unit with 17 beds at Arumana hospital in the city, and provides outpatient services at four government hospitals.

In 2016, the mobile teams made 6,397 home visits. Some patients are starving and Pallium India currently provides 225 families with a monthly food kit, containing basic supplies, and supports the education of 300 children, in addition to supplying free drugs.

The work of creating the voluntary groups starts with talking to local people, explaining that hospitals are no place for the dying and that caring for the terminally ill is the community's responsibility. The concept of palliative care has been extended to include the chronically ill and the paraplegic, such as stroke survivors and people with complications of diabetes, including blindness and amputation, who now constitute up to half the patients.

Once a group is formed, Pallium India encourages the organisers to register it – for the sake of transparency and to gain tax advantages on donations – and offers support with regular visits from a doctor or nurse. But the aim is that the groups should ultimately go it alone.

Their origin in the communities they represent is their strength. But the absence of any top-down organisation is also a weakness. It means there is no mechanism for spreading the concept to other parts of Kerala, or other parts of India. Organic growth is slow growth.

Out of frustration with the lack of progress, Dr Raj established Pallium India to act as an agency to spread palliative care more widely, beyond the state's borders. "What has happened in Kerala is beautiful. But it should not be stuck in Kerala. It could be 1,000 years before we get universal pain relief [across India]," he says.

With the help of grants from foundations, donations from well-wishers and support from the Tata group, Pallium India has established 23 palliative care centres across India by providing initial funding to interested groups, training doctors and nurses, and giving support.

Kerala has been a pioneer in other ways. Its government launched the first state Palliative Care Policy in 2008. Two other states, Maharashtra and Karnataka, have followed suit and a National Palliative Care Strategy for India was published in 2012. A working group appointed by Pallium India drew up a list of essential standards, including a minimum 10 days' training in palliative care for doctors and nurses, an uninterrupted supply of morphine, and documentation of patients' pain scores.

But Dr Raj, who lobbied for the strategies, is not satisfied. "I am upset when the palliative care community boast about what we have achieved. We are not doing nearly enough. 99 per cent of people in India do not get access to palliative care."

He pauses to reconsider this bleak assessment. "Okay, if I want to be optimistic, I can put it another way. 1 per cent of people do have access to palliative care. That is 12 million people."

Central to the provision of care for the dying is the alleviation of pain. But even this is not being satisfactorily achieved. India is the world's largest legal producer of opium for medical purposes. But most is exported to the West. Over 90 per cent of the world's morphine consumption is in the countries of North America and Europe. All middle- and low-income countries combined consume just 6 per cent.

Morphine is easy and cheap to produce. It is not the cost that restricts access, but the law. Morphine has been highly restricted in India since 1985. As a result, two generations of doctors have grown up unfamiliar with it. Misplaced fears about drug abuse have condemned millions of terminally ill patients to an unnecessarily painful death.

Kerala has again proved more enlightened than other Indian states. Since 1998, palliative care centres in Kerala have been permitted to administer the drug orally. Much more recently, in 2014, the law was finally relaxed to allow access to morphine across India.

But Dr Raj is again unimpressed. "Changing the law is not translated into practice unless someone is pushing it. The new law has not had a big effect. Figures show India uses 320 kg of morphine a year. To meet the need we would need to use 30,000 kg."

He added: "This is why it is vital to seize this moment, when the iron is hot. If we do not act now, it may be too late."

Volunteers are the linchpin of the Kerala model. Krishnaraj Manikoth, a retired chartered accountant who now helps at Arumana hospital, says the work offers a sense of purpose. "I worked for 30 years in Dubai. I had a comfortable life, two wonderful children – I was blessed. What bothered me was that I had not done anything for society. I wanted to give something back."

Sintu Suresh, a former journalist and speechwriter whose father died a painful death in an intensive care unit, says she wanted to protect others from overtreatment. "Doctors don't see the whole patient, the human being. They see only the disease," she says.

"I begged those treating my father to give him something for the pain. I told them they could keep sending the same bills but to stop torturing him. Only on the last day did they mention palliative care."

In the UK, it has been estimated that there are more than 100,000 volunteers working with hospices (and nearly 500,000 in the US). Few, however, visit patients in their homes. An exception is the Hospice Neighbours scheme run by St Nicholas Hospice in Bury St Edmunds, Suffolk.

Established in 2011, the service helps between 120 and 150 people with terminal illnesses in their homes at any one time, supported by more than 150 volunteers who provide comfort, companionship and assistance with household tasks. The scheme, started by chief executive Barbara Gale, won the Queen's Award for Voluntary Service in 2014.

Gale interviewed 16 volunteers for a paper published in BMJ Supportive and Palliative Care in 2015. She found what chiefly motivated them was the opportunity to "make a difference". Many said they found the patients "inspiring", death became "less scary" and the experience made them think differently about life.

Death and dying are taboo topics in many countries. Essential medicines are in short supply and there is little spending on palliative care research. Dying is seen as a failure of the health system to successfully cure.

The pain of dying is compounded when families desperate to find a cure but ignorant of the poor prognosis are aided by doctors ready to impose high charges for ever more interventionist, but useless, treatments. The result is increased suffering for the patient and often penury for the surviving relatives.

The Kerala model helps protect its citizens from the excesses of the medical system by enlisting the support of the community to comfort the dying, enabling the terminally ill to be cared for at home, where most prefer to be, and providing support to bereaved families in their hour of loss. It is one from which the world can learn.

**Since this article was written, Surendran has died.*

What's Motivating Hundreds in Kerala to Spend Time with Dying Patients?

Photography By S. Ramesh Kurup

Dr.K. Suresh Kumar with Baby Fathima, a volunteer at the Institute of Palliative Medicine.

Sitting in a bare room on the first floor, Dr. K. Suresh Kumar, director of the institute, recounts an experiment that has translated into a movement, bursting out of hospital walls and seeping into the soul of the community. He is wary of individual attention and gently says he is merely part of the core team that began the Pain and Palliative Care Society at Calicut Medical College in 1993. "It is about community ownership," he says.

But as the director of the first World Health Organisation Collaborating Centre for Palliative Care in the developing world, and a pioneer in the field who watched over the unprecedented growth of palliative care, he has become the face of the initiative in the Malabar - an area of southern India lying between the Western Ghats and the Arabian Sea.

THE KERALA MODEL

Suresh Kumar now tours the world giving lessons in the Kerala model of palliative care, replicating and remodeling it for other regions. "We are now disseminating our experiences in Bangladesh, Thailand, Sri Lanka, Jordan, Ethiopia and Seychelles. In India we are taking it beyond Kerala — to Tamil Nadu and are working with a group in Karnataka," he says. The hallmark of palliative care here is the community involvement, says Suresh Kumar, who was an anaesthetist before turning full-time to palliative care.

"All of us have to die," he says. "Only 15 per cent die suddenly. The rest 85 per cent have to tackle pain, debility or chronic illness. The medical establishment is not equipped to address the issues which are not merely physical. After the age of 65, most live with illness or dementia. It is important to build a system to look after these people for our own sake, for we are candidates for this situation down the line." Suresh Kumar, an Ashoka Fellow, believes making palliative care a universal issue has touched a chord with

The Foundation

The Pain and Palliative Care Society was registered in September 1993 with seven members — Dr. M.R. Rajagopal (then the Head of Department of Anaesthesiology, Calicut Medical College), Dr. K. Suresh Kumar, Dr. E.K. Ramadas, Dr. Molly Joseph, Dr. Ganapathi Rao, Thikodiyan and P.K. Ashok Kumar. Four of them were anaesthetists. The society was formed after a series of meetings and different experiences each member had with terminally ill patients. Supported by two volunteers, they started in a small room of the college previously used as a store for nurses' gloves.

people. "What a doctor or a nurse can do is limited. It is everybody's business. Terminal illnesses can strike the very old and the young. One can make a difference by simply sitting and talking to the patient."

The wind beneath the wings of palliative care in Kerala is the numerous volunteers. Those like Suresh Kumar know people come to the initiative with different motives — political, religious or social. The motivation can be anything, he says, as long as "they can make a difference to the way people die." He adds, "Out of the 925 palliative centres in India, 850 are in Kerala."

Vibrant panchayats and local self-government have all given palliative care a boost, he says. With 20 years' engagement in the field, he says, there are many lessons learnt on the way. When they began, palliative care hardly had a blueprint in the developing world. "As doctors, we address the pain of a patient with the needle. But when you start talking you realise there are a lot of other issues to be addressed, many of which are not medical." So what began as an institution-based approach soon expanded to the community.

The first two volunteers of the Society were homemakers. The volunteers take on a two-pronged approach, first handling physical problems like bed sores and second talking to the patient. An important task is to improve the quality of life of the patient, he says. "The task is to reduce the gap between a patient's expectation and his reality. There can be a 40-year-old terminally ill patient who wants to see the wedding of her 12-year-old daughter, which is unlikely. Little by little, we get them to accept reality. Some accept while some keep looking for a cure."

Hamsa lay on the bed, his arm propping up his head. His tall frame nearly filled the entire bed. His wife Jasmine stood behind him, her hand resting on his shoulder. Both smiled and nodded as they listened to the young visitors in their hospital room.

Every few months, Hamsa and Jasmine leave their own home and take up residence in this quiet corner of the Medical College campus in Kozhikode, Kerala. After more than a decade of visits, this room at the Institute of Palliative Medicine is like a second home and the doctors, nurses and staff like family members. Volunteers – high school and college-age men and women – from the area's well-established palliative care network make frequent visits to chat with the couple. Fifteen years ago, life was very different for Hamsa and Jasmine. They were newly married. Befitting his strength and stature, Hamsa was a karate instructor. But an accidental fall from a bridge left him paraplegic. For years, they visited hospitals and specialists searching for a cure, until realising that his paralysis was permanent. The physical and psychosocial care at the palliative care institute

> "After the age of 65, most live with disease or dementia. It is important to build a system to look after these people for our own sake, for we are candidates for this situation down the line."

Photography By S. Ramesh Kurup

helped them to accept his condition and create a new yet still meaningful life.

For the incurably and terminally ill and those who are dying, palliative care is a holistic attempt not only to relieve physical pain but to address the patient's emotional and spiritual well-being. But the effects of palliative care don't only benefit the patient. It is also a way for volunteers and society at large to see death and dying as part of the natural process of living, according to Dr Suresh Kumar. And this is a transformative process for anyone who spends time with a person who may have months, weeks or even just days left. "Once you start talking to the patient, start listening to the patient, you also tend to change. It's an opportunity to experience life from a different point of view. If you keep your ears and eyes open, this has immense potential to change you. I've seen a transformation happening in many people when they go and sit with the patient. They come back and say that they see a different world now," explained Dr Kumar.

The backbone of this vast, decentralised network – one of the largest in the world – is more than 10,000 volunteers, many under 30.

After many days of rain, a deep stream obscured the red dirt of the road. The palliative care team hitched up their clothes as they crossed over a fast-moving section to land in the dry front yard of a modest home.

They had already visited three other patients at various houses on the outskirts of Kozhikode. Anju Sebastian, a staff nurse, checked on an elderly man as his family watched. She asked his son to fetch a thin yellow record book to make notes on his treatment. Two volunteers, Shajan P.B. and Leena P. stood nearby. The old man's face scrunched in pain and he winced as the nurse gave him an injection. Leena held his hand tight to help him keep it still.

"My motivation is to do for others what I can do during my life," she said.

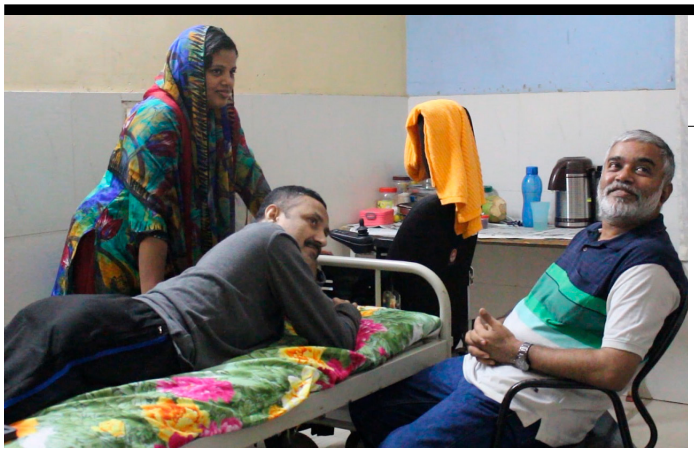
Leena has volunteered for four years. Her son is a volunteer and her now-deceased husband was also a volunteer. Before her retirement, Leena would volunteer after work on Saturdays and also take time off from her job in a bank to help.

"This makes me happy," she continued. Her voice softens a bit as she wonders about her own life: "Tomorrow, we don't know what will happen to us."

Staff nurse Anju Sebastian and volunteers Leena P. and Shajan P.B. make a home visit in Kozhikode, Kerala

This branch of the palliative network cares for 173 patients, with small teams of nurses and volunteers making home visits to treat the terminally ill and offer some conversation and comfort to their often weary families. Someone from the network is available at any time, every day of the year.

"After the age of 65, most live with disease or dementia. It is important to build a system to look after these people for our own sake, for we are candidates for this situation down the line."



Photography By S.Ramesh Kurup

Dr. Suresh Kumar with Hamsa and Jasmine at the Institute of Palliative Medicine. *(Left)*
Staff nurse Anju Sebastian and volunteers Leena P. and Shajan P.B. make a home visit in Kozhikode, Kerala *(Right)*

Central to the success of the volunteer is a feeling of ownership, according to Dr. Kumar. Once they are trained, they are not compelled to participate in the network and can join and leave at will.

"People will do it in a much better way, more creative way, a more innovative way, they'll apply their heart and mind to it when they own it," he said. "This is not the institution or the society or the palliative care network. This is owned by local people. There is no hierarchy. For the work to carry on, there should be more owners, more stakeholders, more people who are interested."

Strangely enough, for a caregivers' network, a seeming self-interest may motivate many of the dedicated volunteers.

"When you have time to spend, don't waste that time," said Shajan, who is now retired and a volunteer for the last year. "I don't have any other motivation other than the self-satisfaction I get from doing this. And one day the question will be asked of me, 'What did I do to help someone else?'"

Dr. Kumar began his journey in palliative care when he was an anaesthesiologist administering nerve blocking injections. Then, realising pain was just one small part of a complex interweaving of issues.

But a hospital, nurse and doctor could really only address the physical issues. Social, emotional and spiritual aspects were best left to volunteers. Working as a team, Dr. Kumar explains, they could alleviate most of the patient's unnecessary suffering.

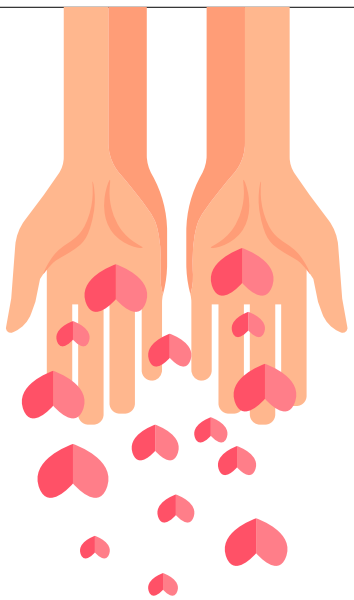
What motivates so many people to spend time with bedridden or dying patients?

"The whole thing is based on empathy," explained Dr. Kumar. "The compassion that you show is with the hope that tomorrow when you are in the same position, somebody else will also show this to you."

Anchoring the network, continued Dr. Kumar, is a rights-based approach to palliative care, as a necessity not a privilege. "You're not offering this because the other guy is a poor chap who is about to die. You're offering it because it's a responsibility as a member of society, to make sure the other person's right is covered." And in his 24th year of spending countless hours with thousands of dying patients, Dr. Kumar reflects on what it means to have a good death.

"Unless you discuss death, you will not be able to realise the value of your own life, how fragile it is and also how valuable it is," he said. "What I've seen so far is that you cannot have a really good death unless you have lived a meaningful life."

In India, Dispensers of Balm Travel to Death's Door



A white van coursed through narrow roads along the monsoon-soaked coastline of Kerala, a state in southwestern India. Inside, Radha Upasarna, a volunteer, and two nurses looked over the roster of patients they would visit, most of whom had cancer or heart disease or were paraplegic.

by **Ankita Rao**

As they bumped along through the area's villages, the women shared snacks, stopped for roadside chai, and sang film songs in Malayalam, Kerala's official language. Around midday the van parked outside a whitewashed home where four out of the five members of the family there were chronically or terminally ill. As they did at each home, Upasarna and the nurses quickly got to work: they checked for bedsores, filled prescriptions, delivered kits of lentils and rice, and often just listened to stories.

Bolstered by pillows on a daybed in the living room, Alikoya Karathattya, a snowy-haired 62-year-old was in high spirits, despite recovering from a recent chemotherapy treatment. Karathattya supported the family by driving a motorized rickshaw until he suffered a stroke in 2008; shortly afterward, his bladder cancer was diagnosed. His daughter Semina, a 34-year-old single mother, was receiving chemotherapy for cancer of the cheek, and his wife, Ayshabhi, was trying to control her diabetes, a widespread problem in Kerala.

Upasarna, a tiny woman wrapped in a cotton sari, sat at Karathattya's bedside, holding his hand and assessing his pain. Working with a nonprofit in the Ernakulum district called Apium, she is one of 15,000 volunteers in Kerala who assist a network of physicians and nurses in extending palliative care to tens of thousands of people who are incurably ill, bedridden or nearing the end of their lives. Upasarna said this work was not only a service to her community, but a way to overcome the loneliness she experienced after her husband died last year.

"It doesn't feel like work," she said. "It's just something I want to do."

Volunteers like Upasarna are the linchpin in Kerala's palliative care system — one that was singled out as "a beacon of hope" in The Economist's "Quality of Death" study in 2010. Kerala's achievement is especially significant at a time when richer Indian states and wealthy countries like the United States are struggling with the same challenge: How can health systems offer the possibility of a dignified death to everyone?

Most people want to die the same way — pain-free and at home, surrounded by family. But in reality, most people in high-income countries die in a hospital, while in many lower-income countries they suffer in pain without medicine or facilities.

Countries take different approaches to their chronically or terminally ill. In Britain, ranked highest this year in The Economist's "Quality of Death Index," the government has invested $703 million on palliative care. In the United States, starting this year under the Affordable Care Act, doctors will be paid for time spent in conversations with patients about end-of-life care. And in Uganda, the health system has invested in nurses, instead of doctors, for pain management and hospice care.

"It's the universal experience," said Ellen Goodman, co-founder of The Conversation Project, an organization that guides people to talk about end-of-life decisions and pain management (pdf). "When you get this right, you get something big right."

In Kerala, it has taken a generation to make that conversation, and palliative care, a household norm and a government priority, according to Dr. Anil Paleri, director of the Institute of Palliative Medicine, a medical and training organization in northern Kerala.

"Suffering is the common denominator," he said. "But this way, the community has a tool in their hands."

The movement in Kerala gained steam in the 1990s. Inspired by Dr. Lucito Desouza, a cancer surgeon in Mumbai who introduced hospice care to India in 1986, two doctors, M.R. Rajagopal and Suresh Kumar, teamed up with an activist friend, Asoka Kumar, with the goal of spreading knowledge and practices about that kind of care across Kerala, where more than 33 million people live – nearly half of them in urban areas, and the rest in 1,400 villages.

Working through the nonprofit organization they founded, the Pain and Palliative Care Society, and later alongside other nonprofit groups, physicians, village leaders and journalists, they spent years taking their message from house to house. Today, about 100 nurses, 50 doctors and 300 nonprofit groups are involved in palliative care in Kerala, according to the World Health Organization.

Kerala had an advantage: The state has a long history of community organizing and unionism. (One of the world's earliest democratically elected Communist governments was in Kerala). It also has the highest literacy rate in India. Paleri, who

Working through the nonprofit organization they founded, the Pain and Palliative Care Society, and later alongside other nonprofit groups, physicians, village leaders and journalists, they spent years taking their message from house to house.

has worked in the movement for almost a quarter-century, said Kerala's history made it easier to start at the village level and trickle up to the government.

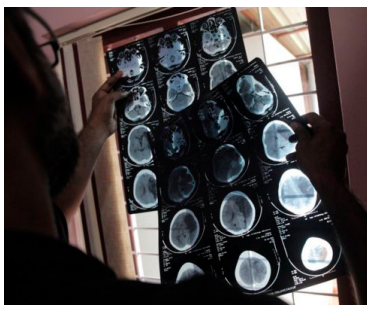
Offering palliative care "had gained momentum as a social movement," he said. "It was hard for the government not to notice." By contrast, the state of Maharashtra, where officials began efforts to spread palliative care 20 years ago, has seen much slower progress, according to Dr. Mary Ann Muckaden, who directs the palliative care program at the Tata Memorial Hospital in Mumbai.

Still, it took time for palliative care to become an official part of Kerala's health system. That happened in 2008, when the state government declared such care a basic right. It allotted 10 percent of the state's share of national health funding to that kind of care, mandating that each government hospital include a doctor and nurse trained in delivering it, and giving local panchayats, or groups of villages, control over their own programs.

"Kerala's model is now setting national standards," said Dr. Kamalakannan Ellangovan, the principal secretary of health for the state government. "We will be strengthening these programs, not only through the elected local bodies, but also some of the well-known NGOs like Pallium India."

In the early years, however, an important piece to the policy puzzle had not fallen into place. Morphine, an opioid used to manage pain, has been highly restricted in India since 1985. Most states still require a specially trained doctor to distribute the drug — a big obstacle to widespread care, given India's shortage of doctors.

But Kerala has made the most progress of any Indian state in expanding access to morphine. In 1995, with guidance from the World Health Organization, the state's lawmakers began allowing palliative care centers to administer the drug orally. In 2008, a new policy went even further: requiring access to morphine where needed for palliative care.



Photography By **Atish Patel**

1. Most Indians who need palliative care simply don't get it and die in excruciating pain.
2. Radha Upasarna (right) assists specially trained physicians and nurses treating patients at home
3. The movement in Kerala gained steam in the 1990s
4. Today, about 100 nurses, 50 doctors and 300 nonprofits groups are involved in palliative care in Kerala

"The sad part is that despite growing awareness, we have not made much progress in terms of the number of people actually getting palliative care in the last 10 years,"

"I have hope, so I keep moving forward."

1. Kerala has more palliative care centres than the rest of India put together
2. Dayal Durlav (right), who is battling oral cancer, has benefitted from a palliative programme in West Bengal
3. Morphine is available in Kerala's hospitals and at homes for patients who need it

The difference between states is now stark: Lotika Rajuwal, 34, is struggling with acute lymphoblastic leukemia and a harsh regimen of chemotherapy. But she can't get morphine for the pain because she lives in West Bengal, rather than Kerala. "When I'm in pain, I feel hopeless," she said. "Especially in the night, the pain is unbearable."

As the Apium van made its way along the Ernakulum coast in Kerala, Upasarna and the nurses monitored the morphine doses for patients struggling with paraplegia or chemotherapy treatments. Alikoya Karathattya, who has gone through six rounds of chemotherapy, said morphine allowed him to sleep at night.

"I'm not as tense as before," he said. "I have hope, so I keep moving forward."

Today, six million people in India need palliative care each year but only a tiny fraction — less than 3 percent — get it.

"The sad part is that despite growing awareness, we have not made much progress in terms of the number of people actually getting palliative care in the last 10 years," Rajagopal said.

As an example for makers of national policy, however, Kerala's model has been gaining traction. In 2012, the government of India issued a policy paper urging states to develop palliative care programs, according to Dr. Sudhir Gupta, a director at the Ministry of Health & Family Welfare in New Delhi. And in 2014, the government took steps to amend the 1985 Narcotics Act to expand access to morphine, although most programs are just getting going, Rajagopal said.

Gupta said that only seven of India's 36 states and union territories had been allocating funds for palliative care so far, but he expects that number to grow. "This is a humble beginning but will certainly pave the way forward," he said.

In "Being Mortal," a manifesto on how to take care of patients at the end of life, Dr. Atul Gawande, a physician and journalist, writes: "The only way death is not meaningless is to see yourself as part of something greater: a family, a community, a society. If you don't, mortality is only a horror."

For families like the Karathattyas, it is the ability to live together, sharing occasions like the Muslim festivals of Eid with their friends and serving snacks to their neighbors, that make the heavy shadow of illness and death more bearable. Rather than being a moving hospital, the little van that comes to their house every month is a reminder that they're not suffering alone.

"There's always pain," Karathattya said, leaning back on his bed. "But there's always happiness."▼▲

by **Dr M R Rajagopal**
Director, WHO Collaborating Centre for Policy And Training on Access to Pain Relief and Founder-Chairman, Pallium

THE CURRENT STATUS OF PALLIATIVE CARE IN INDIA

Less than 1% of India's 1.2 billion population has access to palliative care.

Shutterstock

The efforts by pioneers over the last quarter of a century have resulted in progress, some of which may hold lessons for the rest of the developing world. In recent years, a few of the major barriers have begun to be overcome. The South Indian state of Kerala, which has 3% of India's population, stands out in terms of achieving coverage of palliative care. This has been achieved initially by non-government charitable activity, which catalysed the creation of a government palliative care policy. The nongovernment action, by involving the community, serves to strive for quality of care as the government system improves coverage. On the national level, recent years saw several improvements, including the creation of a National Program for Palliative Care (NPPC) by the government of India in 2012. The year 2014 saw the landmark action by the Indian Parliament, which amended India's infamous Narcotic Drugs and Psychotropic Substances Act, thus overcoming many of the legal barriers to opioid access. Education of professionals and public awareness are now seen to be the greatest needs for improving access to palliative care in India.

Home to one-sixth of the World's population, India has a huge burden of suffering from life-limiting diseases. Less than 1% of its population has access to pain relief and palliative care (1). It has a federal system of Government, health and drug control being responsibilities of its 29 states and six Union Territories. Provision for health care and for opioid access varies from state to state, and as can be expected, this created difficulties especially when one state had to depend on a manufacturer of opioids in another state or when palliative care provisions had to be made a part of Government's health system.

Palliative care was born in India as the Shanti Avedna Sadan in Mumbai, a hospice, in 1986 (2). Over the next five years, it established two more branches, one in Delhi and one in Goa; but patients outside these institutions had no access to palliative care. Two major developments occurred in the 1990s. One was the formation of the Pain and Palliative Care Society (PPCS) in Calicut in the South Indian state of Kerala in 1993. The other was the formation of the Indian Association of Palliative Care in 1994.

PPCS was formed as a registered charitable trust. It followed the work of the author over the previous six years to provide a pain management service in the Government Medical College Hospital. It was obvious that for any person with pain, the suffering goes way beyond pain as a symptom.

They often have other symptoms along with psychological, social and spiritual issues often complicated by impoverishment. Typically, all treatment costs were out of pocket for the patient. It was not easy to watch families getting destroyed, including the generation that follows the patient. This experience and teachings of visiting pioneers, particularly Ms Gilly Burn, a British nurse, brought to light the need for total care of the patient. Two doctors and one layman got together to form PPCS (3). From the point of involvement of this lay person, Mr Asok Kumar, the community was seen as an integral part of palliative care in Kerala.

The organization was started with practically no resources and was done purely based on volunteerism. As more volunteers got involved, PPCS grew as an out-patient service later adding on a home visit programme as the need became apparent. Dr Jan Stjernsward, then Chief of Cancer and Palliative Care at the World Health Organization (WHO), and Dr Robert Twycross, the director of the WHO Collaborating Center, Oxford, were major catalysts in this process.

This duo also catalyzed the formation of the Indian Association of Palliative Care (IAPC). Doctors from various parts of India, with a predominance of anaesthetists involved in pain management, formed the majority of founding members. From the beginning, the association envisaged a multidisciplinary approach and welcomed volunteers as members.

Over the next few years, in the latter part of 1990s, several new palliative care initiatives were started, such as the Guwahati Pain and Palliative Care Society in Assam, the Jivodaya Hospice in Chennai, Cansupport in Delhi, the Lakshmi Palliative Care Trust in Chennai and the Karunasraya Hospice in Bangalore. Some regional cancer centres like Trivandrum, Bangalore and Delhi which already had pain management programmes, also included palliative care in their service. Though every year a few centres were added, the growth was limited considering the enormity of Indian population.

At this time, access to opioids was not easy. Possibly as a response to the global war on drugs, India had formed, in 1985, the Narcotic Drugs and Psychotropic Substances (NDPS) Act (4). This draconian legislation brought in stiff penalties which could even be applicable for minor clerical errors and gradually pharmacies stopped stocking morphine.

This Act also mandated several different licenses, typically four to five, all of which needed to be valid at the same time. Typically again, these licenses had to be issued with the concurrence of several Government departments making the system next to nonfunctional. In the 13 years which followed the enactment of the NDPS Act, morphine consumption in the country fell by an alarming 92% – from around 600kg to a mere 48kg. In 1997, India's per capita consumption of morphine ranked among the lowest in the world (113th of 131 countries). During the same period, global consumption of morphine had increased by 437% (5).

In 1995, Mr David Joranson, the Founder Director of Pain and Policy Studies Group in Madison Wisconsin, another WHO Collaborating Centre, entered into a partnership with palliative care pioneers in India. They analyzed the NDPS Act, identified barriers and submitted a proposal to the Government of India for simplification. Health as well as control of opioid medicines are both "state subjects" in India's federal system of governance; it was necessary for each state to act independently (6).

In 1998, the pharmacologist Ravindra Ghooi approached the Delhi High Court seeking access to morphine for his mother in pain from cancer. The High Court passed an order expressing sympathy for the cause and asking Delhi Government to take prompt action. Following this and representations from the Pain and Policy Study Group, the Government of India prepared a model rule for the modification of existing state regulations and asked all states to change their regulations accordingly. By India's constitution, the state government is not obliged to follow the central government in this matter. Most states did nothing. The collaborators, namely the Pain and Policy Studies Group and Indian palliative care activists worked together through state governments. Eighteen workshops were organized in various states resulting in many of them changing the state regulations following the central government instruction.

Of these, Kerala showed a remarkable improvement in access to opioids during the subsequent years. Some states like Tamil Nadu, Karnataka and Delhi showed a modest improvement while in most other states the change was minimal. It appears that wherever there was existing palliative care activity resulting in a demand for pain relief and for morphine, the amendment of the state rules did improve the situation. It also became very clear that without such activity, the regulatory reforms make no impact.

Since the beginning of the Pain and Palliative Care Society in 1993, the community's involvement in palliative care was steadily growing in Kerala. By the turn of the century, this was given structure and growth with the name "Neighborhood Networks in Palliative Care" (NNPC) (7). An international conference on community participation in palliative care gave great visibility to NNPC, the media were supportive, public interest grew and truly the people of Kerala embraced palliative care. Trained volunteers are involved in palliative care, organizing palliative care services, doing nursing chores, educating families in care and in spreading awareness. Questions have been raised about the quality of services that such community-based services can give (8), but the system has indeed succeeded in providing a link between the patient and medical institutions (9), adding the "meso" element of the social capital that is being eroded in much of the world (10).

In 2003, the charitable organization called Pallium India was created to improve access to palliative care outside Kerala. Since then, palliative care centres have been established in 11 states where until then practically no such service existed. Whether they followed the complicated old "narcotic" rules or the simpler new ones in some states, access to morphine became a reality in all these centres soon after the initiative.

In 2005, Pallium India submitted a representation to the Government of Kerala and to the Government of India for the creation of palliative care policy. The Kerala state government acted on it and created a task force to formulate a draft policy. Many meetings and discussions later, in 2008, the Government of Kerala declared a palliative care policy integrating it into health care (11). This has since then been a huge success so that today each of about 900 local selfgovernment institutions called panchayats employ one nurse trained in palliative care. The funds for this came through the National Rural Health Mission which, by the very function of its being, had to serve rural areas and therefore had to restrict their activities to community health centres and primary health centres. No budget allocation, unfortunately, was made for much of the activities envisaged in the palliative care policy, namely, the creation of palliative care centres in district hospitals and in tertiary referral centres.

This has resulted in the anomalous situation in which the patient has to go through intolerable pain and other distress for weeks, months or years

THE GOVERNMENT OF INDIA FORMED A COMMITTEE IN 2006

The Government of India formed a committee in 2006 involving experts from various parts of the country to create a national policy for palliative care. The committee worked together to create a draft policy document. However, following a change in one official, this did not see the light of the day. Representations to the Medical Council of India and Indian Nursing Council for the incorporation of palliative care into the undergraduate curriculum also were unsuccessful during that decade.

of treatment in major hospitals, to get palliative care only in the last few weeks at home through the primary health centre. The monitoring committees planned in the state policy were also not established and hence there was no forum for review and modification of strategy.

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Following the initial growth in the 1990s, there appeared to be a plateauing of improvements in palliative care access at the national level in India. In 2007, palliative care activists took the matter to the Supreme Court of India. The petitioners were the Indian Association of Palliative Care (represented by the Chairman of its Opioid Availability Committee), Dr Ravindra Ghooi who had earlier taken the matter to Delhi High Court and Ms Poonam Bagai, a cancer survivor and founder of Cankids, a child cancer organization and Vice Chair of Pallium India. Two Supreme Court lawyers, Mr Ashok Chitale (one of the trustees of Pallium India) and Niraj Sharma, gave their services gratis for this purpose. The Supreme Court accepted the case in file which in itself was a success because only about 7% of all submitted petitions are usually accepted by the Supreme Court. The petitioners argued that lack of access to palliative care violated an individual's fundamental right to life with dignity that was guaranteed by the constitution of India and asked essentially for three things:

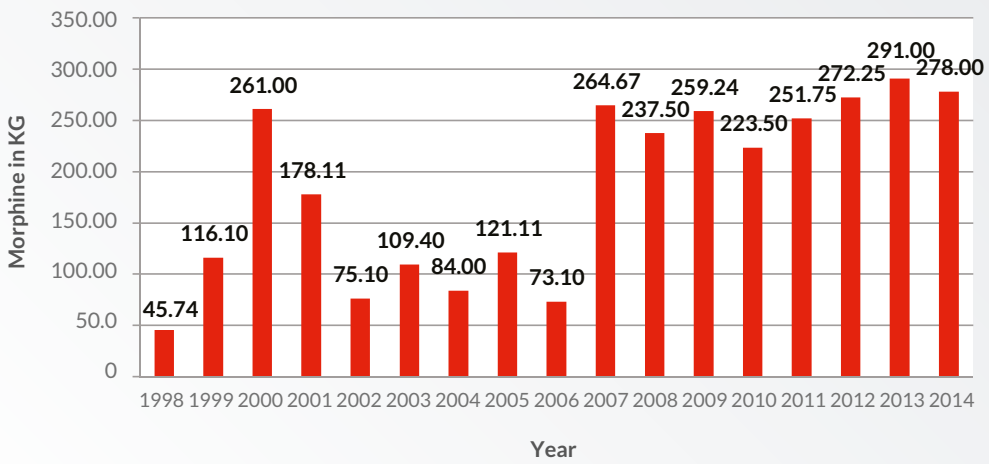
- the central and state governments should develop palliative care policies;
- the NDPS Act of India must be simplified ensuring access to opioids for those who need them; and
- palliative care must be made a part of undergraduate medical and nursing curricula. During periodic hearings of the case which is yet to be settled, the court's questions to the central and state governments have been a significant factor in catalyzing action.

A further development occurred in Kerala between 2005 and 2008. Acting on a request from Pallium India, the Government of Kerala appointed a committee to draft the Palliative Care Policy for the state. The policy came into being in April 2008. It accepted palliative care as an essential part of health care in the state. However, the Government made no budget allocation for palliative care and the implementation of palliative care was left to the National Rural Health Mission (NRHM). This has been largely successful.

Kerala, though it covers only 1% of India's land mass and cotains 3% of India's population, has now more palliative care services than the rest of the country put together. In a study published in 2008 (12), McDermott E et al found Kerala to have 83 palliative care services as against 139 in the whole of the country. As of 2014 in Kerala, more than 170 institutions stock and dispense oral morphine. International advocacy has always had a major role in supporting palliative care efforts in India. In 2009, the Human Rights Watch published the results of their research, namely "Unbearable pain: India's obligation to ensure palliative care" (13). One of its recommendations was to International Narcotics Control Board (INCB) to plan a factfinding mission to India, with the availability of controlled substances for medical and scientific purposes as one area of focus. INCB did take up the suggestion and a delegation came to India and interacted with Government officials and representatives of palliative care associations. Its recommendations had a major role in persuading further government action. India, till around this time, did not have a proper system in place for assessing opioid consumption and reporting it to INCB and for many years, it either failed to send reports or sent clearly inaccurate reports. Following the INCB visit, the Government put into place a new functional system and from that year, we have had reasonably reliable statistics on consumption of opioids.

Recognizing that education of professionals was the key to improvement of palliative care in the country, palliative care activists had, from the beginning, conducted educational programmes. After several trials with courses of two, four and six weeks, the six week courses in Palliative Medicine and Nursing started by PPCS became widely popular and has been replicated in several institutions in the country. A oneyear fellow-

FIGURE 1: CONSUMPTION OF MORPHINE, 1998–2014



ship programme was also started by several institutions, though none had the approval of the Medical and Nursing Councils of India.

Continued advocacy by the palliative care community bore fruit in 2010, when the Medical Council of India accepted palliative medicine as a medical specialty and announced a postgraduate course in the subject.

Subsequently, in 2012, the first Doctor of Medicine (MD) course was started at the Tata Memorial Hospital in Mumbai with two places per year. Unfortunately, most of the palliative care service available at this time was in the charitable sector, and there are not many academic institutions with the capacity to start palliative care courses.

Designation of the Institute of Palliative Medicine at Calicut, Kerala, as a WHO Collaborating Centre for Community Participation in Palliative Care and Long Term Care in 2010 and of Pallium India's Trivandrum Institute of Palliative Sciences (TIPS) as a WHO Collaborating Centre for Training and Policy on Access to Pain Relief in 2012 were two significant events contributing to further progress.

In 2013, following his attendance of a side-event held at the World Health Assembly in Geneva organized by Human Rights Watch and others, the Principal Secretary of Health of Government of India, Mr Keshav Desiraju, called a meeting to create a palliative care strategy for the country's five-year plan. Health ministry officials and palliative care activists worked together to create this strategy, the National Program in Palliative Care (NPPC), which was declared in 2012. Unfortunately, the proposed budget allocation did not materialize and hence, the implemented part of NPPC turned out to be a skeleton of the envisaged programme, with about 2% of the originally proposed budget, some money being allocated to a minority of states by the Government of India for implementing some of the parts of the NPPC.

Pallium India found the resources and organized a working group to create an implementation framework for NPPC, spelling out strategies, action items, and timelines. This was submitted both to the WHO India Office with a request for undertaking operational analysis and to the Ministry of Health. Though the operational analysis did not materialize, the document continues to be available for guidance in implementation of NPPC (14).

In addition to implementing the establishment of palliative care services, the NPPC had recommended undergraduate medical and nursing education as one of its targets. Pallium India subsequently organized a working group involving experts from various parts of the country, Ministry of Health officials and representatives of the Medical Council. The committee, over a six-month period of time, developed curricula for undergraduate medical and nursing education, and prepared a scheme for its inclusion in the existing medical and nursing curricula. Action on this by the respective councils is yet to happen.

The Pain and Policy Studies Group at Madison, Wisconsin, in 2012, included three fellows from India in its fellowship programme and also invited two officials from the Government of India, Mr Rajesh Nandan Srivastava, Director of Narcotics in the Department of Revenue, and Dr Sudhir Gupta, Deputy Director General of Health Services.

Their interactions had a positive impact, and in the subsequent year, the department of revenue, working with palliative care activists, developed a draft docu-

ment for amendment and simplification of the existing NDPS Act. The voluntary services of a lawyer, Ms Tripti Tandon of the nongovernmental organization "The Lawyers' Collective" had given precious input to the drafting of this document. The Amendment would have the effect of uniform NDPS rules for the whole country, as it would shift the powers of legislation from the state government to the central government. The resultant document was placed before the Parliament of India in 2013. It was on the agenda for all three sessions of the Indian Parliament during 2013, but never got the required priority to be dealt with, despite advocacy campaigns by the palliative care community. Finally, during an extended winter session of the Parliament in February 2014, the Parliament passed the NDPS Amendment Act. The new Act transferred the powers for legislation on "essential narcotic drugs" (ENDs) from the state governments to the central Government. It is necessary now for the Government of India to announce the uniform simplified state rules.

These rules and the standard operating procedures were already prepared by the government, in consultation with the department officials with the support of Ms Tripti Tandon of Lawyers' Collective and palliative care activists. In May 2015, the Government of India concluded the process with notifications regarding the rules to be followed by the state governments. It is up to palliative care activists and state governments to ensure that the amended rules are implemented.

If we take morphine consumption in the country as the index of access to palliative care, there has been little progress in last few years as can be seen in Figure 1 (15).

Considering that the official reporting of data to INCB has been erratic until recently, this graph has used the officially communicated record of the quantity of morphine sold by the Government opium and alkaloid factory to manufacturers of formulations of morphine. Considering that morphine is the only oral opioid belonging to step III of the WHO analgesic ladder, these figures are likely to be representative, with some exceptions. In 2000, the peak was caused by a large scale purchase of morphine by the Government of India using funds from World Health Organization for free distribution to Regional Cancer Centres. We know for a fact that the bulk of it was never used and was eventually destroyed after expiry date. The drop in consumption from 2002 to 2006 was caused by a breakdown in the Government Opium and Alkaloid Factory, following which production of morphine was reduced.

There has been a lot of progress in palliative care in India, but the fact remains that despite the passing of almost a quarter of a century of palliative care activity in the country, even today palliative care reaches only about 1% of the people in India.

SUMMARY

There has been a lot of progress in palliative care in India, but the fact remains that despite the passing of almost a quarter of a century of palliative care activity in the country, even today palliative care reaches only about 1% of the people in India. If we take per capita consumption of opioids belonging to the step III of the WHO ladder as a criterion, this has been on a plateau for many years now.

India is still at that phase when it seems poised to leap forward, though the dynamism is yet to be manifest, in the following three areas:

- The NDPS Amendment Act is simplified now, but needs to be implemented by state governments. Nongovernment palliative care organizations, who already are struggling with paucity of resources, will have to take on the onerous task of finding funds and personnel for catalyzing government action, state by state, through 29 states and

six union territories.

- Despite a submission before the Supreme Court of India expressing willingness to incorporate palliative care in undergraduate curricula, and despite the palliative care community preparing the curricula and giving a framework for implementation, the Medical Council of India and the Indian Nursing Council are yet to act on the matter.
- Though the National Program in Palliative Care was created in 2012, due to lack of budget allocation, only a tiny part of the programme has been implemented. Even for the part that is funded, considerable catalytic work is needed with the state governments to ensure that proper plans are made and implemented.

In short, some major barriers to access to palliative care in India have been overcome, but implementation of created policies and laws still requires massive efforts by both the government system and non-government organizations. The non-government organizations do have the commitment but would need international support to effectively facilitate government activity. The recent declaration by the World Health Assembly (16) asking all member states to integrate palliative care with routine health care comes as a major tool in advocacy and hopefully will boost the current efforts. ▾▴ing of almost a quarter of a century of palliative care activity in the country, even today palliative care reaches only about 1% of the people in India. If we take per capita consumption of opioids belonging to the step III of the WHO ladder as a criterion, this has been on a plateau for many years now.

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Research

Comparison of Risk Scoring Systems for Patients Presenting with Upper Gastrointestinal Bleeding: International Multicentre Prospective Study *– Page 34*

Relative Effectiveness of Insulin Pump Treatment Over Multiple Daily Injections and Structured Education During Flexible Intensive Insulin Treatment for Type 1 Diabetes: Cluster Randomised Trial (Repose) *– Page 44*

The primary outcomes were a change in glycated haemoglobin (HbA1c) values (%) at two years in participants with baseline HbA1c value of ≥7.5% (58 mmol/mol), and the proportion of participants achieving an HbA1c value of <7.5%. Secondary outcomes included body weight, insulin dose, and episodes of moderate and severe hypoglycaemia. Ancillary outcomes included quality of life and treatment satisfaction.

Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study

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Abstract

Objective To compare the predictive accuracy and clinical utility of five risk scoring systems in the assessment of patients with upper gastrointestinal bleeding.
Design International multicentre prospective study.
Setting Six large hospitals in Europe, North America, Asia, and Oceania.
Participants 3012 consecutive patients presenting over 12 months with upper gastrointestinal bleeding.
Main outcome measures Comparison of pre-endoscopy scores (admission Rockall, AIMS65, and Glasgow Blatchford) and post-endoscopy scores (full Rockall and PNED) for their ability to predict predefined clinical endpoints: a composite endpoint (transfusion, endoscopic treatment, interventional radiology, surgery, or 30 day mortality), endoscopic treatment, 30 day mortality, rebleeding, and length of hospital stay. Optimum score thresholds to identify low risk and high risk patients were determined.
Results The Glasgow Blatchford score was best (area under the receiver operating characteristic curve (AUROC) 0.86) at predicting intervention or death compared with the full Rockall score (0.70), PNED score (0.69), admission Rockall score (0.66, and AIMS65 score (0.68) (all P<0.001). A Glasgow Blatchford score of ≤1 was the optimum threshold to predict survival without intervention (sensitivity 98.6%, specificity 34.6%). The Glasgow Blatchford score was better at predicting endoscopic treatment (AUROC 0.75) than the AIMS65 (0.62) and admission Rockall scores (0.61) (both P<0.001). A Glasgow Blatchford score of ≥7 was the optimum threshold to predict endoscopic treatment (sensitivity 80%, specificity 57%). The PNED (AUROC 0.77) and AIMS65 scores (0.77) were best at predicting mortality, with both superior to admission Rockall score (0.72) and Glasgow

Blatchford score (0.64; P<0.001). Score thresholds of ≥4 for PNED, ≥2 for AIMS65, ≥4 for admission Rockall, and ≥5 for full Rockall were optimal at predicting death, with sensitivities of 65.8-78.6% and specificities of 65.0-65.3%. No score was helpful at predicting rebleeding or length of stay.

Conclusions The Glasgow Blatchford score has high accuracy at predicting need for hospital based intervention or death. Scores of ≤1 appear the optimum threshold for directing patients to outpatient management. AUROCs of scores for the other endpoints are less than 0.80, therefore their clinical utility for these outcomes seems to be limited.

Trial registration Current Controlled Trials ISRCTN16235737.

INTRODUCTION

Upper gastrointestinal bleeding is a common cause of admission to hospital worldwide, with a UK incidence of 103-172 per 100 000 adults each year and mortality of 8-14%.[1 2 3] Many risk assessment scores have been developed to predict clinically relevant outcomes, including mortality, need for hospital based intervention, rebleeding, and length of hospital stay.[4 5 6 7 8 9] Several of these, including the Rockall score and recently described progetto nazionale emorragia digestive (PNED) score require endoscopy before calculation.[4 5] The Rockall score has been widely reported and it has been suggested that the PNED score is superior to it, although it has not been externally validated.[5] Other endoscopy based scores have been described but are not appropriate for unselected patients with upper gastrointestinal bleeding, have not been externally validated, or have been shown to be inferior to the Rockall score or PNED score.[10] However, requiring endoscopy to calculate a score might delay risk assessment in some healthcare settings, as there can be considerable delays in performing endoscopy out of hours or on weekends.[11]

Recently, much interest has been shown in pre-endoscopic risk scores for upper gastrointestinal bleeding, which can be calculated shortly after presentation to hospital. The most widely studied scores are the abbreviated "admission" Rockall score, Glasgow Blatchford score, and recently described AIMS65 (albumin level <30 g/L (A), international normalised ratio >1.5 (I), altered mental status (M), systolic blood pressure ≤90 mm Hg (S), and age >65 years (65)) score.[7 8] These scoring systems use clinical, haemodynamic, and (for Glasgow Blatchford and AIMS65 scores) readily available laboratory variables. Some studies have suggested that these scores could be used to identify patients at very low risk who could be managed as outpatients.[12 13 14] Studies have also suggested that these scores could identify patients at higher risk who might require urgent endoscopy or management in high dependency or intensive care units.[15 16]

Several studies have compared scores in their ability to predict various outcomes.[12 16 17 18 19] Although the Glasgow Blatchford score seems useful in identifying very low risk patients in the UK many studies have been small and single centre and no international study has compared all the commonly used scores. Recent guidelines have suggested use of risk scores for patients with upper gastrointestinal bleeding, but uncertainty remains about their exact role in clinical practice.[20 21 22 23] In this prospective international study we compared five endoscopic and pre-endoscopic risk assessment scores for their ability to predict clinically relevant endpoints. In addition we assessed the clinical utility of these scores, by determining optimal thresholds for identifying patients at very low risk who could be managed as outpatients, and higher risk patients who might require specific management strategies aimed at improving outcome.

METHODS

The study was undertaken in Yale-New Haven Hospital (USA), Glasgow Royal Infirmary (Scotland), Royal Cornwall Hospital Truro (England), Odense University Hospital (Denmark), Singapore General Hospital (Singapore), and Dunedin Hospital (New Zealand).

The predetermined clinical endpoints were the composite endpoint of need for hospital based intervention (red blood cell transfusion, endoscopic treatment, interventional radiology, or surgery) or death, endoscopic treatment, 30 day mortality, rebleeding within seven days, and length of hospital stay.

Patient management

Patients were included if they presented to the hospital with evidence of upper gastrointestinal bleeding defined by haematemesis, coffee-ground vomiting, or melaena. We excluded patients who developed upper gastrointestinal bleeding while an inpatient for another reason.

All patients presenting to each hospital with upper gastrointestinal bleeding were initially assessed in the emergency department or acute assessment unit. Two centres (Glasgow and Odense) had a policy of non-ad-

mission for those with Glasgow Blatchford scores of 1 or less, and one centre (Truro) for those with Glasgow Blatchford scores of 2 or less and aged less than 70 years, unless required for other reasons. Outpatient endoscopy was arranged in all three centres. Proton pump inhibitors (PPIs) were not routinely given to all admitted patients before endoscopy. The practice in all centres was to perform endoscopy within 24 hours in all admitted patients where possible. After endoscopy, the policy in all centres was to administer high dose PPIs by intravenous bolus followed by infusion to patients with high risk ulcer stigmata who required endoscopic treatment, and to other selected patients depending on clinical judgment.[20 21 22 23] For patients with suspected variceal bleeding, the policy in all centres was to give intravenous vasopressors and antibiotics before endoscopy.[21 24]

The endoscopic practice in all centres for patients with high risk stigmata of non-variceal bleeding was by injection of dilute adrenaline (epinephrine) into and around the bleeding point, thermal contact or clips, or both, but not adrenaline alone.[20 21 22 23] Band ligation or injection of tissue glue with or without transjugular intrahepatic portosystemic stent shunt was performed in cases of oesophageal or gastric variceal bleeding, respectively.[21 24] In line with recent evidence and guidelines, the policy was to administer red blood cells at a haemoglobin threshold of 70-80 g/L (7-8 g/dL), or as guided by the clinician in patients with severe haemorrhage.[24 25]

Data collection

At each centre, data on consecutive, unselected patients presenting to the hospital with upper gastrointestinal bleeding were collected over a 12 month period between March 2014 and March 2015. Data on patients managed as outpatients in Glasgow, Truro, and Odense were also included. A dedicated research nurse, doctor, or medical student collected data at each site. The data collected included patient characteristics and haemodynamic and laboratory variables at presentation necessary to calculate the full Rockall, admission Rockall, Glasgow Blatchford, AIMS65, and PNED scores (see supplementary table 1). Endoscopic findings were recorded.

Blood transfusion, endoscopic treatment, and interventional radiology or surgery were recorded, as was rebleeding within seven days, as previously defined (see supplementary table 2),26 30 day mortality, and length of hospital stay. Supplementary table 3 shows the collected data.

Statistical analysis

We compared each scores' ability to predict the predetermined outcomes, using calculation of area under the receiver operating characteristic curves (AUROCs) and 95% confidence intervals. All comparisons were based on patients in whom all the compared scores could be calculated. The AUROCs were considered dependent and were compared based on the method by Delong et al.[27] The optimal score thresholds to predict patients at very low risk who are potentially suitable for outpatient management were identified based on a sensitivity of 95% or more. For the other outcomes, we considered thresholds associated with maximum Youden index[28] to be optimal. In addition, the performance of the scores was assessed by calculation of sensitivity, specificity, positive predictive value, negative predictive value, and proportion of patients classified as low risk or high risk. We calculated rates of transfusion, endoscopic treatment, and mortality for those classified as low risk. Proportions were compared using Pearsons 2 test and Fischer's exact test. Medians were compared using the Mann-Whitney U test and the Kruskal-Wallis equality of populations rank test.

We aimed for an adequate sample size to compare all the predetermined outcomes. Existing data indicated that the highest power was needed for comparative analyses on mortality. Therefore assuming AUROCs of 0.86 for mortality, 0.78 for AIMS65 score8 20 and full Rockall score,[10 21] with an α of 5%, power of 90%, rank correlation of 0.5, and mortality of 5%,13 we determined that we required a sample size of 2814 patients. We used a two tailed significance level of 5%. Data analysis was undertaken using STATA 11.0 (StataCorp, College Station, TX).

Only the local principal investigator and dedicated nurse, junior doctor, or medical student had access to the identifiable data from their centre, with the anonymised data sent to SBL and AJS for central analysis. Our report follows STROBE guidelines.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Table 1. Characteristics, treatment, and outcome of patients (n=3012). Values are numbers (percentages) unless stated otherwise

Characteristics	Data
Median (95% CI) age (years)	65 (24 to 90)
Men	1750 (58)
Comorbidity:	
Ischaemic heart disease	580 (19)
Liver disease	453 (15)
Renal failure	266 (9)
Any malignancy	430 (14)
Median (95% CI) systolic blood pressure (mm Hg)	125 (90 to 170)
Median (95% CI) pulse	89 (61 to 126)
Median (95% CI) haemoglobin level (g/L)	112 (58 to 162)
Findings at endoscopy:	
Nothing abnormal	297 (14)
Erosive disease*	583 (28)
Gastric/duodenal ulcer	572 (28)
Variceal bleeding	143 (7)
Upper gastrointestinal cancer	70 (3)
No endoscopy	937 (31)
Median (95% CI) time to endoscopy (hours)	19 (3 to 72)
Treatment:	
Median (95% CI) No of transfusions	1.3 (0 to 6)
Endoscopic treatment	574 (19)
Surgery/interventional radiology	37 (1.2)
Outcome:	
No need for intervention, or death	1636 (55)
Rebleeding	144 (5)
Mortality	208 (7)
Mean (95% CI) score:	
Glasgow Blatchford	6.6 (0 to 14)
AIMS65	1.0 (0 to 3)
Admission Rockall	2.7 (0 to 5)
Full Rockall	3.9 (1 to 7)
PNED	3.0 (0 to 8)

*Oesophagitis, gastritis, or duodenitis.

RESULTS

Patient characteristics and baseline scores

A total of 3012 patients were included in the study, with 2868 (95%) followed up for 30 days. The median age of patients was 65 years, and 58% were men. Table 1 shows the patients' characteristics, endoscopic findings, interventions, and outcomes. A total of 1348 (45%) patients needed hospital based intervention or died within 30 days. Endoscopic treatment was performed in 574 (19%), 37 (1.2%) required interventional radiology or surgery, and 144 (5%) rebled within seven days. The median length of stay was 3 days (95% confidence interval 0 to 16 days), and 30 day mortality was 7%. Overall, the mean Glasgow Blatchford score was 6.6 (95% confidence interval 0 to 14), mean AIMS65 score was 1 (0 to 3), mean admission Rockall score was 2.7 (0 to 5), mean full Rockall score was 3.9 (1 to 7), and mean PNED score was 3.0 (0 to 8). Supplementary table 4 show these data by centre.

Comparison of scores' ability to predict outcomes Intervention or mortality

The Glasgow Blatchford score had the highest discriminative ability (AUROC 0.86) at predicting need for intervention or death compared with the PNED score (0.69; P<0.001), full Rockall score (0.70; P<0.001), admission Rockall score (0.66 P<0.001), and AIMS65 score (0.68; P<0.001) (table 2 and fig 1). The Glasgow Blatchford score performed consistently well in all centres, with AUROCs ranging between 0.85 and 0.91 (see supplementary table 5). However, performance of AIMS65 and the full Rockall scoring systems varied by centre, with AUROCs ranging from 0.54-0.75 and 0.57-0.79, respectively. AUROCs among centres were 0.59-0.72 for admission Rockall score and 0.70-0.76 for PNED score (see supplementary table 5).

Tables 3 shows the ability of the three pre-endoscopic scores to predict patients at very low risk who did not require intervention and survived at optimal cut-offs. A Glasgow Blatchford score of 1 or less had a sensitivity of 98.6%, specificity of 34.6%, positive predictive value of 96.6%, and negative predictive value of 56.0% for this combined endpoint. Intervention or death was recorded in 3.4% of the 564 patients with Glasgow Blatchford scores of 1 or less, compared with 14% of the 436 patients with admission Rockall scores of 0, and 25% of the 865 patients with AIMS65 scores of 0 (see table 3). The most common intervention in those with Glasgow Blatchford scores of 1 or less was blood

Table 2. Discriminative ability of evaluated scoring systems

Outcome by scoring system	AUROC (95% CI)
Intervention or death:	
Glasgow Blatchford	0.89 (0.87 to 0.90)
AIMS65	0.70 (0.68 to 0.72)
Admission Rockall	0.69 (0.67 to 0.71)
Full Rockall	0.69 (0.67 to 0.71)
PNED	0.71 (0.70 to 0.73)
Need for endoscopic treatment:	
Glasgow Blatchford	0.75 (0.73 to 0.77)
AIMS65	0.63 (0.60 to 0.65)
Admission Rockall	0.61 (0.59 to 0.64)
Rebleeding:	
Glasgow Blatchford	0.70 (0.66 to 0.74)
AIMS65	0.62 (0.57 to 0.66)
Admission Rockall	0.62 (0.57 to 0.66)
Full Rockall	0.63 (0.58 to 0.68)
PNED	0.85 (0.83 to 0.88)
Mortality:	
Glasgow Blatchford	0.69 (0.66 to 0.72)
AIMS65	0.78 (0.75 to 0.81)
Admission Rockall	0.76 (0.73 to 0.79)
Full Rockall	0.72 (0.68 to 0.77)
PNED	0.79 (0.76 to 0.82)

AUROC=Area under receiver operating characteristic curve.
Values represent all patients with available data.

Figure 1

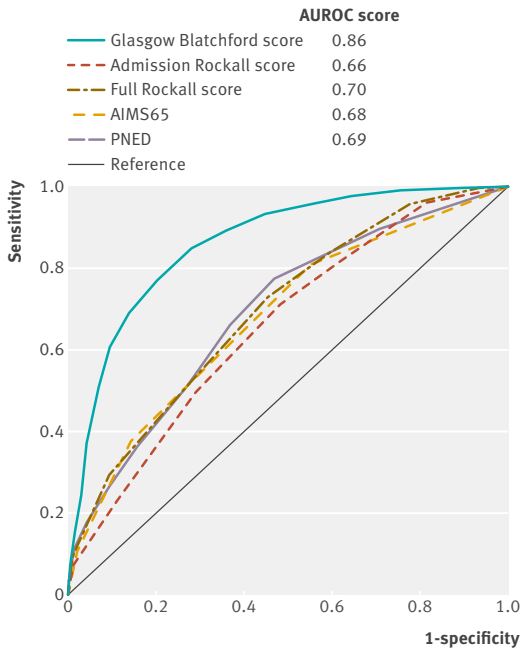

Fig 1 | Comparisons of scores in prediction of need for any intervention (transfusion, endoscopic treatment, interventional radiology or surgery) or 30 day mortality (n=1704). All figures compare patients with complete data for all compared scores. AUROC=area under the receiver operating characteristic curve

transfusion, with endoscopic treatment performed in 1.4% and overall mortality 0.4%. The proportion of low risk patients defined by Glasgow Blatchford scores of 1 or less varied by site, ranging from 9% in Dunedin to 31% in Glasgow.

Endoscopic treatment

The Glasgow Blatchford score (AUROC 0.75) performed better in predicting need for endoscopic treatment than the other pre-endoscopic scores: AIMS65 (0.62) and admission Rockall (0.61; P<0.001 for both; fig 2). The Glasgow Blatchford scoring system performed equally well in predicting this endpoint in all centres (see supplementary table 5). A threshold Glasgow Blatchford score of 7 or more was best at predicting endoscopic treatment, with a sensitivity of 80.4%, specificity of 57.4%, positive predictive value of 31.3%, and negative predictive value of 92.4% (table 4).

MORTALITY

The AIMS65 score (AUROC 0.77) and PNED score (0.77) had similar discriminative abilities for predicting 30 day mortality (table 2α and fig 3). The PNED score was better at predicting mortality than the admission Rockall score (0.72; P=0.05), full Rockall score (0.72; P=0.05), and Glasgow Blatchford score (0.64; P<0.001). AIMS65 was better at predicting mortality than the Glasgow Blatchford score (P<0.001) and admission Rockall score (P=0.05). Furthermore, the AIMS65 score had a near statistically significantly higher AUROC compared with the full Rockall score (P=0.06). The best score thresholds at predicting 30 day mortality were 4 or more for PNED, 2 or more for AIMS65, 4 or more for admission Rockall, 5 or more for full Rockall, and 5 or more for Glasgow Blatchford. Table 5 shows the predictive ability of all five scores to identify high risk patients.

Rebleeding and length of stay

PNED, which includes rebleeding in the score, was best (AUROC 0.85) at predicting rebleeding compared with the Glasgow Blatchford score (0.66; P<0·001), full Rockall score (0.64; P<0·001), admission Rockall score (0.62; P<0.001), and AIMS65 (0.60; P<0.001). The Glasgow Blatchford score was better at predicting rebleeding compared with the AIMS65 score (P=0.04). All risk scores had poor discriminative abilities for predicting length of stay for more than three days. The AUROCs were 0.68 for PNED score, 0.65 for full Rockall score, 0.64 for admission Rockall score, 0.63 for Glasgow Blatchford score, and 0.61 for AIMS65 score.

Missing values

Values were missing for the Glasgow Blatchford score (n=80), AIMS65 score (n=511), admission Rockall score (n=43), full Rockall score (n=1000), PNED score (n=178), comorbidity (n=1), systolic blood pressure (n=41), pulse (n=38), haemoglobin concentration (n=28), findings at endoscopy (n=2), true low risk status (n=28), total units of blood transfused (n=23), performance of endoscopic treatment (n=20), performance of surgery or interventional radiology (n=5), rebleeding (n=51), and mortality (n=1). Comparisons of AUROCs were undertaken using complete case analysis. Data for all pre-endoscopic scores (admission Rockall, AIMS65, Glasgow Blatchford) were available in 2495 (83%) patients, and data for both post-endoscopy scores (full Rockall, PNED) in 1922 (64%). Data for the endoscopic treatment endpoint and the composite endpoint were available in 2478 (82%) and 1707 (57%) patients, respectively.

Patients with missing values for full Rockall or AIMS65 had lower Glasgow Blatchford scores (mean: 4.8 (95% confidence interval 0.0 to 13.0) v 7.8 (1 to 14); P<0.001), PNED scores (mean: 2.6 (0.0 to 7.0) v 3.2 (0.0 to

Table 3. Outcomes at optimal thresholds of Glasgow Blatchford score, AIMS65, and admission Rockall score in prediction of need for intervention, or death. Values are numbers (percentages) unless stated otherwise

Scoring system	Cut-off	Low risk patients*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Received transfusion	Endoscopic treatment	Surgery or interventional radiology†	Mortality‡
Glasgow Blatchford	≤1	564 (19.2)	98.6	34.6	96.6	56.0	10 (1.8)	8 (1.4)	2 (0.4)	2 (0.4)
AIMS65	0	865 (34.6)	81.5	49.9	74.7	59.9	165 (19)	107 (12)	9 (1.0)	6 (0.7)
Admission Rockall	0	436 (14.7)	95.6	23.4	86.5	50.9	41 (9.4)	29 (6.7)	0 (0)	1 (0.2)

PPV=positive predictive value; NPV=negative predictive value.
Several patients fulfilled more than one endpoint.
*Classified as low risk according to risk scoring system.
†Number (%) of patients needing surgery, or arterial embolisation among patients classified as low risk.
‡Number (%) of patients dying within 30 days from presentation among patients classified as low risk.

8.0); P<0.001), and admission Rockall scores (mean: 2.5 (0 to 5) v 2.9 (0 to 5); P<0.001) compared with patients without missing data for these two scores. Patients with missing values for full Rockall score or AIMS65 less often underwent hospital based intervention or died (27% v 58%; P<0.001) but had similar 30 day mortality (7.5% v 6.5%; P=0.32) compared with patients without missing values for these scores. Analysis from the centre with the lowest missing data on AIMS65 and full Rockall scores (Odense, at 1.9% and 8.3% respectively) showed that the Glasgow Blatchford score had a higher discriminative ability to predict need for intervention, or death, and need for endoscopic treatment, compared with all other risk scores (P<0.001; see supplementary table 5).

Figure 2

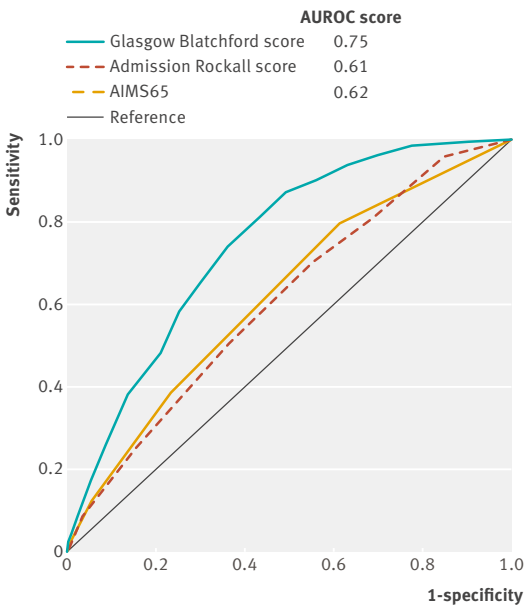

Fig 2 | Comparisons of pre-endoscopic scores in prediction of need for endoscopic treatment (n=2478). AUROC=area under the receiver operating characteristic curve

DISCUSSION

This international multicentre study shows that the Glasgow Blatchford score is an accurate risk score at all sites for predicting need for clinical intervention, or death, after upper gastrointestinal bleeding. Although scores for AIMS65 and PNED are the best for predicting mortality and the Glasgow Blatchford score is best for predicting endoscopic treatment, accuracy and clinical utility is relatively low for these endpoints.

Strengths and limitations of this study

Strengths of our study include its international multicentre design and large number of consecutive patients studied. By assessing the five pre-endoscopy and post-endoscopy scores that appeared most promising for clinical use, we could investigate the optimum way to risk assess patients with upper gastrointestinal bleeding, both early after presentation and after endoscopic diagnosis and treatment. We believe our choice of several clinically relevant endpoints in addition to a composite endpoint to compare the scores provides clinicians with useful information. Clinicians may be keen to identify those at high risk for need of endoscopic treatment, to direct such patients to urgent endoscopy. Similarly, those at high risk of death could be moved to areas of higher level care. While a potential weakness of composite endpoints is that they may be driven largely by one or two components and thus might not provide useful information if the components are not clinically appropriate to combine, we believe our composite endpoint is clinically useful because it includes the outcomes that generally would necessitate admission to hospital. Furthermore, this composite endpoint has been used in several previous studies in this area.[12 13 29] Using our composite endpoint, if patients can be identified as unlikely to need transfusion or haemostatic intervention, or die, then most doctors would be comfortable discharging them from the emergency department for outpatient management.

A weakness of our study was that we excluded patients who were already inpatients when they developed upper gastrointestinal bleeding. These patients are already known to be at high risk of poor outcome. In

Table 4. Need for endoscopic treatment at optimal score thresholds of each of the pre-endoscopic scores: Glasgow Blatchford score, AIMS65, and admission Rockall score

Scoring system	Cut-off	No (%) of patients classified as high risk	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Glasgow Blatchford	≥7	1456 (50)	80.4	57.4	31.3	92.4
AIMS65	≥1	1619 (65)	79.7	38.7	25.9	87.6
Admission Rockall	≥3	1686 (57)	69.8	45.9	23.5	86.5

PPV=positive predictive value; NPV=negative predictive value.

addition, 31% of patients did not undergo endoscopy. In three centres, there was a guideline to not admit patients with Glasgow Blatchford scores of either 1 or less or 2 or less and aged less than 70 years, and many did not attend for outpatient endoscopy. In addition, some clinicians decided endoscopy was not required after an apparent trivial bleed, or was deemed inappropriate for some ill patients with multiple comorbidities. Interestingly, the UK national audit on upper gastrointestinal bleeding reported that 26% of patients notified to gastroenterologists did not have inpatient endoscopy.[11] We do not believe this had a major effect on our study findings, as 95% of patients were followed up for 30 days after presentation. Importantly, the usefulness of risk scores that require endoscopy is limited because endoscopy (if undertaken) is often delayed for up to 24 hours or more, whereas clinicians generally want risk stratification early after presentation.

A fairly large number of patients had missing values for full Rockall score (largely as a result of not undergoing endoscopy) or AIMS65 score (largely due to lack of measurement of albumin). Although 30 day mortality was similar in patients with and without missing values for both scoring systems, those with missing values had lower values of the other scores and less often underwent intervention, which could lead to an underestimation of the ability of the AIMS65 score to identify low risk patients. However, in the centre with the lowest missing values for AIMS65 score (Odense at 1.9%), subgroup analysis confirmed our main finding that the Glasgow Blatchford score had a higher discriminative ability to predict need for intervention or death compared with other risk scores, including AIMS65.

All data on patients managed as outpatients were included. In these outpatients, apart from performance of endoscopy they were otherwise assessed, investigated, and managed in the same way as all others and were followed up at 30 days using patient records. None of those managed as outpatients died and none required transfusion, surgery, or interventional radiology; endoscopic treatment was undertaken in one (a 28 year old with a minor Mallory-Weiss tear.). Therefore we do not believe that these policies had a major impact on our conclusions.

The power calculation for mortality was based on AIMS65 and full Rockall scores. Using our baseline assumptions, the number of patients in our study with full data on AIMS65 and full Rockall scores still provided 80% power to predict mortality. For our primary endpoint of intervention or death, using previous AUROC data for AIMS65 score of 0.7 and for the Glasgow Blatchford score of 0.8 (worst case value) and power of 90%, we needed only approximately 500 patients.30 Therefore we believe we achieved sufficient power in this study, which is the largest prospective study on this topic to date.

COMPARISON WITH OTHER STUDIES

A recent single centre retrospective study from Australia of 424 patients with upper gastrointestinal bleeding compared all these scores apart from PNED.31 The researchers reported that the AIMS65 score was best at predicting mortality with a similar AUROC to ours, although lower than other smaller studies.[16 19 29] They also found that AIMS65, Glasgow Blatchford, and full Rockall scores were similar at predicting their composite endpoint, which unlike ours did not include blood transfusion. However, we believe this is an important endpoint to assess, particularly for identification of low risk patients for possible outpatient management. A variety of low and high risk score thresholds have been suggested for clinical use by these and other small studies.

Published guidelines suggest outpatient management for patients with a Glasgow Blatchford score of 0.[20 21 23] Some authors, however, have suggested that this low risk threshold could be extended to 1 or less or to 2 or less.[13 14 22] We identified a Glasgow Blatchford score of 1 or less as the optimum score threshold to identify patients who would not require intervention or die, with a sensitivity of 98.6%. The accuracy of this threshold was consistently high across international sites, which comprised 19% of all patients in our study, compared with the 8.6% patients who had a Glasgow Blatchford score of 0. Of the patients with a Glasgow Blatchford score of 1 or less, all cause mortality was only 0.4%. This compares favourably with accepted low risk thresholds of commonly used scores for other medical conditions, including CURB65 for chest infection and

Table 5. 30 day mortality at optimal score thresholds of Glasgow Blatchford score, AIMS65, PNED, and full Rockall score

Scoring system	Cut-off	No (%) of high risk patients*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
AIMS65	≥2	672 (26.9)	65.8	76.2	18.0	96.6
PNED	≥4	1065 (37.6)	77.3	65.3	14.1	97.5
Admission Rockall	≥4	1130 (38.1)	78.6	65.0	14.3	97.6
Full Rockall	≥5	815 (40.5)	74.0	61.7	11.1	97.3
Glasgow Blatchford	≥5	1812 (61.8)	88.7	40.2	9.9	97.9

PPV=positive predictive value; NPV=negative predictive value.
*Classified as high risk according to risk scoring system.

the pulmonary embolism severity index.[32 33] Other studies have reported more accurate prediction of death, rebleeding, or length of stay using these scores, but our study has the advantages of a multicentre design and large numbers of participants and suggests these outcomes are not well predicted by the studied scores.

The median length of hospital admission for a patient presenting with upper gastrointestinal bleeding in the UK is four or five days,[3 12] and a recent study showed the mean in-hospital cost to be £2458 ($3087; €2909) per patient.[34] Use of an accurate score within emergency departments or acute assessment units, to identify very low risk patients with upper gastrointestinal bleeding not requiring admission has clear benefits. Interestingly, sites varied in the proportion of very low risk patients defined by a Glasgow Blatchford score of 1 or less. The differences are probably due to different models of healthcare provision, including extent of primary care services. At the other end of the spectrum of severity of upper gastrointestinal bleeding, early identification of high risk patients who might benefit from urgent endoscopy or higher level care could help guide management. An observational study suggested that patients with a Glasgow Blatchford score greater than 12 have decreased mortality if endoscopy is undertaken less than 13 hours after presentation.19 Our data suggest that a Glasgow Blatchford score of 7 or more and AIMS65 score of 2 or more have the highest combination of sensitivity and specificity for predicting endoscopic treatment or 30 day mortality, respectively, but the positive predictive value for both is low. Therefore the clinical utility of these scores to direct care in high risk patients seems limited.

Figure 3

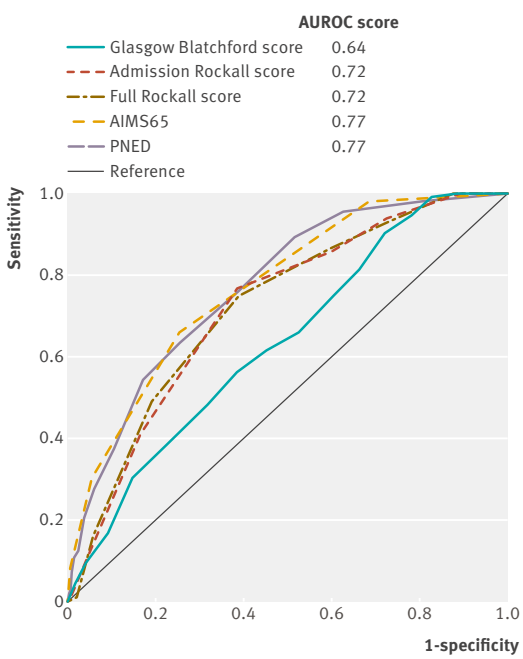

Fig 3 | Comparisons of scores in prediction of 30 day mortality (n=1707). AUROC=area under the receiver operating characteristic curve

CONCLUSIONS AND POLICY IMPLICATIONS

The Glasgow Blatchford score is accurate at predicting need for clinical intervention, or death in patients with upper gastrointestinal bleeding in all countries studied. A score of 1 or less is the optimum threshold for identifying very low risk patients suitable for outpatient management. A Glasgow Blatchford score of 7 or more is best at predicting need for endoscopic treatment, and a PNED score of 4 or more and AIMS65 score of 2 or more are best at predicting mortality, although accuracy in predicting these endpoints is relatively low. No score seems accurate at predicting rebleeding or length of hospital stay. This information can help direct management of very low risk patients with upper gastrointestinal bleeding, but further studies using these, or new scores, are required to clarify their role in directing management of higher risk patients.

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Ethical approval: This study was approved by the west of Scotland ethics committee (reference 14/WS/0012; project No 145837) and each centre obtained approval from their local research committee or review board. Owing to the observational, non-interventional nature of the study, the ethical committee (and local committees and boards) agreed that individual patient consent was not required.

Data sharing: Patient level data and/or full dataset available from the corresponding author AJS. Consent was not obtained but the presented data are anonymised and risk of identification is low.

Transparency: The study guarantor (AJS) affirms that the manuscript is an honest, accurate and transparent account of the study being reported. No important aspects of the study have been omitted and no discrepancies identified.

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Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE)

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Abstract

Objective To compare the effectiveness of insulin pumps with multiple daily injections for adults with type 1 diabetes, with both groups receiving equivalent training in flexible insulin treatment.

Design Pragmatic, multicentre, open label, parallel group, cluster randomised controlled trial (Relative Effectiveness of Pumps Over MDI and Structured Education (REPOSE) trial).

Setting Eight secondary care centres in England and Scotland.

Participants Adults with type 1 diabetes who were willing to undertake intensive insulin treatment, with no preference for pumps or multiple daily injections. Participants were allocated a place on established group training courses that taught flexible intensive insulin treatment ("dose adjustment for normal eating," DAFNE). The course groups (the clusters) were then randomly allocated in pairs to either pump or multiple daily injections.

Interventions Participants attended training in flexible insulin treatment (using insulin analogues) structured around the use of pump or injections, followed for two years.

Main outcome measures The primary outcomes were a change in glycated haemoglobin (HbA1c) values (%) at two years in participants with baseline HbA1c value of ≥7.5% (58 mmol/mol), and the proportion of participants achieving an HbA1c value of <7.5%. Secondary outcomes included body weight, insulin dose, and episodes of moderate and severe hypoglycaemia. Ancillary outcomes included quality of life and treatment satisfaction.

Results 317 participants (46 courses) were randomised (156 pump and 161 injections). 267 attended courses and 260 were included in the intention to treat analysis, of which

235 (119 pump and 116 injection) had baseline HbA1c values of ≥7.5%. Glycaemic control and rates of severe hypoglycaemia improved in both groups. The mean change in HbA1c at two years was −0.85% with pump treatment and −0.42% with multiple daily injections. Adjusting for course, centre, age, sex, and accounting for missing values, the difference was −0.24% (−2.7 mmol/mol) in favour of pump users (95% confidence interval −0.53 to 0.05, P=0.10). Most psychosocial measures showed no difference, but pump users showed greater improvement in treatment satisfaction and some quality of life domains (dietary freedom and daily hassle) at 12 and 24 months.

Conclusions Both groups showed clinically relevant and long lasting decreases in HbA1c, rates of severe hypoglycaemia, and improved psychological measures, although few participants achieved glucose levels currently recommended by national and international guidelines. Adding pump treatment to structured training in flexible intensive insulin treatment did not substantially enhance educational benefits on glycaemic control, hypoglycaemia, or psychosocial outcomes in adults with type 1 diabetes. These results do not support a policy of providing insulin pumps to adults with poor glycaemic control until the effects of training on participants' level of engagement in intensive self management have been determined.

Trial registration Current Controlled Trials ISRCTN61215213.

INTRODUCTION

People with type 1 diabetes mellitus require lifelong treatment with insulin to prevent diabetic ketoacidosis and to optimise blood glucose levels to minimise vascular complications.1 Insulin is generally administered by multiple daily subcutaneous injections, using different insulins to cover background and meal requirements. Doses are adjusted according to eating, physical activity, and blood glucose level. This approach and its integration within flexible lifestyles is promoted in "dose adjustment for normal eating" (DAFNE)2 and similar structured training courses.3 Despite this training and best efforts, many people struggle to achieve glycaemic targets and a considerable proportion go on to develop serious complications, reducing both the length and the quality of their lives.1 4

In continuous subcutaneous insulin infusion, a pump delivers insulin continuously under the skin through a small plastic tube and cannula.5 6 Pumps are filled with quick acting insulin to supply both background insulin and insulin replacement after meals.

Potential advantages include more precise insulin delivery and the ability to adjust basal insulin levels. Observational studies have reported improved glucose control, reduced risk of hypoglycaemia, and enhanced quality of life. Pump treatment is more expensive than multiple daily injections, with pumps costing around £2500 ($3041; €2800) each plus £1500 a year for consumables (cannulas, reservoirs, and batteries).7

In the UK, pump use is approved in adults with type 1 diabetes who have high glycated haemoglobin (HbA1c) values (>8.5%) or an inability to achieve reasonable control without "disabling hypoglycaemia."8 An estimated 6% of UK adults with type 1 diabetes use pumps, which is lower than in many comparable countries.9 Around 40% of people with type 1 diabetes in the USA use pumps,10 and proponents of pumps suggest that far more people should be offered them in the UK.11

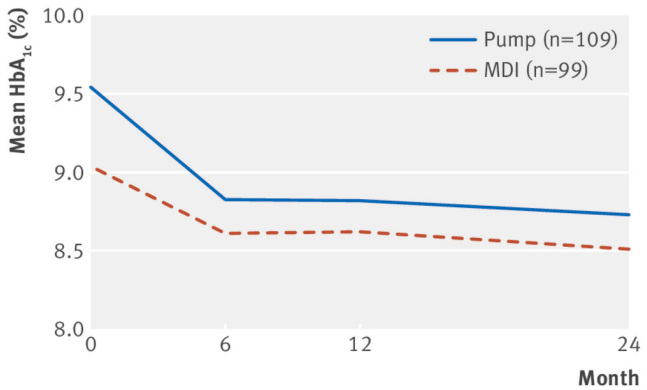
One weakness of existing evidence is that patients allocated to pumps are likely to have received more training and attention than those using multiple daily injections. A recent observational study12 of pump treatment and injections, where both groups received intensive education in insulin usage, concluded that the training might have made the most difference. To our knowledge, no randomised trials in adults have compared pump treatment with multiple daily injections where the same structured training in insulin adjustment has been provided, so the added benefit of pump technology remains unclear.

In the Relative Effectiveness of Pumps Over MDI and Structured Education (REPOSE) trial we assessed the effectiveness of adding pump treatment to high quality equivalent structured education in flexible intensive insulin treatment for people with type 1 diabetes, comparing pump plus education with multiple daily injections plus education. Our hypothesis was that much of the benefit of pump treatment might come from the re-training and education in insulin use given to enable patients to use pumps safely. We present the clinical effectiveness and quantitative psychosocial results of this pragmatic trial.

METHODS

Trial design

The study protocol has been previously published.13 In brief, we conducted a multicentre, parallel group, open label, confirmatory, cluster randomised controlled trial. Eight secondary care centres (three in Scotland and five in England) recruited up to 40 participants to three pump and three multiple daily injection courses (with five to eight patients on each course) over 11 months. Participants were allocated a place on a one week DAFNE skills training course, with a further visit at six weeks. The course groups (clusters) were



Mean change (%) in glycated haemoglobin (HbA1c) over time in participants with baseline HbA1c ≥7.5% (58 mmol/mol) (including only participants with data at all four time points, n=208). MDI=multiple daily injections

randomly allocated in pairs to either pump or multiple daily injections. After the courses, participants received the trial treatment for two years. We collected outcome measures at baseline (up to three weeks before the DAFNE course) and at six, 12, and 24 months. A cluster design was chosen to address the challenge of randomising participants and then finding suitable times for their attendance on a course of the correct allocation. We believe this approach reduced both recruitment bias and attrition rates before the course.

Participants

We recruited adults with a diagnosis of type 1 diabetes for at least 12 months, and who were willing to undertake intensive insulin treatment with self monitoring of blood glucose levels, counting of carbohydrate intake, and insulin self adjustment, with no preference for either pump or multiple daily injections. Participants were those with clinical indications for structured education in insulin treatment to optimise diabetes control who had not participated previously in structured training. We excluded those with a strong desire for pump treatment, those already using optimised multiple daily injections and meeting the criteria of the National Institute for Health and Care Excellence for pump treatment, those needing a pump in the opinion of the investigator, those with serious diabetic complications, and those unable to communicate in English. Courses (clusters) required between five and eight participants to maintain optimal course dynamics.

Interventions

Participants using multiple daily injections attended standard DAFNE structured education courses,2 which were conducted over five consecutive days and delivered to groups of five to eight adults as outpatients. The participants took insulin aspart, a quick acting insulin analogue, for meals, and twice daily injections of insulin detemir for background replacement. They used the Accu-Chek Aviva Expert Bolus Advisor System (Roche Diagnostics Ltd, Burgess Hill, UK) as a bolus calculator, as there is evidence that bolus advisers can improve glycaemic control, presumably by helping patients calculate the appropriate meal related bolus.14

Participants allocated to pump treatment attended a modified DAFNE course, previously validated in pump users.15 That course maintained the five day structure and the principles of insulin dose adjustment in the standard DAFNE course, but also incorporated the practical skills and learning outcomes needed to use pumps successfully. This necessitated an additional group session, delivered one to three weeks before the main course. Standard DAFNE includes a rigorous quality assurance programme. For the pump courses, fidelity testing was undertaken to assess incorporation of appropriate pump training. Participants used a Minimed Paradigm Veo insulin pump (model X54; Medtronic, Watford, UK) with insulin aspart. The bolus wizard in the pumps was activated as part of the course.

The curriculum (and associated patient workbook) was adapted specifically to make better use of pump features, compared with standard (multiple daily injections) DAFNE. This included general pump management (infusion sets, cannulas, filling reservoirs, changing batteries, and troubleshooting). During the five day course participants were also taught use of the bolus wizard, basal testing and adjustment (including fasting during the day and overnight glucose profiles), use of temporary basal rates for physical activity or alcohol intake (reduced) and illness (increased), use of alternative bolus "waves" (extended, multiwave), prevention of diabetic ketoacidosis ("sick day rules" eg, when to use a pen to inject insulin in case of cannula/pump failure, how much insulin to give and how often).

All participants (multiple daily injections and continuous subcutaneous insulin infusion) were invited to the course follow-up session at six to eight weeks, and those who required additional input were offered further one-to-one appointments. These appointments were supported by meter or pump downloads (Diasend: www.glooko.com/diasend; CareLink: www.medtronicdiabetes.com/products/carelink-personal-diabetes-software), depending on local availability. Participants were encouraged to maintain paper record diaries to facilitate discussion and adjustments, according to the principles taught on the course and supported by the workbook. Some might have already sought additional help in between these planned appointments. We recorded diabetes related contact with educators outside the course and at the six week follow-up.

OUTCOMES

Primary outcomes

We specified two primary outcomes. One was the change in HbA1c (%, measured centrally) after two years in participants whose baseline HbA1c was ≥7.5% (58 mmol/mol). HbA1c is the

accepted ideal surrogate measure of glycaemic control and provides a measure of efficacy and a means of modelling long term cost effectiveness. Our choice of this primary outcome was based on our concern that HbA1c values might not decrease in those who entered the trial with low baseline values, but who might be experiencing problematic hypoglycaemia. Success for such individuals would be an HbA1c value that was maintained or even increased but with a reduced frequency of severe hypoglycaemia (an important secondary endpoint).

The other primary endpoint was the proportion of participants reaching the 2004 NICE target of HbA1c ≤7.5% (58 mmol/mol).

Secondary outcomes

Secondary biomedical outcomes measured at six, 12, and 24 months were moderate hypoglycaemia (an episode that could be treated by the individual, but where hypoglycaemia caused a significant interruption of current activity leading to impaired performance, or embarrassment, or being woken during nocturnal sleep); severe hypoglycaemia (an episode leading to cognitive impairment sufficient to cause either coma or requiring the assistance of another person to recover); total and high density lipoprotein cholesterol levels; proteinuria; insulin dose; and body weight. Diabetic ketoacidosis was recorded through the assessment of serious adverse events throughout the trial.

Ancillary outcomes

Quantitative psychosocial self completed questionnaires assessed generic and diabetes specific quality of life: SF-12 (12 item short form health survey); WHOQOL-BREF (World Health Organization quality of life–BREF); EQ-5D (EuroQol five dimensions questionnaire); DSQOL (diabetes specific quality of life), fear of hypoglycaemia (HFS: hypoglycaemia fear scale), satisfaction with treatment (DTSQ: diabetes treatment satisfaction questionnaire), and emotional wellbeing (HADS: hospital anxiety and depression scale) at the same time points.13

A health economic evaluation to address the question "What is the cost effectiveness of pump treatment compared with multiple daily injections in patients receiving the DAFNE structured education programme?" was undertaken. It has been submitted for publication. It included a within trial and a modelled patient lifetime analysis, the latter being the primary focus of the evaluation.

Sample size

We calculated the sample size using a minimally clinically important difference of 0.5% (5.5 mmol/mol) in HbA1c values. To detect this difference with a standard deviation of 1% at 80% power and 5% two sided significance required 64 participants with an HbA1c of ≥7.5% in each group. To allow for clustering of educators, an average of seven participants per group, a within course intraclass correlation coefficient of 0.05, and a 10% dropout rate, we required a sample size of 93 in each group. In the DAFNE database,15 75% of participants had an HbA1c value ≥7.5%, so we required 124 participants per group. We planned to recruit 280 participants, which increased the power to 85% but allowed for some variation in dropout rates and the proportion of participants with HbA1c of ≥7.5%. However, monitoring of baseline data showed the actual proportion of participants with an HbA1c of ≥7.5% was around 90%. A modelling exercise undertaken during recruitment with conservative estimates of 85% (HbA1c ≥7.5%) and dropout rate of 15% suggested the trial would require at least 240 participants with primary outcome data at two years to preserve a power of at least 85%.

Randomisation

After providing consent, participants were allocated to a training course, depending on their availability. Courses were randomised in pairs either to DAFNE plus pump or to DAFNE plus multiple daily injections. Simple randomisation in a block size of two, stratified by centre, was used for the first four courses. Courses 5 onwards were allocated in pairs using minimisation; the number of participants with baseline HbA1c values ≥7.5% and the total number of participants were used as minimisation factors. A statistician within Sheffield Clinical Trials Research Unit conducted the randomisation by a user written Stata code produced to generate allocation. The trial coordinator revealed the allocation to study sites. Participants who were unable to attend their original course were allowed to attend a later course in the same treatment arm, to reduce selection bias.

Statistical analysis

Analyses were performed in Stata 13 after a prespecified approved statistical analysis plan. All analyses were by intention to treat, with participants analysed in the groups to which they were randomised, unless otherwise specified. Participants were included in the intention to treat analysis if they had at least one post-baseline HbA1c measure. Those who dropped out before receiving the intervention were substituted where possible, to ensure the courses were run with adequate numbers of participants, but these individuals were not included in the analysis. Statistical tests were two sided at the 5% significance level.

We analysed the change in HbA1c (%) at two years using a mixed effects model, with centre and baseline HbA1c treated as fixed effect covariates, and course (cluster) as a random intercept. For the primary analysis we used multiple imputation to impute missing HbA1c data for participants with at least one follow-up HbA1c measure but without two years outcome. We also performed a per protocol sensitivity analysis that excluded participants who had switched treatment. Changes in HbA1c values at six months and one year were analysed in the same way.

The proportion of participants reaching an HbA1c of <7.5% was compared between groups using a logistic regression

model adjusted for baseline HbA1c, and centre and modelling separate courses within centre as random intercepts.

We used negative binomial mixed effects regression (to account for over-dispersion and clustering) on the number of moderate hypoglycaemic episodes in the four weeks before each follow-up, and occurrence of at least one moderate episode in the four weeks before courses as a covariate and the same covariates described previously. The number of severe hypoglycaemic episodes in two years was analysed as for moderate hypoglycaemic episodes, with the addition of study follow-up as the exposure. Incidence rate ratios were calculated using negative binomial random effects regression with participant as the random effect, adjusted for baseline HbA1c value and centre, based on the full intention to treat set (n=260).

Secondary continuous outcomes (insulin dose, body weight, high density lipoprotein and total cholesterol levels) were analysed as for the primary outcome. We categorised proteinuria as macroalbuminuria, microalbuminuria, or normal and analysed using mixed effects ordered logistic regression adjusted for clustering by course (random effect), centre, and baseline HbA1c (fixed effects).

Changes in psychological outcomes were analysed using a mixed model adjusted for course (random), centre, baseline HbA1c, and baseline score, with the exception of the diabetes treatment satisfaction questionnaire, which we compared between groups using a non-parametric Wilcoxon-Mann-Whitney U test. No adjustments for multiple testing were made to the significance level for all exploratory secondary objectives.

A retrospective subgroup analysis used mixed effects regression modelling with the primary outcome, change in HbA1c (%), including main effects of treatment group and subgroup, an interaction term between treatment and subgroup, and covariates of centre (fixed effect) and course (random effect). All categories for the subgroup analysis were prespecified in the statistical analysis plan but not in the original protocol, and are reported in full.

Patient involvement

Fifteen people, who had previously attended DAFNE courses (including pilot courses on pump treatment) but were not participating in the trial, were recruited to act as a user group and contribute to different aspects of the work. We invited two members to join both the steering group and the other investigator meetings. In addition, one of the project team (a doctor) is a pump user. They provided input to the trial design, implementation, and dissemination, including all participant materials. This included a discussion of the most appropriate research questions and whether individuals who were willing to try pump treatment could be successfully recruited into a trial where they could be randomised to multiple daily injections.

RESULTS

Study participants

Participants were recruited between November 2011 and April 2013. Follow-up continued until June 2015. The CONSORT flowchart (fig 1) shows the flow of patients through the trial. Forty six courses were randomised. Of the 317 participants included in the randomisation, 50 were excluded from any analysis; 40 withdrew before giving baseline data and 10 before their course. All randomised courses were delivered. Of 267 participants randomised and attending the baseline assessment and the course, 260 (pump=132; injections=128) made up the intention to treat set. Two hundred and forty eight participants had complete primary outcome data at 24 months.

Primary outcomes

HbA1c

At 24 months in participants whose baseline HbA1c was ≥7.5% (n=119 in pump group; n=116 in multiple daily injections group) the mean change in the pump group was a decrease of 0.85% (9.3 mmol/mol) compared with 0.42% (4.5 mmol/mol) in the multiple daily injections group. After adjusting for centre, course, and baseline HbA1c, the mean difference in HbA1c change from baseline was −0.24% (95% confidence interval −0.53% to 0.05%) (−2.7 mmol/mol, −5.8 to 0.5) in favour of pump treatment (P=0.10). The treatment difference was larger for the per protocol analysis; mean difference −0.36% (−0.64% to −0.07%) (−3.9 mmol/mol, −7.0 to −0.8) in favour of pump treatment (P=0.02), although this point estimate was still smaller than the prespecified minimal clinically important difference. Estimate of the intraclass correlation coefficient was approximately 0.5%.

At 24 months, for the treatment groups combined (n=248), in all participants with complete HbA1c data there was a decrease of 0.54% (95% confidence interval 0.38% to 0.69%) (5.9 mmol/mol, 4.2 to 7.6) and for participants with baseline HbA1c ≥7.5% (n=224) the decrease was slightly greater, at 0.64% (95% confidence interval 0.48% to 0.80%) (7 mmol/mol, 5.2 to 8.8).

Proportion of participants reaching HbA1c ≤7.5% (58 mmol/mol)

The proportions of participants reaching an HbA1c ≤7.5% (58 mmol/mol) after two years, regardless of baseline HbA1c value, were 25.0% for the pump group and 23.3% for the multiple daily injections group (odds ratio 1.22, 95% confidence interval 0.62 to 2.39, P=0.57, table 2). The results were similar at six and 12 months.

The primary analysis at 24 months was repeated for six and 12 month follow-up visits (table 3). The results for these interim time points were consistent with the primary outcome analysis. The largest difference in HbA1c change from baseline was observed at six months, with an adjusted mean difference of −0.25% (95% confidence interval −0.52% to 0.02%) (−2.7 mmol/mol, −5.6 to 0.2), P=0.07. Figure 2 displays the change in HbA1c for participants with data at all four time points by treatment group.

Secondary outcomes

Hypoglycaemia

Relatively few severe hypoglycaemic episodes were observed post-baseline: 49 in 25 participants. The rate of severe hypoglycaemia during the 24 month follow-up did not differ between the treatment groups, adjusted for centre, course, baseline HbA1c, and presence of at least one severe hypoglycaemic episode in the 12 months before baseline (incidence rate ratio 1.13, 95% confidence interval 0.51 to 2.51, P=0.77).

Across both treatment groups, the number of severe hypoglycaemic episodes was reduced. The average number of episodes for each patient per year in the study reduced from 0.17 before baseline to 0.10 during follow-up. The incidence rate ratio for the number of severe hypoglycaemic episodes in the 24 month follow-up, compared with the year before baseline, was 0.46 (0.24 to 0.89, P=0.02).

Across both treatment arms, on average, three moderate hypoglycaemic episodes were recorded for each patient over a four week history at six months. By 24 months this number was slightly lower (2.6 for pump group, 2.3 for multiple daily injections group) but there was no statistically significant difference between the groups in rates of moderate hypoglycaemic episodes at any time point.

Other biomedical outcomes

Body weight remained roughly constant throughout the study period, and was not statistically significantly different between the treatment groups at any time point (table 4). A slight increase in high density lipoprotein cholesterol and a slight decrease in total cholesterol levels were observed in both groups, with no evidence of a difference between treatment groups in change from baseline (P values ranged from 0.22 to 0.86). Insulin dose decreased in both arms. At 12 months, participants in the pump group had a 0.07 IU/kg greater reduction in insulin dose than those in the multiple daily injections group (95% confidence interval 0.01 to 0.13 decrease, P=0.02). The difference was slightly smaller at six and 24 months and was not statistically significant. There was no statistically significant difference in the odds of proteinuria between the treatment groups at any time point (table 5).

Diabetic ketoacidosis

The number or type of serious adverse events did not differ between the groups, with the exception of diabetic ketoacidosis, which was greater in the pump group compared with multiple daily injections group (17 v 5). More patients using pumps than using multiple daily injections had several episodes (5 v 2) and the differences were confined to the first year, with four episodes in each group during the second year. Three episodes occurred in two participants who switched to pump treatment, and one in a participant who switched to multiple daily injections. Most episodes of ketoacidosis were caused by infections and 18% by set failure in those using pumps. Only five episodes occurred when participants implemented all sick day rules.

Ancillary outcomes

High levels of completion of the psychosocial questionnaires were observed across all questionnaires and time points (around 90% completed at each time point). The completion rate was slightly higher for participants allocated to the pump compared with multiple daily injections, which reflects the relative dropout rates in the two groups. No between group differences were found in the generic quality of life and health status instruments SF-12, WHOQOL-BREF, and EQ-5D, and the HADs score for depression and anxiety at six, 12, and 24 months (tables 6-8).

The overall diabetes specific quality of life (DSQOL) (on a 100 point scale) showed that both groups improved at 24 months, by a mean of 8.2 (SD 13.1) points in the pump group and 4.2 (SD 13.2) points in the multiple daily injections group. Both groups showed improvements in the DSQOL subdomains, which were greater in the pump group although not always reaching statistical significance.

The improvement in DSQOL diet restrictions was larger for the pump group compared with multiple daily injections group at both 12 and 24 months (12 month adjusted mean difference in change from baseline −4.1 (95% confidence interval −7.2 to −1.0, P=0.01); 24 month adjusted mean difference in change from baseline −5.1 (−8.6 to −1.6, P=0.004); lower scores represent better outcomes. The pump group also had greater improvement in DSQOL daily hassle or functions at both 12 and 24 months; at 24 months the score had decreased by 10 points in the pump group, compared with 4 points in the multiple daily injections group (adjusted mean difference −6.3, −10.9 to −1.8, P=0.01).

Participants in the pump group had better improvement in treatment satisfaction at all time points (table 9) but the difference was statistically significant at 12 and 24 months only (P=0.07 at six months, P<0.001 at 12 and 24 months).

Retrospective analyses

Participants achieving the updated NICE recommendation of HbA1c ≤6.5%

A retrospective analysis showed that eight (3%) of all participants (4/128 pump group and 4/120 multiple daily injections group) reached an HbA1c of ≤6.5% (47 mmol/mol) after two years (table 10). Of these, two participants (both in the pump group) experienced one or more episodes of severe hypoglycaemia during follow-up.

Participant contacts

A retrospective analysis showed that, on average, those allocated to pumps had around double the number of contacts with professionals for diabetes between baseline and the end of year 1, both face to face and by telephone. Between months 12 and 24, those using pumps had more face-to-face contacts, which were of longer duration (mean 1.6 v 1.3 contacts), but fewer telephone contacts (0.7 v 1.2).

Blood glucose testing

Mean difference in change of psychosocial outcomes from baseline to six months

Outcomes	Pump treatment		Multiple daily injections		Adjusted difference* (95% CI)	P value
	No	Mean (SD) change	No	Mean (SD) change		
SF-12 physical component summary†	127	1.2 (6.1)	116	0.5 (8.6)	0.3 (−1.4 to 2.0)	0.72
SF-12 mental component summary	127	0.2 (8.8)	117	0.9 (9.9)	−0.8 (−2.9 to 1.3)	0.45
DSQOL:						
Total score†	128	−5.2 (12.2)	117	−4.4 (11.2)	−0.1 (−2.8 to 2.6)	0.94
Social relations	128	−2.2 (11.8)	117	−3.0 (13.2)	1.5 (−1.2 to 4.2)	0.28
Leisure time restrictions and flexibility	128	−5.1 (16.6)	117	−4.4 (18.5)	−0.1 (−3.8 to 3.7)	0.97
Physical complaints	128	−6.0 (17.0)	117	−4.8 (13.8)	−0.1 (−3.5 to 3.3)	0.95
Worries about the future	128	−7.9 (20.4)	117	−7.5 (19.4)	−0.7 (−5.5 to 4.1)	0.78
Daily hassle of functions	128	−6.3 (18.9)	117	−5.0 (18.7)	−0.8 (−5.0 to 3.4)	0.70
Diet restrictions	128	−11.3 (18.3)	117	−6.4 (16.0)	−3.3 (−6.9 to 0.2)	0.06
Treatment satisfaction (PWTSS)†	118	2.1 (4.4)	109	2.1 (4.8)	0.1 (−0.7 to 1.0)	0.79
WHOQOL-BREF:						
Physical health†	127	0.4 (2.3)	117	0.2 (2.3)	0.1 (−0.4 to 0.6)	0.74
Psychological	128	0.1 (1.9)	117	0.4 (2.2)	−0.3 (−0.7 to 0.2)	0.23
Social relationships	127	−0.3 (2.7)	117	0.3 (3.0)	−0.7 (−1.3 to 0.1)	0.03
Environment	128	0.1 (1.7)	117	0.4 (1.6)	−0.3 (−0.7 to 0.1)	0.17
HFS behaviour score‡	127	−1.7 (4.9)	117	−0.2 (4.8)	−0.9 (−2.0 to 0.1)	0.07
HFS worry score§	128	−4.0 (10.9)	117	−2.8 (9.5)	−0.1 (−2.4 to 2.1)	0.91
HADS anxiety score¶	128	−0.2 (3.0)	117	−0.6 (3.3)	0.4 (−0.3 to 1.1)	0.26
HADS depression score	128	−0.3 (2.9)	117	−0.2 (2.5)	0.1 (−0.5 to 0.7)	0.74
EQ-5D**	127	−0.02 (0.17)	117	−0.01 (0.18)	−0.02 (−0.06 to 0.02)	0.38

SF12=12 item short form health survey; DSQOL=diabetes specific quality of life; PWTSS=preference weighted treatment satisfaction score; WHOQOL-BREF=World Health Organization quality of life-BREF; HFS=hypoglycaemia fear survey; HADS=hospital anxiety and depression scale; EQ-5D=EuroQol five dimensions questionnaire.

*Calculated using mixed effects regression adjusted for baseline quality of life score, centre, course, and baseline HBA1c.

†Scored from 0 (poor) to 100 (good).

‡Scored from 10 to 50 (higher score=greater fear).

§Scored from 17 to 85 (higher score=greater fear).

¶Scored from 0 (good) to 21 (poor).

**Scale from −0.56 to 1.00 (good health).

A retrospective analysis indicated that there was no difference in the mean frequency of blood glucose testing between treatment groups at 24 months after adjustment for baseline number of blood glucose tests, centre, and DAFNE course. The adjusted mean difference in blood glucose tests was 0.22 (95% confidence interval −0.24 to 0.68) per day or 3.1 (−3.4 to 9.6) over two weeks; P=0.35. Overall, the number of blood glucose tests increased from 3.6 per day at baseline to 4.1 per day at 24 months (95% confidence interval 0.33 to 0.82, P<0.001).

Subgroup analysis

A retrospective analysis found no reliable statistical evidence of any subgroup effects or interactions between group (figs 3 and 4). However, there was some indication that participants with qualifications up to A level or equivalent did better in the pump group than in the multiple daily injections group (mean difference in HbA1c change (%) at 24 months −0.7% (95% confidence interval −1.2% to −0.1%) (−7.4 mmol/mol, 95% confidence interval −13.2 to −1.5)), although the interaction test was not statistically significant (P=0.07).

DISCUSSION

In a group of adults with type 1 diabetes referred for structured training in flexible insulin treatment because of suboptimal diabetes control, participation in the REPOSE trial achieved a clinically worthwhile decrease in HbA1c of 0.6% (7 mmol/mol) at two years in those with a baseline HbA1c of >7.5%. However, in terms of the primary outcomes, there were no statistically significant differences in change from baseline to 24 months

between those randomised to pump treatment or those using multiple daily injections, nor in the proportion of participants reaching an HbA1c of ≤7.5%, indicating that pump treatment provided no clear biomedical benefit over training in DAFNE skills.

Rates of severe hypoglycaemia were halved in both groups (despite lower HbA1c values), a benefit maintained to 24 months with no difference between the groups in this or in rates of moderate hypoglycaemia. There were no other differences in biomedical outcomes apart from slightly greater reductions in insulin doses in those randomised to pump treatment. Both groups showed improved satisfaction with treatment and diabetes specific quality of life. Treatment satisfaction and two subdomains of the diabetes specific quality of life scale improved to a greater extent at two years in those allocated to pump treatment.

Strengths and limitations of this study

Compared with previous trials of pump treatment our study had a robust, multisite design, involved much larger numbers, and had a clinically meaningful period of follow-up pump treatment. Participants in both groups used analogue insulins and bolus calculators. The study was conducted in experienced secondary care centres and involved attendance at a structured education intervention that is well established across the UK. It included a comprehensive psychological evaluation with high levels of data completeness. The pragmatic study design thus provides good external validity, particularly as participating in the educational course led to sustained improvements in glycaemic control and reduced rates of severe hypoglycaemia.

It is not possible to blind a trial where insulin delivery systems are fundamentally different and this imposes limitations on any randomised controlled trial involving pumps. However, for the primary outcomes, HbA1c was objectively assessed using a central laboratory.17 A trial studying people who have expressed a desire for pump treatment is likely to struggle to recruit participants if one arm continues to use multiple daily injections. Those randomised to the injections arm might also either drop out or exhibit poor outcomes because of "disappointment" and lack of motivation. We recruited individuals who had not specifically requested pump treatment but were awaiting a course in diabetes self management to help them improve their metabolic control. Thus, our aim was to determine any added benefit of pumps over multiple daily injections while controlling for the training itself.

A potential limitation is that those randomised to pump treatment might have been insufficiently motivated to make the most of any technological benefit since they had not expressed a particular wish to use a pump. A common reason given by patients for not wanting to participate in REPOSE was reluctance to use an insulin pump. However, educators encouraged participants to use additional technological pump features (eg using more sophisticated bolus delivery) and provided extra input when this training was requested. Overall, we reasoned that since participants had signed up for a course to improve their glucose control, any added benefits of pump treatment would emerge.

In this pragmatic trial we did not collect detailed information about pump basal rates, how often patients adjusted and tested these, and time spent with pump participants. Our study was not designed to establish which features of pumps determine success in lowering HbA1c values in those doing "well" with pump treatment. An explanatory trial would have required a different study design. We therefore cannot be sure why those allocated to pump treatment failed to show a greater decrease in HbA1c.

We recorded the average number of blood glucose tests each day in both groups over the previous two weeks, both at baseline and at 24 months. Both groups had increased the number of daily tests from 3.6 before training to more than four each day at 24 months, but this did not differ between the groups. Perhaps this frequency of testing reflects a level of engagement in self management that was insufficient for participants in the pump group to take full advantage of the technology. One interpretation was that the educators were unable to provide adequate training in use of the pump during the one week course. However, it is just as likely that provision of pump treatment in a group of patients who had not been previously trained in delivery of flexible intensive insulin treatment included many who subsequently found it too challenging to implement and maintain the intensity of self management that both pump treatment and multiple daily injections demand.

Comparison with other trials

Two appraisals of pumps by NICE have reviewed the evidence on clinical and cost effectiveness. One18 noted that there were no trials of pumps against "best multiple daily injections" with long acting and short acting analogue insulins; that some trials had unequal amounts of education in the arms (with more in the pump arms); and that the trials had focused on easily measurable outcomes such as HbA1c, rather than on benefits in terms of flexibility of lifestyle and quality of life. The report recommended trials of pumps against analogue based multiple daily injections. A more recent report19 found only three trials in adults, one a pilot and the other involving 39 adults with type 1 diabetes, already using pump treatment who were randomised to continue with the pump or to switch to glargine based multiple daily injections. Patients received four months treatment with each. A third trial recruited 57 adults randomised to pump or analogue injections in an equivalence study. None showed any difference in HbA1c. Thus, the evidence base from trials for comparing pumps and "best multiple daily injections" was weak in terms of numbers, with a total of only 103 patients and short follow-up.

The assessment for the second appraisal19 reviewed observational studies of adults switching to pumps for clinical indications. These have the advantage of measuring change in glycaemic control and hypoglycaemia in those who have most to gain, and these studies showed improved HbA1c of the order of around 0.5%. Bias in observational studies is more of a problem, and results must be treated with caution. Furthermore, of 48 observational studies, only nine reported quality of life. Study numbers were small, with at most 35 patients. Duration was usually short. The longest study noted that initial benefits from pump treatment might not be sustained. The present study has thus addressed several of these concerns with large numbers in an adequately powered trial and a virtually complete dataset for both biomedical and psychological outcomes.

Clinical and policy implications

Our study suggests that extending the availability of pumps to adults with type 1diabetes with suboptimal glycaemic control and no desire to use this form of insulin delivery is unlikely to result in either lower levels of glycaemia as measured by HbA1c or lower rates of hypoglycaemia. The absence of a control arm in which structured training was not provided, means we cannot be certain that participation in training explains the considerable decreases in HbA1c and severe hypoglycaemia in both groups. Yet, it seems unlikely that mere trial participation led to sustained decreases in HbA1c and severe hypoglycaemia for up to two years, particularly as allocation to such a control arm, in previous trials involving the DAFNE intervention, showed no effect on HbA1c.2

The results would appear to support the current clinical pathway as proposed by NICE, in which people desiring improved diabetes control undergo structured training in flexible insulin treatment with multiple daily injections alone. The trial outcomes, together with the review for NICE of observational pump studies, suggest that pumps might usefully be reserved to support those who actively engage in self management after structured education. Those who find that despite their best efforts, injections fail to deliver the expected benefits could then be offered the additional technological advantages of an insulin pump.

Clearly some patients improved more than others in terms of glucose control or hypoglycaemia and we explored whether there were any demographic differences in those who did particularly well. There was no reliable evidence of any plausible subgroup effects or interactions between the pump and multiple daily injections group, and the baseline characteristics of those whose glycaemic control changed to <7.5% during the trial were no different from the pump population as a whole. We observed modest centre effects but no systematic differences according to greater experience in pump treatment.

Those using insulin pumps did show some quality of life benefits, reporting less restriction in diet and daily hassles in the DSQOL scale and greater treatment satisfaction. Nevertheless, the differences were modest and observed in comparison with a group given no novel technology. Since they were not associated with other positive treatment outcomes, those observations are probably insufficient to justify a major alteration in guidelines for the use of pumps.

One of the more striking results of this trial was the generally high level of HbA1c among adults in the UK enrolling for self management training in flexible insulin treatment. Participation in the courses produced important and sustained decreases, but for most participants still fell well short of the target recommended by NICE, recently reduced from 7.5% to 6.5%.20 The high levels of HbA1c among people with type 1 diabetes in UK centres compared with most other European countries have also been noted in a recent study.21 There is an urgent need to explore the barriers to successful self management in adults with type 1 diabetes in the UK and to understand why referral for appropriate training is often left so long. This was also the conclusion of our recently completed research programme.15 Our results suggest that these problems cannot be overcome merely by providing additional technology in the form of pumps.

CONCLUSIONS

People with type 1 diabetes might be better served by ensuring far greater availability of high quality, structured self management training, which is currently only accessed by around 10% of adults in the UK.22 Participants might only recognise the limitations of insulin delivery by multiple daily injections if they start actively managing their diabetes after training. Those individuals could then be offered pump treatment to help them reach the stringent glucose targets necessary to achieve an HbA1c of 6.5% or to overcome problematic hypoglycaemia.

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Cindy Cooper, Gemma Hackney, Diana Papaioannou, Emma Whatley, and David White provided central trial management, oversight, and monitoring. Mike Bradburn, Michael Campbell, Munya Dimairo, and Ellen Lee contributed to the statistics. Hasan Basarir, Alan Brennan, Simon Dixon, and Daniel Pollard contributed to the health economics. Nina Hallowell, Jackie Kirkham, Julia Lawton, and David Rankin designed and undertook the qualitative work. Katharine Barnard led the quantitative psychosocial work. Timothy Chater and Kirsty Pemberton provided data management. Fiona Allsop and Lucy Carr provided central administration. Pamela Royle conducted literature searches and exploratory analyses. Gill Thompson and Sharon Walker provided central DAFNE support. Pauline Cowling conducted the fidelity assessment. Henry Smithson provided user representation on the management group.

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Ethical approval: The protocol was approved by the Research Ethics Committee North West, Liverpool East (11/H1002/10). Each participating centre gave NHS Research and Development approval. The protocol received MHRA clinical trials authorisation. All participants provided written informed consent before taking part in the study.

Data sharing: Requests for patient level data and statistical code should be made to the corresponding author and will be considered by the REPOSE trial management group who, although specific consent for data sharing was not obtained, will release data on a case by case basis following the principles for sharing patient level data as described by Smith et al. 23 The presented data do not contain any direct identifiers, we will minimise indirect identifiers and remove free text data, to minimise the risk of identification.

Transparency: The guarantor (SH) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Features

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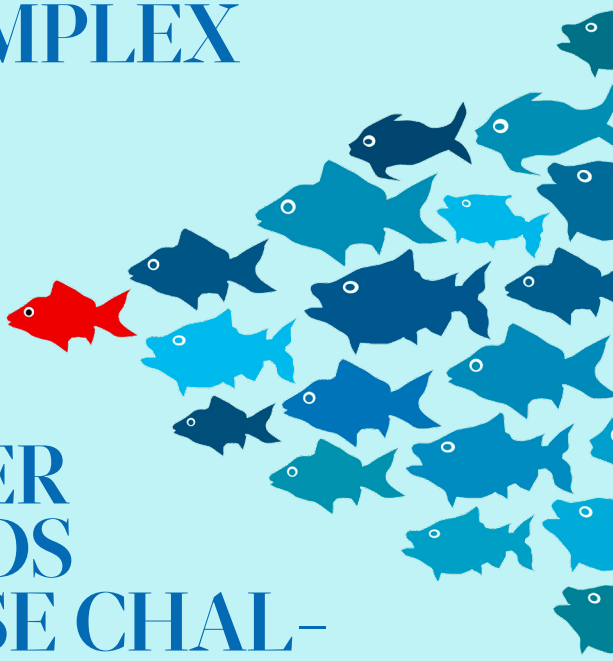
HEALTHCARE HAS BECOME EXTRAORDINARILY COMPLEX — THE BALANCE OF QUALITY AGAINST COST, AND OF TECHNOLOGY AGAINST HUMANITY, ARE PLACING EVER INCREASING DEMANDS ON CLINICIANS. THESE CHALLENGES REQUIRE EXTRAORDINARY LEADERS.



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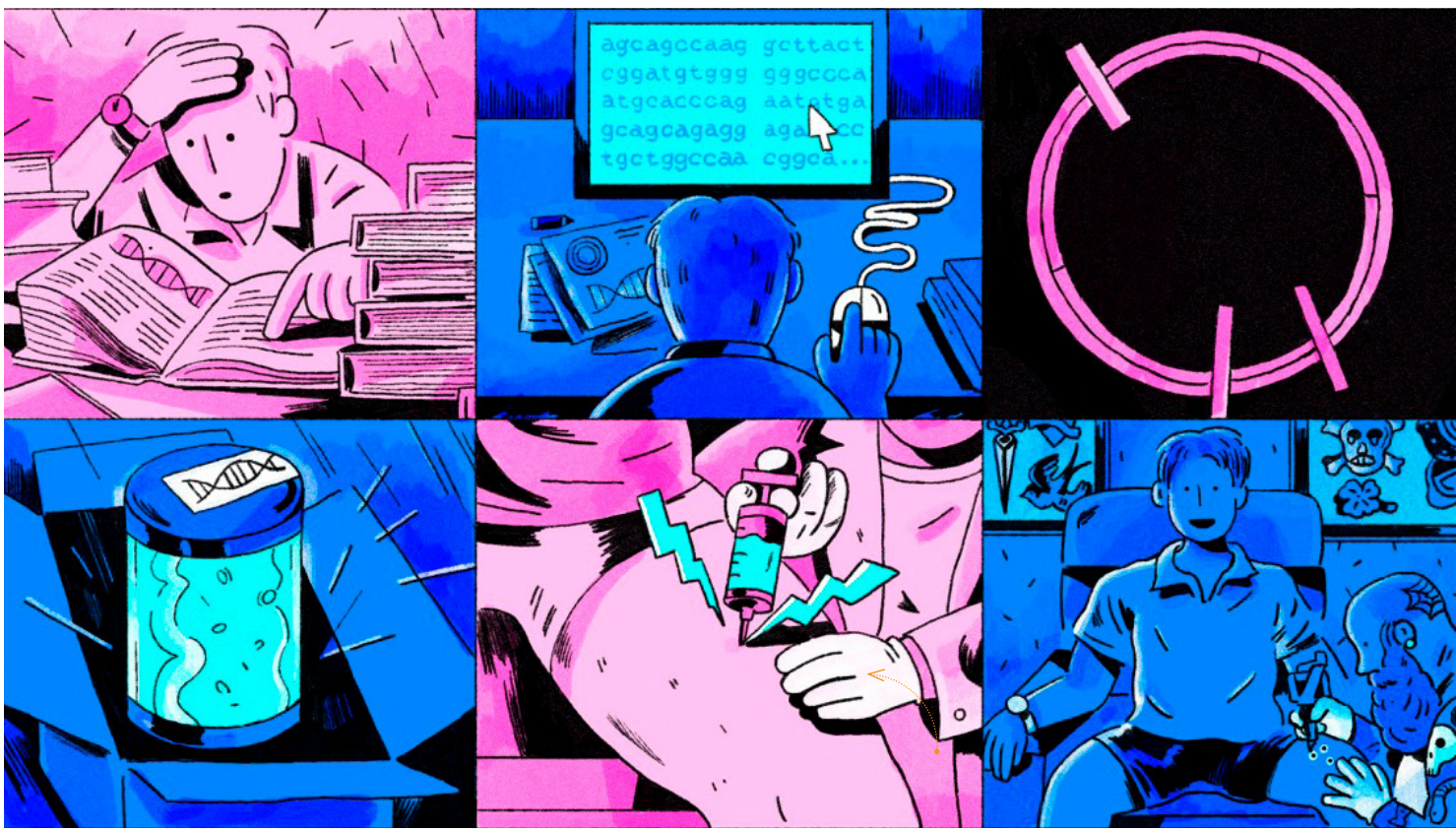
One Man's Quest to Hack His Own Genes

When Brian Hanley set out to test a gene therapy, he started with himself.

by **Antonio Regalado**



In a dream Brian Hanley told me about, he's riding a bus when he meets a man in dark leather clothing. Next thing he knows, he is splayed across a tilted metal bed, being electrocuted. The dream was no doubt connected to events that took place last June at a plastic surgeon's office in Davis, California. At Hanley's request, a doctor had injected into his thighs copies of a gene that Hanley, a PhD microbiologist, had designed and ordered from a research supply company. Then, plunging two pointed electrodes into his leg, the doctor had passed a strong current into his body, causing his muscle cells to open and absorb the new DNA.

The effort is the second case MIT Technology Review has documented of unregulated gene therapy, a risky undertaking that is being embraced by a few daring individuals seeking to develop anti-aging treatments. The gene Hanley added to his muscle cells would make his body produce more of a potent hormone—potentially increasing his strength,

stamina, and life span.

Hanley, 60, is the founder of a one-man company called Butterfly Sciences, also in Davis. After encountering little interest from investors for his ideas about using DNA injections to help strengthen AIDS patients, he determined that he should be the first to try it. "I wanted to prove it, I wanted to do it for myself, and I wanted to make progress," says Hanley.

Most gene therapy involves high-tech, multimillion-dollar experiments carried out by large teams at top medical centers, with an eye to correcting rare illnesses like hemophilia. But Hanley showed that gene therapy can be also carried out on the cheap in the same setting as liposuction or a nose job, and might one day be easily accessed by anyone.

In an attempt to live longer, some enthusiasts of anti-aging medicine already inject growth hormone, swallow fullerenes, or gulp megavitamins, sometimes with disregard for mainstream medical thinking. Now unregulated gene therapy could be the next frontier. "I think it's damn crazy," says Bruce Smith, a professor at Auburn University who develops genetic treatments for dogs. "But that is human nature, and it's colliding with technology."

To pull off his experiment, Hanley used his scientific knowledge and part of his life savings. He put his insider know-how to work to procure supplies, order blood tests, win the sign-off of a local ethics committee, and engage a plastic surgeon who helped give him two treatments, a small dose in 2015 and then a larger one last June.

Hanley, who drives a battered sedan humming with Hindu rave music, fits the profile of an underappreciated genius on a self-improvement quest. He's a prolific online commenter whose opinions touch on everything from radiation to electric cars and street pickup of leaf piles. But his scientific thinking seems generally sound, and he says the meaning of his dream is straightforward too: he'd become Dr. Frankenstein's monster. "My unconscious is really not that subtle," says Hanley. "I had become something else, not entirely me."

Hanley's undertaking has caught the attention of big-league scientists. His blood is now being studied by researchers at Harvard University at the laboratory of George Church, the renowned genomics expert. Church, who provided MIT Technology Review with an introduction to Hanley, says he knows of a handful of other cases of do-it-yourself gene therapy as well. "And there are probably a lot more," he says, although no one is quite sure, since regulators have not signed off on the experiments. "This is a completely free-form exercise."

In 2015, we wrote about the case of Liz Parrish, an entrepreneur without a background in biology who claimed to have received a dose of gene therapy in Latin America. Parrish briefly worked for Hanley, whom she knew from anti-aging meetings. At least one additional person who underwent self-administered gene therapy is a U.S. biotech executive who did not want his experience publicly known because he is dealing with the U.S. Food and Drug Administration on other matters.

HANLEY'S UNDERTAKING HAS CAUGHT THE ATTENTION OF BIG-LEAGUE SCIENTISTS. HIS BLOOD IS NOW BEING STUDIED BY RESEARCHERS AT HARVARD UNIVERSITY GENOMICS EXPERT.

Hanley says he did not secure the approval of the FDA before carrying out his experiment either. The agency requires companies to seek an authorization called an investigational new drug application, or IND, before administering any novel drug or gene therapy to people. "They said 'You need an IND' and I said, 'No, I don't,'" recalls Hanley, who traded e-mails with officials at the federal agency. He argued that self-experiments should be exempt, in part because they don't pose any risk to the public.

That's not to say gene therapy is without dangers, such as immune reactions. "I spent years doing very little else other than iterating designs and thinking of all the ways something could go wrong," he says. When I met him on Stanford University's campus to discuss his project, Hanley zipped open his cargo pants to show me three black dots tattooed on his left thigh, marking the site of one of the injections. Had the gene therapy gone haywire, he says, his fail-safe option was to have the affected tissue surgically removed.

Informed consent

During a day I spent with Hanley in Menlo Park, he seemed to burst with energy, several times colliding with me as we tried to walk through doors. Was it the gene therapy at work, an excitable personality, or just a show? "I think getting near Spider-Man-like transformations of people is potentially possible," he says of gene therapy.

Most often, this approach relies on viruses to shuttle DNA into a person's cells. Hanley opted instead for a simpler method called electroporation. In this procedure, circular rings of DNA, called plasmids, are passed into cells using an electrical current. Once inside, they don't become a permanent part of person's chromosomes. Instead, they float inside the nucleus. And if a gene is coded into

the plasmid, it will start to manufacture proteins. The effect of plasmids is temporary, lasting weeks to a few months.

Because of its relative simplicity, the same technique is now eyed as a novel way to quickly deliver vaccines in response to emerging diseases. In August, the U.S. National Institutes of Health began dosing volunteers with a plasmid containing parts of the Zika virus.

Hanley took the technique in a different direction, poring over decade-old studies by a company called VGX Animal Health that had tried zapping plasmids into the muscles of cows, dogs with kidney disease, and baby piglets. They'd explored adding extra copies of the gene for growth-hormone-releasing hormone (GHRH)—a molecule that is normally made in the brain. One of its roles is to travel to the pituitary gland, where it acts as a regulator of growth hormone itself, telling the body to make more. It also appears to have an array of other roles, including enhancing the immune system.

"We never did try it in humans, but from everything that I saw in dogs, cats, cattle, pigs, and horses, it seems like a reasonable leap forward," says Douglas Kern, a veterinarian who worked at VGX. "It has very profound positive effects in most species."

Hanley says he designed a plasmid containing the human GHRH gene on his computer, with the idea of developing it as a treatment for AIDS patients. But no investors wanted to back the plan. He concluded that the way forward was to nominate himself as lab rat. Soon he located a scientific supply company that manufactured the DNA rings for him at a cost of about $10,000. He showed me two vials of the stuff he'd brought along in a thermos, each containing a few drops of water thickened by a half-milligram of DNA. In planning his study, Hanley skipped some steps that most companies developing a drug would consider essential. In addition to proceeding without FDA approval, he never tested his plasmid in any animals. He did win clearance for the study from the Institute of Regenerative and Cellular Medicine in Santa Monica, California, a private "institutional review board," or IRB, that furnishes ethics oversight of human experiments.

However, in the application by his company to increase "GHRH levels to more youthful levels," Hanley did not indicate that he planned to be the subject himself. He says that's not a problem, because he knows the risks so well after working on the idea for so long. "I am informed consent personified," he says. "There is no one in the world more informed than me."

But ethicists not involved in the study see a significant omission. "If I found out only after I approved a protocol that it was intended to be self-experimentation, I'd be seriously unhappy," says Hank Greely, a law professor at Stanford University. "That is definitely the kind of thing an IRB should know about." He says the issue is one of potentially impaired objectivity, as when a physician proposes to treat family members—except even more so, since Hanley is the designer of the therapy as well as its recipient, and may be financially dependent on the outcome.

"One thing you have when you're experimenting with yourself is a very, very deep conflict of interest," says Greely.

The video

When I asked Hanley for proof the treatment had actually occurred, he obliged by providing documentation and playing for me a video of the experiment he had stored on his laptop. In it, Hanley appears sitting in his undershorts in a doctor's office. The scene, recorded in June, shows the surgeon from the elbows down, wearing shorts, running shoes, and white exam gloves. The two met at a gym working out, Hanley says. Off screen, a female friend of Hanley's makes small talk as large ice packs are laid on his thighs.

Biologist Brian Hanley shows a tattoo on his thigh marking the location where a "DIY" gene-therapy he developed was administered.

"How are you feeling?" the doctor asks.

"A little nervous," Hanley replies.

Also watching the experiment that day, via Skype, was Bobby Dhadwar, a postdoc in Church's Harvard laboratory, which Hanley has kept abreast of his plans. "When I first heard someone is going to electroporate themselves, I thought they had to be kidding. It's usually something we do to animals," says Dhadwar.

The procedure, involving an electrical discharge into the body, is painful. Hanley tried it first in the summer of 2015, with no anesthetic. In a diary he keeps to track his results, he compared the feeling to torture. "Pow!" he noted. "No way is that acceptable. Have to work on that protocol."

This time, Hanley had opted to take six milligrams of the tranquilizer Xanax and got local anesthetic in his thighs. The doctor can be seen placing a plexiglass jig built by Hanley onto the biologist's thigh. The doctor leans in with a hypodermic needle to inject the sticky solution of GHRH plasmids into the designated spot. He also uses the jig to guide the two electrodes, stiff sharp needles the size of fork tines, into the flesh. The electrodes—one positive, one negative—create a circuit, a little like jump-starting your car.

In the video, Hanley's thigh shudders as the current is turned on, his cells open momentarily, and the DNA rings slip inside.

"That was better than last time," he's heard saying.

The results

Three weeks after the treatment in June, Hanley's diary records that he flew to Boston. By the morning of June 28 he had arrived at Church's Harvard lab, where he spent two weeks at a vacant desk. The geneticist, who enjoys millions in NIH grants, has a large program testing 45 different gene-therapy interventions in mice to see which extend their lives the most, or even reverse aging.

Church has said he thinks the gene therapy is "underrated" as a way to conquer old age and believes in a not-so-far-off scenario where "everyone takes gene therapy" not in order to cure hemophilia, sickle-cell anemia, or some other rare disease, but to reverse the results of getting old.

That makes Hanley a person of considerable interest to the lab—he's a sort of visitor from the near future. "We think it's very interesting to hear about people who are self-medicating with gene therapy," says Dhadwar. "It's so easy to acquire these materials; it's just one step to say 'I am going to start treating myself.'"

Dhadwar told me the lab had received blood samples from both Hanley and Parrish and was carrying out measurements to determine whether new genes were active in their bodies. He said in Hanley's case levels of GHRH appeared elevated, suggesting that the treatment had had an effect, although he cautioned that his results are not definitive.

With "indie" gene therapists checking in and out of his Harvard lab, I asked Church if it was becoming a sanctuary for people flouting medical convention, if not the law. One real risk is that gene therapy could become a zone of reckless and unproven treatments. "We certainly don't encourage people to do this; in fact, we encourage them not to," Church says. But he doesn't see why he should give up the chance to offer scientific feedback or assistance: "I don't think of it as offering a haven so much as a critique."

Invictus

In many conversations and e-mails with Hanley, I frequently wondered what his deepest motive was, and whether he even knew it himself. Was it to "develop products people will love," as he told me, as if he were the Steve Jobs of plasmids? When I described the experiment to Greely, the legal ethicist, he said it reminded him of the treacly 19th-century poem "Invictus," by William Ernest Henley. It's the one that ends, "I am the master of my fate: I am the captain of my soul."

Maybe doing gene therapy on himself was Hanley's way to take control of his business, his health, and his identity. Altering your DNA, in a very literal way, alters who you are. It also let him play in a big scientific pond alongside people doing "real science," like those in the Church lab. "To be in that game, you need to be hooked into NIH or Google's billions," says Hanley. "Someone like me, I look for things that are proven and that I am convinced of, and then how do we implement it?"

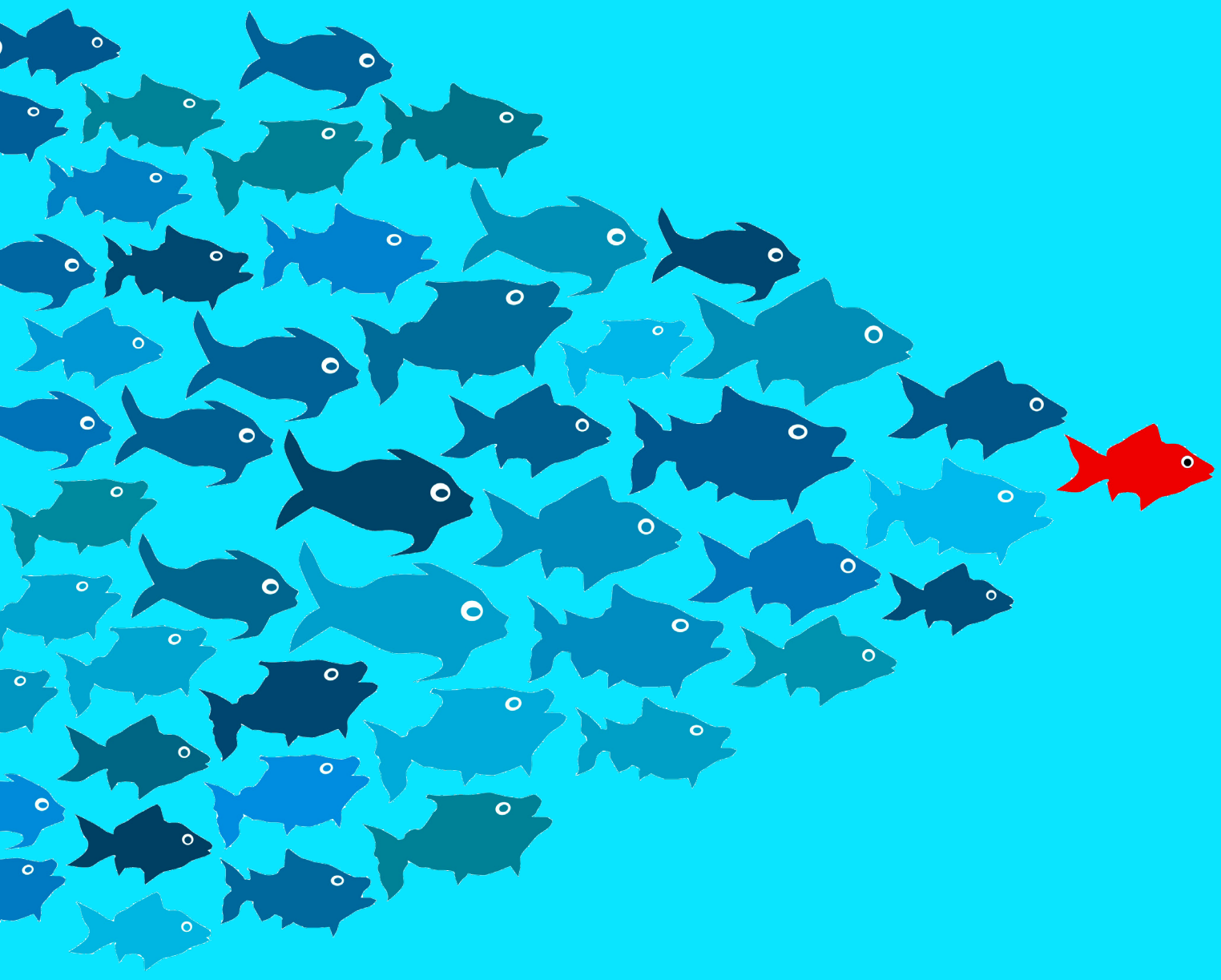
Should people be able to experiment on themselves using gene therapy without the FDA's sign-off? Tell us what you think.

So what happens next? The U.S. Food and Drug Administration could get involved, intervening with warning letters or site visits or auditing his ethics board. The plastic surgeon—whose name Hanley wished to keep confidential—could face questions from California's medical board. Companies that supply plasmids might start taking a closer look at who is ordering DNA and what they plan to do with it. Or perhaps authorities will simply look the other way because Hanley experimented on himself.

The kind of attention Hanley is hoping for, he says, is from investors. Maybe someone will fund a larger study, or perhaps there is a wealthy person interested in paying for his treatment.

THE U.S. FOOD & DRUG ADMINISTRATION COULD GET INVOLVED, INTERVENING WITH WARNING LETTERS OR SITE VISITS OR AUDITING HIS ETHICS BOARD. THE PLASTIC SURGEON—WHOSE NAME HANLEY WISHED TO KEEP CONFIDENTIAL—COULD FACE QUESTIONS FROM CALIFORNIA'S MEDICAL BOARD.

Hanley is proud of what he's done. He created a company, secured patents, made new contacts, identified a gene therapy that has plausible benefits for people, thought in detail about the risks, and offered himself up as a pioneering volunteer. Doing gene therapy to yourself, Hanley says, "focuses the mind, it really does." ▾▴



Why The Best Hospitals Are Managed by Doctors

Healthcare has become extraordinarily complex — the balance of quality against cost, and of technology against humanity, are placing ever-increasing demands on clinicians. These challenges require extraordinary leaders.

by **James K. Stoller, Amanda Goodall, and Agnes Baker**

DOCTORS WERE ONCE VIEWED AS ILL-PREPARED FOR LEADERSHIP ROLES BECAUSE THEIR SELECTION AND TRAINING LED THEM TO BECOME "HEROIC LONE HEALERS." BUT THIS IS CHANGING.

The emphasis on patient-centered care and efficiency in the delivery of clinical outcomes means that physicians are now being prepared for leadership.

The Best Hospitals. The Mayo Clinic is America's best hospital, according to the 2016 US News and World Report (USNWR) ranking. Cleveland Clinic comes in second. The CEOs of both — John Noseworthy and Delos "Toby" Cosgrove — are highly skilled physicians. In fact, both institutions have been physician-led since their inception around a century ago. Might there be a general message here?

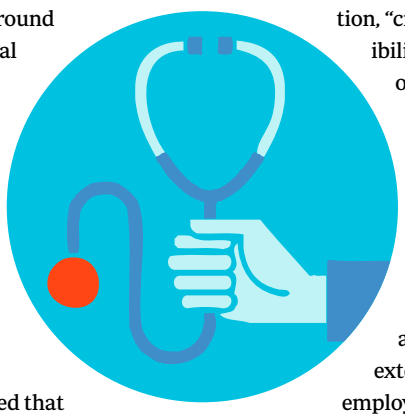
A study published in 2011 examined CEOs in the top-100 best hospitals in USNWR in three key medical specialties: cancer, digestive disorders, and cardiovascular care. A simple question was asked: are hospitals ranked more highly when they are led by medically trained doctors or non-MD professional managers? The analysis showed that hospital quality scores are approximately 25% higher in physician-run hospitals than in manager-run hospitals.

The findings of course do not prove that doctors make better leaders, though the results are surely consistent with that claim. Other studies also find this correlation. Research by Nick Bloom, Raffaella Sadun, and John Van Reenen revealed how important good management practices are to hospital performance. But they also found that it is the proportion of managers with a clinical degree that had the largest positive effect; in other words, the separation of clinical and managerial knowledge inside hospitals was associated with worse management.

Support for the idea that physician-leaders are advantaged in healthcare is consistent with observations from multiple other sectors. Domain experts – "expert leaders" (like physicians in hospitals) — have been linked with better organizational performance in settings as diverse as universities, where scholar-leaders enhance the research output of their organizations, to basketball teams, where former All Star players turned coaches are disproportionately linked to NBA success, and in Formula One racing where former drivers excel as team leaders.

Why doctors make good managers...

What are the attributes of physician-leaders that might account for this association with enhanced organizational performance? As leaders, do physicians create a more sympathetic and productive work environment for other clinicians, because they are "one of them"? Does being a physician inform leadership through a shared understanding about the motivations and incentives of other clinicians? When asked this question, Dr. Toby Cosgrove, CEO of Cleveland Clinic, responded without hesitation, "credibility ... peer-to-peer credibility." In other words, when an outstanding physician heads a major hospital, it signals that they have "walked the walk," and thus have earned credibility and insights into the needs of their fellow physicians. But we would argue that credibility may also be signaled to important external stakeholders — future employees, patients, the pharmaceutical industry, donors, and so on.



The Mayo website notes that it is physician-led because, "This helps ensure a continued focus on our primary value, the needs of the patient come first." Having spent their careers looking through a patient-focused lens, physicians moving into executive positions might be expected to bring a patient-focused strategy.

In a recent study that matched random samples of U.S. and UK employees with employers, we found that having a boss who is an expert in the core business is associated with high levels of employee job

The Analysis

A study published in 2016 examined CEOs in the top-100 best hospitals in three key medical specialties: cancer, digestive disorders, and cardiovascular care. A simple question was asked: are hospitals ranked more highly when they are led by medically trained doctors or non-MD professional managers? The analysis showed that hospital quality scores are approximately 25% higher in physician-run hospitals than in manager-run hospitals.

satisfaction and low intentions of quitting. Similarly, physician-leaders may know how to raise the job satisfaction of other clinicians, thereby contributing to enhanced organizational performance.

Our research suggests that if a manager understands, through their own experience, what is needed to complete a job to the highest standard, then they may be more likely to create the right work environment, set appropriate goals and accurately evaluate others' contributions.

Having an expert leader at the helm, such as an exemplary physician, may also send a signal to external stakeholders, such as new hires or patients, about organizational priorities. These factors are revealed in new work soon to be released.

Finally, we might expect a highly talented physician to know what "good" looks like when hiring other physicians. Cosgrove suggests that physician-leaders are also more likely to "tolerate crazy ideas" (innovative ideas like the first coronary artery bypass, performed by René Favaloro at the Cleveland Clinic in the late '60s). Cosgrove believes that the Cleveland Clinic unlocks talent by giving safe space to people with extraordinary ideas and importantly, that leadership tolerates appropriate failure, which is a natural part of scientific endeavor and progress.

...and how training can make them even better ones. Physician-leaders appear to be the most effective leaders precisely because they are physicians. Yet, great leadership also takes social skills. Medical care is one of the few sectors where lack of teamwork might actually cost lives, yet physicians are not trained to be team players. Nor is there evidence that it is the team players who select into medicine. Indeed, the favored nature of physician leadership of hospitals is even more remarkable for the leadership and followership handicaps that physicians must overcome in becoming doctors. In view of this handicap, Dr. Victor Dzau, President of the National Academy of Medicine, considers those successful physician-leaders (who largely lack formal leadership training) as "accidental leaders."

Physicians have traditionally been trained in "command and control" environments as "heroic lone healers" who are collaboratively challenged. In the context of this paradox, that medical training on the whole conspires against great leadership, there is a clear need to train physicians more systematically.

One model has been pioneered by Paul Taheri, CEO of Yale Medicine, who has been engaging doctors in management training for some time. He has focused on a two-tier approach: the first introduces physicians to the fundamental principles of business in the delivery of healthcare, and personal leadership development, through a day a month programme spread over a year. Taheri sends around 40 medical faculty annually. For those physicians who stand out as emergent leaders, the next step is an MBA. Taheri insists that in the executive programs physicians are always trained with other physicians, but by design they are taken away from their hospital environment into the safe learning environment of the business school.

The Cleveland Clinic has also been training physicians to lead for many years. For example, a cohort-based annual course, "Leading in Health Care," began in the early 1990s and has invited nominated, high-potential physicians (and more recently nurses and administrators) to engage in 10 days of offsite training in leadership competencies which fall outside the domain of traditional medical training. Core to the curriculum is emotional intelligence (with 360-degree feedback and executive coaching), teambuilding, conflict resolution, and situational leadership. The course culminates in a team-based innovation project presented to hospital leadership. 61% of the proposed innovation projects have had a positive institutional impact. Moreover, in ten years of follow-up after the initial course, 43% of the physician participants have been promoted to leadership positions at Cleveland Clinic.

In-house programs have been developed in many healthcare institutions (including Virginia Mason, Hartford Healthcare, the University of Kentucky, etc.), by medical societies like the American Association of Physician Leadership, and by business schools (including Wharton, Harvard Business School, the Weatherhead School of Management, and soon at Cass Business School in London). There seems to be a widening consensus that training physicians for leadership matters. Such training promises to enhance the pipeline of physician-leaders so that the benefits of physician leadership can be more broadly realized.

Searching for Ebola's hideout

After the recent epidemic, Ebola disappeared. But this relief is only temporary: the virus is hiding somewhere – maybe in forest animals, maybe closer to home. Leigh Cowart joins the hunt.

© Owen Davey at Folio Art

There was a certain kind of quiet hopefulness when, in late April this year, the last Ebola patient of the West African epidemic – a two-year-old boy – walked out of a treatment facility in Monrovia, Liberia. With the smouldering embers of the outbreak fading, there was cause for celebration. But there remains the impotent fear of the unseen: Ebola is still out there, lurking. We just don't know where it's hiding or when it will be back. And if we're going to stop Ebola in the future, we have to find its hiding places.

Ebola is a zoonotic disease, meaning that it can spread between animals and humans. It burns hot and fast through people. Its ruthless nature means that we are often the end of the line for the virus: a host like us that gets too sick too fast, that dies too quickly, cuts down the virus's ability to jump into a fresh body. To remain a threat, Ebola needs a safe house in which to lie low and hide.

Such a long-term host, the quiet refuge of a pathogen, is known as a reservoir species. If a reservoir species is Ebola's safe house, we are its luxury retirement property, a place for it to live out its last days with a bang. The trouble is that we aren't sure where the safe house is. If we are going to be vigilant against Ebola's re-emergence, we need to find it.

Searches so far have focused on forested parts of Africa, the home of a number of possible reservoirs. Classically, bats have been considered the most likely culprits, given that they overlap with humans geographically and can carry Ebola infection without symptoms. Based on research that has tested a wide variety of small mammals, bats, primates, insects and amphibians, several species of fruit bat have emerged as possible candidates. A 2005 study published in Nature and helmed by Eric Leroy tested over 1,000 small vertebrates in central Africa and found evidence of symptomless Ebola infection in three species of fruit bat, suggesting that these animals – which are sometimes hunted for bushmeat – might be Ebola's reservoir. An editor's summary ran alongside the paper, titled simply: 'Ebola virus: don't eat the bats'.

But not everyone is convinced that fruit bats are to blame. Some researchers, like Fabian Leendertz of the Robert Koch Institute in Berlin, are working with circumstantial evidence that points to the insectivorous bat Mops condylurus. The first – or 'index' – case of the 2014 Ebola epidemic was traced to a two-year-old boy in Guinea who may have spent time inside a large hollow cola tree near his house before falling ill. The tree was a known roost for these bats and a popular neighbourhood play spot. The boy died in December 2013, and by the following March, officials were alerting the public to the brewing outbreak. However, by the time researchers arrived in April to examine the tree and its inhabitants, it had been burned down.

Still others are looking elsewhere for Ebola's home, sceptical that bats are to blame. Virologist Jens Kuhn of the US National Institute of Allergy and Infectious Diseases at Fort Detrick, Maryland, has told Nature that he thinks bats live much too close to humans: if they were the reservoir, it would be curious that there have been so few emergences of Ebola since we first discovered the virus 40 years ago. Instead, he believes insects or fungi could be possibilities. As he told National Geographic in 2015, he's betting on finding Ebola in a "strange host", explaining that perhaps the virus is hiding in a tick or a flea that intermittently bites bats, which only sometimes initiates the virus's move from the wild into human communities.

Nevertheless, bats are largely considered to be our best bet, even if a lot of the incriminating evidence is circumstantial. The fact that certain bat species can harbour an Ebola infection is important. A screening test in 1996, during which researchers injected live Ebola virus into 24 species of plant and 19 species of animal – such as pigeons, cockroaches, small mammals and lizards – found that bats could test positive for Ebola infection for at least 12 days. None of the bats died from the virus, and none of the other species showed such potential as hosts.

This capacity to handle the virus adds to the argument that bats could be Ebola's hideout. But without further evidence, we can't be sure that they are.

The reason we need to be sure has to do with prediction and prevention: if we know the reservoir

species and where they live, we can allocate resources to areas at risk, help the local communities better prepare, and cut down on potential exposure to the virus by educating those who might stumble through its territory.

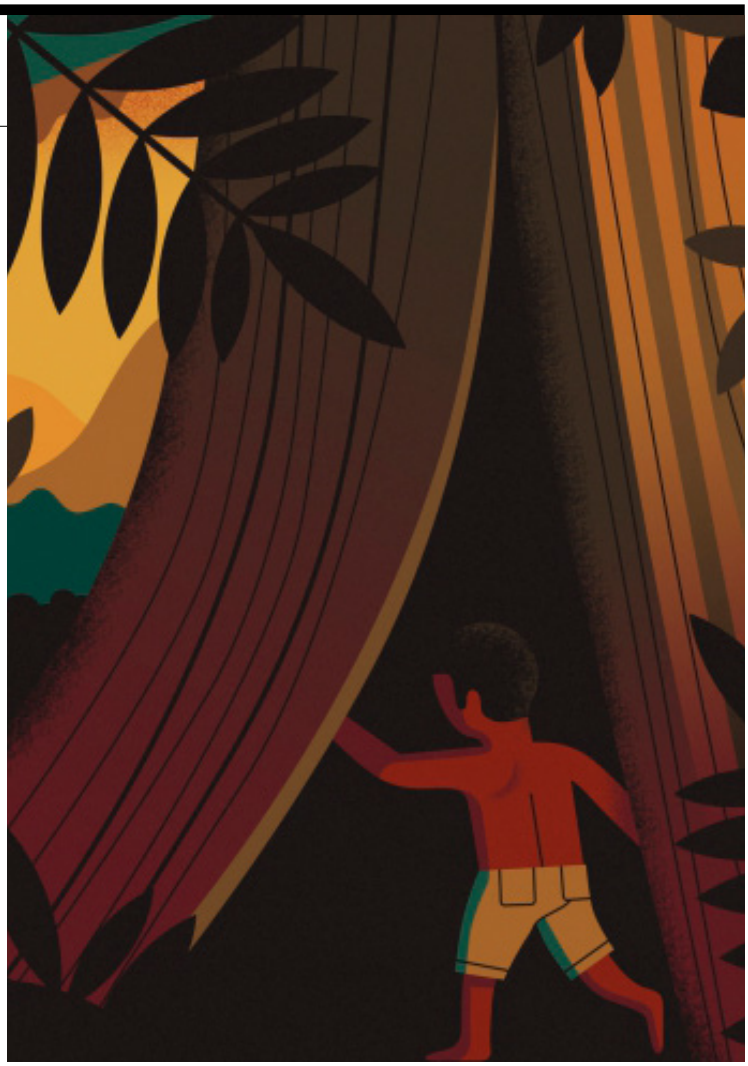
And that's where zoonotic niche mapping comes in.

These maps are a way to look for patterns in where Ebola comes out of the forest and into the homes that line the wilderness – scenarios known as 'spillover' events. By studying Ebola spillover, we can better predict where the virus might emerge in the future. Researchers like spatial epidemiologist David Pigott are combining measures of ecological features like vegetation, elevation and the presence of suspected reservoir species with the exact geospatial coordinates of index cases to create an algorithm that describes who might be at risk.

"We wanted to know where else in Africa could potentially be in the same situation as Guinea in 2013 and early 2014," says Pigott, lead author of the newly updated zoonotic niche map of Ebola in Africa. Back then, doctors were seeing cases of Ebola virus disease but not diagnosing them correctly, "because no one thought that Ebola could be circulating in that area".

Curiously, in Pigott's model, the presence of bats is not the strongest clue precipitating a spillover event. Instead, he says, the main predictor of where Ebola may emerge is the vegetation index. The amount of vegetation "could influence a variety of different species," he explains. Though bats were included in the model, "it was vegetation that dominated the profile". Translation: among areas that had experienced a spillover event, there was a critical pattern of plant cover that stands to be very helpful in identifying areas that might be at risk from Ebola in the future.

While ecological niche mapping can help in predicting spillover, there's also another, less well explored hiding place to consider: people. Ebola has an incredible ability, unknown until recently, to stake out a claim in bodily fluids of men who have survived infection, long after they have returned to health. In fact, a recent study found that over half of male survivors tested positive for Ebola in their semen one year or longer after they'd recovered, with one survivor's semen testing positive a full 565 days post-recovery. Because of the risk of spreading infection, male survivors are recommended to avoid unprotected sex until their semen has twice tested negative for Ebola.



Despite this, Pigott thinks it's worth bearing in mind that most outbreaks historically have followed a narrative of human–animal interaction. "The other big unknown in terms of future outbreaks is how long is the transmission route viable." It's hard to incorporate transmission by survivors into a predictive model because we simply don't know how long people can carry the virus and remain infectious.

This potential for human-to-human transmission means that Ebola has opportunities to re-emerge without a spillover event from the forest. And this means you don't even need to be near the forest to get it. Ebola's persistence in semen means we now have to track this curious villain in two ways. We must look for both patterns of emergence in our messy data streams.

So to be prepared for Ebola in the future, we need to discover how the virus moves through the wild and the city alike. We must find out where it thrives and how it spills over, and we must track it to all of the places it goes when we are not watching from the hospital bedside. With Ebola, there remain too many questions for us to rest easy. ▾▴

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Cameron Harding is one of the first children to survive spinal muscular atrophy.

PHOTOGRAPH BY LEIGH WEBBER

How a Boy's Lazarus-like Revival Points to a New Generation of Drugs

Drugs made from RNA may be the next great class of medicine. by **Karen Weintraub**

Shortly after Cameron Harding's one-month check-up, his mother, Alison, saw that her newborn seemed to stop moving. She'd unwrap him from a swaddle and his arms would flop to one side. He wouldn't kick his legs or turn his head.

The diagnosis: spinal muscular atrophy. The inherited illness, which destroys the motor neurons that control movement, often kills children before they turn two. Cameron's case was severe enough he'd probably never even have a birthday.

But when he was seven weeks old, Cameron's parents enrolled him in a clinical trial for an experimental drug. In videos shot two months later, he could move his head and reach for a toy. No child with his condition had ever made such a recovery before.

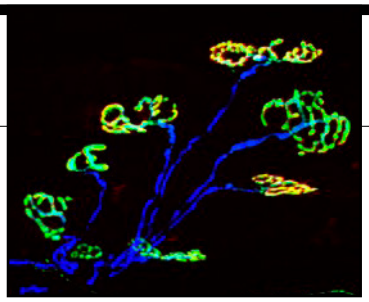
The drug Cameron received, Spinraza, was approved in the U.S. just before Christmas and may become the first blockbuster in a novel category of drugs called RNA therapeutics, after the genetic messenger molecule from which they are constructed.

Drugs made of RNA have been in development for more than 20 years. But Cameron's remarkable trajectory is a sign they could be ready to join familiar pharmacy chemicals and biotech proteins as the next great class of drug types, proponents say.

"Right now, RNA therapeutics—that's the future of medicine," says Steven Dowdy of the University of California, San Diego, School of Medicine. Dowdy admits to being a partisan—his lab works on RNA—but says advances in chemistry have finally made this type of drug feasible. "We still have a lot of work to do, but it's going to be huge," he says.

Some investors think so, too. One private company, Moderna Therapeutics, has reportedly managed to raise nearly $2 billion to develop what it calls a "platform" for inventing new RNA treatments. Overall, more than 150 clinical trials under way are using RNA to treat cancer, infection, hormone problems, and neurologic diseases, including Huntington's disease.

Inside our cells, the genes in our DNA code are translated into copies



An image of the junction between the nerve fibers and muscles of a mouse.

made of RNA. These copies, in turn, float into the cell body, where they serve as the information template from which proteins are manufactured. Most drugstore pills act directly on proteins. Gene therapy, meanwhile, seeks to replace DNA instructions with new ones.

What drugs like Spinraza seek to do instead is use RNA to block, modify, or add to, the existing RNA messages in a cell. The most serious challenge to this approach, says Dowdy, is that cells evolved billions of years ago to keep RNA from the environment out. Overcoming this "delivery" problem has cost company chemists many years of effort.

While the science of RNA has unfolded since the 1960s to a drumbeat of Nobel Prizes, the advance into real medicine hasn't been quick. Ionis, then known as Isis Pharmaceuticals, got the first RNA treatment approved in 1998 to counter an eye virus afflicting AIDS patients. But the drug became irrelevant once anti-HIV drug cocktails proved successful.

RNA drugs have also been beset by serious side effects, and several have been pulled from human tests over safety concerns. In October, the biotech company Alnylam had to stop a large study of one drug, Revusiran, after unexplained deaths in volunteers being treated for a hereditary metabolic disease, ATTR amyloidosis.

Alnylam, which works with a technique for blocking RNA messages, has spent about $1.5 billion since being founded in 2002 but is still working toward its first product. In January, in a paper published in the New England Journal of Medicine, it showed that one of its drugs could lower cholesterol levels for six months with one shot. Rachel Meyers, previously a senior executive at Alnylam, says one problem facing RNA drugs is that companies have too often tried to use them to treat diseases where other options exist. Instead, she believes, RNA therapeutics are more likely to find success in situations, like Cameron's, that can't easily be treated in any other way. "The dirty secret of RNA therapies is that most people are working on stuff where there is competition and there are other molecules," she says. "It's those ones that don't have a good alternative where you say, 'Oh my gosh, we can really change the world, or someone's life, with this.'"

Ionis's drug, which is being commercialized by its partner, Biogen, works through a mechanism called "antisense." The drug is a chemically enhanced strand of RNA that, by matching up with a mirror copy present in Cameron's cells, allows his body to correctly assemble a protein his nerve cells need.

Last year, two drugs that work along these lines were approved in the U.S. The other, Exondys 51, developed by Sarepta Therapeutics, was approved to treat muscular dystrophy after becoming the focus of impassioned lobbying by parents of affected boys, who prevailed on the U.S Food and Drug Administration to allow it on the market despite limited evidence of its benefits.

There are no such questions about the drug Cameron receives. Its effects are "Lazarus-like," according to one expert, but it is not simple and is not a permanent cure. It's delivered through a spinal tap once every four months, and Cameron will need it for the rest of his life. The cost of the injections: $375,000 a year.

"This has given us a glimpse into a future that's really quite profound, at least in serious disorders of the central nervous system," says Biogen executive vice president Michael Ehlers.

What happens next for Cameron is not clear. Since Spinraza just started being tested in children five years ago, doctors aren't sure what will occur as Cameron grows older. C. Frank Bennett, senior vice president of research at Ionis, says the company is now studying the results if the drug is given even earlier, just after birth, and before symptoms start. So far, he says, these kids are meeting their developmental milestones by rolling over and crawling on time.

Cameron's mother, an employee of a bank's IT department, says her son is still learning to control his muscles well enough to walk. It's "a ton of work," she says. "If there's anything I've learned this last three years, it's that the medication is not going to work by itself. If you do not work the muscles, you will not see progress." The toddler has a physical therapist, an occupational therapist, a speech therapist, a swim therapist, and a chiropractor in addition to "a lot of doctor's appointments."

Now that he's talking a mile a minute, Cameron's speech therapist is working to help make his words more understandable. He still hasn't learned how to control his facial muscles. But there's a little twitch at the corner of his mouth when he's happy. It's the beginnings of a smile.

Alison Harding and her son Cameron play at home. He was treated in a clinical trial with a novel type of drug made from RNA.

ART BY PING ZHU

Determined Parents are Moving the Needle on Gene Therapy

Families of patients are starting advocacy groups, raising money for research, and founding biotech companies to advance cures for rare diseases. by **Emily Mullin**

Alison Frase remembers the first moment when she thought gene therapy had a chance of curing patients like her son Joshua of a rare genetic muscle disease called X-linked myotubular myopathy. It was 2007, and she was viewing a video of a crippled mouse on her home computer. Four weeks earlier, the mouse had been injected with an engineered virus carrying a new strand of DNA intended to correct a genetic mutation that made its muscles limp and weak.

Frase watched in awe and began to cry as the mouse's limbs started to twitch. Eventually, it picked itself up and walked for the first time. "I thought, who cries watching a video of a mouse?" she recalls.

Frase is very likely the reason why the same treatment is now about to be tested in humans. In recent years, gene therapies have become safer and better at hitting their intended targets in the body, leading to a handful of remarkable cures in clinical trials. Advocates for rare-disease patients—especially determined parents like Frase—are increasingly seeking to start gene-therapy programs. They are establishing patient advocacy organizations, raising money for research, and even founding their own biotechnology startups to find treatments where few or none currently exist.

Gene therapy is an experimental technique that attempts to replace a disease-causing gene with a healthy copy. Because many rare diseases are monogenic—caused by a mutation in one gene—the approach could potentially be used to treat any disease where the precise genetic mutation is known.

"The prospect of being able to correct these genetic abnormalities with gene therapy has become a topic of great interest in the rare-disease community," says Mary Dunkle, vice president of educational initiatives at the National Organization for Rare Diseases. "The idea of being able to 'cure' a rare disease by addressing the underlying problem is alluring."

Joshua Frase's X-linked myotubular myopathy was diagnosed shortly after he was born in 1994. Cases vary in severity, but many affected children die before age two. Alison Frase began researching the disease but found only a handful of published studies, and patient advocacy organizations didn't know much about the disorder at the time. So in 1996, she and her husband, Paul Frase, a former NFL football player, created the Joshua Frase Foundation to raise awareness.

Eventually, Frase partnered with Alan Beggs at Harvard to establish a patient registry and encourage families to participate in medical research. Beggs's lab was collaborating with a group at the nonprofit

Alison Frase, with her son Joshua at age five in 2000, first learned about gene therapy more than 10 years ago.

Généthon in France when researchers sent her the video in 2007. Mice had been engineered to carry a mutation in MTM1, the gene involved in X-linked myotubular myopathy. Alterations in that gene disrupt the role of a protein called myotubularin, which is involved in muscle-cell development.

After the mouse experiments, Beggs and his colleagues published a study in 2010 that identified a group of Labrador retrievers with an MTM1 mutation, which displayed muscle weakness similar to symptoms in children with X-linked myotubular myopathy. Frase tracked down the owner of one of the dogs, named Nibs, in Canada. Back in the U.S., Nibs became the start of the first dog colony for myotubular myopathy, which the Joshua Frase Foundation helped fund.

The dogs became central to research by Martin Childers, a professor of rehabilitation medicine at the University of Washington. Childers, who has been working with Beggs and the Généthon group to develop and test gene therapy in the dogs bred from Nibs, says the results have been remarkable. "We were able to find a dose that completely reversed the disease in dogs. You could not tell the difference between the dogs with this fatal disease and the normal ones," he says. The findings were published in February.

A San Francisco company, Audentes Therapeutics, has licensed the technology and says it will begin a clinical trial this year. It will be the first human gene-therapy trial for X-linked myotubular myopathy.

Joshua died in 2010 at age 15, having lived years longer than his doctors expected. Though he will never be able to benefit from the therapy, Alison Frase hopes her years of advocacy will be able to help other children.

Racing toward a cure

Historically, much of the research on rare diseases has been driven by patients and patient organizations that have raised funds for grants and reached out to medical researchers, says Dunkle. "It's not surprising that parents of children with devastating diseases would be doing whatever they could to try to save the lives of their children," she adds. "For them, the clock is ticking, and there is a powerful sense of urgency."

Ilan Ganot knows that feeling well. He's determined to cure his six-year-old son Eytani of Duchenne muscular dystrophy, a degenerative muscular disease, and he thinks gene therapy could be the way to do it. Most boys born with the disorder only live into their 30s.

A former J.P. Morgan banker, Ganot moved his family from London to the Boston area, raised $17 million, and in 2013 founded Solid Biosciences to develop drugs for Duchenne. The company considered more than 200 different treatment approaches before making gene therapy its top priority.

Its therapy aims to restore dystrophin, a key protein that keeps muscles intact, which is missing in Duchenne patients. The dystrophin gene is too large to fit inside a traditional engineered virus, a problem that hindered previous efforts to develop gene therapy for the disease. So the company is using what it calls "micro-dystrophin," a DNA sequence that acts like the full-size gene but is small enough to fit inside a virus. Ganot says he hopes to begin clinical trials of the therapy this year.

The promise of gene therapy

Patient advocate Laura King Edwards is excited about gene therapy for its potential to correct disease at its root, even though it might not come in time to save her 18-year-old sister, Taylor, who has an extremely rare and fatal neurological disorder called Batten disease. "The beauty of gene therapy is that to a certain extent you can put any gene into a viral vector and get it to the gene you need to fix," says Edwards.

Taylor was a thriving seven-year-old when her condition was diagnosed in 2006. For years, she continued to excel in school, ran 5Ks, and competed in talent shows, Edwards says. Now, she is blind and has lost the ability to walk or communicate.

The same year as Taylor's diagnosis, Edwards and her mother, Sharon King, founded a patient advocacy organization called Taylor's Tale to focus on the disease. In 2011, King connected with a young researcher named Steven Gray at the University of North Carolina at Chapel Hill, whose lab was working on gene therapy for other rare diseases. Two years later, Taylor's Tale and other organizations raised enough money to fund a grant for Gray to expand his work on gene therapy for Batten disease.

Would you want your child to get an experimental gene therapy if no other treatments existed? **Tell us your thoughts.**

Dallas-based Abeona Therapeutics licensed the technology from Gray's lab last September and is now moving toward clinical trials. Gray says rare-disease patients and their families are becoming interested in gene therapy because of recent successes in clinical trials of other rare diseases.

"I'm seeing a transformation where there's a sense of patients and patient advocates being enabled to fight for the development of new treatments," he says. And as the falling costs of genetic testing make it possible to diagnose these conditions at ever younger ages, Gray says, there's an opportunity to intervene early. ▼▲

Lab-in-a-Box

A $150,000 instrument being tested in gene-therapy studies of cancer. It automatically adds a new gene to a person's blood cells.

Image courtesy of Prodigy

This Lab-in-a-Box Could Make Gene Therapy Less Elitist

Genetic repairs are curing patients—but only at a few elite centers. by **Antonio Regalado**

Jennifer Adair carried out her first gene therapy experiment several years ago. A cancer treatment, it involved collecting blood from a patient, and then adding to these cells a new strand of DNA—a gene—that would protect them from a powerful chemotherapy.

The altered cells were then reinfused into their veins. The study, involving 11 patients, proved fairly successful. But Adair, who runs a gene-therapy lab at the Fred Hutchinson Cancer Research Center in Seattle, says it took three sleepless scientists around 96 hours just to process a single person's cells in a multimillion-dollar clean room. "I said, 'Wow, we really need to simplify this,' " Adair recalls.

Gene therapy is moving quickly from experiment to medical reality. But with potential treatments for cancer and rare diseases now showing promise, scientists are worried that the technology is so complex that patients will not benefit as quickly as they should because of a shortage of trained technicians and suitable facilities. For the most successful gene therapies, those that require modifying blood cells outside the body, the procedures are offered only by a dozen or so research centers, all in major cities like New York, Seattle, Milan, and Paris.

Bottlenecks and ethical dilemmas are arising already as some patients able to afford it buy plane tickets and travel across the globe to seek out cures, while the vast majority of people have no possibility of accessing these treatments.

Just last week, French scientists working with the U.S. biotech company BlueBird Bio described

how they'd replaced the gene that causes sickle cell disease in a boy at a Paris hospital. It was yet another technical success. But no one asked how it would reach those who need it. Most cases of sickle cell disease—about 57 percent of the 300,000 new cases each year—are in Nigeria, the Democratic Republic of the Congo, or India.

In October, Adair demonstrated a new technology she thinks could democratize access to gene therapy. Tweaking a cell-processing device sold by German instrument maker Miltenyi, she mostly automated the process of preparing blood cells with a gene therapy for HIV that her center is also testing. Cells dripped in one end came out the other 30 hours later with little oversight needed. She even added wheels. Adair calls the mobile lab "gene therapy in a box."

Adair thinks a key job for the mobile gene-therapy lab is to extend experimental studies to the developing world, including Africa, where most HIV cases are. "We wanted to show that we could make the trial mobile, because we are kidding ourselves that treating someone in Seattle is going to have the same risks and outcomes as in South Africa," she says.

Cancer treatment

Helping to drive interest in portable gene-therapy devices is a new form of cancer therapy, known as CAR-T, that reprograms the DNA of immune system sentinels called T cells so they attack tumors. A growing pack of biotech companies has raised billions of dollars to test these treatments, which also require taking a person's blood and performing the gene addition in a specialized facility.

One of the first CAR-T treatments to reach the marketplace will probably come from Novartis. The Swiss drug giant last year completed a global test of children with leukemia in which 82 percent of the kids saw their tumors evaporate, and many stayed cancer-free.

"We want to make cell therapy less elite than it is right now. I don't think every rural hospital will be able to do it, but it doesn't have to only be for people able to pay $500,000,"

Novartis will apply for permission to sell the treatment this year, but the company isn't too happy with how the therapy is made. For its study, Novartis says that it air-shipped patients' cells back and forth to a single cell-processing factory it owns in Morris Plains, New Jersey, with the help of Cryoport, a company specializing in shipping frozen cells. It's logistically complex, labor-intensive, expensive, and potentially unpredictable, since no two people's cells are the same. What's more, Novartis isn't certain how many patients it will actually be able to treat.

"We are limited in the number of patients we can treat given the cumbersome supply chain that we have going," says Philip Gotwals, chief of exploratory immune-oncology at Novartis. "If we don't do anything to automate the process, you would have to [build more of] these large factories, and I don't know if the industry would do that."

Less elite

Miltenyi, the German device maker, says its instrument, called Prodigy, can already largely automate CAR-T production, and is now being tested by a few companies. The instrument, which weighs about 150 pounds, looks a little like a machine from Willy Wonka's factory, with bright pastel casements, neatly placed dials, and twists and turns of disposable tubing covering its surface. Instead of hot chocolate, a patient's cells move through the tubes, mixing with chemicals that stimulate them and, eventually, a load of DNA-carrying viruses used to alter their genetic code.

The instrument costs about $150,000, and a kit of supplies to process one patient's cells costs another $12,000. Katharina Winnemöller, a marketing manager based in Germany, says doctors in London will use the box to treat cancer patients with CAR-T cells in coming months. "We want to make cell therapy less elite than it is right now. I don't think every rural hospital will be able to do it, but it doesn't have to only be for people able to pay $500,000," says Winnemöller, citing a potential price for this type of cancer treatment. "I think the price has to go down."

Novartis's Gotwals says Miltenyi's gadget is just one of several devices under development. Last summer, after predicting CAR-T cancer treatments could generate $10 billion in sales by 2021, General Electric acquired a company called Biosafe that specializes in cell handling. The research organization Draper is working on microfluidics devices to prepare CAR-T treatments and a California startup, Berkeley Lights, has new ways to sort through blood cells to zero in on just the right ones.

Gotwals expects that, at first, gene therapy in a box will be useful to companies that want to expand manufacturing, or to academic centers that want to start offering it. Eventually, it may be that when a person is diagnosed with cancer or born with sickle cell disease, doctors in Lagos, Mumbai, or Seattle simply go online and order the right gene-therapy kit. "The aspiration is to have a device by the bedside. You would just plug the patient in and give them whatever makes sense," says Gotwals.

The winner of the 2008 Nobel Prize in Physiology or Medicine, French scientist Francoise Barre-Sinoussi (L), receives her medal and diploma from Sweden's King Carl XVI Gustaf in the concert hall in Stockholm December 10, 2008. Barre-Sinoussi was awarded the prize for the discovery of the human immunodeficiency virus, HIV.

THE woman WHO discovered HIV

REUTERS/Fredrik Sandberg/Scanpix

"We were very naïve. More than 30 years after, we still do not entirely understand why the CD4 cells are disappearing."

Dr. Françoise Barré-Sinoussi, Nobel Laureate

Interview by **Mary Engel**

Nobel Laureate Dr. Françoise Barré-Sinoussi, the French virologist who has been a leader in HIV research since her 1983 co-discovery of the virus, In addition to her research, Barré-Sinoussi, the director of the Regulation of Retroviral Infections Unit at the Institute Pasteur in Paris, is equally known for her advocacy for people with HIV.

Mary Engel: **When you discovered the retrovirus that turned out to be HIV, did you have any idea what it meant and how it was going to change your life and career? Did you have any idea how big this was?**

Françoise Barré-Sinoussi: I had the idea that it was an important discovery because I was convinced that it was a new virus, never identified before. I called one of my best friends in the United States, to share with someone. He said, "Oh, my God. If what you are telling me, Francoise, is true, I would take this virus and I would put it in the garbage immediately because you are going to be in a mess for the rest of your life!" He was right!

He was joking, but he made me realize how important was this discovery.

Of course it took additional months to make the link between the virus and the disease itself. But there is something that I and others at that time did not realize -- none of us in 1983 had any idea of the magnitude of the epidemic, and none of us had any idea about the complexity of the interaction between the virus and the body. I remember saying, "Oh, this is very clear. We infect CD4 cells with this virus, and the cells are dying, so this is the explanation of the loss of CD4 cells." We were very naïve. More than 30 years after, we still do not entirely understand why the CD4 cells are disappearing.

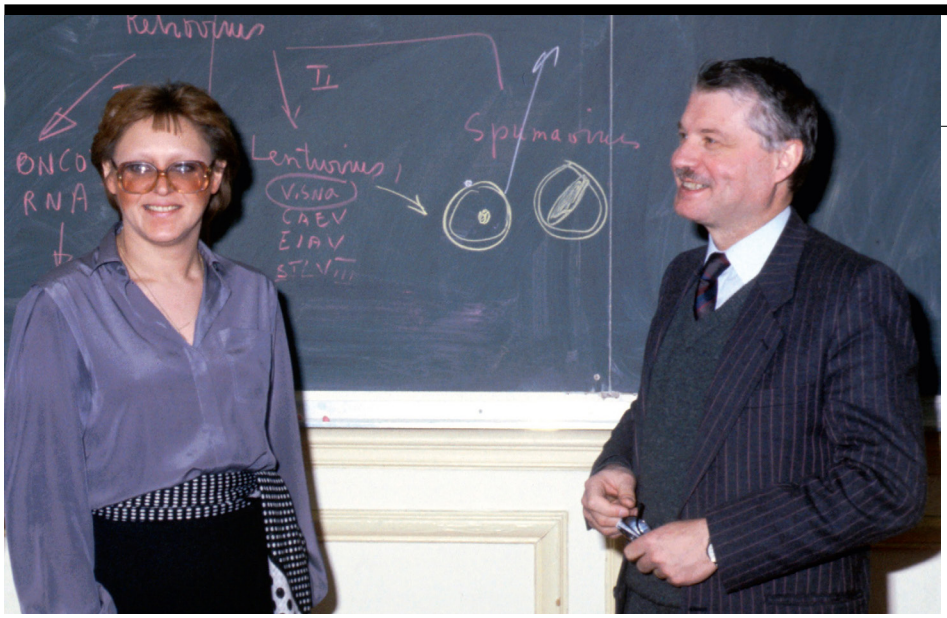
Are any other viruses this complex, that after 30 years, you still don't understand?

There are very complex viruses, but this one is particularly complex probably because it affects the cells of the immune defense, all the cells that are critical for immunity.

One way that this changed your life was how, as a PhD scientist, not a medical doctor, you hadn't expected to work with patients. Yet after your discovery became known, people with HIV started coming to your lab at the Pasteur Institute. Yesterday you mentioned two men in particular. Could you tell that story?

It was probably in 1984 - in '83 we had a few people coming, but they were all French. But in '84, after the announcement in the United States [that the AIDS virus had been found] by [Health and Human Services Secretary] Margaret Heckler, then people started to come to us in Paris thinking that we may have a treatment or something to propose. Among them I remember two that came to Pasteur. They were really in terrible shape. They should have been in hospital. They were very depressed, ready to suicide. And so I felt in a very difficult situation. I asked if they'd like me to call a doctor because I was not a doctor. And they said no. And so I said to myself, "You have to be careful about what you say because they can go out and suicide in the street." I said, "Look, I cannot feel what you feel because I'm not myself affected by this disease.

But you have to realize that you are not alone. There are many others, unfortunately, affected by this disease. I myself am starting to work with NGOs, with communities. Maybe you should be involved with



REUTERS/Copyright Institut Pasteur

communities because you will find out new objectives. You will see that that it is useful for you to talk with others that are in the same situation as you." They left. I did not know what happened until 2008, after the announcement of the Nobel Prize. Among the thousands of mails that I received, I saw two.

They were from these people that I met. They wrote me: "Maybe you don't remember us, but you gave the advice to work for communities. We did. And we're still alive. We had time to wait for the treatment. And we're doing well."

You said of all the mail you'd received, it meant more to you than any of the others.

Yes. I said, "My God. They are alive." And that was really wonderful.

Where do you find your passion to keep working toward stopping HIV? What gets you up in the morning and back to work each day?

People living with HIV. I mean, it's them. More generally, life is so wonderful. I think the best motivation that you have is to fight for life. Like everybody, I have some times in my life when I'm pessimistic. I wonder whether I should continue, like everyone, I guess. Then I go and have a trip to Africa or Southeast Asia and have a small meeting with people affected by HIV, and I forget my mood. I say, "OK, let's go on. Let's continue. This is real life. Don't think about yourself."

When you started out, were there many other women doing this kind of research? How have you seen that change?

There were already women making science at that time, especially in the field of HIV, by the way. We were several women involved, in the early '80s and still today. Of course, I was young, but when I look back in the '80s, the number of women who were professor, for example, at Institute Pasteur, probably maybe five maximum. So there were women, but they were not at the highest level. Now fortunately it has changed. We are not far from 50 percent. The balance is much better now than it was 30 years ago. It was very hard then for a woman to be convincing. Both the fact that I was relatively young and the fact that I was a woman, it was hard for the male to believe that what I was saying was true. (Laughter.)

I'd say you showed them!

But a few of them were convinced. I remember giving my first talk at Cold Spring Harbor in New York. Several people at the end of my talk came to me, including males, for example some people from the CDC, and asked, "Can you come to Atlanta and tell us a little bit more about your story?" So some people were convinced, even if I was young and female.

When you come to a conference like this, it seems like there's a line that you have to walk between encouraging scientists to work towards a cure or remission and not overpromising to people who have HIV, not raising false hopes. How do you walk that line?

For me, it's very simple: Just try to say the truth. I mean, in science, you have to try. You have to try with a kind of rationale. I say to people living with HIV, "Look, we think that [at least a permanent remission] is feasible. It will not be for tomorrow because we have a lot of work to do, many approaches to try, which will take time."

What I know is if people and scientists are working better together - like it is the case here, by the way, people coming from the field of transplantation and others to work together with HIV researchers - I'm convinced it is the way to go. [We have to] try to go faster. But faster does not mean that it will not be long because unfortunately there's a lot to be done.

Wilderness doctor Matt Lewin in the field in the Philippines.

Expedition Doctor Combines Medicine and Adventure

Wilderness doctor Matt Lewin, M.D., Ph.D., has traveled to the ends of the Earth treating scientists who work in remote and dangerous locations.

As an expedition doctor with the California Academy of Sciences, he's handled dehydration in the Gobi Desert, poisonous spider bites in Papua, New Guinea, and altitude sickness in Argentina. But one of the biggest challenges, Lewin says, is saving victims of venomous snakebites, which he deems the world's most neglected tropical disease.

Neglected, he says, because 75% of snakebite victims who die never make it to a hospital. When you're deep in a rainforest or high atop a mountain on a scientific expedition, medical treatment can be hours or even days away, Lewin explains. When a venomous snake bites, it can send paralyzing neurotoxins coursing through the victim's veins.

The nervous system becomes progressively disabled, and death comes when neurotransmission ceases. With no instructions to breathe, the muscles of the diaphragm are stilled and the victim asphyxiates. Hospitalization can provide anti-venom and respiratory support to counter these effects, but in the most remote regions of the globe, there often is no antivenom, no respirator and, sometimes, no way out.

To protect scientists on future expeditions, Lewin invented a portable, field-friendly nasal spray that contains an antidote to some snake venoms that cause paralysis. Typically, anti-venom is administered through an intravenous (IV) injection, but Lewin thinks clinical trials will prove the nasal spray to be quicker, cheaper and likely equally as effective. It's easy to administer in the field, he says, because no needles are required.

And unlike IV anti-venom, it doesn't have to be refrigerated. Lewin tested the treatment on himself in an experiment that took place at the University of California San Francisco Medical Center. Surrounded by several anaesthesiologists and an emergency room doctor, he was paralyzed while still awake with a toxin that mimics cobra venom. The team then administered the nasal spray, and within 15 minutes Lewin completely recovered, though the paralyzing toxin was still being delivered into his bloodstream.

In India, where an estimated 1 million people are bitten by snakes every year, the nasal spray was successfully used to treat a patient who did not respond to anti-venom therapy. The spray has also been successfully tested in laboratory mice that were injected with high doses of cobra venom. Clinical trials are in the works, and when made widely available, the spray is expected to save tens of thousands of lives each year.

A CAREER-DEFINING MOMENT

Matt Lewin was exposed to science as a small child by his father, an industrial chemist, and his aunt, who worked at New York's American Museum of Natural History, where she would often bring her dinosaur-obsessed nephew. But Lewin's career-defining moment came when Carleton Gajdusek came to his second-grade classroom. Gajdusek had just won the 1976 Nobel Prize in medicine for unmasking a bizarre disease in Papua New Guinea called kuru, a byproduct of ritualistic cannibalism. His presentation was dazzling, with wild stories of jungle adventure. The laureate acted out stages of kuru,

NEJM | 23 Mar 2017 | Vol 376

Pregabalin for sciatica

There's nothing quite so personal as pain. If you have severe pain and take something for it and it goes away, your brain will insist that you take the same thing if it returns. This poses a number of problems for trials of pain relieving drugs. The obvious one is that pain may abate on its own: we can solve that by placebo controlled randomised trials like this one of pregabalin for acute and chronic sciatica. It shows that, overall, most sciatica resolves spontaneously, and that for the weeks during which it persists, pregabalin provides no better aggregated pain relief than placebo and causes more adverse effects. But the question still lurks: hidden in the disappointing overall figures, were there a few people for whom it worked really well? For enduring pain, the real world strategy is to try one thing, then another. The ideal trial method should therefore be a cluster of n-of-one trials. Instead, the editorial suggests a different approach, based on mechanistic biology: "This trial highlights a need in the field of pain treatment—namely, to identify biomarkers that could link the efficacy of a drug with the biologic causes of diverse types of pain." Until that far off day, I'll stick with just trying different things until the pain goes away.

The more stents you put in now, the fewer you'll put in later

Stents are so satisfying. They have won a place in our hearts. But should our hearts be stented simply because the coronary arteries look narrow? No, no, say the stenters: we are more sophisticated now, and use measures of fractional flow reserve (FFR). Does this really improve the selection of patients, or is it just a trick to keep this popular intervention common? We'll come on to that in the next item. This trial selected people who were having heart attacks and asked if they would mind being randomised to have just their culprit artery stented or to have any other narrowed ones with reduced FFR done at the same time. The composite primary outcome lumped together death from any cause, non-fatal myocardial infarction, revascularization, and cerebrovascular events at 12 months. As you might expect, those who had more stents at the time of myocardial infarct PCI "needed" fewer later. This may be significant, inasmuch as they were truly needed, but this is hard to pick out from the summary data. And, unfortunately, the trial was underpowered to detect differences in the most important outcomes: myocardial infarction and all cause death.

JAMA | 21 Mar 2017 | Vol 317

Treatment outcomes for localised prostate cancer

The first intensive work on shared decision making took place over 25 years ago and dealt with surgical options for benign prostatic hyperplasia (BPH). Nowadays BPH has slid into the background amid a PSA-driven epidemic of localised prostatic cancer. But two key outcomes described in this cohort study are the same as in that early work at Dartmouth: urinary incontinence and sexual function. In this sample, the 60% of men who opted for radical surgery were generally fitter physically and had better sexual function than those who opted for external beam radiotherapy (23%) or observation (17%). The surgical group, however, suffered the worst decline in sexual ability and an increase in urinary incontinence. This is not new news, but will help to inform the decision aids that need to be used in the future.

More fractures with warfarin?

If people taking warfarin are at greater risk of osteoporotic fractures than people taking dabigatran, that would be useful knowledge to share with patients starting anticoagulation. But we don't know. Observational studies using propensity matching can send signals, but unless the signal is deafening, it needs confirmation by other means—ideally by a randomised controlled trial. A population wide database managed by the Hong Kong Hospital Authority sends a signal that warfarin may be associated with more osteoporotic fractures than dabigatran. There have been several RCTs comparing dabigatran with warfarin, and perhaps the full individual participant data from these could shed further light on this issue.

“ I’ve always had mixed feelings about this ingrained ritual, and so it seems have those who are appointed to guide us.”

The Lancet
25 Mar 2017 | Vol 389

Cardiovascular disease and the noble savage

“Trope” is an annoying word introduced by literary academics to describe a recurring image or concept, such as people living happily in the wild. The noble savage trope appears in various guises from the earliest literature (Sumer, 3000 BC) to the present: we love to think that in some age or in some place, humans might live long healthy lives in perfect harmony with Nature. Sadly, we never have and never will, although we might do much better if we tried a bit harder. The Tsimane who live in the Bolivian Amazon practice a mixture of hunting, gathering, fishing, and farming. Although they show a high burden of chronic inflammation as shown by elevated C-reactive protein levels, they have the lowest reported levels of coronary artery disease of any population recorded to date, as assessed by coronary artery calcium scoring. “These findings suggest that coronary atherosclerosis can be avoided in most people by achieving a lifetime with very low LDL, low blood pressure, low glucose, normal body mass index, no smoking, and plenty of physical activity.”

The BMJ | 25 Mar 2017 | Vol 356

Wine that makes glad the heart of men

Ah, another observational study to end the week’s tally. This one is huge and sophisticated, and attempts to address the link between alcohol consumption and 12 common symptomatic manifestations of cardiovascular disease, including chronic stable angina, unstable angina, acute myocardial infarction, unheralded coronary heart disease death, heart failure, sudden coronary death/cardiac arrest, transient ischaemic attack, ischaemic stroke, intracerebral and subarachnoid haemorrhage, peripheral arterial disease, and abdominal aortic aneurysm. It is based on data from nearly two million people, using inputs from the Clinical Practice Research Datalink, married up with other large UK databases. Data about endpoints is therefore probably reasonably complete. But as someone who used to enter data into the CPRD, I wouldn’t vouch at all for the GP data about alcohol consumption. Most of it will be what patients wanted their doctors to believe. There’s the usual signal here of a threshold above which alcohol intake ceases to show any association with reduced CVD and starts to show an association with increased risk, not just for ischaemic disease and stroke but also for heart failure. But I’d suggest that whether you believe this or not, other factors should determine how much wine you have with your cheese.

JAMA Intern Med
Mar 2017 | Vol 177

Vague recommendations for cancer follow-up

“OK, we’ve treated your cancer: see a doctor you’ve never met before at the end of a busy outpatient clinic and have some tests every six or 12 or 24 months, just in case it comes back.” I’ve always had mixed feelings about this ingrained ritual, and so it seems have those who are appointed to guide us. This study looks at 41 guidelines on surveillance after treatment for nine common cancers, published between 1 January 2010 and 1 March 2016. European guidelines trump American for containing ambiguous recommendations: 100% vs 68%. But given the general lack of evidence, that probably just means that the American ones have a 32% higher level of meaningless certainty.

"In the cramped space Eva rocked back and forth," Dr. Ofri writes.

Doctor Feel bad

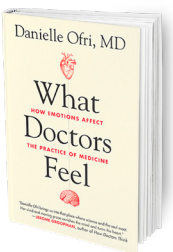
In *What Doctors Feel,* pain is not just the realm of patients.

In her new book, "What Doctors Feel," Dr. Danielle Ofri tells the unforgettable story of a pediatrician she interviewed, a woman she calls Eva.

In taut, vivid prose, Dr. Ofri describes a tragic event that occurred during Eva's residency. She helped deliver a baby doomed to asphyxiation within minutes of birth because of a severe lack of amniotic fluid in the womb. The traumatized parents knew the outcome in advance, and made it clear they did not want to see the baby. After the delivery, the room leaden with silence, Eva wrapped the baby in a blanket and wondered where to go. The hospital had no room set aside for this. So the young physician, consumed with sadness for a child who would never be held by anyone but her, took the dying newborn into a supply closet.

There, knowing she would be reprimanded for not observing the precise moment at which the umbilical cord ceased pulsing, she gathered the baby in her arms. "In the cramped space Eva rocked back and forth," Dr. Ofri writes. " 'I love you, baby,' she whispered as the heart began its slow, cratering descent."

In the hands of a less agile and intelligent writer, such a scene could easily grow maudlin. Indeed, calling attention to a physician's emotional pain might be seen as distracting and self-indulgent. It is, after all, the physician's role to ease the suffering of others.



What Doctors Feel: How Emotions Affect the Practice of Medicine
Danielle Ofri, M.D
Beacon Press
226 pages
$24.95

Yet as Dr. Ofri points out, how doctors feel matters. And while she does write of joy, pride and gratitude, her emphasis is on negative emotions — which exert the strongest influence on medical care, particularly when a case grows unexpectedly complicated, frustrating or unyielding. "This is where factors other than clinical competency come into play," she writes. An unwell doctor is a bad doctor.

Dr. Ofri is an internist at Bellevue Hospital Center in New York City, which cares for legions of indigent, uninsured patients, as well as a large population of immigrants. The author of three previous books and a frequent contributor to The New York Times, she writes for a lay audience with a practiced hand.

This book's hallmark is her honesty, particularly when it comes to the emotional fallout of her medical mistakes. When she dismisses a patient's litany of vague symptoms as stress-related, only to miss a blood clot in each lung, she is overwhelmed by shame and remorse.

She is also frank about her prejudices, particularly toward the worried well. Early in her career, during a summer job at a tony practice on Long Island, Dr. Ofri refused a woman's request for weight-loss pills. "After three years of round-the-clock AIDS, cancer, congestive heart failure and cirrhosis, it was hard to get worked up over a couple of middle-aged pounds," she writes.

But later she rethinks her reaction. "I wasn't able to step past my own issues," she writes. "Maybe underneath the seemingly superficial concerns were serious issues that were crying out for attention."

Then there is the constant thrum of death: Eva and the dying newborn; a young patient under Dr. Ofri's care with heart disease whose stormy course appears to end with a successful heart transplant, only to be followed by a fatal stroke.

It does make one wonder how doctors cope. A study of oncologists cited by Dr. Ofri found that these specialists learned to compartmentalize their grief. Yet the most striking finding of the study was how poorly that strategy worked. Grief spilled into the physicians' daily lives and sapped them of their inner strength.

After the newborn's death, Eva walled herself off from all emotions, only to have them return many months later with full-blown post-traumatic stress disorder.

Bitterness is here, too. Dr. Ofri devotes much of one chapter to malpractice lawsuits. She describes her own harrowing experiences of being sued — in one instance, by the family of a woman she had not just grown close to, but gone well out of her way to care for. "Dealing with a lawsuit is often likened to having a death in the family," she writes. "Doctors end up (often unconsciously) grieving for the doctors they used to be."

Counterintuitively, perhaps, Dr. Ofri is at her most compelling when telling other physicians' stories. It's almost as if she still needs to keep a slight cool distance from her own experiences. But this is not necessarily a sign of weak writing. It is an indication of just how raw the inner life of a doctor can be.

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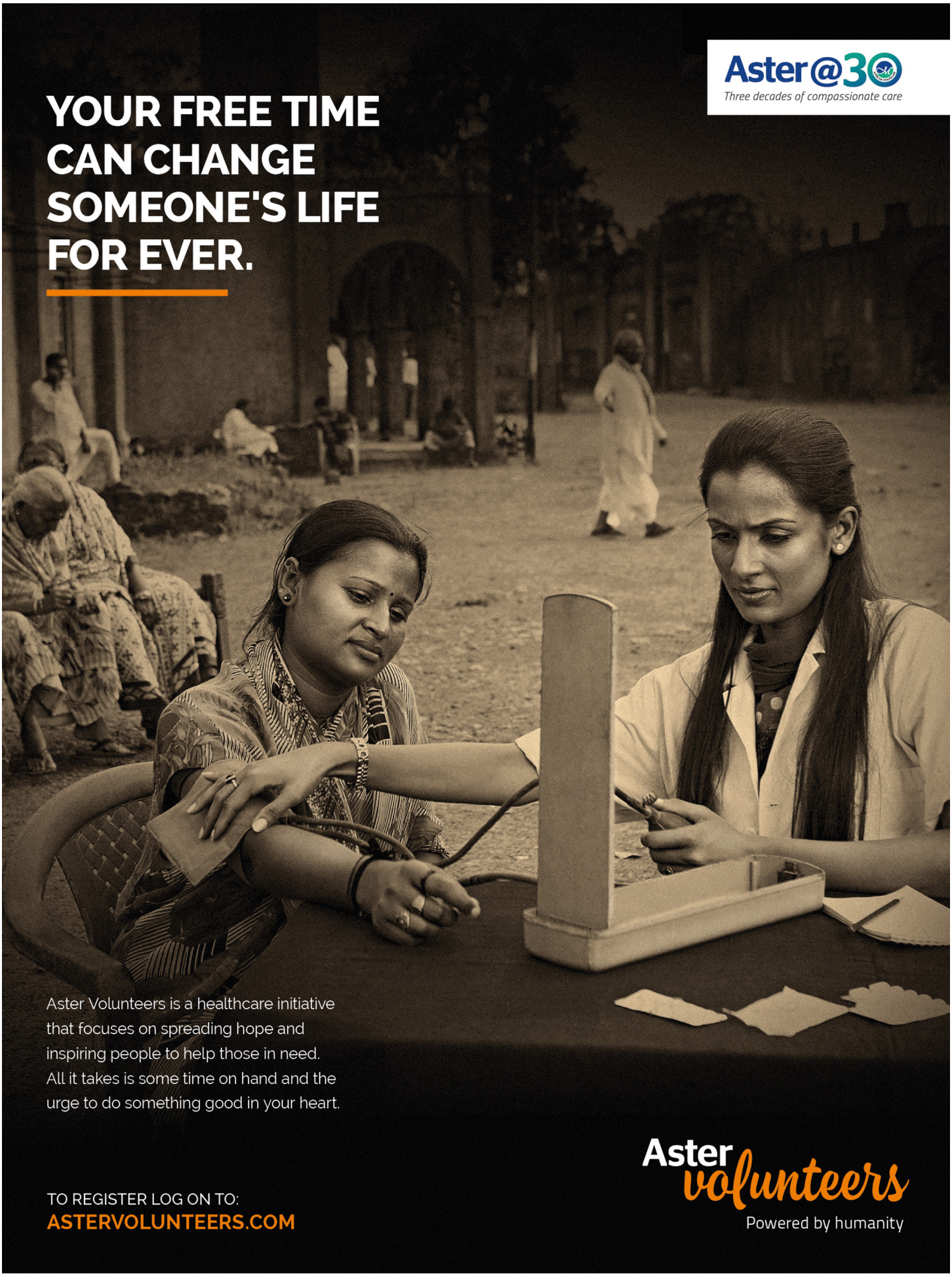
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