

Big Science, better care

Only massive collaboration can produce evidence that works for patients

Advancing problematic situations requires clinicians and patients to draw from their experience, expertise, and evidence. Working together, they should be able to find a way forward that makes intellectual, emotional, and practical sense.¹ How research is conducted, however, offers challenges to achieving patient centred care. The solution may lie in Big Science.

For many situations, funders prefer to obtain answers efficiently, and researchers win the competition for resources when they propose the smallest and briefest study. To succeed, these Little Science trials must enrol high risk patients, use comparators that favour the experimental intervention, and use responsive—surrogate or composite—endpoints. Hiding unflattering results completes the illusion. Clinicians and patients must deal with imprecise, inconsistent, and incomplete results about the effect of impertinent comparisons on endpoints of unclear relevance to the experience and destiny of patients. Little Science may work to support regulators and new drug marketers but falls short of what patients and clinicians need for care.

Big Data

Database observational research, or Big Data, can explore the effect of disease and care on many patients (with enough participants with rare conditions or from important subgroups), across many outcomes (with enough occurrence of rare outcomes), at a low cost per question. Big Data are more representative of the “real world” than Little Science trials that recruit a few patients from referral centres. Clinical trialists can use Big Data to design more efficient and useful trials, and to formulate and validate prediction models to support decision making and individualise care.² Sophisticated analyses cannot overcome inaccurate



data—common in these large clinical and administrative repositories—or permit causal inferences. Too often, Big Data are not-so-great data.

Patient centred care

Patient centred care demands trustworthy evidence that applies directly and confidently to patients. Studies designed to practically meet the needs of decision makers³ will need to be much bigger and longer than Little Science trials. Systematic reviews can help, but only when the body of small trials is trustworthy. Rather, randomised mega-trials, prospective meta-analyses, and other designs—some yet to be invented—respond better to the demands of care.

When these designs include thousands of patients and follow them completely for long periods, they can compare options as used in the “real world” and estimate their effect on outcomes that really matter to patients. Their design and conduct can be planned to protect against bias, rendering their results more trustworthy than Big Data studies. Their feasibility requires massive collaboration between scientists, academic institutions, clinics and health systems, patients, and communities. This is Big Science.

To work, Big Science requires generous collaboration. We have no evidence that relying on competition to cull ideas worth funding produces the best science. A zero-sum game

Competition produces rivals where we need partners; secrecy, redundancy, and waste where we need transparency and efficiency

favours competitors who offer timid improvements; bold innovators or reproducers of previous studies need not apply.⁴ Competition produces rivals where we need partners; secrecy, redundancy, and waste where we need transparency and efficiency. Young talents are convinced—through repeated failure that underinvestment makes more likely—their ideas are not worthy of realisation.

Problem solved

Competition hinders our progress to Big Science. Funders, scientific, and health agencies must bring together a few talented people in a room and thousands online to share ideas, methods, and protocols. Promotion and recognition programmes must be engineered to foster fearless collaboration. The ownership of ideas, resources, data, results, and credit in this culture must remain subsidiary to the celebration of problems solved.

The evaluation of new methods and the testing of alternative interventions will require a close and trusting partnership between clinical research and practice. Mega-trials must take place across diverse systems, on which scientists must impose the smallest possible footprint. Learning healthcare systems must engage with this minimally disruptive research and participate in Big Science, but they must apply its results.

For instance, healthcare systems can prevent suffering and waste by forgoing the use of inefficient or unsafe interventions and instead implement better options. Big Science is most likely to produce the kind of nuanced comparative data necessary to support shared decision making conversations.⁵ Patient centred care demands practical evidence. To produce it, we must shift from competition to collaboration: from Little Science and Big Data to Big Science.

Victor M Montori,
Mayo Clinic,
Rochester,
Minnesota
montori.victor@
mayo.edu

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Hope is a therapeutic tool

Don't be afraid to use it

Everyone who has been a patient, or accompanied a relative to see a doctor, recognises the importance of the doctor-patient relationship. At its heart is the patient's need to understand what is wrong, be understood, and be offered hope. Although it is common sense that hope is a fundamental element of overcoming any illness, the clinician's role in encouraging hope has been framed as one of the distinctive elements of the "art of medicine," relying on personal experience and instinct.¹⁻⁴ However, hope is in fact a practical therapeutic tool that can be optimised just like any other.

Despite the considerable attention given to the doctor-patient relationship during medical training, hope has been neglected. Many doctors still don't have a clear idea about how to use hope as therapy while at the same time being realistic and truthful about the potential for poor outcomes. Communication skills training tells us to avoid saying, "You are going to get better," because there is rarely such certainty and, in the case of poor outcomes, unfulfilled expectations will erode trust. Clinicians are apprehensive about offering false hope and can end up ignoring the question of hope altogether. This is particularly challenging for those of us caring for patients with chronic and progressive diseases—we fear looking incompetent when we have no curative treatments to offer.⁵

Hope versus optimism

When tackling these difficulties, it is important to differentiate hope from optimism. Optimism is an individual's confidence in a good outcome, whereas hope is a goal oriented way of thinking that makes an individual invest time and energy in planning how to achieve their aims. It consists of two interactive components: first, routes to achieve



A study of young people with type 1 diabetes found hope, but not optimism, was a predictor of improvement in glycaemic control

the desired goals and, second, agency, or the individual's goal directed intention and persistence.⁶ For example, an optimistic person with asthma would expect few attacks and not carry an inhaler, while a hopeful person would aim for good outcomes but still ensure an inhaler was available.

Powerful predictor

A study using the Children's Hope Scale showed that hope was a powerful predictor of asthma treatment adherence.⁷ Another more recent study⁸ followed young people (aged 10-16) with type 1 diabetes over six months to explore the associations between patients' hope and optimism—measured with validated scales—and treatment adherence. The study found that change in hope (but not optimism) was a significant predictor of improvement in both glycaemic control and self monitoring of blood glucose levels.

Therapeutic benefits are biologically plausible if hope is viewed as a kind of placebo effect. We know that placebos are sometimes associated with therapeutic benefits across a range of diseases. Effect sizes can be large, as observed in studies of pain management and Parkinson's disease, and a neurobiological basis is emerging. Studies using positron emission tomography and functional MRI suggest placebos are associated with a change in neurotransmitter

levels and activation of brain regions involved in reward and attention.⁹

Hope has been shown to protect against anxiety, and a recent study of functional MRI in 231 adolescents reported that it also mediates the association between anxiety and activity in the orbitofrontal cortex.¹⁰ This part of the cortex aids motivation, problem solving, and goal directed behaviours—brain functions relevant to pathways and agency, the two core elements of hope.

Mutual understanding

Can clinicians influence a patient's hope? There is preliminary evidence that brief, hope based intervention using guided imagery, goal-directed and pathways thinking can be effective in pain management.¹¹ However, doctors often believe patients expect substantial improvement or cure and do not always see a patient's capacity to process disability and adapt their treatment goals.⁵ This is evident in schizophrenia, for example. Whereas psychiatrists are preoccupied with reducing symptoms and attaining previous functioning, the patient's perspective is more on achieving independence and maintaining hope. Encouraging hope means negotiating a clear understanding of the aims of treatment through dialogue, mutual understanding, and a process of adjustment and acceptance.⁵⁻¹³

Hope may be one of the most powerful therapeutic aspects of the doctor-patient relationship.²⁻¹³ Framing the concept as part of the art of medicine risks making it intangible and potentially unattainable. Understanding that hope is a measurable psychological construct, associated with a plausible neurobiological mechanism and clinical benefits, should help clinicians use hope to its full potential in all clinical encounters.

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Rodrigo A Bressan, professor of psychiatry rodrigo.bressan@kcl.ac.uk

Eduardo Iacoponi, honorary senior clinical lecturer, Institute of Psychiatry, Psychology and Neuroscience, King's College London

Jorge Candido de Assis, vice president, Brazilian Association of Families, Friends and People with Schizophrenia, São Paulo

Sukhi S Shergill, professor of psychiatry and systems neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London

Feel the heat: a short history of body temperature

Time to let go of our cherished 37°C reference for normal

Before the 16th century, patients' temperatures could be monitored only by placing the hand on the forehead, cheek, or other body surface. The process took a scientific turn in 1592, when Galileo invented a primitive (air) thermometer during his tenure at the University of Padua in Italy.¹ However, it was not until Carl Wunderlich published his magnum opus, *Das Verhalten der Eigenwärme in Krankheiten* (The Course of Temperature in Diseases)² in 1868, that clinical thermometry reached the sophistication and importance it now enjoys among both the medical profession and the public.³

Ups and downs

Das Verhalten is remarkable for its content, clarity, and, perhaps most particularly, longevity. Wunderlich gave 37°C its special importance as the reference temperature in humans; demonstrated diurnal variation of body temperature; and established that "normal temperature" is in fact a range of temperatures that varies by anatomical site and time of day. He showed that women have a slightly higher average temperature than men, and that old people have slightly lower temperatures than young people.⁴

Until the advent of digital "big data," the size of Wunderlich's dataset was unequalled—estimated to have included several million observations from 25 000 subjects. The sheer volume of his data discouraged others from critically appraising his observations and conclusions, to the extent that, for over a century, his concepts survived largely intact in lay thinking and medical writing.

Philip A Mackowiak, emeritus professor, Department of Medicine, University of Maryland School of Medicine, Baltimore philip.mackowiak@va.gov

Daniel J Morgan, associate professor, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore

Many of his dictums have since been corroborated, including diurnal oscillation of body temperature,^{5,6} the slightly higher temperature of women compared with men,^{7,8} and the progressive slight diminution of average temperature with advancing age.^{9,10}

However, Wunderlich's most cherished and durable dictum, that in normal conditions "the general temperature of the body maintains itself at the physiological point: 37°C=98.6°F," has since been repudiated, most recently in the linked article by Obermeyer and colleagues (doi:10.1136/bmj.j5468).¹¹ In healthy young adults at least, 37°C is not the overall daily mean temperature, the mean temperature at any particular time of day, or the most commonly recorded temperature.⁸

Selective reporting

Though Wunderlich's dataset was enormous, he could have analysed only a small fraction of it. He reported only anecdotal glimpses of his raw data, and we have no way of knowing how he chose the data for analysis.

We do know that he used an unorthodox thermometer that systematically overestimated axillary temperatures, producing measurements more consistent with modern oral readings.³

Like Wunderlich, Obermeyer and colleagues had to deal with a vast number of clinical observations of variable quality and uncertain precision.

But whereas Wunderlich lacked the techniques needed to process his data, Obermeyer and colleagues challenge the average reader's understanding by choosing an analysis notable for

a confusing mixture of complicated modelling techniques.¹¹ Their analysis has as much to say about the promise and the perils of big data mining as it does about clinical thermometry or the legacy of Wunderlich.

A particular problem common to analyses of big data is a reliance on data collected for purposes different from those of the study authors.¹² Obermeyer and colleagues, for example, analysed data recorded for financial purposes in the form of ICD-9 codes, which provided little information on critical variables such as use of medications that might have influenced temperature recordings, including antipyretics and drugs acting on the central nervous system. Moreover, the temperature measurements came from several different clinics, where temperatures were taken at varying anatomical sites by technicians with unspecified levels of training using different types of thermometers.

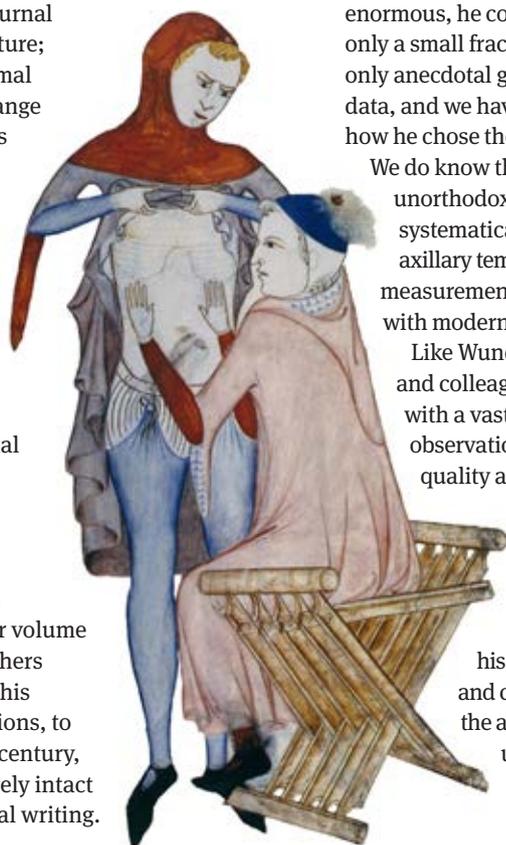
Wunderlich's most cherished and durable dictum, on the general temperature of the body in normal conditions, has since been repudiated

Obermeyer and colleagues used a host of statistical techniques to try to minimise the distorting effects of unmeasured variables, but much of what they discovered simply corroborated Wunderlich's less sophisticated observations nearly a century and a half ago. Their most provocative finding—that "temperature correlates with mortality"—is unconfirmed, though intriguing enough to merit further study. More intriguing still is our apparently unshakable faith in Wunderlich's original reference temperature, despite all the evidence that has since accumulated against it.

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● NATURAL PHENOMENA, p 428



THE BMJ CHRISTMAS APPEAL

Help MSF bring essential care to war torn Yemen

Médecins Sans Frontières is providing medical aid to millions of Yemenis facing the dangers of violence, cholera, and malnutrition, writes **Richard Hurley**

“Yemen is one of MSF’s biggest missions, partly because of the medical need and partly because of lack of capacity,” Djoen Besselink, the head of mission, said by phone from the capital Sana’a, pausing for the occasional explosion.

More than three million people have fled their homes after two years of civil war. Some 15 million civilians, half the population, lack healthcare and are facing cholera and malnutrition as food costs rise. Healthcare facilities have been destroyed, and many workers have fled. Add in water shortages, food insecurity, air strikes, and a fuel blockade and the necessity of MSF’s work is clear.

“Healthcare was bad before; now it’s really bad,” says Besselink. “After two years of conflict it cannot deal with cholera outbreaks or diphtheria. It can’t even deal with pneumonia and malaria. It’s a massive humanitarian crisis. A healthy health system should be able to deal with cholera. People shouldn’t die from pneumonia.”

In the first three months of this year in Yemen, MSF saw 97 216 emergency department inpatients, carried out 5826 surgical procedures, and admitted 2786 children to hospital. Most staff are volunteers. To remain independent MSF relies almost entirely on private donations. “In the papers you see a lot of political discussion, diplomatic talk, the blockade,” says Besselink. “We want to show the human impact. The fighting that’s become a normal part of life.”

Richard Hurley is features and debates editor, *The BMJ*

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