

A high NNT should not be taken to imply that a drug works really well for a specific, narrow subset of people. It could simply mean that a drug is just not that effective across all individuals.

Subsequence, not consequence. All of the errors discussed so far lead to the assumption that what has happened, for good or ill, has been caused by what was done before — that if a headache disappeared, it was because of the drug. It is ironic that the evidence-based-medicine movement, which has done so much to enthrone the randomized clinical trial as a principled and cautious way of establishing causation across populations, consistently fails to establish causation in the context of personalized medicine.

WAY FORWARD

These warnings are not intended to discourage researchers from pursuing precision medicine. Rather, they are meant to encourage them to get a better sense of its potential at the outset.

How to improve? One thing we need more of are *N*-of-1 trials. These studies repeatedly test multiple treatments in the same person, including the same treatment multiple times (see ‘Compare each patient at least twice’).

With such designs, we can assess differences between the same drug being administered on many occasions, and compare those data with differences seen when different drugs are administered in the same way. They are being used, for example,

in trials of fentanyl for pain control in individuals with cancer⁹ and of temazepam for people with sleep disturbances¹⁰.

When medicines are given on many occasions for a chronic or recurring condition, *N*-of-1 studies are a good way of establishing the scope for personalized medicine¹¹. When drugs are given once or infrequently for degenerative or fatal conditions, careful modelling of repeated measures can help. Whatever their approach, trial designers must hunt down sources of variation. To work out how much of the change observed is due to variability within individuals requires more careful design and analysis¹².

Another advance would be to drop the use of dichotomies⁵. Statistical analysis of continuous measurements is straightforward but underused. More-widespread uptake of this approach would mean that clinical trials could enrol fewer patients and still collect more information⁶.

Perhaps the most straightforward adjustment would be to avoid labels such as ‘responder’ that encourage researchers to put trial participants in arbitrary categories. An alternative term — perhaps ‘clinical improvement’ or ‘satisfactory endpoint’ — might help. Better still, sticking with the actual measurement would reduce the peril of all the pitfalls mentioned here.

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It has been a long, hard struggle in medicine to convince researchers, regulators and patients that causality is hard to study and difficult to prove. We are in danger of forgetting at the level of the individual what we have learnt at the level of the population. Realizing that the scope for personalized medicine might be smaller than we have assumed over the past 20 years will help us to concentrate our resources more carefully. Ironically, this could also help us to achieve our goals. ■

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Why academic freedom is needed more than ever

For a century, the Haldane principle has enabled government scientists to speak truth to power without fear of retribution — cherish it, urges **Ehsan Masood**.

One hundred years ago this month, shortly after the guns of the First World War fell silent, a German-speaking Scottish lawyer-turned-politician sent an 80-page report to his prime minister. In it was an idea whose echo still shapes the way in which many nations fund research — an idea arguably as important to the soul of modern science as the secular state is to modern democracy.

That idea has come to be called the Haldane principle, after its proponent, Richard Burdon Haldane. This principle says that scientists should mostly be left alone to decide which research projects should receive government

funding^{1–3}. (It is not to be confused with the rule about speciation, formulated by evolutionary biologist J. B. S. Haldane.) In many nations, the Haldane principle is near-totemic — regarded as the scholar’s last defence against more powerful interests.

But the definition used today does not reflect the depth of vision in the original. Haldane argued in his 1918 report⁴ that politicians need to do more than stay out of funding decisions. He urged them to listen to expertise, and to take time to think and reflect before reaching a conclusion. And he wrote that politicians who ask scientists for advice should resist telling

them what that advice should be.

The difference matters. Today, from Istanbul to Islamabad, from Rome to Rio de Janeiro, a parade of authoritarian leaders is advancing policies that fly in the face of evidence — on energy, emissions, the environment, economics, immigration and more. Worse, these leaders are demanding that academics march to the beat of their drums.

Even in seemingly healthy democracies, the direction of travel is unmistakable. In the United Kingdom last year, a ‘Haldane principle’ was passed into law for the first time — but as part of a package of measures that saw universities lose the protection ▶

► of the royal charters that have enshrined scholarly autonomy for centuries⁵.

Today, it is researchers who are demanding protection for their ability to speak truth to power. What is remarkable about Haldane's incarnation of this idea is that it originated, not from scientists, but from the heart of government in the darkest of times.

A NEW WORLD

Britain in 1918 was a different place. The small island nation controlled about one-fifth of the world's population and one-quarter of global land area from Canada to New Zealand, including many nations in Africa, Asia and the Middle East.

The First World War had been a wake-up call. In 1917, Haldane was asked by the UK government to chair the Orwellian-sounding Machinery of Government Committee. Its remit was to re-engineer Britain's ministries to cope with peacetime, the rising powers of Germany and the United States, and the citizens of various colonial states, who would soon be demanding freedom. The seven-member committee included Edwin Montagu, secretary of state for India, and the economist and social reformer Beatrice Webb, a co-founder of the London School of Economics and Political Science.

Haldane was an unusual politician but the ideal chairperson for this task. He had top-level experience of government as Lord Chancellor, the person responsible for the country's judiciary. And he was available: he'd lost the post of minister for war in 1915 after a campaign in the popular press painted him as a German sympathizer. He had praised the organization of education and science in Germany, noting how its culture, industry, research and policymaking came together. For this, the newspapers called him an enemy of the British state. He was doorstepped by journalists and insulted on the street⁶.

Haldane could just as easily have worked in academia. He studied philosophy at the University of Göttingen in Germany and wrote several books on the topic, including *The Reign of Relativity* in 1921, about the implications of Albert Einstein's physics. But his heart lay in public policy. He was an early advocate of expanding education and, after he left the government, helped to create a wave of civic universities in cities including Birmingham, Bristol, Leeds, Liverpool and London⁶.

THINK THEN DO

The Haldane report's key recommendations included something that we take for granted today: cabinet-level ministries for health and education. In another innovation that is also now mainstream, Haldane advised that these

ministries would need access to the best available advice. For example, an education ministry would need counsel from experts in childhood development, and a health ministry would need guidance from scientists working on infectious diseases. His ideal ministers were people whose time was freed from operational matters to be able to think and plan.

The most radical suggestion in the report was for an entirely new ministry of "research and information". Haldane dared to suggest that its leader should be not a party politician (the convention then, as now), but "essentially a trained thinker".

The report envisaged this ministry as a blend of government think tank and research funder. It urged that "better provision should be made for enquiry, research and reflection before policy is defined and put into operation".

The historian David Edgerton has rightly pointed out that the original report does not mention a 'Haldane principle' (see go.nature.com/2qyb7bn). So where did the moniker arise? In an unpublished memo written probably in February or March of 1918, six months into the inquiry, Haldane mentions three "principles" for reorganizing government⁷. The first — a "new principle to be recognised as fundamental" — is for government and policymakers to develop "a habit of mind, a disposition to insist on the systematic study of questions before [policy] action is taken". (The other two focused on the rationale for different ministerial jobs and better financial accountability from government departments.) The memo's tone is much more direct than that of the final report, suggesting that its intended

audience was probably Prime Minister David Lloyd George.

In words that ring true today, Haldane adds: "A Prime Minister is chosen as the leader of the nation largely because of his gifts as its spokesman... But he has to shape policy, and to this end requires the most highly skilled assistance, if he is not to be a bungler."

Despite this progressive thinking, there is no sugar-coating the fact that Haldane was an imperialist⁸. The needs of the British Empire were a strong factor in his calculations for science in government. There were railways to be built, botanical and geological surveys to be done, new languages and legal systems to be mastered — and catastrophic famines and outbreaks to be tackled, notably in India. All of this demanded engineers and scientists⁹.

Haldane's wish for an over-arching ministerial research department never materialized. It is a brave government that would prioritize study, thought and reflection in the making of policy. But traces of the Haldane ideal can be seen in what was to follow.

His ideas are reflected today in the work of the scientists attached to the ministries dedicated to science, technology, innovation and higher education. These are largely responsible for organizing and funding teaching and research in universities and in public laboratories. They also seek expert counsel. In a few countries — notably Germany and the United Kingdom — they are also involved in industrial policy.

The ideal of independence also informs the work of chief science advisers, whose offices might be attached to those of heads of government or to departments from food to forestry, transport to trade. Since 2014, they

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Students in Budapest protest in April 2017 over government interference in universities.

BERNADETT SZABO/REUTERS



Richard Burdon Haldane advised in 1918 that governments need access to the best expert advice.

have been part of the International Network for Government Science Advice (INGSA), created to hone practice. The difference is that Haldane wished for such expertise to operate closer to the apex of government, and to be accountable to Parliament.

INDEPENDENCE DAY

When Haldane's report landed on the prime minister's desk, it had little impact: the end of the First World War was a busy time for statecraft. There were peace treaties to be agreed and a domestic economy to be steadied. The Ottoman empire was collapsing, and Britain and France were competing for influence in its former territories.

It was in the years during and after the Second World War that Haldane's idea of independent advice resurfaced. Scientists and engineers from many countries had created the technologies that were crucial to the Allies' victory, such as radar and the atomic bomb. These needed a degree of operational distance from politicians — a hard-won achievement, as writer C. P. Snow describes entertainingly in his 1961 book *Science and Government* (Harvard Univ. Press; see also J. Baker *Nature* 459, 36–39; 2009).

US scientists who had held prominent policy roles during the Second World War — such as Vannevar Bush — spied an opportunity. Bush's post-war report, *Science: The Endless Frontier*, was an appeal to US leaders that if scientists could help to win the war, they could also help to hold the peace¹⁰. Bush

noted that they would need federal funding and, crucially, would require politicians to stay at arms' length.

And so it proved. Year after year, when governments respected the independence of the scientists they tapped for advice, the results were genuinely world-changing. Examples include the first generation of scientists who created Green Revolution agricultural technologies in the 1950s and 1960s, and the researchers whose findings led to the Montreal Protocol to protect the ozone layer in 1987. The Kyoto climate protocol of 1997 was a direct result of the efforts of the Intergovernmental Panel on Climate Change, whose members, although nominated by governments, fight hard to work without their paymasters peeping through the keyhole¹¹.

But Haldane's world of the honest broker starts to break down when governments stop keeping their side of the bargain.

BEWARE BUNGLERS

That is what is happening now, as an expanding network of populist political movements derides independent scholarship. For instance, Britain's staunchest supporters of the campaign to leave the European Union ('Brexiters') disdained expert warnings of the economic and environmental costs. In his election campaign, Brazil's new president, Jair Bolsonaro, pledged to roll back the country's historical commitments on deforestation and climate change. And last month, Michael Ignatieff, rector of the Central European

University in Budapest, announced that the university will be relocating to Vienna because of sustained interference in its operations by Hungary's right-wing government.

Meanwhile, some scientists are so concerned by the ransacking of the US Environmental Protection Agency (EPA) by President Donald Trump's White House that they have reportedly set up a shadow EPA in preparation for the next administration, so that valuable knowledge isn't lost. And in Australia, former education minister Simon Birmingham was unapologetic when it emerged that he had vetoed 11 grants worth Aus\$4.2 million (US\$3 million) that had been cleared for funding by the Australian Research Council.

There are other examples, and there will be more as populism strengthens its grip on those who suffered as a result of the 2008 financial crisis. And that is what makes the original Haldane report a remarkable document, worth recalling now. With national security under threat, Haldane's committee could have demanded fealty from scientists and engineers. It could have insisted on ideological litmus tests. It did no such thing.

Today, more than ever, the authentic Haldane principle — and its origin story — must be cherished. In a world laid waste by war, a politician argued persuasively for a check on the power of the very corridors he walked. Haldane died in 1928, having no inkling that his Machinery of Government report would be talked of a century later. Its lasting legacy is the insight that the truth, often expendable in politics, must not be so in science advice. ■

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