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Gary Taubes

“The (Political) Science of Salt”

Science

Part Two: Crystallizing a debate

The case against salt begins with physiological plausibility. Eat more salt, and your body will maintain its sodium concentration by retaining more water. "If you go on a salt binge," says Harvard Medical School nephrologist Frank Epstein, "you will retain salt and with it a proportionate amount of water until your kidneys respond and excrete more salt. In most people, you will detect a slight increase in blood pressure when body fluids are swollen like this, although there is a very broad spectrum of responses."

Behind this spectrum is a homeostatic mechanism that has been compared to a Russian novel in its complexity. The cast of characters includes some 50 different nutrients, growth factors, and hormones. Sodium, for instance, is important for maintaining blood volume; potassium for vasodilation or constriction; and calcium for vascular smooth muscle tone. Increase your caloric intake, and your sympathetic nervous system responds to constrict your blood vessels, thus raising your blood pressure. Decrease your calories, and your blood pressure falls. To make matters still more complicated, the interplay of these variables differs with age, sex, and even race. Most researchers believe that a condition known as salt sensitivity explains why the blood pressure of some individuals rises with increased salt but not others, but even that is controversial, says Harlan. No diagnostic test exists for salt sensitivity other than giving someone salt and seeing what happens, which still won’t predict whether the sensitivity is lifelong or transitory. Despite this complexity, most researchers still believe it makes physiological sense that populations with high-salt diets would have more individuals with high blood pressure than those with low salt diets, and that lowering salt intake would lower blood pressure.

> "You can say without any shadow of a doubt that the [NHLBI] has made a commitment to salt education that goes way beyond the scientific facts."
>
> — Drummond Rennie

By the 1970s, when the government began recommending salt reduction to treat hypertension — defined as systolic blood pressure higher than 140 mmHg and diastolic higher than 90 mmHg (140/90 mmHg) — the physiological plausibility had been supplemented by a grab bag of not particularly definitive studies and clinical lore. In the 1940s, for instance, Duke University clinician Wallace Kempner demonstrated that he could successfully treat hypertensive patients with a low-salt, rice-and-peaches diet. For years Kempner’s regimen was the only nonsurgical treatment for severe hypertension, a fact that may have done more than anything to convince an entire generation of clinicians of the value of salt reduction. In a seminal 1972 paper, Lewis Dahl, a physician at Brookhaven National Laboratory in Upton, New York, and the primary champion of salt reduction in this country until his death in 1975, claimed it was proven that a low-salt diet reduced blood pressure in hypertensives. When it didn’t, he said, that only proved that the patient had fallen off the diet, "all protestation to the contrary, notwithstanding." Whether it was low salt that explained the diet’s effect is still debatable, however. Kempner’s regimen was also extraordinarily low in calories and fat and high in potassium, factors that themselves are now known to lower blood pressure.

Dahl furthered the case for a salt-blood pressure link by breeding a strain of salt-sensitive hypertensive rats. Researchers still cite this work as compelling evidence for the role of salt in human hypertension. As Simpson pointed out in 1979, however, Dahl’s rats became hypertensive only if fed an amount of salt equivalent to more than 500 grams a day for an adult human — "probably outside the area of relevance," Simpson noted. Lately, researchers have been touting a 1995 study of chimps fed a high-salt diet. But Harlan notes that "it’s unlikely" that any existing animal models of hypertension are particularly relevant to humans.

Throughout the early years of the controversy, the most compelling evidence against salt came from a type of epidemiologic study known as an "ecologic" study, in which researchers compared the salt intake of indigenous populations — the Yanomamo Indians of Brazil, for instance — that had little or no hypertension and cardiovascular disease to that of industrialized societies. Inevitably the indigenous populations ate little or no salt; the industrialized societies ate a lot. While the Yanomamo ate less than a gram of salt daily, for instance, the northern Japanese ate 20 to 30 grams — the highest salt intake in the world — and had the highest stroke rates. Such findings were reinforced by migration studies, in which researchers tracked down members of low-salt communities who had moved to industrialized areas only to see both their salt intake and blood pressure rise.

The findings led researchers to postulate an intuitive Darwinian argument for salt reduction: Humans evolved in an environment where salt was scarce, and so those who survived were those best adapted to retaining salt. This trait, so the argument goes, would have been preserved even though we now live in an environment of salt abundance. By this logic, the appropriate intake of salt is that of the primitive societies — a few grams a day — and all industrialized societies eat far too much and pay it for it in heart disease and stroke.

The catch to this accumulation of data and hypotheses was that it only included half the data. The other half was the half that didn’t fit — in particular, data from the epidemiologic studies known as intrapopulation studies. These compared salt intake and blood pressure in individuals within a population — males in Chicago, for instance — and invariably found no evidence that those who ate a lot of salt had higher blood pressure than

those who ate little. Among the intrapopulation studies that came up negative were an analysis of 20,000 Americans conducted by the National Center for Health Statistics around 1980.

> "All I'm trying to do is save some lives."
>
> — Ed Roccella

Neither kind of study was capable of giving a definitive answer, however. The ecologic studies were certainly the least sound scientifically, and epidemiologists today put little stock in them. The potentially fatal flaw in ecologic studies is always the number of variables other than the one at issue that might differ between the populations and explain the relevant effect. Populations that eat little salt, for instance, also consume fewer calories; eat more fruits, vegetables, and dairy products; are leaner and more physically active; drink less alcohol; and are less industrialized. Any one of these differences or some combination of them might be responsible for the lower blood pressure. Indigenous people also tend to die young from infectious diseases or trauma, notes Epstein, while industrialized societies live long enough to die of heart disease.

Both ecologic and intrapopulation studies also suffer from the remarkable difficulty of accurately assessing average blood pressure — which can vary greatly from day to day — or a lifetime intake of salt. Most of the early ecologic studies based their assessments of salt intake on guesses rather than measurements. In 1973, when University of Michigan anthropologist Lillian Gleibermann published what's still considered a seminal paper linking salt and blood pressure, she based her conclusions on 27 ecologic studies, only 11 of which actually tried to measure sodium intake. A 24-hour collection of urine is considered to be the best assessment of salt intake, because we quickly excrete in our urine all the salt we consume. But even that will only reflect the salt intake of those 24 hours, not necessarily of an entire month, year, or lifetime. "You need at least five to 10 measures of sodium in urine collected on different days to get a measure of habitual intake," says Daan Kromhout, a nutritional epidemiologist at the National Institute of Public Health and the Environment in the Netherlands. "You can't do that in an epidemiologic field situation."

To researchers who accept the salt-blood pressure hypothesis, these measurement problems served to explain why intrapopulation studies wouldn't see an association even if one existed. Quite simply, the link between salt and blood pressure, however potent, would likely be washed out by the measurement errors. Moreover, any experiment large enough to have the statistical power to overcome these errors would be prohibitively expensive.

In the early 1980s, London School of Tropical Medicine and Hygiene epidemiologist Geoffrey Rose suggested another reason why the intrapopulation studies might fail to detect benefits of salt reduction that could still have a significant public health impact. Rose speculated that if the entire developed world consumed too much salt, as ecologic studies suggested, then epidemiology would never be able to link salt to hypertension, regardless of how causal the relationship. Imagine, he wrote, if everyone smoked a pack of cigarettes daily; then any intrapopulation study "would lead us to conclude that lung cancer was a genetic disease ... since if everyone is exposed to the necessary agent, then the distribution of cases is wholly determined by individual susceptibility." Thus, as with salt and high blood pressure, the clues would have to be "sought from differences between populations or from changes within populations over time." By the same logic, cutting salt consumption a small amount might have little effect on a single individual — just as going from 20 cigarettes to 19 would — but a major impact on mortality across an entire population.

Although Rose's proposition made intuitive sense, it still rested on the unproven conjecture that avoiding salt could reduce blood pressure, a conjecture that was beginning to seem extraordinarily resistant to any findings that might negate it. In 1979, for instance, Stamler and his Northwestern colleagues tested the hypothesis in an intrapopulation study of Chicago schoolchildren. They compared blood pressure in 72 children to salt intake, estimated from seven consecutive 24-hour urine samples, enough to reliably reflect habitual sodium intake. They reported a "clear-cut" relationship between sodium and blood pressure in the children but then tried twice to reproduce the result and failed twice.

Opinions on one study range from "reads like a New Yorker comedy piece" and the "worst example of a meta-analysis in print by a long shot" to "competently done and competently analyzed and interpreted."

"A variety of potential explanations of this phenomenon could be advanced," the authors wrote, one of which was the obvious: "No relationship in fact exists between sodium and [blood pressure]. ..." They then listed five reasons why they might have missed the expected relationship — insensitive measurement techniques, for instance, or genetic variability obscuring the role of sodium, or the possibility that "the true relationship is not yet evident in children." Because the first of the three studies was positive, Stamler and his colleagues concluded that their data were "not wholly negative" and "do in fact suggest a weak and inconsistent relationship."

This logic served to manifest what Simpson called "the resilience and virtual indestructibility of the salt-hypertension hypothesis. Negative data can always be explained away."

> "Another thing I must point out is that you cannot prove a vague theory wrong. ... Also, if the process of computing the consequences is indefinite, then with a little skill any experimental results can be made to look like the expected consequences."
>
> — Richard Feynman, 1964

Through the early 1980s, the scientific discord over salt reduction was buried beneath the public attention given to the benefits of avoiding salt. The NHBPEP had decreed since its inception in 1972 that salt was an unnecessary evil, a conclusion reached as well by a host of medical organizations, not to mention the National Academy of Sciences and the Surgeon General. By 1978, the Center for Science in the Public Interest, a consumer advocacy group, was describing salt as "the deadly white powder you already snort" and lobbying Congress to require food labeling on high-salt foods. In 1981, the FDA launched a series of "sodium initiatives" aimed at reducing the nation's salt intake.

Not until after these campaigns were well under way, however, did researchers set out to do studies that might be powerful enough to resolve the underlying controversy. The first was the Scottish Heart Health Study, launched in 1984 by epidemiologist Hugh Tunstall-Pedoe and colleagues at the Ninewells Hospital and Medical School in Dundee, Scotland. The researchers used questionnaires, physical exams, and 24-hour urine samples to establish the risk factors for cardiovascular disease in 7300 Scottish men. This was an order of magnitude larger than any intrapopulation study ever done with 24-hour urine samples. The BMJ published the results in 1988: Potassium, which is in fruits and vegetables, seemed to have a beneficial effect on blood pressure. Sodium had no effect.

With this result, the Scottish study vanished from the debate. Advocates of salt reduction argued that the negative result was no surprise because the study, despite its size, was still not large enough to overcome the measurement problems that beset all other intrapopulation studies. When the NHBPEP recommended universal salt reduction in its landmark 1993 report, it cited 327 different journal articles in support of its recommendations. The Scottish study was not among them. (In 1998, Tunstall-Pedoe and his collaborators published a 10-year follow-up: Sodium intake now showed no relationship to either coronary heart disease or death.)

The second collaboration was Intersalt, led by Stamler and Rose. Unlike the relentlessly negative Scottish Heart Health Study, Intersalt would become the most influential and controversial study in the salt debate. Intersalt was designed specifically to resolve the contradiction between ecologic and intrapopulation studies. It would compare blood pressure and salt consumption, as measured by 24-hour urine samples, from 52 communities around the globe, from the highest to the lowest extremes of salt intake. Two hundred individuals — half males, half females, 50 from each decade of life between 20 and 60 — were chosen at random from each population. In effect, Intersalt would be 52 small but identical intrapopulation studies combined into a single huge ecologic study.

After years of work by nearly 150 researchers, the results appeared in the same 1988 BMJ issue that included the Scottish Heart Health Study. Intersalt had failed to confirm its primary hypothesis, which was the existence of a linear relationship between salt intake and blood pressure. Of the 52 populations, four were primitive societies like the Yanomamo with low blood pressure and daily salt intake below 3.5 grams. They also differed, however, in virtually every other imaginable way from the 48 industrialized societies that had higher blood pressure. The remaining 48 revealed no relationship between sodium intake and blood pressure. The population with the highest salt intake, for instance — in Tianjin, China, consuming roughly 14 grams a day — had a median blood pressure of 119/70 mmHg, while the one with the lowest salt intake — a Chicago African-American population at 6 grams a day — had a median blood pressure of 119/76 mmHg. Only body mass and alcohol intake correlated with blood pressure in this comparison.

The Intersalt researchers did derive two positive correlations between salt and blood pressure. One weak association appeared when they treated the 10,000-plus subjects as a single large population rather than 52 distinct populations. It implied that cutting salt intake from 10 grams a day to four would reduce blood pressure by 2.2/0.1 mmHg. The more potent association was between salt intake and the rise in blood pressure with age: Populations that ate less salt experienced a smaller rise than did populations that ate more salt. If this relationship was causal, Intersalt estimated, then cutting salt intake by 6 grams a day would reduce the average rise in blood pressure between the ages of 25 and 55 by 9/4.5 mmHg.

These findings made Intersalt Rorschach-like in its ability to generate conflicting interpretations. John Swales wrote off the results in an accompanying BMJ editorial, saying the potential benefit, if any, was so small it "would hardly seem likely to take nutritionists to the barricades (except perhaps the ones already there)." Today, the majority of the researchers interviewed by Science, including Intersalt members such as Daan Kromhout and Lennart Hansson, see it as a negative study. Says Hansson, "It did not show blood pressure increases if you eat a lot of salt."

Stamler and other Intersalt leaders vehemently disagree. When the results were published, Stamler described them as "abundant, rich, and precise confirmation" of the sodium-blood pressure association and used them to advocate a 6-gram "reduction in salt intake for everyone." In this view, the definitive positive finding was the correlation between salt consumption and rising blood pressure with age. Intersalt's Hugo Kesteloot, for instance, an epidemiologist at the Catholic University of Leuven in Belgium, says this was "the most interesting finding" and "confirmatory." Officials at the NHBPEP and NHLBI sided with this interpretation. In 1993, the NHBPEP report on primary prevention of hypertension cited Intersalt for confirming the "strong positive relationship" between sodium intake and blood pressure reported by Dahl in 1972, which was precisely what it did not do. NHLBI's Cutler still describes the results as "overwhelmingly positive."

> "The most slender piece of evidence in favor of [a salt-blood pressure link] is welcomed as further proof of the link, while failure to find such evidence is explained away."
>
> — Olaf Simpson

Critics, however, noted that the association Stamler and his colleagues found so telling — between salt intake and blood pressure rise with age — was not included among the hypotheses that Intersalt had clearly delineated in prestudy publications describing its methodology. This made the finding appear to be a post hoc analysis, a practice known pejoratively as "data dredging." In such situations, the researchers are no longer testing hypotheses, as the scientific method requires, but are finding hypotheses that fit data already accumulated. Although this doesn't mean the new hypotheses are not true, it does mean they have not been properly tested.

Because Intersalt wasn't designed to test a link between salt and a rise in blood pressure with age, explains NIH's Bill Harlan, the association reported later could be treated as no more than an inference: "If you [were going] in with that as a specific hypothesis, you would have set the study up differently," for example, by including a wider range of ages and a larger sample of each population. David Freedman, a UC Berkeley statistician, puts it more bluntly, saying that the conclusion about salt and rising blood pressure with age looked like "something they dragged in when the primary analyses didn't go their way."

Although Intersalt members agree that testing a hypothesized link between salt and rising blood pressure with age was not in their proposals, they insist it was always part of the plan. "It just wasn't in by omission. Stupidly," says Intersalt's Paul Elliot, an epidemiologist at London's Imperial College School of Medicine. Alan Dyer of Northwestern University, the collaboration's biostatistician, says, "It just was one of those things that didn't get written down." Stamler insists it was recorded in the minutes of a meeting and in an early publication, and that the accusations of "retrospective data-dredging" are "factually wrong" and should be retracted.

Far from delivering the last word on salt, Intersalt had dissolved in ambiguous data and contradictory interpretations. And that was just round one.