The science of obesity: what do we really know about what makes us fat?

The history of obesity research is a history of two competing hypotheses. Gary Taubes argues that the wrong hypothesis won out and that it is this hypothesis, along with substandard science, that has exacerbated the obesity crisis and the related chronic diseases. If we are to make any progress, he says, we have to look again at what really makes us fat.

Since the 1950s, the conventional wisdom on obesity has been simple: it is fundamentally caused by or results from a net positive energy balance—another way of saying that we get fat because we overeat. We consume more energy than we expend. The conventional wisdom has also held, however, that efforts to cure the problem by inducing undereating or a negative energy balance—either by counselling patients to eat less or exercise more—are ineffective.

Put these two notions together and the result should be a palpable sense of cognitive dissonance. Take, for instance, The Handbook of Obesity, published in 1998 and edited by three of the most influential authorities in the field. “Dietary therapy,” it says, “remains the cornerstone of treatment and the reduction of energy intake continues to be the basis of successful weight reduction programs.” And yet it simultaneously describes the results of such dietary therapy as “poor and not long-lasting.”1

Rather than resolve this dissonance by questioning our beliefs about the cause of obesity, the tendency is to blame the public (and obese patients implicitly) for not faithfully following our advice. And we embrace the relatively new assumption that obesity must be a multifactorial and complex disorder. This makes our failures to either treat the disorder or rein in the burgeoning epidemics of obesity worldwide somehow understandable, acceptable.

Another possibility, though, is that our fundamental understanding of the aetiology of the disorder is indeed incorrect, and this is the reason for the lack of progress. If this is true, and it certainly could be, then rectifying this aetiologic misconception is absolutely critical to future progress.

Energy balance hypothesis

Despite its treatment as a gospel truth, as preordained by physical law, the energy balance or overeating hypothesis of obesity is only that, a hypothesis. It’s largely the product of the influential thinking of two physicians—the German diabetes specialist Carl von Noorden at the University of Michigan was crediting him with the theory of the German physiologist Max Rubner. By the end of the 19th century, the American scientists Wilbur Atwater and Francis Benedict had confirmed that these laws held for humans as well: that the calories we consumed would be burned as fuel, stored, or excreted.2 This revelation then led von Noorden to propose that “the ingestion of a quantity of food greater than that required by the body, leads to an accumulation of fat, and to obesity, should the disproportion be continued over a considerable period.”

By the late 1920s, Newburgh had taken up the energy balance banner at the University of Michigan and was promoting it based on what he believed to be a fundamental truth: “All obese persons are alike in one fundamental respect—they literally overeat.” As such, he blamed obesity on either a “perverted appetite” (excessive energy consumption) or a “lessened outflow of energy” (insufficient expenditure). If the obese person’s metabolism was normal, he argued, and they still refused to rein in their intake, that was sufficient evidence to assume that they were guilty of “various human weaknesses such as overindulgence and ignorance.”

By 1939, Newburgh’s biography at the University of Michigan was crediting him with the discovery that “the whole problem of weight lies in regulation of the inflow and outflow of calories” and for having “undermined conclusively the generally held theory that obesity is the result of some fundamental fault.”

As sceptics pointed out at the time, though, the energy balance notion has an obvious flaw: it is tautological. If we get fatter (more massive), we...
have to take in more calories than we expend—that’s what the laws of thermodynamics dictate—and so we must be overeating during this fattening process. But this tells us nothing about cause. Here’s the circular logic:

Why do we get fat? Because we overeat.

How do we know we’re overeating? Because we’re getting fatter.

And why are we getting fatter? Because we’re overeating.

And so it goes, round and round.

“The statement that primary increase of appetite may be a cause of obesity does not lead us very far,” wrote the Northwestern University School of Medicine endocrinologist Hugo Rony in 1940 in Obesity and Leanness, “unless it is supplemented with some information concerning the origin of the primarily increased appetite. What is wrong with the mechanism that normally adjusts appetite to caloric output? What part of this mechanism is primarily disturbed?” Any regulatory defect that drove people to gain weight, Rony noted, would induce them to take in more calories than they expend. “Positive caloric balance would be, then, a result rather than a cause of the condition.”

Endocrinological hypothesis

The alternative hypothesis that Newburgh’s work had allegedly undermined was the idea that some “intrinsic abnormality”—Rony’s words—was at the root of the disorder. This was an endocrinological hypothesis. It took the laws of physics as a given; it rejected aberrant behaviour or ignorance as causal. It existed at the time as two distinct hypotheses.

One was the brainchild of Wilhelm Falta, a student of von Noorden and a pioneer of the science of endocrinology. Falta believed that the hormone insulin must be driving obesity on the basis, as he noted as early as 1923, that “a functionally intact pancreas is necessary for fattening.” Once insulin was discovered, Falta considered it the prime suspect in obesity. “We can conceive,” he wrote, “that the origin of obesity may receive an impetus through a primarily strengthened function of the insular apparatus, in that the assimilation of larger amounts of food goes on abnormally easily, and hence there does not occur the setting free of the reactions that in normal individuals work against an ingestion of food which for a long time supersedes the need.”

The other version of the hypothesis was bound up in a concept known as lipophilia. It was initially proposed in 1908 by Gustav Von Bergmann, a German authority on internal medicine, and then taken up by Julius Bauer, who did pioneering work on endocrinology, genetics, and chronic disease at the University of Vienna. Von Bergmann initially evoked the term lipophilia (“love of fat”) to explain why fat deposition was not uniform throughout the body. Just as we grow hair in some places and not others, according to this thinking, we fatten in some areas and not others and biological factors must regulate this. People who are constitutionally predisposed to fatten, Von Bergmann proposed, had adipose tissue that was more lipophilic than that of constitutionally lean individuals. And if fat cells were accumulating excessive calories as fat, this would deprive other organs and cells of the energy they needed to thrive, leading to hunger or lethargy. These would be compensatory effects of the fattening process, not causes.

“Like a malignant tumor or like the fetus, the uterus or the breasts of a pregnant woman,” explained Bauer, “the abnormal lipophilic tissue seizes on foodstuffs, even in the case of undernutrition. It maintains its stock, and may increase it independent of the requirements of the organism. A sort of anarchy exists; the adipose tissue lives for itself and does not fit into the precisely regulated management of the whole organism.”

Erich Grafe, director of the Clinic of Medicine and Neurology at the University of Würzburg, discussed these competing hypotheses in his seminal textbook Metabolic Diseases and Their Treatment, which was published in an English translation in 1933. Grafe said he favoured the energy balance model of obesity, but acknowledged that this model failed to explain key observations—why fat accumulates in certain regions of the body. “The energy conception certainly cannot be applied to this realm,” Grafe wrote. The lipophilia hypothesis could.

By 1938, Russell Wilder of the Mayo Clinic (later to become director of the National Institute of Arthritis and Metabolic Diseases) was writing that the lipophilia hypothesis “deserves attentive consideration,” and that “the effect after meals of withdrawing from the circulation even a little more fat than usual might well account both for the delayed sense of satiety and for the frequently abnormal taste for carbohydrate encountered in obese persons... A slight tendency in this direction would have a profound effect in the course of time.”

Two years later, Rony wrote in Obesity and Leanness that the hypothesis was “more or less fully accepted” in Europe.

Language barrier

Maybe so. But it was lost with the second world war and the embracing of English as the lingua franca of science afterwards. In Grafe’s chapters on obesity, over 90% of the 235 references are from the German language literature. In Rony’s Obesity and Leanness, this is true for a third of the almost 600 references. But post-war, the German language references fall away quickly. In Obesity... published in 1949 by two Mayo Clinic physicians—Edward Rynearson and Clifford Gastineau—only 14 of its 422 references are from the German language literature, compared with a dozen from Louis Newburgh alone. By the late 1960s and 1970s, when the next generation of textbooks were written, German language references were absent almost entirely, as were the clinical observations, experience, and intuitions that went with them.

By then, obesity had evolved into an eat-
ing disorder, to be treated and studied by psychologists and psychiatrists, while laboratory researchers focused (as they still do) on identifying the physiological determinants of hunger, satiety, and appetite: why do we eat too much, rather than why do we store too much fat? Two entirely different questions.

What makes this transition so jarring in retrospect is that it coincided with the identification of the hormone insulin in the early 1960s as the primary regulator of fat accumulation in fat cells.13 Had Falta’s ideas and the lipophilia hypothesis survived the second world war, this discovery would have served to bring these two hypotheses together. And because serum insulin levels are effectively driven by the carbohydrate content of the diet, this hypothesis would implicate refined, high glycemic grains and sugars (sucrose and high fructose corn syrup, in particular) as the environmental triggers of obesity. They would be considered uniquely fattening, just as Falta had suggested, not because we overeat them—whatever that means—but because they trigger a hormonal response that drives the partitioning of the fuel consumed into storage as fat.

This might have been perceived, although it was not, as a medical triumph: the elucidation of both the biological underpinnings of obesity as well as an explanation for what was until then the conventional wisdom on the cause. “Every woman knows that carbohydrate is fattening,” as Reginald Passmore and Yola Swindells wrote in the British Journal of Nutrition in 1963: “this is a piece of common knowledge, which few nutritionists would dispute.”

Academic backlash
That this insulin-carbohydrate hypothesis never gained traction can be explained, paradoxically, by the fact that it was embraced by practising physicians, who read the physiology and biochemistry literature and then designed carbohydrate restricted diet plans that seemed to work remarkably well. Indeed, the sessions on dietary therapy for obesity in the scattering of obesity conferences held from the end of the second world war through the mid-1970s invariably focused on the surprising efficacy of carbohydrate restricted diets to reduce excess adiposity.

When those physicians then wrote diet books based on their regimens, and these books then sold exceedingly well—Dr Atkins’ Diet Revolution (1972) most notably—the result was a backlash from academic nutritionists and obesity researchers. Fred Stare, for instance, head of the Harvard nutrition department, testified in 1972 Congressional hearings that physicians prescribing such diets were “guilty of malpractice,” on the basis that these diets were rich in saturated fat at a time when the medical community was coming to believe that high fat diets were the cause of heart disease. Exacerbating the dietary fat issue was the fact that these diet plans encouraged obese individuals to eat to satiety, effectively as much as they wanted (so long as they avoided carbohydrates), when the conventional wisdom had it that they got fat to begin with precisely because they ate as much as they wanted.

By the mid-1970s, the diets had been successfully tarred as dangerous fads (despite a history of common use in hospitals, including the Harvard Medical School,15 and a provenance going back at least to the 1820s) and the physician authors as quacks and confidence men. The notion that obesity is not an eating disorder or an energy balance disorder, but a fat accumulation disorder—a hormonal, regulatory disorder—triggered not by energy imbalance but the quality and quantity of the carbohydrates in the diet, has been routinely dismissed ever since as unworthy of serious attention.

Calories or carbohydrates?
Current attempts to blame the obesity epidemics worldwide on increased availability of calories typically ignore the fact that these increases are largely carbohydrates and those carbohydrates are largely sugars—sucrose or high fructose corn syrup. And so these observations shed no light on whether it’s total calories to blame or the carbohydrate calories. Nor do they shed light on the more fundamental question of whether people or populations get fat because they’re eating more, or eat more because the macronutrient composition of their diets is promoting fat accumulation—increased lipogenesis or decreased lipolysis, in effect, driving an increase in appetite.

The same is true for bariatric surgery, which is now acknowledged to be a remarkably effective means of inducing long term weight loss. But does weight loss occur after surgery because of the rearrangement of the gastrointestinal tract resulting in hormonal effects that minimise appetite or directly minimise fat accumulation? Does it occur because the patient reduces total calories consumed after surgery or reduces carbohydrate calories and, specifically, refined grains and sugars? The observation that bariatric surgery works doesn’t answer these questions.

Sugary beverages are another example of how these different hypotheses lead to different conclusions that are relevant to solving the obesity epidemics worldwide. The conventional wisdom has it that sugary beverages are merely empty calories that we consume in excess, although it is possible that the metabolism of fructose (a key carbohydrate component that makes these sugars sweet) in the liver somehow circumvents leptin signalling, leading us to consume these beverages and their calories even when we’re not and shouldn’t be hungry. The hormonal or regulatory hypothesis also focuses on the metabolism of fructose in the liver, but rather than leptin it uses evidence suggesting that fructose metabolism can induce insulin resistance, leading in turn to raised insulin levels and trapping fat in fat cells—increasing, in effect, lipophilia.

Shortcomings of obesity and nutrition research
Another problem endemic to obesity and nutrition research since the second world war has been the assumption that poorly controlled experiments and observational studies are sufficient basis on which to form beliefs and promulgate public health guidelines. This is rationalised by the fact that it’s exceedingly difficult (and inordinately expensive) to do better science when dealing with humans and long term chronic diseases. This may be true, but it doesn’t negate the fact that the evidence generated from this research is inherently incapable of establishing reliable knowledge.

The shortcomings of observational studies are obvious and should not be controversial. These studies, regardless of their size or number, only indicate associations—providing hypothesis generating data—not causal relations. These hypotheses then have to be rigorously tested. This is the core of the scientific process. Without rigorous experimental tests, we know nothing meaningful about the cause of the disease states we’re studying or about the therapies that might work to ameliorate them. All we have are speculations.

As for the experimental trials, these too have been flawed. Most conspicuous is the failure to control variables, particularly in free-living trials. Researchers counsel participants to eat diets of different macronutrient composition—a low fat, a low carbohydrate, and a Mediterranean diet, for instance—and then send them off about their lives to do so. In these trials, carbohydrate restricted diets almost invariably show significantly better short term weight loss, despite allowing participants to eat as much as they want and being compared with calorie restricted diets that also reduce the quantity of carbohydrates consumed and improve the quality. In these trials, the ad libitum carbohydrate restricted diets have also improved heart disease and diabetes risk factors better than the diets to which they’ve been compared. But after
a year or two, the results converge towards non-
significance, while attempts to quantify what
participants actually eat consistently conclude
that there is little long term compliance with any
of the diets.16-18

Rather than acknowledge that these trials are
incapable of answering the question of what
causes obesity (assumed to be obvious, in any
case), this research is still treated as relevant,
at least, to the question of what diet works best
to resolve it—and that in turn as relevant to the
causality question. Should we restrict calories
or carbohydrates to lose weight? If the answer
is that it doesn't seem to matter because the par-
ticipants eventually fail to adhere to any of the
diets, this is perceived as somehow a confirma-
tion that the only way to lose weight is to reduce
calories, and so the energy balance hypothesis
is the correct one.19

Ultimately what we want to know is what
causes weight gain. That's an entirely different
question from whether advising someone to fol-
low a Mediterranean diet is more or less effica-
cious than a low fat or a carbohydrate restricted
diet or some variation thereof.

In metabolic ward studies, in which the diets
of the participants have been well controlled,
researchers typically restricted the calories in
both arms of the trials—feeding participants,
say, 800 calories of a low fat versus a low carbohy-
drate diet—and so building into the study design
one of the hypotheses that is ultimately being
tested. What we want to know, again, is what
causes us to gain weight, not whether weight
loss can be induced under different conditions of
both semistarvation and carbohydrate restriction.

What can we do about this? It seems we have
two choices. We can continue to examine and
debate the past, or we can look forward and start
anew.

A year ago, working with Peter Attia, a phy-
sician, and with support from the Laura and
John Arnold Foundation in Houston Texas, I
cofounded a not-for-profit organisation called
the Nutrition Science Initiative (NuSI.org). Our
strategy is to fund and facilitate rigorously well
controlled experimental trials, carried out by
independent, sceptical researchers. Our hope is
that these experiments will answer definitively
the question of what causes obesity, and help us
finally make meaningful progress against it.

We believe that ultimately three conditions
are necessary to make progress in the struggle
against obesity and its related chronic diseases—
type 2 diabetes, most notably. First is the accept-
ance of the existence of an alternative hypothesis
of obesity, or even multiple alternative hypoth-
eses, with the understanding that these, too,
adohere to the laws of physics and must be tested
rigorously.

Second is a refusal to accept substandard
science as sufficient to establish reliable knowl-
edge, let alone for public health guidelines.
When the results of studies are published, the
authors must be brutally honest about the possi-
ble shortcomings and all reasonable alternative
explanations for what they observed. “If sci-
ence is to progress,” as the Nobel prize winning
physicist Richard Feynman said half a century
ago, “what we need is the ability to experiment,
honesty in reporting results—the results must
be reported without somebody saying what
they would like the results to have been—and
finally—an important thing—the intelligence to
interpret the results. An important point about
this intelligence is that it should not be sure
ahead of time what must be.”20

Finally, if the best we’ve done so far isn’t good
enough—if uncontrolled experiments and obser-
vational studies are unreliable, which should be
undeniable—then we have to find the willingness
and the resources to do better. With the burden
of obesity now estimated at greater than $150bn
($100bn; €118bn) a year in the US alone, virtu-
ally any amount of money spent on getting nutri-
tion research right can be defended on the basis
that the long term savings to the healthcare sys-
tem and to the health of individuals will offset
the costs of the research by orders of magnitude.

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**CASE REPORT**

**A man with pain in his right ear**

1. This patient has right otitis externa with cellulitis of the pinna and surrounding soft tissue.
2. Risk factors for this condition include dermatological conditions such as eczema and psoriasis; trauma, particularly scratching and use of, or abrasion by, cotton buds; a compromised immune system; diabetes; foreign bodies or hearing aids; and environmental factors, such as humidity and water in the ear canal.
3. The most common causative organisms are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Less common causes include coliforms, fungal infections, and rarely viral infection.
4. General treatment measures in adults include analgesia; strict water precautions (avoidance of water and use of ear plugs); and topical antimicrobial ear drops, such as a fluoroquinolone (eye drops) or aminoglycoside (with or without steroid). Aural toilet is important. Wick insertion may be needed in cases of oedema of the ear canal, and patients may require admission for intravenous antibiotics (flucloxacillin) to treat cellulitis of the pinna and surrounding skin.

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**PICTURE QUIZ**

**Visual impairment**

1. Left homonymous superior quadrantanopia.
2. Right inferior occipital (or occipitotemporal) region.
3. Long term oral anticoagulation is needed to prevent further cardioembolic stroke episodes.

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**STATISTICAL QUESTION**

**Simple linear regression**

Statements a and c are true, whereas b and d are false.