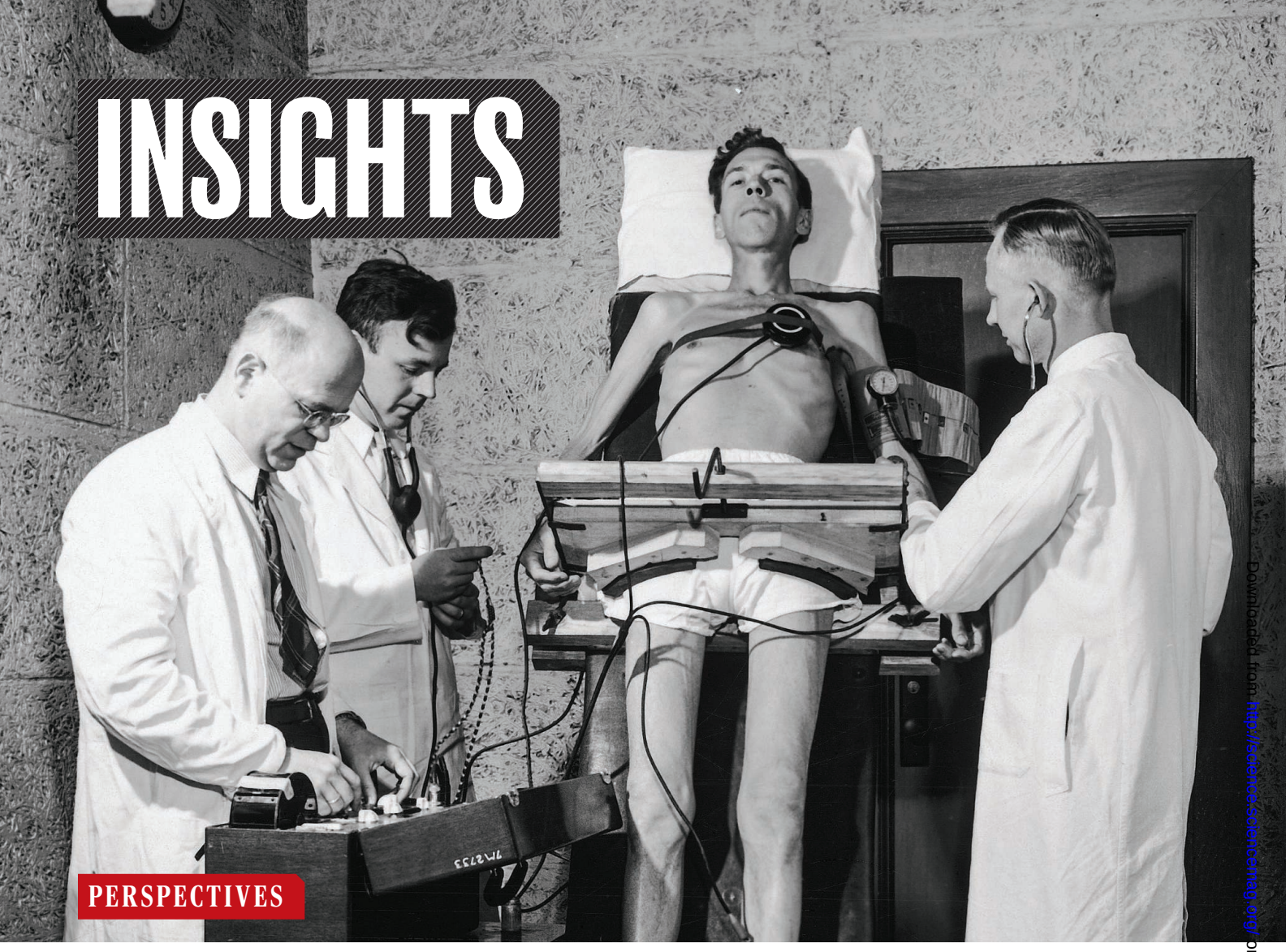

PHYSIOLOGY

Challenges of human nutrition research

Facilities to house and feed subjects could increase rigor and advance nutrition science

By **Kevin D. Hall**

Nutrition is fundamentally important for human health (*1*), but there is widespread public confusion about what constitutes a healthy diet. Flip-flopping headlines report conflicting information about whether individual foods (e.g., butter, eggs, meat), nutrients (e.g., saturated fat, cholesterol, sodium), or eating patterns (e.g., Mediterranean versus ketogenic diets) result in improved, worsened, or unchanged health. However, public confusion about nutrition belies expert consensus regarding important aspects of healthy diets. For example, it is widely agreed that Western diets high in ultra-processed food are deleterious and that considerable health improvements would likely result from shifting the population toward eating mostly minimally processed foods (*2*). But expert consensus erodes when discussing detailed questions of optimal human nutrition or the physiological mechanisms underlying the body's response to diet changes. Rigorous controlled feeding studies would help to address such questions and advance human nutrition science, a field whose overall veracity has recently been questioned (*3*, *4*).

Much of the criticism of nutrition science has been directed at nutritional epidemiology, a field that investigates associations between diet and health outcomes in large numbers of people. Although nutritional epidemiology has ardent defenders (*5*, *6*), its critics suggest that it is plagued by measurement error, reverse causality, selection bias, weak effects, analytical flexibility, and unmeasured or residual confounders that can result in spurious relationships between diet variables and health outcomes (*7*). Increased funding for large, long-term randomized diet intervention trials has been suggested as a way to mitigate reliance on nutritional epidemiology and improve causal inference about the effects of diet on human health (*8*). However, such trials have their own challenges, including the impracticality of randomizing large numbers of people to eat different diets for months or

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In 1945, a domiciled feeding study carried out at the University of Minnesota involved participants being fed a semistarvation diet.

years while ensuring high levels of adherence throughout.

Indeed, most randomized diet intervention trials do not actually study the effects of different diets; rather, they investigate the effects of differing diet advice. In other words, subjects are randomized to receive education and support to consume diets that are assigned by the investigators. Although diet-advice trials assess real-world effectiveness, their results conflate adherence to a given diet with the effects of that diet.

Knowledge about the effects of diet per se is required for advancement of fundamental nutrition science. However, studies in free-living people have a limited ability to provide such knowledge because it is not currently possible to accurately and objectively quantify their food intake. Indeed, most human nutrition studies rely on self-reported diet measures that are known to have systematic biases, such as underestimation of energy intake. Furthermore, errors in self-reported diet measurements may be associated with other variables (e.g., socioeconomic status) or health outcomes (e.g., obesity) that can result in biased associations (*9*).

Rather than relying on self-reported diet assessments, some diet intervention trials provide food to their free-living subjects, but these studies seldom verify whether all the food is eaten. Even when subjects are instructed to eat only the food provided by the study, substantial quantities of off-study food may be consumed amounting to several hundred kilocalories per day that can confound study results (*10*, *11*). To understand how these challenges impede the progress of human nutrition science, imagine trying to develop a new drug without being confident that researchers could administer known quantities of the drug or measure its pharmacokinetics, pharmacodynamics, or dose response. Successful pharmaceutical development requires such studies because they investigate benefits and risks of the drug under highly controlled conditions where questions of patient adherence are minimized because the researchers administer the drug. The inability to conduct such trials would severely impede the drug development process. Why should human nutrition science be expected to advance without the benefit of well-controlled diet efficacy studies?

Therefore, it is important to conduct human nutrition studies where subjects can comfortably reside at a research facility, thereby allowing investigators to control and objectively measure their food intake. Subjects enrolled in such domiciled feeding studies are required to stay at the research facility for periods of days, weeks, or months without leaving to ensure that they consume the provided food under observation while avoiding exposure to off-study food.

Domiciled feeding studies have a long history of yielding important discoveries about human nutrition and metabolism. For example, many of the physiological responses to starvation and nutritional rehabilitation were revealed in a controlled feeding study of 32 male volunteers who simultaneously resided at the University of Minnesota for a continuous 48-week period during the Second World War (*12*) (see the photo). The subjects were fed a baseline diet for 12 weeks followed by a 24-week semistarvation diet, after which they were fed several rehabilitation diets for the final 12 weeks. The resulting detailed physiological and psychological measurements in response to known diets would have been impossible had the subjects not been domiciled during this classic study.

Unfortunately, domiciled feeding studies have become prohibitively expensive in the United States since the National Institutes of Health ceased directly funding Clinical Research Centers (*13*). Very few centers around the world currently conduct domiciled feeding studies, and their study populations often comprise students, staff, and faculty, which limits their generalizability. Furthermore, the few facilities conducting domiciled feeding studies are typically limited to housing and feeding only a handful of subjects at a time, which restricts their power and duration.

Such limitations are surmountable. Investment in research facilities for domiciled feeding studies could provide the infrastructure and staff required to simultaneously house and feed dozens of subjects comfortably and safely. One possibility would be to create centralized domiciled feeding facilities that could enable teams of researchers from around the world to recruit a wide range of subjects and efficiently conduct rigorous human nutrition studies that currently can only be performed on a much smaller scale in a handful of existing facilities.

Well-designed domiciled feeding studies can increase the rigor of human nutrition science and elucidate the fundamental mechanisms by which diet affects human physiology. For example, such studies can investigate complex interactions among changes in diet, the microbiota, and its role in modulating host physiology. The effects of meal timing and circadian biology could be advanced by enabling precisely controlled periods for eating and sleeping. Personalized nutrition and nutrient-genomic interaction studies could be facilitated by reducing the usual noise of unknown diet variability to focus on individual physiological variability in response to controlled diets. Nutrient requirements and their dependence on overall dietary and physical activity patterns could be assessed in a variety of populations of men and women of different ethnicities and ages. The effects of diet on physical and cognitive performance could also be carefully evaluated. Comprehensive assessment of the effects of diet interventions on common health conditions such as obesity, metabolic syndrome, and type 2 diabetes, as well as rare diseases such as those that result from inborn errors of metabolism, could also be rigorously determined in domiciled subjects.

Although domiciled feeding studies can provide important mechanistic insights, their artificial environment may limit generalizability and application to free-living populations. Furthermore, domiciled feeding studies alone are insufficient for determining what constitutes a healthy diet because it is impossible to continuously house for several years the large numbers of subjects that would be required to objectively measure both food intake and clinical endpoints, such as cardiovascular events or diabetes progression. Therefore, long-term nutrition studies in free-living people will always be required.

Nonetheless, domiciled feeding studies can help to improve long-term human nutrition studies. For example, the development and validation of objective diet assessment technologies requires domiciled feeding studies because the only way to objectively know what people eat is to house them continuously in a research facility and directly measure their food intake. Advancement of objective diet assessment technologies has been identified as a top priority for human nutrition science (*14*) and promising new technologies are emerging, such as sensors and cameras that detect food intake. Biomarkers of diet are also being developed, such as plasma concentrations of vitamin C and carotenoids as indicators of fruit and vegetable intake. Domiciled feeding studies can validate objective diet assessment technologies and biomarkers in diverse subject groups consuming a variety of known diets. These validated technologies and standardized biomarkers can then be deployed in large, long-term nutrition studies to monitor diet adherence and improve understanding of the relationships between diet and disease, and diet and health.

Domiciled feeding studies can also help researchers to design and interpret large, long-term nutrition studies. For example, surrogate biomarkers of disease risk often change rapidly in response to controlled diet interventions. When surrogate markers are causally related to disease risk, then it may be possible to cautiously extrapolate the re-

sults of domiciled feeding studies, especially those that test dose responses, and to estimate the effects of diet changes on long-term disease risk. Such information can be useful for planning long-term randomized diet trials by helping to avoid underpowered studies whose null statistical results might be misinterpreted to conclude that the diet had no real effect when even a small undetected effect might be important, especially on the population scale.

For example, prior to devoting many millions of dollars to a large, long-term randomized trial of a Westernized Mediterranean diet intended to prevent cardiovascular disease, domiciled feeding studies could be used to help develop and validate biomarkers of varying degrees of adherence to the dietary pattern while also evaluating surrogate markers of disease risk in response to known diet changes. For a relatively small fraction of the overall investment, data from such a domiciled feeding study could be used to help plan and interpret the results of the large, long-term randomized trial.

The advancement of human nutrition science has enormous benefits for health and the economy (*15*). Knowledge of nutrition requires triangulation of evidence from a variety of study designs, including observational studies and randomized trials in free-living people. Facilitating more domiciled feeding studies will lead to fundamental new discoveries about the mechanistic physiological responses to diet and will improve human nutrition research in all its forms. ■

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NEUROSCIENCE

Is it worth the effort?

Individual variation in dopamine affects the weighting of benefits relative to costs

By **Amy C. Janes**

Before undertaking any task, humans implicitly determine whether reaching the goal is worth the effort. Weighing costs and benefits is a fundamental brain function that often occurs unconsciously, allowing for the adaptive use of resources to attain goals. The neurotransmitter dopamine is a key player in this process (*1*). On page 1362 of this issue, Westbrook *et al.* (*2*) clarify the role of dopamine by showing that increasing an otherwise weak dopamine signal shifts attention toward the rewarding outcome, resulting in greater readiness to perform cognitive effort to reach the goal. As such, increasing dopamine appears to be beneficial specifically for those individuals with relatively lower dopamine function. This finding may explain the efficacy of dopamine-enhancing medications such as Ritalin (methylphenidate), which is prescribed to treat attention deficit hyperactivity disorder (ADHD) and has been used without a prescription by students as a "study enhancing drug."

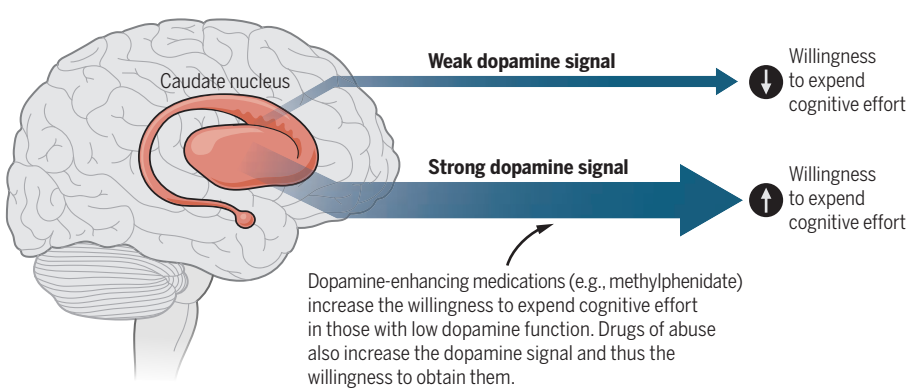
Dopamine is found throughout the brain in several neurobiological pathways that mediate processes including movement, reward, and cognitive functions such as learning and working memory (*3*). Given the range of functions influenced by dopamine, there is a need to better understand how dopamine within distinct brain regions affects nuanced elements of cognition and behavior. For example, Westbrook *et al.* expand on the finding that a blunted dopamine signal can result in cognitive dysfunction (*4*). Specifically, they show that the willingness to expend cognitive effort is diminished in those with lower dopamine function in the caudate nucleus, a portion of the brain involved in goal-motivated behavior (*5*). This finding blends two known roles of dopamine—motivation and cognition—by indicating that goal-related attention drives the motivation to engage cognitive resources.

Westbrook *et al.* also show that a blunted willingness to expend cognitive effort can be increased by pharmacologically enhancing the dopamine signal using the dopamine agonist methylphenidate. This is consistent with prior findings that dopamine enhancement leads to increased willingness to expend effort in patient populations who have disorders with an underlying dopamine deficit, such as ADHD and Parkinson's disease (*6*, *7*). Thus, dopamine-enhancing medications may not improve cognitive ability per se, but drive the willingness to expend cognitive effort (*8*).

More precisely, this greater willingness to expend effort occurs because dopamine-enhancing medications raise the salience of, and attention to, goal-related stimuli that would otherwise evoke a response too weak to warrant the expenditure of cognitive effort (*8*). Methylphenidate and similar drugs

Caudate dopamine affects the weight of benefits

Individual differences in dopamine function in the caudate nucleus relate to one's willingness to expend cognitive effort, which can be influenced both by medications and drugs of abuse that enhance the dopamine signal.



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