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Keynote address

Nonexercise activity thermogenesis: a way forward to treat the worldwide obesity epidemic

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Obesity is an epidemic with already catastrophic consequences [1]. When a doctor sees a patient with obesity, not only does the doctor need to be cognizant that obesity affects every organ system, but the doctor also needs to be aware that it affects the patient's self-perception [2]. Patients think about their obesity and the discrimination they experience because of it approximately 5 times every hour [3,4]. It is unfortunate, because it is the combination of the patient with, not only their inbuilt genetic makeup, but also the environment in which they find themselves [5] that is preventing the patient from moving and has precipitated their obesity.

Obesity not only results in the patient experiencing medical issues, discrimination, and negative feelings, the costs, to corporate America are staggering. Obesity alone raises annual per capita medical costs by $2741 (in 2005 dollars) [6]. However, a patient with obesity with multiple complications can cost a company $7000–$10,000 per person per year more than their lean counterpart [7].

One and one half billion people have obesity [1]. One half of the children in Beijing are obese [8]. The rate of accentuation of obesity in India is so rapid that it has the capability of slowing its growing economy. The rapid increase in obesity is a global issue [9].

There is debate as to whether it is the chair or the knife and fork that has caused the increase in obesity rates. During the past 150 years, data from multiple studies have shown that food intake has remained relatively constant. The U.K. data have suggested that as the obesity rates doubled since the 1980s [10], the caloric intake actually declined. However, concomitantly with that there has been a progressive and systematic decline in energy expenditure, first with urbanization and now with the computer and car revolutions. Obesity occurs in the persistence of positive energy balance, such that energy intake is consistently greater than energy expenditure. The National Health and Nutrition Examination Survey has shown that the combined effect of access to low-priced food, concomitantly with the inactive lifestyle, has resulted in sustained positive energy balance and obesity [11]. With this realization, it becomes of great interest to examine the progressive decline in daily energy expenditure.

Energy expenditure [12] is composed of the basal metabolic rate, thermic effect of food, and physical activity. The basal metabolic rate accounts for approximately 60% of the total energy expenditure in a sedentary individual. Approximately 73% of the variance in basal metabolic rate is determined by body size, with the lean body mass positively correlated with the basal metabolic rate. Thermic effect of food accounts for about 11% of the total; this is the energy expenditure associated with the ingestion and absorption of food and its conversion into intermediary metabolites. The remainder of energy expenditure is physical activity.

The energy expenditure associated with physical activity is either associated with purposeful exercise, accounting for 20% of Americans who participate regularly, or nonexercise activity thermogenesis (NEAT), the energy expenditure of everyday living [13]. The energy expenditure of everyday living is of great interest, because the vast majority of individuals with obesity have no exercise activity thermogenesis; thus, their entire bout of activity-associated energy expenditure is NEAT.

Data from the United Kingdom display the vast distribution in total daily energy expenditure across an industrialized population [14]. Thus, if body size accounts for basal metabolic rate and the thermal effect of food are small, the only explanation for how an individual of similar body size can expend 2000 kcal/d more than another individual of similar body size is through the variability in their activity energy expenditure.

Similar to the United States, most people in Britain do not use fitness centers [15,16]. Most people do not exercise

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regularly; thus, the only way to explain why, across a population, some people can expend 2000 kcal/d more than other individuals of similar size is because their NEAT is so variable. How can NEAT vary by 2000 kcal/d between two individuals of similar size, both living in civilized countries? The answer is because work practices differ greatly between individuals, and leisure time activities also differ tremendously between individuals.

If one studies, using calorimetry, the energy expenditure of work, one sees that a chair-bound job can be associated with a NEAT of 300 kcal/d [14]. If one were to take, theoretically at least, a group of individuals working in a modern office and transfer them into an environment in which agriculture was the primary work-related endeavor, the energy expenditure theoretically associated with work would increase from 300 kcal/d of NEAT to 2300 kcal/d. Work is a tremendous driver of the energy we expend through nonexercise activity. The energy expenditure of leisure time activities also has great variance [17–19]. An activity that many of us engage in for most of our days is gum chewing [20]. Such an activity is associated with an excursion of energy expenditure versus resting of about 20 kcal/hr. The point is not necessarily that one should chew gum all day, but to make the point that the trivial activities actually have a significant thermogenic effect [21]. When a person engages in multiple low-level activities throughout the day, this can aggregate to a significant amount of energy expended [22].

Conversely, there are NEAT activities that can be considered high-effect activities. These high-effect activities occur when an individual becomes upright. As soon as one starts to walk, even at 1 mile/hr, equivalent to "shopping speed," a person doubles their metabolic rate [23]. At 2 mile/hr, which is equivalent to purposefully walking to a meeting, a person increases their metabolic rate by about 150–200 kcal/hr, depending on their size. Rushed walking, which is equivalent to racing to an airport gate, can triple one's metabolic rate above the basal level. Thus, what a person does in their leisure time can dramatically affect their total daily energy expenditure. For instance, a person could return from work at 5:00 PM in the evening and sit in front of the television until falling asleep at 11:00 PM at night. That entire evening of leisure activity would expend approximately 50 kcal. In contrast, a person could return from work at 5:00 PM in the evening and start raking leaves or paint the basement, and in so doing, expend 100–150 kcal/hr. For that evening of avid home redecoration, one would expend 500–600 kcal compared with sitting in front of the television for 50 kcal. It is that combined effect of what one does during one's day as an obligate job combined with what one chooses to do in the evening that can account for why 1 individual of similar size can burn 2000 kcal more through NEAT than another individual of similar size [24].

If so much variability exists in NEAT, is that variability relevant to weight gain? In a previous research study, we studied a group of lean individuals and determined exactly how much energy each individual required to remain weight stable. Each individual was then overfed by an excess of 1000 kcal/d for 8 weeks [25]. That degree of overfeeding was maintained for 8 weeks, resulting in each individual receiving 56,000 excess kcal for that period. Although the degree of overfeeding was the same for each participant, the variability in how much fat each person gained was great. As shown in other studies [26], individuals appear to gain weight at variable levels, regardless of the amount of energy consumed in excess. Those people who store excess energy as body fat are those who do not activate their NEAT with overfeeding [25]. Those who eat 56,000 kcal greater than their energy needs and do not gain body fat appear to expend it through NEAT.

To understand the mechanism of NEAT activation, the experiment was repeated with different subjects by our laboratory [27]. These results were reaffirmed. The reason, however, an individual can consume 56,000 kcal and not gain excess weight is because this individual intuitively begins to walk [27]. As an individual is overfed an excess of 1000 kcal a day, they take it on themselves, without necessarily realizing it or joining the gym, to increase their walking. The median free-living velocity of walking is 1.1 mile/hr, and overfed individuals increase walking by ~2.5 extra hours daily. Thus, individuals who do not respond with changes in NEAT to overfeeding gain excess body fat. Individuals who activate NEAT stay lean, even when they are overfed.

Our next question was, are there drivers that stimulate the NEAT response? To address this, our laboratory conducted studies on rats in which putative chemicals were injected into the paraventricular nucleus of the hypothalamus [28,29]. The rats were then placed inside of a calorimetry chamber and their movements were monitored continuously in the X, Y, and Z axis, in all axes of movement.

Similar studies have been conducted using numerous different chemicals that potentially drive NEAT. One chemical that became of particular interest to our laboratory was orexin, an arousal protein [28,29]. In 1 study, we compared rats that were inbred for leanness over multiple generations to those that were inbred for obesity [29]. Before the orexin injections, the baseline measurements of physical activity for the rats inbred for obesity showed they had lower NEAT than the rats inbred for leanness. Even more intriguing is that when progressive doses of orexin were injected, the response of the rats with obesity was far less than that of the lean rats injected with similar doses. The brains of the obese rats appeared to have a diminished responsiveness to the same dose of chemical as those rats inbred for leanness. Other neuromediators have also been similarly implicated in the integration of NEAT into energy balance [30].

If NEAT is variable, centrally regulated, and implicated in fat gain, is NEAT important in obesity? To understand the role of NEAT in daily living, our laboratory developed a physical activity monitoring system (PAMS) [31,32]. This system enables us to track all the movements and postures of free-living individuals. Using this system, we are able to ascertain body posture. When an individual is standing, the body posture sensors indicate a vertical/vertical position; when sitting, the sensors indicate a horizontal/vertical position, and when lying, the sensors indicate a horizontal/horizontal position. Because the motion sensors are associated with all the posture senses, PAMS allows for all movements of a person in a 24-hour period to be captured by the laboratory.

In an analysis of the PAMS data from free-living individuals while they were awake, we examined every walk that a free-living person took. A walk was defined as a standing posture that involved movement for at least half a second. This analysis allowed for a unique glimpse into how individuals choose to move throughout their day. That study showed that most walks taken by free-living people were of short duration, with the average walk lasting <12 minutes [27]. Similarly, the walks are of low velocity. Thus, the average walk of a person is about 1.1 mi/hr and lasts for just <12 minutes. Therefore, it is the sum of all the different walks that explains how 1 person can expend by walking 850 kcal/d more of NEAT than another person who is taking slightly shorter, slower walks.

Our movements throughout the day might not therefore be purely volitional but might be underpinned by a deep biology that determines movement. Perhaps some people choose jobs as post office workers and others choose sedentary jobs. Such decisions might be driven by subtle brain mechanisms.

An individual with obesity, living in the same environment as an individual with more NEAT, is reasonable 2.25 hr/d more than their lean counterpart [33]. A lean individual, living in the same environment as a person with obesity, is exploiting opportunities to be up and walking for 2.25 hr/d [31,34]. Somehow subtle "be active" responses in the obesity-prone person might differ from those of lean-prone individuals whose brains are responding to the same signals differently.

How can one take advantage of this information to help individuals with obesity who might want to lose weight? The first question is what are the maximum capabilities of the human to move? To address this question, we conducted similar studies using the PAMS technology in Jamaica [35]. We were interested in individuals working in agriculture and individuals who had migrated into urban Kingston who now worked in offices. We found ambulation in the rural, lean Jamaican individuals to be twice as great as that of lean individuals living in Kingston or lean individuals living in the United States [35]. Similarly, people who were lean, working in the agricultural communities in Jamaica were seated for one half the amount of time as lean Americans. Thus, people in the United States are capable of potentially moving twice as much. Thus, here is the putative therapeutic window, an opportunity to increase calorie expenditure 350–750 kcal or more daily—if only we can get people out of their chairs.

To exploit this 350–750-kcal window, we started to examine how we might build high-volume, low-cost sensors that would be amenable to a wider audience. We took the Micro ElectroMechanical Systems accelerometer technology and integrated it into an MP3 player earpiece [36]. We then took that technology and linked it with a cellular telephone, which would enable people to start competitively "gaming" with respect to physical activity [37]. Next, we built a standalone device for consumers to use throughout their day [38]. As all of this was being done, however, a significant advance occurred in the technology. Both the iPhone (Apple Computer, Cupertino, CA) and Smartphone platforms incorporated a 3-axis Micro ElectroMechanical Systems accelerometer. These accelerometers are inside cellular telephones to rotate the screen as the machine is rotated. Suddenly, we had a mass marketed technology that enabled daily physical activity to be measured. These technologies have been validated in the laboratory [37] with energy expenditure, and these devices are precise and accurate physical NEAT sensing devices. We deployed an application (App), and 28,000 users used it within 6 months [37], which provided data similar to that of Westerterp [39] (Fig. 1). This demonstrated the feasibility of using accelerometers for population-wide assessment of energy expenditure.

Once we had the capability of measuring NEAT and access to the behavioral techniques to promote it [40–42], we wanted to design environments that were permissive to movement. Our first office of the future was developed in 2005. It was a standard office space populated with treadmills, bicycles, and a walking track. A total of 304 people worked there temporarily. There were desks; however, they were least favorably positioned in the space. This environment heralded the concept of walk while you work.

However, the treadmill desk was only a visual representation of the concept [34,43]. A person does not need a treadmill desk to be active during the workday. A stepping device with the same technology integrated into it [44] will also allow for increased physical activity while at work. It is placed under a desk and can be pulled out and used at will; for instance during a telephone call. The technology intergraded into the device can provide a daily printout of how many miles a person has stepped. This technology cost just under $50.

Less expensive and ubiquitously successful is the lanyard worn around the neck, "Walk and Talk Meeting in Progress"[34]. In each company in which it has been deployed, a protocol is put in place such that employees know not to interrupt people who are conducting walking meetings.

Other office elements include moving printers away from where things are printed from (this is rarely popular), mov-

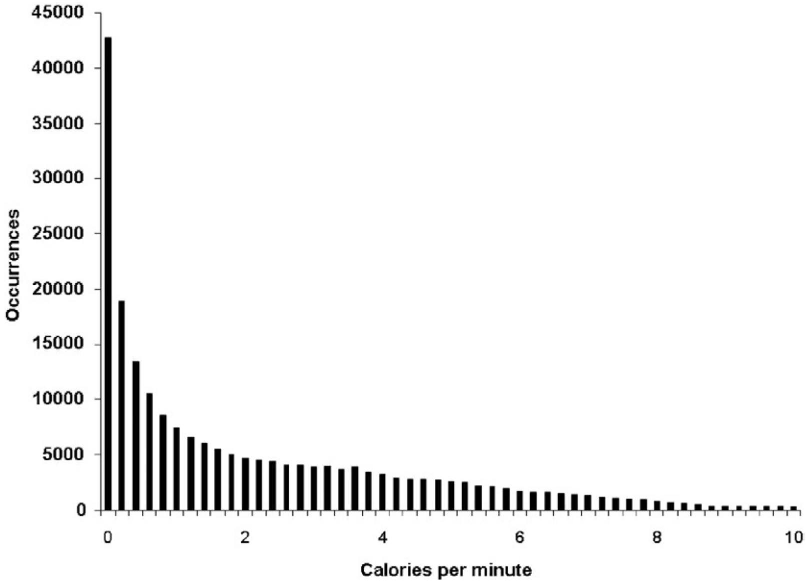

Fig. 1. Cellular telephone application data for 7346 cellular telephone users.

ing trash cans further away, and having walking tracks laid out with floor tape.

Importantly, each of these intervention elements has been validated in the laboratory and assessed for safety and utility by people with obesity. These interventions have therefore been validated and are accessible by most people. For instance, most people, regardless of weight, can complete a 30-minute walk-and-talk meeting and use a stepper during telephone calls. We have focused on designing, testing, and validating all-inclusive methods of promoting daily physical activity.

Moreover, we have validated comprehensive programs to promote office-based health and optional weight loss by building laboratories inside office complexes [45]. Subjects generally reach their weight goals and fat mass decreases while the lean mass increases. Full-scale deployments, however, require the need, not only for behavioral scientists, but also lawyers, company economists, healthcare providers, information technology personnel, janitorial staff, and managers. Companies do not want wellness initiatives unless an entire plan is in place with respect to ensuring their productivity objectives are met.

Having developed these approaches for adults in offices, it was straightforward to take them into schools [46]. We interviewed focus groups of 11-year-old children and asked them to design their own school. The students devised this school environment akin to a Socratic village-style living environment (Fig. 2). We found that children like to study in hockey nets—akin to fort-building behaviors. The students also devised and designed white boards, which weighed 1.5 kg; light enough for them to carry around the environment. The space was decorated by their artwork, which was suspended from the ceiling. We used a number of mobile electronic technologies, wheeled desks, and pre-existing toys, such as the Dance Dance Revolution [47,48]. Interestingly, a hierarchical development occurred in which the students became group advocates for their own health. We have had success with students taking on specific roles in a class-based health environment.

Students also became proactive advocates beyond the classroom. One boy, for instance, wrote and met with leadership from a major cereal company to address the amount of sugar in children's cereals. One girl designed a desk that was converted into a commercial prototype.

We examined the effect of the redesigned school using validated physical activity sensors. The students in the redesigned school moved twice as much as those in a traditional classroom [49]. In another classroom in Idaho Falls,

Fig. 2. Design of school of the future.

Fig. 3. Mobile dual-energy x-ray absorptiometry unit.

the entire classroom was redesigned and mobile desks and measurement matrices were put in place by a student's mother—community-based participatory research. In this example, the entire process was internally driven and successful.

As school-based activity and nutrition programs expanded, it proved to be a challenge to validate these programs using robust measures. Thus, we built a bus containing a dual-energy x-ray absorptiometry scanner and a host of activity sensors and educational materials (Fig. 3). Thus, we can drive the laboratory to assess any given program's efficacy.

However, the most important metric for school-based health programs is often educational attainment (similar to the productivity in offices). In schools that engage in active learning programs, educational attainment has improved.

Conclusion

The human being was designed over 2.5 million years to walk. It was a feat of glorious engineering. Within a miniscule, in genetic terms, period, a mere 200 years, humans have been compressed into chairs. It is an unnatural position for this version of *Homo sapiens*. Sitting is an unhealthy way of spending our days, and, simply put, we are not designed to do it. There is a calling, to raise the sedentary from their chairs and let good health abound.

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