Special Article

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The importance of clinical research: the role of thermogenesis in human obesity[1–5]

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ABSTRACT The hypothesis that human obesity is caused by deficient thermogenesis has been proposed by many investigators throughout the 20th century. Supporting evidence was obtained from epidemiologic studies of dietary intake, animal models with aberrant brown adipose tissue (BAT) function, and genetic studies of human polymorphisms of genes involved in BAT function. Supporting evidence was also obtained from clinical studies of the thermogenic effect of meals, but these measures capture only a short portion of the day and may miss some of the thermogenic effect. To capture the effects throughout the day and to move the studies out of the metabolic ward, investigators have used the doubly labeled water (DLW) method to measure total daily energy expenditure. DLW studies have not supported the above hypothesis. Increases in total energy expenditure (TEE) during overfeeding have been small (0.9 ± 0.8 MJ/d) and account for an average of only 18 ± 18% of the excess energy intake. Most of this increase is in the resting metabolic rate. Moreover, these studies showed little variation in the changes in resting metabolic rate or in thermogenesis from meals during overfeeding. Instead, the component that is most variable and that accounts for the variability in weight gain during overfeeding is the energy expended in physical activity. This component of TEE deserves greater attention in future studies. These studies of thermogenesis have shown the importance of clinical research as part of a comprehensive approach to understanding the etiology of human obesity. *Am J Clin Nutr* 2001;73:511–6.

KEY WORDS Energy metabolism, doubly labeled water, thermogenesis, stable isotopes, Robert H Herman Memorial Award in Clinical Nutrition

The hypothesis that weight gain, and ultimately obesity, results from a deficit in energy expenditure has been a central hypothesis of many studies for much of the past century. Examples begin with the work of Neumann (1) and Gullick (2), who performed overfeeding studies on themselves, and continue through human genome searches for linkages between various uncoupling protein loci and obesity. Investigative methods have been wide-ranging and have included epidemiologic studies, animal model studies, clinical studies, and basic biochemical, molecular, and genetic studies. These studies provided much evidence supporting the hypothesis; however, recent clinical studies in which total energy expenditure (TEE) was measured did not support the hypothesis.

As reviewed by Heymsfield et al (3), several epidemiologic studies indicated strongly that the energy requirements of obese participants are lower than those of nonobese control subjects and that these requirements decrease with increasing obesity. The results of 2 of the larger studies that typify these findings are shown in **Figure 1**. Keen et al (4) collected 3-d records of dietary intake using semiquantitative dietary questionnaires from 1488 middle-aged male civil servants from central London. When energy intake was regressed on body mass index (BMI), energy intake was found to decrease with increasing adiposity ($r = -0.14$, $P < 0.001$). Braitman et al (5) evaluated the 24-h diet recalls of 2700 US males and 3519 US females in the first National Health and Nutrition Examination Survey and found a similar relation, except for an upward trend in the heaviest group. These results, and the results of many similar epidemiologic studies, indicate that obese individuals maintain their obese states with energy intakes that are on average less than those of lean individuals; this has been interpreted as evidence that obesity is associated with reduced energy expenditure. To pursue this interpretation further, Braitmen et al (5) performed a second data analysis in which they adjusted the energy intake data for the participants' reported physical activity. This eliminated the negative correlation in men but not in women ($r = -0.16$), suggesting that although some of the decrease in energy expenditure was related to physical activity, there must also be reductions in the other components of energy expenditure.

Work with animal models of obesity strongly supported the results of human epidemiologic studies. Specifically, it was found that energy expenditure varies little between genetically obese rodents and their lean controls (6). A striking similarity between many of these obese animal models is their abnormally

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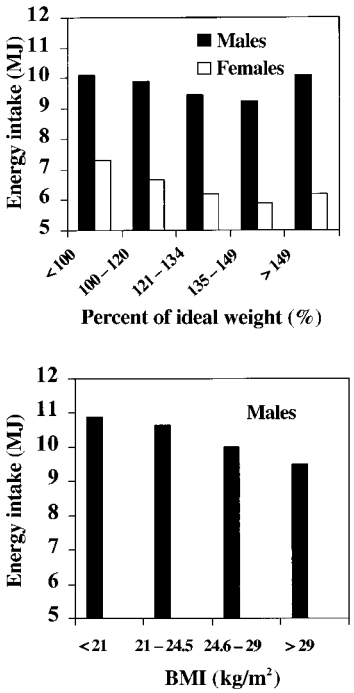

FIGURE 1. Representative estimates of energy intake based on dietary questionnaires of groups with different degrees of obesity. Adapted from Keen et al (4) and Braitman et al (5).

low thermogenic response to cold or feeding (6, 7). Zucker rats, *ob/ob* mice, and *db/db* mice do not respond to cold exposure or excess energy intake by increasing heat production. This results in dramatic differences in the efficiency of weight gain when these animals are fed an energy-dense diet. Zucker rats store 90% of their energy intake in excess of maintenance energy needs as body fat, and *ob/ob* mice store 70%. In contrast, wild-type control animals increase their energy expenditure while consuming these diets and store only ≤10% of the excess energy intake as fat. In addition to the decreased thermogenesis, many, but not all, of the animal models show hyperphagia, especially early in life when weight gain is most rapid (7).

Morphologic and biochemical studies traced the deficit in the thermogenic response to aberrant brown fat function. Brown adipose tissue (BAT), long known as a thermogenic tissue, was identified as the site of uncoupling protein 1 (UCP1) expression (8). Biochemical studies further elucidated the mechanism of UCP1 by showing that this protein uncouples mitochondrial oxidation from phosphorylation by discharging the proton gradient that is produced across the inner mitochondial wall during oxidation without producing ATP (8). Thus, BAT can oxidize energy substrates, particularly fatty acids, to produce heat without producing ATP. In this way, animals with active BAT can partition excess energy intake toward oxidation and thus away from storage as body fat.

Although BAT has been identified by morphologic examination in adult humans, proof of its existence in humans remained elusive until molecular studies showed the expression of UCP1 in human fat tissue (9). Genetic studies have continued to look to relations between thermogenesis and obesity by searching for relations between BMI and known genetic mutations. For example, Clement et al (10) found that the Trp64Arg mutation in the β_3-adrenergic receptor that mediates BAT response predicts elevated BMI in obese individuals, suggesting that this particular etiology of deficient thermogenesis indeed contributes to obesity.

The quantitative contribution of thermogenesis, however, has remained an issue. Many clinical studies were performed during the 1960s and 1970s to assess the quantitative importance of thermogenesis in humans. Most studies were designed to investigate potential differences in postprandial thermogenesis between lean and obese adults. The increase in resting energy expenditure (REE) was measured for 3–6 h after a meal. Although not all studies showed differences, most showed that obese individuals had a smaller thermic effect of a meal (TEM) than did lean individuals (11). Some of the clearest results were those of Segal et al (12), who carefully controlled for the effects of fasting, diet, and body composition. For example, in one study of 35 young men who were given a 3-MJ liquid meal, thermogenesis was measured for 3 h after a meal and found to be strongly inversely correlated with percentage body fat ($r = -0.64$; **Figure 2**). Differences, however, averaged only 145 kJ/3 h, or ≈5% of the energy content of the meal, and thus were not as large as those observed in animal models. Moreover, a study by Brunden et al (13) even questioned whether these differences were truly due to thermogenesis. These investigators controlled for obesity-related differences in thermal insulation of the abdominal cavity while measuring heat loss through the abdominal wall during the postprandial period. From this, they concluded that most of the difference between lean and obese subjects could be explained by increased heat loss across the abdominal wall in the less-insulated lean individuals rather than by thermogenesis per se.

The above studies, however, generally measured only thermogenesis over a small part of the day and thus might not have detected total thermogenesis. Two approaches, whole-room respiratory chamber measurements and doubly labeled water (DLW), have been used to avoid the limitations of short-term respiratory gas exchange measurements. Most clinical studies using these techniques have challenged the hypothesis that obesity is a result of a deficit in thermogenesis. The proliferation of respiratory chambers has enabled investigators to perform 24-h measurements of energy expenditure. Typically, such chamber studies showed that energy expenditure in obese subjects, rather than being lower, was actually greater with greater weight (14). The increase was found to be correlated with either body mass or fat-free mass and this began to raise doubts among some investigators regarding the

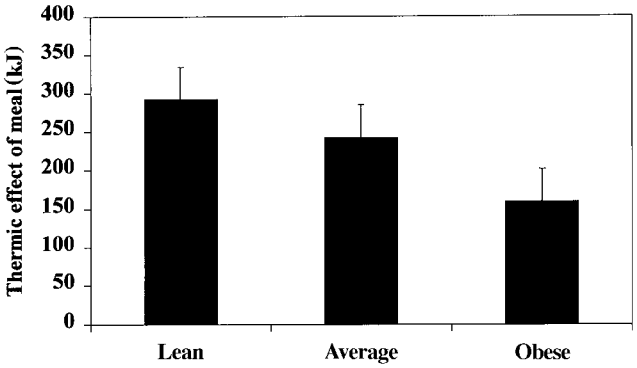

FIGURE 2. The thermic effect of a meal measured for 3 h after the meal in subjects with different degrees of obesity. Adapted from Segal et al (12).

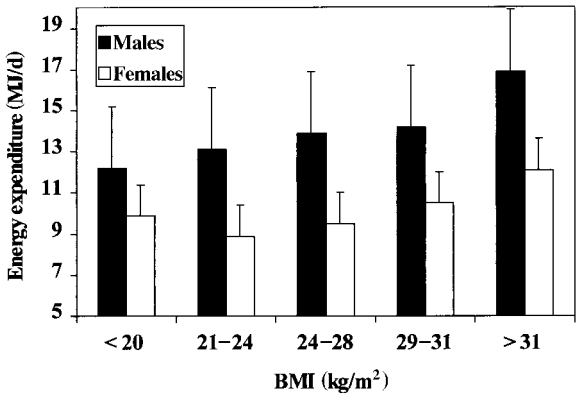

FIGURE 3. Increase in energy expenditure as measured by doubly labeled water in groups with different degrees of obesity. Adapted from Schulz and Schoeller (19).

accuracy of the self-reported energy intakes that gave rise to the relations between obesity and energy expenditure that are shown in Figure 1 (3). The chamber data, however, like short-term respiratory gas exchange measurements, do not mimic normal free-living conditions. The 24-h respiratory measures come closer to free-living conditions than do the 3–6-h open canopy measurements, but participants are limited in their activities and are also aware that their behavior is being monitored.

The development of the DLW method obviated this limitation, allowing investigators to assess the effects of overfeeding under free-living conditions. In 1983, our laboratory published the results of the first use of the DLW method in humans (15). This method, which was developed by Lifson and McClintock (16), used water labeled with tracers for hydrogen and oxygen. The doubly labeled loading dose was given orally and quickly equilibrated with body water. Over the next 2 wk, the hydrogen tracer washed out of the body as water and the oxygen tracer washed out as water and carbon dioxide. The difference between the 2 washout rates therefore provided a measure of carbon dioxide production and thus energy expenditure. Multiple validation studies showed that the DLW method is accurate to within a few percent and has a precision of 3–7%, depending on the dose, the length of the washout period, and the precision of the isotopic analyses (17, 18). The DLW method finally provided an accurate and objective means of investigating the hypotheses that deficient energy expenditure and thermogenesis are at the root of human obesity.

Numerous investigators used the DLW method to measure energy expenditure in lean and obese humans. Summaries of these studies clearly confirmed the results of the respiratory chamber studies by showing that obese subjects have a greater average energy expenditure than do lean and normal-weight subjects (19, 20). The increase with BMI is dramatic (**Figure 3**) and sharply contrasts with the self-reported energy intakes shown in Figure 1. This increase in TEE with increasing weight or BMI has been reported in children and adolescents (21, 22). The results of these DLW studies show conclusively that the self-reported energy intakes of individuals are biased and that this bias increases with BMI (3, 23). Further discussion of the bias problem with self-reported intake is beyond the scope of this article, but the implications of this problem are important for the hypotheses that there are large deficits in energy expenditure in obese individuals. It is now clear that obese individuals generally have a higher energy requirement than do those who weigh less. Thus, rather than obesity being associated with low energy requirements, it is now evident that most obese individuals consume more dietary energy than do sex- and height-matched lean control subjects (3, 19, 20). Thus, any model of the role of energy expenditure in the etiology of obesity can no longer just depend on a finding that indicates a low energy expenditure but must also explain how expenditure increases above that of lean control subjects during or after the development of obesity.

These DLW energy requirement studies, however, do not rule out the possibility that the obese are deficient with regard to a thermogenic response to overfeeding and that the efficiency of weight gain during overfeeding may be at the root of human obesity. To test the hypothesis that there are differences in thermogenesis between lean and obese individuals, investigators have performed studies in which energy expenditure was measured in subjects while they were consuming a maintenance diet and again while they were consuming a diet with an energy intake that exceeds maintenance energy requirements. This design should provide a definitive test of the thermogenesis hypothesis because any adaptive increase in energy expenditure would be detected regardless of the time of day or the component of energy expenditure involved. However, only 2 overfeeding studies have been published that included both obese and nonobese control subjects and 1 of these included only 3 obese subjects (22, 24). Four other studies were performed in nonobese subjects to look for evidence of thermogenesis that protects these individuals from weight gain (25–28). These 6 studies are summarized in **Table 1** and **Figure 4**.

None of these studies provided evidence for a thermogenic response that is comparable with the BAT response in rodents and thus is protective against weight gain during overfeeding. The average increase in TEM observed in the 4 studies that included a TEM measure after a standard meal was only 0.2 ± 0.4 MJ/d, which accounted for $4.8 \pm 6.9\%$ of excess energy intake. Resting metabolic rate (RMR) also increased during the overfeeding period. The increase was larger than that in TEM (0.8 ± 0.7 MJ/d), but this too accounted for only $12.1 \pm 6.2\%$ of the excess energy intake. Indeed, during overfeeding, TEE increased by only 0.9 ± 0.8 MJ/d, or $18 \pm 18\%$ of excess energy intake. Although the 18% increase in TEE helps to mediate energy storage and weight gain, the average increase was small in humans and would not prevent weight gain. Furthermore, when viewed across studies, there was no evidence that the change in energy expenditure increased with greater excess energy intake ($r = -0.27$, NS).

The absence of an adaptive increase in TEE with increasing excess energy intake was surprising because RMR and TEM, 2 of the 3 components of TEE, are generally considered to increase as excess energy intake increases (29). When analyzed separately, RMR did increase across the studies with increasing excess energy intake ($r = 0.98$, $P < 0.001$), with a slope of 0.26. Across all studies except that of Pasquet et al (27), TEM tended to increase with increasing excess energy intake ($r = 0.37$, $P = 0.4$). The absence of a significant increase in TEM was surprising in light of the large number of studies that showed increases with energy intake. The absence of a significant increase, however, probably reflected methodologic differences, including size and composition of the test meals and the length of measurements after the meals. Given the increase in RMR and the trend toward an increase in TEM observed in these 6 overfeeding

TABLE 1
Summary of human overfeeding and energy balance studies using doubly labeled water[1]

	Reference									
		Bandini et al (22)			Diaz et al (24)					
Variable	Riumallo et al (25)	All	Obese	Roberts et al (26)	All	Obese	Pasquet et al (27)	Levine et al (28)	Average	SD
Length of overfeeding (d)	84	14	14	21	42	42	63	56	46	30
Energy intake (MJ/d)										
Weight maintenance diet	11.2	11.5	12.1	14.0	13.8	11.9	12.7	11.8	12.4	1.0
Overfeeding diet	14.2	17.6	18.5	18.1	20.2	18.5	25.1	16.0	18.5	3.2
TEE (MJ/d)										
Weight maintenance diet	11.4	12.6	12.9	13.9	13.5	12.4	14.1	11.7	12.8	1.0
Overfeeding diet	11.4	12.8	13.9	14.7	15.5	13.5	14.1	14.0	13.7	1.2
RMR (MJ/d)										
Weight maintenance diet	6.2	7.0	7.5	7.5	7.3	7.2	5.1	7.1	6.9	0.8
Overfeeding diet	6.3	7.7	8.4	7.8	8.2	8.3	7.2	7.4	7.7	0.7
TEM (MJ/d)										
Weight maintenance diet	1.1[2]	1.1	1.2	1.2	1.4[2]	1.2[2]	1.3	0.9	1.2	0.1
Overfeeding diet	1.4[2]	1.5	1.3	1.5	2.0[2]	1.8[2]	0.8	3.8	1.5	0.4
PAEE (MJ/d)										
Weight maintenance diet	4.0	4.5	4.2	5.1	4.8	4.0	7.7	5.2	4.8	1.3
Overfeeding diet	3.6	3.6	4.3	5.4	5.2	3.4	6.1	0.4	4.6	1.0
Increase in energy stores (MJ/d)	2.1	2.9	4.6	3.2	4.6	5.1	7.6	1.8	4.0	1.9
Unaccounted for energy (MJ/d)	0.9	3.0	0.7	0.6	−0.2	0.4	4.8	0.1	1.2	1.9

[1] TEE, total energy expenditure; RMR, resting metabolic rate; TEM, thermic effect of a meal; PAEE, energy expenditure of physical activity (calculated by difference).
[2] Not measured, estimated as 10% of energy intake.

studies, the absence of an increase in TEE suggests that the energy expenditure of physical activity (PAEE) must decrease with overfeeding. Calculation of PAEE by difference, however, identified only a trend toward a decrease in the PAEE values across these 6 studies ($r = -0.60$, $P = 0.1$).

Further inspection of the PAEE component of these 6 studies provides some very intriguing details regarding the human response to overfeeding. Indeed, it was only through the use of DLW that it was possible to obtain this term because it can be derived from the difference between TEE, RMR, and TEM. In so doing, it is evident that the PAEE varies between studies. Although the SD of the change in RMR and TEM during overfeeding is ≈6% of excess energy intake across these studies, that for PAEE is 18%. Of particular note, the study of massive overfeeding during Guru Walla by Pasquet et al (27) was associated with a decrease in PAEE of 1.6 MJ/d, whereas PAEE increased in the study by Levine et al (28) by 1.4 MJ/d, a difference of nearly 50% of the excess energy intake. Some of this variability may be an artifact of determining PAEE by difference, because any errors in measuring TEE, RMR, or TEM are accumulated in the calculated PAEE value. A theoretical propagation of error analysis, however, suggests that this should be only 4–8%, given the number of subjects enrolled in each study, if these studies are performed with good precision for DLW (30). Thus, this variability probably reflects physiologic changes in physical activity. In the study of the ritual overfeeding during Guru Walla, the use of activity meters showed a decrease in activity. This may have reflected the cessation of the work of harvesting, a volitional decrease in activity because the goal of Guru Walla is maximal weight gain, or a nonvoluntary decrease in activity secondary to the massive overfeeding (27). In contrast, the increase in PAEE observed during the overfeeding study of Levine et al (28) was not associated with a change in physical activity as measured by activity monitors, but rather must have been due to increases in the activities of daily life, fidgeting, spontaneous muscle contraction, or maintaining posture, which would not be readily detected by the activity monitors.

The variability in the response of PAEE to overfeeding is further illustrated by the fact that the increase in energy expenditure in nonvolitional activities observed by Levine et al (28) was not a typical feature of overfeeding studies in general. A decrease in PAEE was observed in one-half of the other overfeeding studies and the largest increase in PAEE among the other studies was 0.4 MJ/d, or less than one-third of that observed in the study of Levine et al (28). Still, these investigators found that the between-subject variation in the increase in PAEE accounted for 50% of the between-subject variability in fat gain during overfeeding. Diaz et al (24) also found that increased PAEE accounted for the failure of one of their subjects to gain weight during overfeeding. In that subject, however, the increase did not reflect nonvolitional activity. This subject returned to employment and began a regular exercise program. Indeed, Diaz et al (24) reported that 2 of the 3 subjects who gained the least weight increased their levels of physical activity, whereas the subject who gained the most weight decreased his activity between baseline and overfeeding. The changes in TEE accounted for 87% of the variation in weight gain, with most of this change occurring in the PAEE component (24).

These human clinical studies provide a stark contrast to the animal model studies. The animal studies show that variations in thermogenesis explain the major differences in weight gain during overfeeding in rodents and biochemical studies clearly identify BAT as the source of this thermogenic response (8). Human clinical studies find little evidence of a significant thermogenic response. The most consistent response is an increase in RMR, corresponding to 12% of the excess intake. Most of this is due to increases in body size, particularly fat-free mass (14, 29), and thus cannot be taken as strong evidence of thermogenesis. The increase

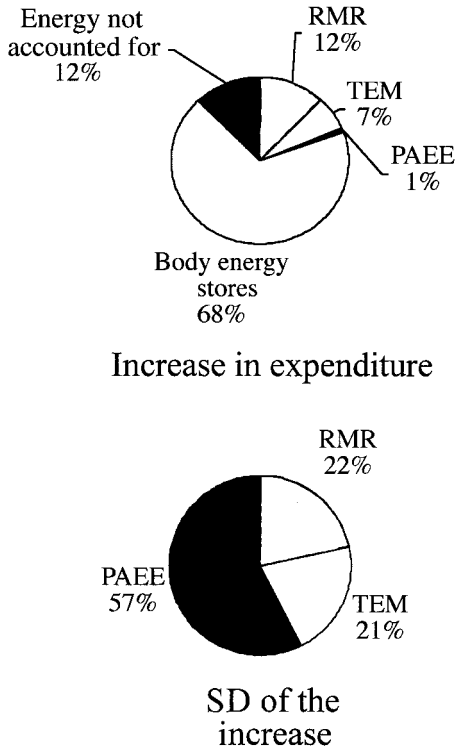

FIGURE 4. Fractional disposition of excess energy intake during overfeeding and SD of the changes in energy expenditure during overfeeding. Average of findings from 6 doubly labeled water studies (22, 24–28). RMR, resting metabolic rate; TEM, thermic effect of a meal; PAEE, energy expenditure of physical activity.

in TEM is not as consistent between studies, but the average is the expected increase in the obligatory cost of storing the extra energy from the larger meals (29) and thus cannot be taken as evidence of thermogenesis. Instead, it is the variability in the PAEE that accounts for the variation in weight or fat gain during overfeeding. This can be due to changes in exercise, activities of daily life, or nonvolitional activity. The changes in PAEE, however, do not appear to result from a decrease in work efficiency (24).

Although the DLW studies did not detect a significant thermogenic response in humans during overfeeding, there was a discrepancy in the net energy efficiency of increased energy stores between the obese and nonobese participants. The number of obese subjects studied, however, is small because only Bandini et al (22) and Diaz et al (24) included an obese cohort in their studies. Nevertheless, the obese subjects had a significantly higher net efficiency of energy storage (84 ± 1% compared with 64 ± 13%; $P < 0.05$). However, these studies did not provide any data that would explain the difference. None of the changes in energy expenditure terms differed between the obese and nonobese subjects. The difference in efficiency lay in the energy that could not be accounted for by either an increase in TEE or body energy stores. Thus, the difference in efficiency appears to be a methodologic problem related to measurement of body composition or metabolizable energy intake.

These human feeding studies show the importance of clinical studies in the study of the etiology of human obesity. Although epidemiologic and basic studies have provided a strong indication that thermogenesis can be an important mechanism in the prevention of obesity, clinical studies provide evidence that thermogenesis plays only a minor role, if any, in the prevention of human obesity. Instead, the clinical studies provide additional support to the growing evidence that physical activity or PAEE plays an important role in protection against weight gain (31–33). However, this is not to say that the epidemiologic studies and basic studies are not as important. Animal studies and basic studies provide the foundation for clinical studies as well as the mechanistic models on which clinical studies must be based. Although beyond the scope of this review, there are also exciting data coming from animal and basic studies regarding the genetics of obesity that will help to identify the mechanisms underlying the development of obesity. In addition, it may be possible to activate thermogenesis by using pharmacologic agents, which may prove vital in the prevention and treatment of human obesity. No single class of research can stand by itself. Rather, all 3 types of research—clinical, animal, and basic—are required if we are to finally understand the etiology and treatment of obesity.

This work was inspired by a large group of collaborators and trainees and was made possible through the efforts of an even larger group of clinical and laboratory staff.

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Erratum

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Reference 1 on page 515 should read as follows: Neumann RO. Experimentelle Beiträge zur Lehre von dem täglichen Nahrungsbedarf des Menschen unter besonderer Berücksichtigung der notwendigen Eiweissmenge. (Experimental contributions to the teaching of man's nutritional requirements under special consideration of the necessary amount of protein.) Arch Hyg Bakteriol 1902;45:1–87 (in German).