Pathophysiology of Weight Loss in Older Persons

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‘...for in old men, even without any disease, owing to their being near the close of life, the appetite is nearly gone.’

Aretaees the Cappadocian

It is now well recognized that a physiological anorexia of aging occurs that is associated with gradual weight loss in older persons [1, 2]. A number of epidemiological studies have shown that weight loss in older persons leads to death (fig. 1) [3–6]. In addition, weight loss has been shown to be associated with hip fracture [7]. When an older person develops a disease, the disease interacts with the propensity for anorexia, leading to severe weight loss and cachexia. The Hebrew physician, Maimorides differentiated between sarcopenia and cachexia: ‘...for wasting which resembles old age (sarcopenia) and wasting which is secondary to fever (cachexia) and wasting which is called doalgashi (starvation)’. The differences between the three forms of weight loss are delineated in table 1.

In nursing home residents who were losing weight, it was shown that those who could reverse their weight loss had a much lower mortality rate than those who continued to lose weight [8]. The Cochrane collaboration found that caloric supplementation decreased mortality [9].

The Physiological Anorexia of Aging

The anorexia of aging is due in part to social factors, especially isolation. Having someone eating with an older persons [10] or enhancing the environment of the dining room [11] have both been shown to enhance food intake.
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With aging there is an increase in taste sensory threshold and a decrease in smell. Both smoking and drugs can further decrease the ability to enjoy food. Zinc deficiency, which is common in diabetics and persons taking diuretics, can lead to hypogeusia. The use of taste enhancers has been shown to reverse weight loss [12]. The major reason for the early satiation that occurs in older persons is altered processing of food in the stomach [13]. Large caloric meals slow gastric emptying. With aging there is a decrease in fundal compliance resulting in more rapid antral filling and earlier satiation [14, 15]. Decreased release of nitric oxide in the fundus in response to food appears to be the reason for the decline in fundal compliance [16, 17].

In addition, older persons have an increase in cholecystokinin levels. This increase is particularly marked in response to fat [18]. Cholecystokinin is also a more potent satiating agent in older animals [19] and humans [20].

We have demonstrated that caloric supplements given 60 min before a meal are more effective at increasing caloric intake than when they are given with the meal [21].

Males develop greater anorexia with aging. This appears to be due to the declining testosterone levels leading to an increase in leptin [22]. Leptin is a peptide hormone that causes anorexia and an increase in metabolic rate. The anorectic effects of leptin are attenuated in the presence of hypertriglyceridemia.

Within the central nervous system a variety of neurotransmitters, such as norepinephrine, neuropeptide Y, serotonin and nitric oxide are responsible for transducing the effects of these peripheral signals.
Sarcopenia

Sarcopenia (lack of flesh) refers to the loss of muscle mass that occurs with aging [23]. Sarcopenia is associated with decreased strength, frailty and disability. Persons who remain obese while losing muscle mass – ‘the obese sarcopenia’ – do particularly poorly as they age.

Numerous factors are involved in the pathogenesis of sarcopenia. A decline in testosterone in males appears to be particularly important in the pathogenesis of sarcopenia [24]. Other factors involved include decreased food intake, decreased physical activity, a decline in muscle insulin-like growth factor-1, lack of appropriate neural input and poor vascular supply. Interleukin-6, the ‘geriatric cytokine,’ has also been implicated in the pathogenesis of sarcopenia.

Cachexia

Cachexia comes from the Greek meaning ‘poor condition’. Cachexia is a condition of severe wasting which occurs in the presence of chronic inflammation. Cachexia is associated with a redistribution of protein, with loss of protein from muscle and an increase in hepatic protein synthesis, leading to an increase in circulating acute phase proteins, such as C-reactive protein and serum amyloid protein. Persons with cachexia lose fat-free mass mainly from muscle as well as an equal amount of fat. They maintain extracellular water. Cachectic patients usually have low serum albumin and cholesterol levels. Cachectic patients have an increase in resting metabolic rate but a decrease in physical activity.

### Table 1. Comparison of anorexia (starvation), sarcopenia and cachexia

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<th>Anorexia</th>
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<td>Physical activity</td>
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<td>Proteolysis</td>
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<td>Insulin resistance</td>
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<tr>
<td>Cortisol</td>
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<tr>
<td>Triglycerides</td>
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<td>Cytokines</td>
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<td>++ +</td>
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<tr>
<td>Leptin</td>
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– = Decrease; + = increase.
Cachexia is triggered by the release of cytokines. Tumor necrosis factor-α, interleukin-1 and interleukin-6 are the major cytokines involved in the pathogenesis of cachexia. Patients with cachexia often have an associated anorexia.

Within cells protein degradation occurs when proteins bind to ubiquitin and are then transported to a proteasome, where proteolysis occurs. Cortisol, tumor necrosis factor-α, and interleukin-1 stimulate this pathway. In addition, cachexia is associated with decreased hepatic lipoprotein lipase activity and increased triglycerides (table 2). An associated insulin resistance decreases glucose going to muscle while making it available for the liver and other organs.

**Pathological Causes of Weight Loss**

The majority of causes of weight loss in older persons are potentially reversible. Nearly a third of older persons with weight loss have depression [25, 26]. Depression classically causes anorexia. Treatment of depression reverses weight loss. In severe cases this requires electroconvulsive therapy.

Numerous medications produce anorexia including digoxin, theophylline, cimetidine, and fluoxetine. Elder abuse occurs in 5% of older persons and may result in weight loss. Late life alcoholism is also a cause of weight loss. Females who had asthenia (anorexia nervosa) when young may redevelop an anorexia tardive in old age. Cholesterol phobia has also been associated with weight loss. Late life paranoia can result in the rejection of food.

Dysphagia can result in aversion to eating. Oral disease can lead to a decrease in intake of about 100 cal/day. Nosocomial infections such as tuberculosis, recurrent *Clostridium difficile*, and *Helicobacter pylori*, are common

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<th>Table 2. Reversible causes of weight loss – the MEALS-ON-WHEELS mnemonic</th>
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<td>Medications&lt;br&gt;Emotional (depression)&lt;br&gt;Alcoholism, elder abuse, anorexia tardive&lt;br&gt;Late life paranoia&lt;br&gt;Swallowing disorders&lt;br&gt;Oral problems&lt;br&gt;Nosocomial infections, no money (poverty)&lt;br&gt;Wandering and other dementia related behaviors&lt;br&gt;Hyperthyroidism, hypoadrenalism, hyperglycemia, hypercalcemia&lt;br&gt;Enteral problems (gluten enteropathy, pancreatic insufficiency)&lt;br&gt;Eating problems&lt;br&gt;Low salt, low cholesterol diet&lt;br&gt;Stones (gallstones), shopping problems</td>
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chronic infections that lead to weight loss. Poverty can lead to insufficient funds to purchase food. Some elderly have problems with shopping or food preparation related to a decline in instrumental activities of daily living. Persons with a decline in basic activities of daily living may require assistance with eating. It can take up to 45 min a meal to feed an older person.

Persons with dementia may forget to eat. They can also develop apraxia of swallowing. Demented persons who wander excessively may need a marked increase in calories.

A number of metabolic conditions are associated with weight loss. Hypercalcemia leads to anorexia. Apathetic hyperthyroidism is a classical cause of weight loss. Persons with Addison’s disease can have abdominal pain, diarrhea and weight loss. Older persons with pheochromocytoma continue to be hypertensive in the face of severe weight loss. Enteral problems leading to malabsorption include gluten enteropathy and pancreatic insufficiency. Persons with Parkinson’s disease and other tremors may find it difficult to get food to their mouth.

Therapeutic diets have been shown to be associated with weight loss. There is no evidence that these diets have positive effects on disease processes [27]. It is no longer recommended to use therapeutic diets in nursing homes.

Gallstones can present with early satiation. Persons with severe cardiac disease cannot only be anorectic, but with hepatic congestion decrease albumin production and lose protein from the gut. Diabetes, when uncontrolled, is associated with weight loss. Persons with chronic obstructive pulmonary disease have an increased resting metabolic rate but decrease their physical activity. These persons become hypoxic while eating because of the oxygen necessary to maintain the thermic energy of eating. This leads to food avoidance and severe anorexia. Cancer accounts for 10% of the causes of weight loss in older persons.

**Conclusion**

Weight loss is a major barometer of impending frailty in older persons. Numerous causes of weight loss are reversible. We have recently found that an appetite questionnaire can predict weight loss. All older persons should have their appetite regularly assessed and if they have a decline in appetite, reversible causes should be considered.

**References**

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Discussion

Dr. Elia: I was particularly interested in your comments on the anorexia of aging which might be expected to produce weight loss. However, we are increasingly seeing
elderly people who are overweight/obese. So, is the anorexia of aging defined in relation to the appetite behavior of younger individuals or to the behavior of those concerned? In addition, do your comments relate to older individuals who are ‘healthy’ or those with disability and disease?

Dr. Morley: The first part of my lecture was about healthy people and we have actually looked at extraordinarily healthy people, and there is no question that if you take a 20- to 30-year-old and a healthy 70-year-old, the 70-year-old eats much less. Now the 70-year-old also exercises much less. So what you are looking at is that over the lifetime food intake should decrease along with the decrease in physical activity which has been shown in many studies. The epidemic of obesity we are seeing at the moment is occurring predominantly in middle-age people, both in the United Kingdom and the United States, and these people are already eating less than you would expect. So now you have got to stop and say what is wrong with the scenario when the CDC in the United States says we have got to eat less. What is wrong with it if that is not the problem? The problem is we are not exercising enough. Our whole lifestyle has changed from the beginning of the 20th century to now. At the beginning of the 20th century most people didn’t sit in a hall for 3 days thinking that this was hard work; basically they would have been out there working hard because the jobs were hard. The jobs have changed; what people do has changed. In the United States no one walks anywhere; a car is taken to every place. We have stopped exercising and I think what we are failing to do is recognize that exercise is the key to weight reduction and it has very little to do with food intake other than that we are over-eating. If you go back to the original studies by Willet in which he showed that high cholesterol was bad for the heart, he couldn’t do this until he took one factor out of his epidemiological analysis. This is why I hate epidemiology because epidemiologists have no trouble in throwing things that they don’t understand out. In his older biography Willet pointed out that they had to take out this one thing: the more you ate the less heart disease you had, and that was very clear in all the early epidemiological studies. Now we know obesity produces heart disease. We know that fundamentally this does not make sense, but it does if you think of it, because people who eat a lot usually exercise a lot as well. So exercise becomes important and food in itself may be protective. What you find here again is that weight loss is bad for you. Now if weight loss is bad for you, ethically we should not be telling people to lose weight by not eating. I think we should be telling them to exercise, and I don’t think that I have seen any data to support that long-term dieting is a good way to do anything. It has been shown that with dieting you lose muscle mass as well as fat mass, and if you are like me when I diet, eventually put it back on. You actually put on more fat than you put on muscle, you put on about 15% muscle when you go back. In our studies in New Mexico we have shown that the obese sarcopenic subjects had by far the worst outcome. All this suggests to me that we are talking about an exercise problem with obesity or a physical activity problem, and I think that is what we should beginning with rather than looking for a food intake problem; lack of food intake is bad for us, exercise is good for us. I don’t know if that answers your question but that is what I have come to terms with because I have to tell all my patients not to diet anymore.

Dr. Elia: In terms of the weight maintenance that is very important. The issue of appetite regulation is very complex.

Dr. Morley: I wouldn’t disagree with that. I have spent 20 years to prove it isn’t and it really is.

Dr. Armstrong: Do you have any data on the effect of exercise on appetite in the elderly or in any populations?

Dr. Morley: There are actually minuscule data on the effect of exercise on appetite in all the people. It is interesting that it suggests that there is an early decline when
you start exercising followed by an increase. Particularly if you have exercised a lot as I have at different times in my life, you recognize basically that you are often very anorexic when you finish exercising at a high level. This is most probably because of an increase in corticotropin-releasing factor (CRF) which occurs in major exercise. The increase in CRF is very anorexic for animals and actually in humans. So I think you get short-term anorexia, long-term with bouts in between you tend to increase your appetite and eat more. That is a long-term effect as perhaps the changes in leptin and issues like that. In addition in Diabetes [1] we very recently showed that hypertriglyceridemia actually blocks the leptin effect. In fact when people try to give leptin to obese people what happens is that basically it doesn’t decrease their appetite unless they were truly leptin-deficient which very few people are. Nobody could understand that. we believe that it is the hypertriglyceridemia in fat people and therefore when you exercise you get rid of some of the fat over time. You lower your hypertriglyceridemia so you start to get an effect of leptin but in the intermediate period you actually have an increase in appetite and then it balances is out. It is extraordinarily complex. The whole problem is that every single thing about appetite and its relationships with the rest of the body are complex, and if you only look at one thing you get the answer wrong.

Dr. Biesalski: Regarding some of the interventions you described in nursing homes: my view of nursing homes is that lots of people are sitting around in chairs not doing very much. Perhaps the sort of chronic exercise you describe is affecting appetite and may also play a role in improving people’s nutritional status.

Dr. Morley: We spent a lot of time in nursing homes trying to get all the people in the nursing homes to be involved in activity, to pull people out of bed. People who stay in bed do poorly; immobility is poor; people need to actually be moved around. A meta-analysis of the long-term effects of exercise basically came to the conclusion that it did nothing. Now the problem here is that long-term effects require people with intention-to-treat to stay on the exercise program, and most human beings are not very good and they should believe in exercise and stay on the exercise program. So in fact the drop off when you stop exercise is very rapid.

Dr. Biesalski: Would you generally recommend that the elderly take multivitamins or multi-micronutrient supplements?

Dr. Morley: That is a very tough question because if you are eating adequately you will get adequate micronutrients. What I try to tell my patients is that they should eat adequately and that I believe, though I have absolutely no evidence, that micronutrients when given in food are better than micronutrients when taken in a tablet. If somebody is anorexic and not eating they certainly need a vitamin supplement, but there is no evidence one way or the other whether or not you should give free radical inhibitors. We use α-lipoic acid rather than vitamin E because some of our basic science studies show that in Alzheimer’s animals it actually reverses Alzheimer’s disease. The animal data are very good for using free radical inhibitors; the human data are not nearly as good and I think that is where we run into problems. There are some data on α-lipoic acid for Alzheimer’s disease now, but at least the Cochrane database [2], which I believe in fundamentally, says that there are insufficient data to say it is good or bad. I think we have to live with that until we have better data. So if people are starving, they need micronutrients. I think we are now giving much more intravenous multivitamins as people come to hospital because almost all of those people over the age of 70 are vitamin-deficient, but again there are no data, just a belief. This field is total belief unfortunately.

Dr. Biesalski: There is an argument frequently used that a diet or an energy intake below 1,500 kcal is not sufficient with respect to micronutrients. Can you ensure that all the elderly in nursing homes have an energy intake that is more than 1,500 up to 2,000 kcal?
Dr. Morley: Again it depends on the diet. The arguments I have seen are that around 1,000 cal are essential and it depends on what is in that diet. Obviously in most of our American nursing home diets 1,000 cal makes the daily allowance, just. So I can say that if we are treating people properly they get about 1,000 cal. If they are not being properly treated, then I need to be aggressively treating them or they need to be on a multivitamin. But as soon as people lose weight they should be on a multivitamin and one exception I didn't mention is calcium and vitamin D. Clearly studies in nursing homes have now shown that calcium and vitamin D decrease hip fracture. There is no excuse for any older person in a nursing home not to be on calcium and vitamin D, and women most probably should be doing this from 50 years old. 85% of the women in nursing homes in the United States are osteoporotic; so with those figures everybody should be getting calcium and vitamin D. But there are no easy answers and the more I look at the literature, the more confused I get. Every time I read an article I change my mind, which says we don't have enough literature.

Dr. Labadarios: How careful should we be in assuming or saying that people who eat adequately don't need micronutrients? I do not subscribe to the believe that everyone who is in an institution needs micronutrients. I am making the comment because if one reads the literature and takes the people or the population in the world that probably eats the most, that is the USA, there is still a significant proportion of that population in which micronutrient intake right across the ages would actually be inadequate if it was not from the ingestion of supplements, that is point number 1. Point number 2, if you look at the data from Europe, particularly from Germany, they are really not much different. Point 3, in view of the emerging evidence on the role of micronutrients, and I am not talking about antioxidant micronutrients only particularly the B group of vitamins, and their role or their possible role in chronic disease, can we afford to assume that people who eat adequately don't need micronutrient supplements?

Dr. Morley: It is a very good point and we don't know the answer. First of all in the United States flours are fortified with folate. If I was in Europe I would have said in answer to you that there is not as much fortification. Certainly folate B12 needs to be looked at much more carefully. We have looked at our patients with B12 deficiency or elevated homocysteine, which is different, and in the United States it appears to be mostly due to renal failure rather than to folate B12 because high doses won't bring it down. B12 cures a lot of things. So I think we have got to think about this, I think we don't know exactly when we are giving people the right amount. The problem I have is giving a tablet to someone who is already on 9 tablets. We did a study 15 years ago in which we looked at people on over 10 drugs, and we reduced the drugs by 5 and reduced hospitalization and death by a third, and the number 1 drug we stopped was multivitamins. The reason was that every older person takes multivitamins. What was happening is they take the multivitamin but they wouldn't take the diuretics, so by stopping it we improved compliance. So every time you add a tablet, even if you think it is totally innocuous, you have got to realize that in an older person this can really interfere with compliance. I don't know the answer.

Dr. Labadarios: My other point relates to weight loss. In the data that you showed us there were two types of weight loss: the involuntary one which had a much higher risk of mortality, and the voluntary one which was associated with a relative risk of 1.78.

Dr. Morley: Most of the data were basically considered as a mix of voluntary and involuntary. The only purely voluntary one was with hip fracture and basically there were twice as many hip fractures in people who had voluntary weight loss as in the involuntary. So it was exactly the opposite way around in the one piece of data that you saw.

Dr. Labadarios: So the weight loss that you were talking about was a disease-associated weight loss?
**Dr. Morley:** Not necessarily and I think it is very important. Now again there are always little bits of disease. These studies are incredibly difficult to do but there is no evidence that truly voluntary weight loss has any advantage at all in older people. If you look at the data Dr. Thomas showed on the first day, older people lose weight. What happens is they can never catch up again, they have a real problem as opposed to younger people who adjust go back to a normal appropriate level for their body, older people don’t seem to be able to do that.

**Dr. Labadarios:** My question still remains. Is there a different mechanism for weight loss in the elderly as opposed to the young adult? Do we know anything about that? The evidence that we are beginning to have now is that weight loss is associated with certain beneficial effects, not necessarily only for heart disease but even at the cytokine level. Now what is the relationship of that to the elderly? If they are obese and lose weight are they still at an increased risk of mortality?

**Dr. Morley:** The answer would appear to be yes, but it is based predominantly on the single hip fracture study [3], which is the best study available looking at voluntary weight loss. You would think with voluntary weight loss in an obese woman that basically they would be less likely to have hip fractures and would do better. Now the problem with that study is that one of the ways to avoid hip fracture is to keep fat on the hips. We now give hip fats to people who are malnourished to try to protect them from fracturing their hips. So I could argue that that is not the answer. The problem with all the weight loss studies that I have seen is that they are all short-term, meaning 1 or 2 years, and it is a little bit like that wonderful drug that lowers cholesterol, increases high-density lipoprotein cholesterol, causes you to have nice wide arteries, but unfortunately increases heart disease. These intermediate end points are frightening things that we tend to use. We use end points that we think are important and then turn out not necessarily to be important, and we must be very careful about that. So I am not aware of long-term starvation studies in a big enough population or weight reduction studies without exercise that have shown anything. What I can tell you is that in our New Mexico population, the people who have done that, almost all of them have gone back to being obese sarcopenics who have by far the highest death rate. So it really worries me because the mechanism of the fat frail or obese sarcopenic is dieting and failing to keep to the diet. Now if the patient can promise me that they can diet, do exercise and keep to it, then I think that we have got a great approach and I would not disagree with that one, but unfortunately human beings are very frail.

**Dr. DeLegge:** I need you to help me to understand something. I am going to pick a specific disease state in the nursing home, which is dementia. There are many people who feel that weight loss is a normal part of the normal process of patients with dementia for whatever reason, whether they forgot how to eat or they can’t swallow or it may be medications, whatever it is, realizing there are many different stages of dementia. Can you give me some advice regarding weight loss in that population on outcome?

**Dr. Morley:** It is not as easy as you would like. First of all there are many different demented patients and a large number of the patients in nursing homes who are demented turn out to be depressed and have a number of treatable diseases because people in nursing homes often have many diseases. So the first thing when you see a demented patient is not to assume that the weight loss is fundamentally because they have dementia. I would say 20–30% of the demented patients I see for the first time with weight loss turn out to have another cause. So that is your starting point, look for all the other causes. We have had a number of people with *Helicobacter pylori* infection in this group who basically, once *H. pylori* is treated, don’t get bad indigestion anymore, and they eat. We have demented patients with severe pain that nobody is recognizing and treating, that is why they are not eating. So the first thing is to treat...
the treatable causes. You are now left with a natural history of dementia which is a hyperphagia often early on in the disease followed by weight loss which eventually becomes lethal, and it is most probably one of the reasons why many of these people die. Now against that you put extraordinarily high quality care. Perhaps the best studies are from a northern Italian nursing home, where everybody was fed, no tubes whatsoever, and they showed that they could actually reverse weight loss and appeared to increase longevity, although the data were not as good. Now increasing longevity in demented patients may or may not be a positive outcome, but if the family has decided they want the person alive we will assume it is a positive outcome. So a lot of the weight loss in demented patients who forget to eat is because nobody feeds them. So much of the answer is that with good feeding weight is not as dramatic. But you do reach a stage eventually in dementia where people lose weight; they lose it appropriately and they are going to die. I don't think it is appropriate at that stage to put a tube in if that is the question; I think it is the worst time. Where I use tube feeding in my demented patients, where I am given the choice as opposed to the family, is in the person who gets sick, has a cytokine excess episode, is in hospital with a pneumonia or something like that, and is doing poorly. In those people if you put a tube in for 4–6 months and feed them they will often do well. They are also the people who do very well with megestrol acetate. So it is looking at that group and saying what is appropriate for each person. But dementia is a huge group of people and I am very hesitant to say there is one approach for everybody. Unfortunately the patients also have adult children, and the pain of my life is adult children. If you look after old people, the problem is that the adult children have totally different ideas about what their parents might have wanted. I don't know if that helps but it is where it is.

Dr. Schwab: I learned quite a few things about appetite regulation in terms of quantity, but I am not quite sure about the quality. I have two questions concerning this. The first is, is there a difference? I guess there must be because my grandparents behave differently according to the selection and preference of food than for instance my children, my wife or myself. The second one is how is this actually regulated? Why is this lady singing because of the ice cream and not because of the roast beef?

Dr. Morley: These are very good questions. For the first one I would refer you to the Seneca data. If you go through Europe looking at different countries there are huge differences in caloric intake that appear to be voluntary, there are differences in the kinds of food, and the amount of macro- and micronutrients, the amount of calcium in the diet is absolutely dramatically different, and it is not always what you would expect. That is part of what I see around and I don't even understand how some of these differences came about. So each individual chooses based on environmental pressure and on a learned pressure to eat something that they think is appropriate for them. There are obviously all manner of decisions on what you are going to eat; what is in the store makes a big difference; how easy it is to prepare, but beyond that there are also studies in animals, and virtually none in humans, that show that food choice is actually controlled by the brain. So for instance a caribou living on the side of Lake Superior will eat two thirds of its food from right on the lake to get enough salt, and then it is going to eat the other third away from the lake because now it has enough salt. So that is a salt-siting behavior, the salt is driving the mix of the two different kinds of food that the caribou eats, so we know there are driving forces. In humans we have virtually no data to tell us what drives that. We do know that there are big differences in what people eat, which is why we aim for a reasonable intake to cover all the micronutrients, hoping that we are covering everything. I don't think we have an idea of what the ideal diet is for any given individual. Does that answer your question? I know it is unsatisfying.
References