Are Older People Starving to
Death in a World of Plenty?

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‘Thousands of patients are annually starved in the
midst of plenty.’

Florence Nightingale, 1859

‘Doctors and nurses frequently fail to recognize
undernourishment because they are not trained to
look for it.’

J.E. Lennard-Jones, 1992

The indictment by Nightingale has persisted for over a century, aided by
the inadequate attention paid by physicians to nutritional status. Dietary
restrictions, improper dietary prescriptions, and keeping patients non per ora
for considerable lengths of time have contributed to nutritional problems in
the healthcare system [1, 2].

The nutritional status of older adults living at home is poor. On average,
persons over the age of 70 years consume one third less calories compared to
younger persons. Energy intakes of older men (40–74 years old) range from
2,100 to 2,300 cal/day compared to younger men (24–34 years old) who con-
sume 2,700 cal/day [3]. Ten percent of older men and 20% of older women
have intakes of protein below the US recommended daily allowance (RDA),
and one third consume fewer calories than the RDA. Fifty percent of older
adults have intakes of minerals and vitamins less than the RDA and 10–30% have
subnormal levels of minerals and vitamins [4]. Sixteen to eighteen percent
of community-dwelling elderly persons consume less than 1,000 kcal daily [5].

The drive to find food, designated by the term ‘hunger’, is essential in all
species. Hunger is controlled by chemical mediators, signaling when to stop
eating (‘satiation’), and when to resume searching for food (‘satiety’) which
defines the interval between meals. 'Appetite', the enjoyment of food for itself, rather than for physiological need, is conditioned by a number of social, cultural, and psychological factors, as well as by disease states. Accumulating evidence points towards 'anorexia', the decline in appetite, as a major contributor to weight loss and undernutrition of older persons [6].

### Sociological and Physiological Causes of Anorexia

Caloric intake in older adults is greatly influenced by sociological, psychological, and physiological factors (table 1) [7]. Sociological factors include food preferences, chiefly determined by cultural circumstances. Older persons modulate food intake by time of day, number of people present, pre-meal stomach contents and their subjective state of hunger in ways similar to that of younger persons. Larger meals (10%) are eaten on weekends than weekdays, and larger meals are eaten later in the day. Provision of pleasant, well-lit, unhurried mealtimes in a social environment increases caloric intake [8]. Socialization greatly increases caloric intake. Women eat more (13%) when men are present, both genders eat more (23%) with family present. Meals eaten in group tend to be up to 44% larger than meals eaten alone [9].

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**Table 1. Conditions associated with undernutrition**

1. Social factors, poverty, lack of socialization, help with meals
2. Mechanical barriers
   - a. Poor oral health status or hygiene, eyesight, motor coordination, taste alterations
   - b. Slow eating pace
   - c. Ethnic preferences or culturally acceptable food
   - d. Therapeutic or mechanically altered diet
3. Medical conditions leading to increased energy requirements
   - a. Cancer
   - b. Infections (acute and chronic)
   - c. Chronic obstructive pulmonary disease
   - d. Wounds, burns, and fractures
4. Medical conditions leading to interference with eating
   - a. Congestive heart failure
   - b. Malabsorption syndromes
   - c. Diabetic gastroparesis
   - d. Cholelithiasis
5. Psychological conditions
   - a. Depression
   - b. Dementia
   - c. Late-life paranoia
   - d. Anorexia nervosa
If the persons delivering meals-on-wheels deliveries stays while the older person eats, nutritional risk is reduced [9].

Physiological changes in the hedonic qualities of food occur universally with aging. The physiological alterations in taste and smell makes food appear less ‘tasty’ as we age. The major change in taste with aging is an increase in the taste threshold. The alteration in the taste threshold means that food presentation and food choice play a more important role than does the actual taste of the food. Flavor amplification may enhance food palatability and acceptance, stimulate salivary flow and reduce complaints concerning the oral cavity. Flavor enhancers have been shown to produce a tendency for ingestion of greater quantities of food and improved food preference [10].

The Influence of Medical Illness on Undernutrition

Acute illness is characterized by a spontaneous decrease in food intake [11], a paradoxical response in the face of a need for increased nutrients during healing. A reduction in food intake accompanying acute illness occurs both before and during hospitalization. In the month before hospitalization, 65% of the males and 69% of the females had an insufficient energy intake, and undernutrition was present in 53% of males and 61% of females by the time of admission to the hospital [12].

Inadequate intake of nutrients often continues during hospitalization. In 286 general medical subjects, 27% became malnourished during hospital admission. These subjects were more likely to consume less than 40% of prescribed food, and were more likely to have lower Mini-Mental Status Examination scores, functional impairment, lower total lymphocyte counts, and lower serum albumin levels [13]. Over 90% of older persons admitted to a skilled care facility after hospitalization either have malnutrition or are at high risk of undernutrition [14]. Similarly, persons returning home from the hospital after an acute illness are at high risk of undernutrition.

The differential diagnosis and management of undernutrition has been published as an algorithm [15]. Depression is one of the most common reversible causes of weight loss in elderly persons, accounting for up to 30% of undernutrition in medical outpatients [16], and 36% of residents in nursing homes [17]. Anorexia is frequently caused by medications [14]. Overzealous restriction in diet by physicians is a common reason for reduced caloric intake [18]. Special or restrictive diets (low cholesterol, low salt, no concentrated sweets) often reduce food intake without significantly helping the clinical status of the patient. For example, a regular diet does not affect glucose control in institutionalized diabetic older adults [19].

Recently evidence has emerged suggesting that inadequate caloric intake is associated with an excess production of cytokines. The syndrome of
cachexia, the cytokine-induced wasting of protein and energy stores, is related to a number of disease conditions including cancer [20], end-stage renal disease [21], chronic pulmonary disease [22], congestive heart failure [23], rheumatoid arthritis [24], and AIDS [25].

Cytokines associated with disease states directly result in feeding suppression and lower intake of nutrients. Interleukin-1β and tumor necrosis factor act on the glucose-sensitive neurons in the ventromedial hypothalamic nucleus (a ‘satiety’ site) and the lateral hypothalamic area (a ‘hunger’ site) [26]. The data suggest that cytokine levels are commonly associated with disease conditions characterized by cachexia, and may play a role in appetite suppression, mortality, and weight loss. Cytokine-induced anorexia is the most common cause of poor caloric intake observed in the acute care setting [27], and affects community-dwelling older persons as well.

### Distinguishing Starvation from Cachexia

Are patients starving in the midst of plenty? Or rather, is the high prevalence of undernutrition reported in hospital and community settings due to disease? Simplistically, the reduction in food intake seen in older adults is often equated with starvation. Worldwide, starvation is most often caused by lack of food. However, a remarkably similar incidence of undernutrition among hospitalized adults has been noted worldwide, suggesting that disease rather than lack of food may be the common denominator in developed countries [28] (table 2). The distinction is important since the strategies to correct cachexia may be different from the simple correction of starvation.

Clinicians frequently confuse the effect of cytokine-induced acute-phase reactants on biochemical variables with undernutrition. However, these biochemical markers are not specific for nutritional status. For example,

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**Table 2.** Distinguishing starvation from cachexia

<table>
<thead>
<tr>
<th></th>
<th>Starvation</th>
<th>Cachexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite</td>
<td>Suppressed in late phase</td>
<td>Suppressed in early phase</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Not predictive of mortality</td>
<td>Predictive of mortality</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Low in late phase</td>
<td>Low in early phase</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>May remain normal</td>
<td>Low</td>
</tr>
<tr>
<td>Total lymphocyte count</td>
<td>Low, responds to refeeding</td>
<td>Low, unresponsive to refeeding</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Little data</td>
<td>Elevated</td>
</tr>
<tr>
<td>Inflammatory disease</td>
<td>Usually not present</td>
<td>Present</td>
</tr>
<tr>
<td>Response to refeeding</td>
<td>Reversible</td>
<td>Resistant</td>
</tr>
</tbody>
</table>
hypoalbuminemia occurs in disease states such as hepatic disease, renal disease, and congestive heart failure [29], stress [30], and occurs after 8 h of bed rest [31]. The total lymphocyte count correlates poorly with both the body cell mass and the nutritional state measured by the Nae to Ke ratio, producing a false-positive rate of 34% and a false-negative rate of 50% for diagnosing undernutrition [32].

In contrast to cytokine-mediated disease states, few changes occur in biochemical markers in simple starvation. Serum albumin remains normal in both short-term and long-term fasting [33]. In fact, after 9 weeks on a diet of about half the normal dietary intake of protein, serum albumin remained normal despite changes in lean body mass and immune status [34]. Serum albumin levels in anorexia nervosa, a condition of chronic energy deficiency, remain normal and serum cholesterol levels increase in one third of anorexia patients. However, chronic inadequate intake of protein (kwashiorkor) does lead to a decline in serum albumin levels.

Use of biochemical markers as nutritional parameters can potentially lead to over-diagnosis of undernutrition [35]. A screening instrument that has less reliance on biochemical markers, such as the Mini-Nutritional Assessment, has been shown to be effective in older adults [36].

**Nutritional Interventions**

The first response to clinical signs of undernutrition, whether due to starvation or cachexia, is to increase nutrient intake. Starvation due to inadequate food sources responds to hypercaloric feeding in both children and adults. Provided absorption is intact, repletion of serum albumin, cholesterol, improved immune function, and weight gain should be achievable in starvation states [37].

Increased voluntary consumption of adequate calories has been effective in producing weight gain. In a meta-analysis of 15 randomized, controlled clinical trials of dietary advice with or without nutritional supplements, the nutritionally supplemented group had a gain in weight (weighted mean difference $-1.14$ kg [95% CI $-1.94$, $-0.33$]) [38]. Oral supplementation improved outcome in older patients with a body mass index of less than the 75th percentile, who were free of cancer or dysphagia. Compared to control subjects, patients who received a sip feed had weight gain and improved energy intake. Mortality and functional status were improved in the most undernourished patients, although total group mortality did not change (odds ratio 0.62, 95% CI 0.35, 1.13).

In contrast to starvation, cachexia is remarkably resistant to hypercaloric feeding (table 3). The provision of additional calories and protein alone has not been shown to be efficacious in patients with cancer cachexia [39], in renal, or in cardiac cachexia [14].
Pharmacological Interventions

Depression is the most common treatable cause of undernutrition, and its treatment may lead to reversal of weight loss. Tricyclic antidepressants and monoamine oxidase inhibitors are more likely to produce weight gain than the selective serotonin reuptake inhibitors or the newer antidepressants. Mirtazapine appears to be particularly useful in stimulating appetite [40].

Orexigenic drugs have shown promise in improving appetite and producing weight gain in older adults. Cannabinoids (dronabinol, marinol, and nabilone) have improved appetite in cancer patients [41, 42] and in AIDS cachexia [43]. Megestrol acetate has been shown to improve appetite and stop weight loss in older adults with cancer, AIDS, and weight loss [44].

Interestingly, an anticytokine effect may be responsible for weight gain in older adults treated with megestrol acetate [45]. Melatonin, at a dose of 20 mg/day, stabilized weight and decreased tumor necrosis factor levels in cancer-related weight loss compared to controls [46]. Treatment with an etanercept, an anticytokine drug, has been demonstrated to results in a significant in left ventricular structure and function and a trend toward improvement in patient functional status in patients with advanced heart failure [47]. These results suggest that anticytokine treatment may be effective in the treatment cachexia-mediated syndromes. Although much work remains to be done, anticytokine drugs appear to be a promising avenue for the treatment of involuntary weight loss.

<table>
<thead>
<tr>
<th>Admission site</th>
<th>Moderate or severe SGA</th>
<th>Country</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hospital (CRI admission)</td>
<td>28% (severe)</td>
<td>Australia</td>
<td>2001</td>
</tr>
<tr>
<td>Acute hospital (n = 2)</td>
<td>36% (severe)</td>
<td>Australia</td>
<td>1997</td>
</tr>
<tr>
<td>Acute hospital</td>
<td>45% (severe)</td>
<td>Netherlands</td>
<td>1997</td>
</tr>
<tr>
<td>Acute geriatric hospital</td>
<td>41%</td>
<td>USA</td>
<td>1999</td>
</tr>
<tr>
<td>Acute hospital (n = 13)</td>
<td>50%</td>
<td>Latin America</td>
<td>2001</td>
</tr>
<tr>
<td>Acute hospital</td>
<td>53%</td>
<td>Sweden</td>
<td>1996</td>
</tr>
<tr>
<td>Acute hospital</td>
<td>61%</td>
<td>Switzerland</td>
<td>2002</td>
</tr>
<tr>
<td>Acute hospital (dialysis)</td>
<td>65%</td>
<td>United Kingdom</td>
<td>1997</td>
</tr>
<tr>
<td>Acute geriatric hospital</td>
<td>69%</td>
<td>Sweden</td>
<td>2002</td>
</tr>
<tr>
<td>Geriatric long-term care</td>
<td>70%</td>
<td>USA</td>
<td>2000</td>
</tr>
<tr>
<td>Oncology [48]</td>
<td>76%</td>
<td>Australia</td>
<td>2002</td>
</tr>
</tbody>
</table>

Undernutrition was assessed using the Subjective Global Assessment (SGA). Several studies reported combined moderate and severe undernutrition, while others reported only severe undernutrition. Adapted from Thomas [28].
Conclusion

It is possible to starve in a world of plenty. However, in the presence of adequate food, the failure to gain weight most often is due to cytokine-associated suppression of appetite. Assessment of changes in appetite are essential to evaluating older persons with weight loss. When anorectic changes are identified, a search for reversible causes should be instituted.

Intervention should first be aimed at the provision of adequate calories and protein, often in the form of high-density nutritional supplements. The chief difference between starvation and cachexia is that refeeding reverses starvation, but is less effective for cachexia. If weight loss continues, use of an orexigenic drug should be considered. Although much work remains to be done, anticytokine drugs appear to be a promising avenue for the treatment of involuntary weight loss.

References

Are Older People Starving to Death in a World of Plenty?

**Discussion**

*Dr. Haschke:* Concerning anti-inflammatory effects, could you elaborate on n-3 fatty acids? Have further studies been done in a more general population? The second question: is there also something in the literature regarding hormonal treatment with testosterone and growth hormone?

*Dr. Thomas:* Testosterone has been looked at in sarcopenic older men and in hypogonadal older men [1, 2]. Testosterone will produce weight gain and increase lean body mass. There are some concerns that limit the use of testosterone in this population, particularly related to the question of prostatic hypertrophy, prostatic cancer, and the effect on the hematological system. Testosterone does not increase appetite. It produces weight gain without necessarily increasing nutrient intake. For that reason it is acting potentially as an anabolic steroid rather than an anti-cytokine drug. The lack of effect on appetite at least suggests that it is probably not suppressing the cytokine-induced anorexia. Testosterone clearly improves functional outcome. Growth hormone will do the same thing, acting as an anabolic steroid to produce weight gain. Growth hormone has been shown to produce small gains in functional outcomes in elderly patients, particularly on knee strength [3, 4]. The problem with the use of growth hormone has been some unpleasant side effects and the obvious problem of the cost of the drug. The chief factor in the United States that has limited the use of growth hormone has been the fact that when it was used in a critical care situation there was an increase in mortality. This leads to some speculation. One universal phenomenon that occurs is that when you get acutely ill, you decrease your food intake. This may be either a side effect of cytokine production or it may be a teleological protective effect, implying that you should go through a period of starvation when you get critically ill. If you are able to suppress the cytokines in that population and you are able to increase nutrient intake, you actually may do some harm. This is speculative but at least there is concern that there may be a protective effect of inflammation in critically ill patients.

*Dr. Ockenga:* One problem is that in acute inflammation we also mobilize a lot of antigen substrates like glucose, etc. In intensive care patients, external energy or external food may not really have a beneficial effect. So I think we also have to focus on the metabolic changes due to chronic inflammation and in this situation we have to think about whether increasing food may really be of benefit to our patients.

*Dr. Thomas:* I think that is a very good point. When we talk about inflammation and cytokine excess we need to distinguish acute from chronic states. I think they are very different fields. I am not sure that I know what we ought to do in the acute setting. If we target decreasing cytokines in an acute setting we may actually do harm. However, in chronic settings, such as in children with chronic inflammatory disease who may not be able to absorb nutrients and in older patients with chronic inflammatory

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disease, we often don’t improve nutritional status even though we supply increased nutrition. So I think that we must distinguish chronic disease from acute illness.

Dr. Ockenga: I would also like to mention the recent article in Science [5] describing the changes in muscle related to age, increasing the fat content of the muscle and increasing peripheral insulin resistance, so there is also a change in the metabolic as well as the hormonal status of these patients. This may also be a link to our failure to improve the nutritional status of the patients.

Dr. Thomas: I agree.

Dr. Schiffrin: If we go back to the aspect of cytokines and sarcopenia, I would like to know what are the most important in terms for inducing sarcopenia? Does that mean a reaction of the cytokines with receptors in muscle cells, and if so what is the effect? Is the intracellular effect due to a lack of synthesis or increased catabolism of proteins? What pathway of proteolytic events are induced by this cytokine reaction?

Dr. Thomas: I don’t think we know the mechanisms as specifically as we would like. At the cellular level I cannot tell you what the pathways are; someone else may have a comment. Most of the literature has been observational associations. In other words, we find that the patients who have elevated C-reactive proteins also have an increase in heart disease. In patients who have renal cachexia, for example, IL-2 and IL-6 are usually associated with weight loss and IL-1 is not. In other studies of renal cachexia, other cytokines have and have not been associated with weight loss. If you look there is a lot of variability in the literature and I don’t think that a specific cytokine can be consistently associated with a specific cachectic state.

Dr. Morley: Major work has been done in this area by Roubenoff [6], suggested that it is low grade proteolysis for sarcopenia as opposed to high grade. In addition there is an alteration in the IgF within the muscle, and the work by Musaro et al. [7] in Rome has shown that if you give old animals stem cells with IgF you can basically reverse the sarcopenia that you see as opposed to cachexia. So it looks as if the IgF and the cytokines are playing a role in sarcopenia. The third component of sarcopenia is testosterone and Herbst and Bhasin [8] have recently shown very nicely that at the stem cell level testosterone actually suppresses the production of adipocytes and increases the production of satellite cells. The satellite cells then fuse with the muscle and allow repair of the muscle. This really leads to one of the conundrums with testosterone and perhaps also with growth hormone. Both of these cause a much bigger muscle mass gain than they do a strength gain, and it appears that repair takes place but you don’t necessarily improve the true quality of the fibers when you repair with hormones.

Dr. Bozzetti: I would like you to expand a bit more on the effect of megestrol in geriatric wasting and especially what the effect on body composition is? We have experience in the oncological field that usually megestrol works to increase body weight but the composition is mainly made up of water or fat tissue. So what is the effect in elderly subjects?

Dr. Thomas: Very interesting question. It was generally assumed that as someone diets or starves, they lose fat mass and then muscle mass. This is the reason why we all diet, to get rid of fat. We maintain our muscle and then we look nice. As you recover from starvation, what should happen teleologically is that you should repair muscle mass first, get strong, and then you should go on to gain fat mass and replace your shortage of fat. Paradoxically, what really happens in recovery from starvation is that fat mass increases first before lean body mass, whether you are doing this nutritionally or with megestrol acetate or some other drugs. This has lead to the idea that we should use anabolic steroids, such as testosterone or growth hormone, to increase lean body mass first because that will give us an improvement in function, and then we can go on to replete the patient nutritionally and regain fat mass. This is a great
scenario but it doesn’t work very well in practice. Regarding megestrol acetate specifically, the gain is predominantly fat mass over lean mass and is not solely due to fluid gain [9, 10]. I suggest that megestrol acetate may suppress a chronic cytokine excess and improve appetite and energy intake. The fat mass increase that occurs may or may not be associated with improvements in outcome, and that is what is not clear.

**Dr. Cynober:** I would like to comment on 3 points. First, the study you mentioned about testosterone supplementation in elderly subjects was a short-term administration, I think up to 1 month, with very impressive results [11]. My concern is that sarcopenia is a long-term disease and nobody can imagine providing intravenous testosterone for years. Second, just a complement to the debate about the mechanism of action of cytokines on muscle protein turnover; it is mainly a proteasome ubiquitin-dependent system but probably not directly mediated by cytokines but by the interaction between cortisol and cytokines at the muscle level. And third, I agree with all the hypotheses discussed about a hormone-related mechanism for sarcopenia including IGF1, human growth hormone, insulin sensitivity, but I would like to call to your attention that to make proteins you need amino acids. It has been repetitively observed by Volpi et al. [12] in the United States and Boirie et al. [13] in Clermont-Ferrand that in elderly subjects the sequestration of amino acids after a meal is doubled compared to young adults. As a consequence the amount of amino acids in the periphery available for protein synthesis is truly decreased in elderly. In addition, when amino acids are provided by the parenteral route, in this condition the fractional synthetic rate of protein in the muscle is normal in these elderly subjects, and this has also been shown in elderly rats.

**Dr. Morley:** Can I just comment on the testosterone studies. The original studies were short-term and one of ours was 3 months, but subsequently we published studies of 1 year in length [1, 14, 15] and there are now 2 studies in the literature of 3 years in length. All show a reversal of sarcopenia and in the middle-aged population. Wang et al. [16] now have follow-up data for up to 5 years I think, so realistically testosterone does remain a possibility as a treatment. There is no good long-term study looking at the side effects which we are left with, and that is a major need to decide whether this is a reasonable approach. But the studies are as long as we see with anything else of the stage.

**Dr. Thomas:** Let me also add that not all men get hypogonadal as they age. In fact bioavailable testosterone stays normal in a fairly substantial number of men as they age. There is little data suggesting that testosterone or other anabolic steroids have a lot of effect in those patients. So we are talking about patients who have true hypogonadism, whose sarcopenia is not due to amino acid problems or starvation problems or other problems, but it is strictly due to the lack of testosterone. In those patients we certainly can improve functional status, muscle mass and produce weight gain. This is limited to patients who have low bioavailable testosterone.

**Dr. Volkert:** I enjoyed your talk very much and would like to emphasize the importance of physical activity besides the supply of amino acids and enough nutrients. Especially in nursing home patients it is very important that they are physically active in order to increase the fat-free mass and body cell mass.

**Dr. Thomas:** Thank you very much for making that point because this is very important. One of the clearly demonstrated things is that physical activity will lower cytokines and that may be the source of the benefit. It is critical to remember that exercise is a good way to lower cytokines without drugs.

**Dr. DeLegge:** I wanted to tap your brain for a second with regard to supplementation that you touched upon in the elderly. I am not aware of any data that have ever shown that enteral supplementation in patients who can swallow changes outcome. In a nursing home population the response of most physicians or caregivers for someone
who is elderly and able to eat is to provide them with some sort of supplementation either in a can or some other consistency. My question is, is that the right approach to these patients?

**Dr. Thomas:** This is one of the problems that catches your attention in the literature on nutritional studies. In a meta-analysis of quality studies, the best evidence is that there is an effect of nutritional supplements in lowering mortality. There is also an effect to produce gain in body weight. Even in persons 90 years old, adding nutritional supplements to physical activity has an effect to improve functional status and weight gain. So I think we have got data. Part of the issue is that the magnitude of the effect is somewhat small. My hypothesis is that we are not properly analyzing the population. We are observing a general population in which we have some people who have no response to nutrition interventions and some people who have a good response, and when we pull them together we observe a small positive effect. What I would like to see us do is to see if we can divide the population who have a cachexia syndrome from the population that does not have cytokine excess and see if there is not a better improvement in the non-cachectic patients. Perhaps the poor improvement occurs only in the cachectic syndrome. We are in the process now of trying to set up a study to do that and hopefully we are going to get some data that will answer this question because I think that is where the real question lies. Clearly you get a positive but small magnitude effect in a general population and I think that the small magnitude effect may be because of the inclusion of cachectic non-responders.

**Dr. Labadarios:** My question relates to the weight gain concept. Should we continue to talk about weight gain or should we in the future be a little bit more fancy as opposed to talking about other things like body composition and particularly muscle mass since we know weight per se, particularly fat weight, may not actually be such a good idea.

**Dr. Thomas:** I agree, and I think it is time that we move on. We have had a lot of studies that measure weight and body composition. I think where we need to start trying to really look at outcome. What we want to be able to do is to either improve quality of life or functional status. Those are the two issues. If we can improve quality of life in our elderly population, does it matter whether they gain weight? If enjoyment of life improves, does it matter whether their body composition is fat or lean? So I think you are right and that is the next step. I think we can, but to do this we need to demonstrate it.

**Dr. Elia:** I agree with you that the most important next step is to try and get evidence of functional benefits as a result of interventions. In relation to the previous question that was raised about enteral tube feeding in those who don’t have swallowing difficulties, we have undertaken a meta-analysis that shows functional improvements and a reduction in complications. The question I wanted to ask was about the issue of lean and fat mass loss during starvation. You indicated that starvation conserves lean mass and depletes fat mass. However, over the years, we and others have proposed alternative models in which lean and fat tissues talk to each other, so that the proportion of lean and fat that is lost during starvation depends on the initial body composition: A lean person loses a greater proportion of lean to fat tissue during starvation than an obese individual. The differences have implications for prolonged survival.

**Dr. Thomas:** Thank you for clarifying that because what we were led to believe was that you would lose fat and conserve lean body mass. In fact, in starvation you lose both lean and fat mass, and there are differences in the portions of how much you lose. But obviously it is not fat followed by lean. You lose both at the same time and you lose functional ability at the same time. This has enormous implications for the
obese person. I have talked mostly about undernutrition but in obese people who lose
weight that is a significant problem.

Dr. Elia: I think it also has implications for certain chronic diseases including HIV
where these issues are being explored.

Dr. Schwab: I would like to come back to the pharmaceutical interventions influ-
encing outcome. I am thinking about an agent that was demonstrated to reduce TNF-α
on the one hand and has another capacity in terms of positively influencing sleeping
disorders, which are actually quite common in elderly people. What I am talking about
is thalidomide which was shown to reduce TNF-α and was used positively in Crohn’s
disease for instance. Could you comment on this agent in a rather low dose because
in inflammatory bowel disease the toxicity is rather large in a high dose of 150–300 mg.
But at a lower dose, let’s say 50 or 100 mg, the toxicity is less. Could you comment on
this agent please?

Dr. Thomas: A very good point and it was one of the drugs I did not mention.
There are very few drugs that we know of that have a strong anti-cytokine effect.
Thalidomide is certainly one of them. My understanding is that we can get some anti-
cytokine suppression and lose some of the side effects if we deal with isomers, but
clearly it is an effective anti-cytokine drug and there are good data suggesting that
you can improve weight in patients who have cachexia syndrome. The other drug is
pentoxifylline, which is another unusual drug that reduces anti-cytokines. In general
what we are seeing is a clinical observation. We have these drugs some of which
improve appetite and weight. What they have in common is an anti-cytokine effect.
None of these drugs were designed to do that. What I would like to see is that the
experts here come up with ideas to develop a better drug that we can give along with
nutritional supplements and thus solve the problem of weight loss.

Dr. Lochs: About the cytokines: are we talking about one single mechanism which
is probably mediated by different cytokines or could it be that we are talking about
different mechanisms? As Dr. Morley said, one cytokine might influence proteolysis,
another cytokine might influence appetite regulation, and a third cytokine might influ-
ence absorption in the intestine. If so, could you tell us which cytokine is doing what?

Dr. Thomas: At least from my standpoint, I think we are in an observational mode
now. As you know great advances in clinical medicine are made by people who just
simply observe things that they see going on clinically. In the current literature what
we are observing is a relationship. We are observing a profound relationship between
C-reactive protein, which is very nonspecific, and heart disease. We are seeing a
profound relationship between certain cytokines and renal cachexia. However, the
relationship is confusing. One study says IL-2, one says IL-6, another says it is TNF-α.
I don’t think we know. The concept is that there is a chronic inflammatory disease that
may be occurring in the gut of malnourished children, and a cachexia syndrome occur-
ring in our older patients. We now have anti-cytokine drugs that can suppress
cytokines, for example in rheumatoid arthritis. It would be wonderful to see what hap-
pens to body weight in that population. Obviously function improves, but does body
weight or appetite improve with these drugs? I don’t think we know. We don’t know all
the cytokines that are involved. Can we manipulate cytokines in such a way that we
could have a positive outcome?

Dr. Labadarios: I enjoyed your comment and your thoughts on the question of
cytokines, the pharmacological manipulation of cytokines. Is it a question of wanting
to be able to alter cytokine profiles or is it a question of whether we are knowledge-
able enough to interfere with the cytokines? In the acute situation we know manipu-
lation with growth hormone is associated with significant adverse clinical outcomes
[17]. Now what do we know in terms of whether it is desirable to actually manipulate
the cytokine balance, and obviously what are the implications of that question?
Dr. Thomas: An excellent observation, I can tell you that we do not know. The state of the art is advancing, but this is obviously very empirical, very observational, and the actual question that needs to be answered is the one you posed. Does manipulation of this chronic inflammatory state improve outcome? We know we can manipulate body composition, we know we can manipulate anabolic hormones, but that may not be good and I think that is where we need to go.

Dr. Ockenga: May I just add a recent article by Schwenk et al. [17] from England as well as one from Paton et al. [18] showing the treatment of chronic tuberculosis. The patients were followed for half a year after sufficient antimicrobial therapy, and it was shown that they gain weight, but they gain fat mass and not muscle mass, so function did not really improve. We can assume that in these patients the inflammatory response is decreased. Still this alone would not explain why they did not gain muscle mass.

Dr. Thomas: It may be related to exercise in that situation. Perhaps you need physical training plus the manipulation of the weight gain.

Dr. Schiffrin: If we can speculate a little bit, one tries to imagine what is feeding this cytokine production. For example, we have discussed previously that the gut or bacterial translocation or endotoxemia could be a factor playing a role here. Do we have any data showing that the gut is probably a source of keeping this low noise inflammatory condition well known in the elderly?

Dr. Thomas: The short answer is I don't think we have a lot of data. We do have some observational data. I asked Dr. Labadarios whether he has tried to treat these young patients with anti-inflammatory drugs to see if we could not remove the problem by treating the cytokines. Do you want to comment on that?

Dr. Labadarios: Very important question, but I don't think in the end we are going to have a simple answer that it is one organ and nothing else, it is the gut and nothing else. I mentioned earlier that we don't know what cholesterol and hypertension or other such risk factors for heart disease have in common. One of the risk factors also for heart disease is periodontal disease. People with periodontal disease have significantly higher C-reactive protein levels than those without periodontal disease [20]. So I think any low grade inflammation is theoretically important in the initiation or progression of disease. Periodontal disease in relation to heart disease makes dentistry and dental hygiene, in terms of environmental influences, crucially important and would be applicable in the elderly.

Dr. Thomas: One of the other examples of anti-cytokine drugs is statins, the cholesterol-lowering agents. It is now clear that if you give one of these drugs to a patient with acute coronary syndrome on admission to the hospital, you can decrease the risk of subsequent myocardial damage by 29%. This has nothing to do with the cholesterol effect. It is postulated now that it is an anti-cytokine effect. So there is another anti-cytokine drug that we ought to think about exploring.

References


