Gastrointestinal Dysfunction and Anorexia: Role of Brain-Gut Axis

Vay Liang W. Go and *Yvette Tache

UCLA Center for Human Nutrition, Los Angeles, California, USA; *CURE: Digestive Diseases Research Center, VA Greater Los Angeles Healthcare System, Los Angeles, California, USA

Nearly a century ago, Pavlov's experimental work confirmed the earlier independent, clinical work by Beaumont and Cabanis demonstrating that the brain influences gut function (1–3). Subsequently, Langley provided the concept of the autonomic nervous system and the notion of an enteric nervous system embedded in the gut wall, distinguishing it from the parasympathetic and sympathetic divisions (4). With advances in anatomical and electrophysiological techniques and the isolation and characterization of regulatory peptides and neuropeptides and their receptors, we have witnessed an explosion of information and increased appreciation of the brain-gut axis and its interrelationship in the regulation of gut function and control of energy homeostasis, and its alteration in various disease stages, including cancer and metabolic disorders like diabetes mellitus, obesity and cancer cachexia (5,76). Recently, we came to appreciate the role of the vagal pathways, both afferent and efferent, in the crosstalk between the brain and the gut (6,7). In this presentation, we shall limit our report to reviewing the: (a) physiologic relevance of corticotrophin-releasing hormone (CRF), stress-related peptides, and its receptors as inhibitors of the vagal outflow to viscera through the vagal efferent pathway; (b) interaction of leptin and cholecystokinin (CCK) through the afferent pathway in food intake regulation; and (c) role of a nutrient—glucose—in the regulation of the various pathways of brain-gut interaction. In addition, we will review a possible pathologic disease state of significance to these pathways.

CORTICOTROPIN-RELEASING FACTOR AND ITS RECEPTORS IN STRESS AND RELEVANCE TO IRRITABLE BOWEL SYNDROME

CRF was first isolated and structurally characterized by Vale et al. Two decades ago as a 41-amino acid peptide and a novel hypothalamic factor stimulating the release of pituitary proopiomelanocortin peptides (8). In recent years, CRF signal pathways have been conclusively documented to coordinate the various endocrine, behavioral, immune, autonomic, and visceral components of the stress response.
(9,10). Other CRF-related family peptides have also been identified: urocortin, urocortin II, and urocortin III, which are located in the periphery as well as in the brain and interact with distinct affinity to the recently cloned CRF receptor namely CRF₁ and CRF₂ (11,12). Specific antagonists for each CRF receptor have also been developed for CRF₁/CRF₂ receptor antagonists, namely α-helical CRF₉₋₄₁, (D-Phe¹², Nle²¹,³⁸)h/rCRF₁₂₋₄₁, and more recently, astressin, cyclo (D-Phe¹², Nle²¹,³⁸, Glu³⁰, Lys³³) CRF₁₂₋₄₁ (13). These CRF antagonists have provided key tools to unravel the neurochemical basis of the stress response, and certainly the role of CRF receptors in the brain mediates almost the entire repertoire of behavioral, neuroendocrine, autonomic, immunologic, and visceral responses characteristic of stress in both rodents and primates (14–16). In particular, the activation of brain CRF receptors modulates autonomic outflow and plays a role in stress-related autonomic alterations of gut function, including the inhibition of gastric emptying and motility (10), somatostatin and other hormones released, and stimulation of colonic motor function. All these effects are mediated exclusively or in part by parasympathetic efferent pathways (17–19).

The brain sites of action of CRF are found in hypothalamic (paraventricular nucleus, PVN) as well as medullary (dorsal vagal complex, DVC) nuclei regulating vagal outflow (Fig. 1). There is now evidence that central CRF inhibits dorsal motor

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**FIG. 1.** Various stressors induce inhibition of gastric emptying and stimulation of colonic motor function. Blockade by central administration of specific nonselective corticotropin-releasing factor (CRF) receptor subtype 1 (CRF₁) or subtype 2 (CRF₂) peptide antagonists and prevention of the colonic but not gastric response by selective CRF₁ antagonists. CSF, cerebrospinal fluid; DVC, dorsal vagal complex; GLP-1, glucagon-like peptide 1; IL-1β, interleukin-1β; ic, intracisternal; icv, intracerebroventricular; iv, intravenous; LCC, locus ceruleus complex; NPY, neuropeptide Y; PVN, paraventricular nucleus of the hypothalamus. From Taché Y, et al. (10).
nucleus of vagus (DMN) neurons activated by exogenous or endogenous thyrotropin-releasing hormone (TRH). Intracisternal injection of CRF induced a dose-related inhibition of gastric vagal efferent discharge. Mapping studies of the distribution of CRF receptor gene expression in the medulla showed the presence of CRF$_2$, particularly in the nucleus tractus solitarius (NTS). There is also a network of CRF immunoreactive fibers, suggesting that CRF may act through activation of NTS inhibitory input to the DMN preganglionic neurons. CRF action in the medulla to decrease vagal outflow to the stomach may be primarily mediated by the CRF$_2$. These results are also consistent with functional studies showing the medullary urocortin-induced inhibition of gastric motor function is mediated by CRF$_2$ as shown by the selective reversal by CRF$_2$ receptor antagonists (20–22).

Brain CRF also activates sacral parasympathetic activity to the colon. CRF injected into the cerebrospinal fluid increases colonic motility, decreases colonic transit time, and induced fecal excretion reproducing colonic motor response to various stressors (10). CRF brain sites of action to stimulate colonic motor function are the PVN and locus ceruleus complex, which have direct projections to the sacral parasympathetic nucleus. The colonic response to central CRF is not altered by hypophysectomy, adrenalectomy, or noradrenergic blockage, but can be abolished by ganglionic and muscarinic blockade (23–26). This pharmacologic characterization of CRF receptor subtypes using selective non peptide CRF$_1$ antagonists (namely CP-154,526 and NBI-27914) indicates that CRF$_1$ is primarily involved in the stimulation of colonic propulsion induced by central administration CRF (27,28) (Fig. 1).

**Pharmacologic Target for Irritable Bowel Syndrome Using CRF$_1$ Receptor Antagonists**

Irritable bowel syndrome (IBS) is a common clinical functional bowel disorder and is associated with changes in bowel habits and increased bowel sensitivity. Colonic distention and abdominal pain are prevalent in the absence of biologic markers (29). IBS is characterized by a symptom complex of diarrhea, constipation, alternating diarrhea and constipation, with or without abdominal pain. Recently, substantial literature has established a high prevalence of co-morbidity with psychiatric disorders with predominantly anxiety or depression and mood disorders in patients with IBS (30). Other studies indicate that stressful life events, including a history of major traumatic events in childhood, are important risk factors in the development of IBS, and influence the onset and severity of symptoms (31). Conversely, stress reduction behavioral techniques and psychotropic agents, including tricyclic antidepressants, result in decreased abdominal pain and bowel symptoms. Clinically, antidepressant therapy has been shown to decrease CRF levels in the cerebrospinal fluid of depressed patients (32). In experiments, the CRF-suppressive effect of antidepressants is well characterized at molecular and cellular levels in animals and humans (33). Antidepressants reduce CRF gene expression at brain sites, eliciting anxiety and colonic motor responses (34,35).

These findings support the clinical testing of CRF$_1$ receptor antagonists to alleviate stress-related psychiatric disorders and depression. The first open-label clinical trial
using the CRF₁ selective antagonist R121919 (formerly BNI 30775, developed by Neurocrine Biosciences, La Jolla, CA) revealed that the administration of the CRF₁ antagonist reduced depression and anxiety scores by 50% in 20 patients with major depressive episodes. Intravenous CRF also decreased threshold of pain sensation to colorectal distention in healthy subjects and induced greater stimulation of colonic motility in patients with IBS than in normal subjects. These findings support the concept that hyperactivity of CRF₁ pathways may contribute to the co-morbidity of anxiety or depression with diarrhea and pain predominant in IBS patients. Therefore, strategies primarily targeted against CRF₁ receptors may provide insight into the underlying mechanisms and provide novel pharmacologic approaches with therapeutic potential for IBS treatment (10,36).

LEPTIN-CHOLECYSTOKININ REGULATION OF FOOD INTAKE THROUGH THE VAGAL AFFERENTS PATHWAY

Our understanding of the hypothalamic control of energy homeostasis increased since the discovery of leptin and other hypothalamic neuropeptides that affect food intake and energy balance. These neuropeptides include CCK, α-melanocyte-stimulating hormones, agouti-related protein, cocaine- and amphetamine-regulated transcript, melanin-concentrating hormone, neuropeptide Y, and pro-opiomelanocortin, and others (37). By studying these molecules and their neuronal systems, receptors, and interactions, we are beginning to unravel the circuitry between peripheral adipogenic signals and hypothalamic effector pathways.

The hypothesis that central effector pathways transduce afferent inputs from adiposity-related humoral signals to regulate long-term feeding behavior and energy balance was strengthened by the discovery of leptin and its subsequent sequencing and cloning. Leptin secretion is in direct proportion to the degree of adiposity. Circulating leptin is transported by a saturable system in an intact form to the brain, where it influences hypothalamic cell groups orchestrating facets of food intake regulation and energy homeostasis through interaction with the Ob-Rb splice variant (long form) of the leptin receptor (38,39).

While these observations provided the dominant conceptual framework for leptin action in the brain as an adiposity signal, our studies using in vitro rat stomach-vagus preparation provided electrophysiologic evidence that leptin can also act peripherally to increase gastric vagal afferent activity and that CCK modulates the sensitivity of gastric afferents to leptin. These findings prompt us to investigate whether such an interaction between leptin and CCK has an implication in the regulation of food intake (40,41).

Evidence now exists that is compatible with the speculation that CCK released during the postprandial state increases the local release of gastric leptin through the CCK-B receptor in addition to the leptin being released into circulation from adipocytes (42). The dual CCK-leptin signals exert their synergistic interaction to reduce food intake through CCK-A receptors. The satiety effect induced by leptin plus CCK may involve sensory signals beginning with the activation of capsaicin-sensitive
vagal afferent fibers that terminate centrally in the NTS. The information is relayed to hypothalamic sites—PVN seems to be the primary target—to integrate signals and orchestrate appropriate food intake alterations (Fig. 2). In addition, leptin, being a long-term adiposity signal, may also increase the efficacy of CCK through interactions initiated at peripheral gastrointestinal sites or at dual sites with central leptin sensitizing the PVN in response to inputs generated by the short-term satiety factor, CCK (43-45).

Based on existing data that points to the PVN as the basis of the central limb of the CCK-leptin interaction, the phenotype of an enhanced number of neurons activated should be explored. In particular, although a multiplicity of hypothalamic endogenous signaling molecules has been implicated in leptin action, CRF neurons in the PVN are promising candidates involved in the biochemical coding of the leptin-CCK interaction. Peripheral CCK activates CRF neurons in the PVN, and leptin injected intracerebroventricularly (icv) or intraperitoneally increases the expression of CRF messenger RNA within 2 hours (46,47). In addition, a CRF receptor antagonist injected icv reduced icv leptin-induced reduction of food intake (48,49). This CRF interaction of leptin-CCK and other neuropeptides may be of physiologic significance, playing a role in obesity and energy metabolism.

THE VAGAL REGULATION OF UPPER GASTROINTESTINAL FUNCTIONS IS MODULATED BY ALTERED BLOOD GLUCOSE CONCENTRATIONS

The vagus nerve is critical in mediating the central control of gastrointestinal (GI) functions. The vagal efferent regulation on gastrointestinal functions is tightly
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regulated by blood glucose concentrations. The DVC neurons are activated by hypoglycemia. However, how altered glucose levels influence the neuronal activation and synthesis/metabolism of the neuropeptides/neurotransmitters in the medullary vagal-regulatory pathways and vagal-innervated gastric enteric plexuses needs further investigation.

Converging evidence suggests that hyperglycemia or hypoglycemia affects GI functions through influencing vagal-cholinergic outflow to the viscera (50,51). The involvement of upper GI tract organs in the delay of gastric emptying corresponds to the distribution of the vagal control in the GI tract. Central vagal efferent activation, such as sham feeding, is well established to induced gastric acid secretion and pancreatic insulin secretion. The vagus nerve displays major autonomic control not only in food digestion and absorption, but also in the control of insulin secretion through the brain-nutrient islet axis (52,53). This control mechanism determines blood glucose level postprandially. The tight control of vagal activity by glucose concentration is important for maintaining energy homeostasis (Fig. 3).

Evidence has now accumulated that the medullary vagal-regulatory pathways respond to altered blood glucose levels, demonstrated by hypoglycemia activation of neurons in the PVN and DVC (54–56). Microinjection of glucose into the DVC prevented the hypoglycemia-induced gastric response, indicating a direct influence of glucose levels on the DVC neurons (57). Acute glucose deprivation by 2-deoxyglucose induces Fos expression in nitric oxide-positive neurons in the NTS and DMN as well as in the catecholamine neurons in the ventrolateral medulla A1/C1 and dorsal medulla C2 and C3 areas (58). Electrophysiologic studies suggest that

![Diagram](image-url)  
**FIG. 3.** Role of glucose levels in the brain-gut interaction and in regulation of food intake and nutrient metabolism. CRF, corticotropin-releasing factor; TRH, thyrotropin-releasing hormone.
some DMN neurons may have an enteroceptor function detecting the change of glucose concentration in their environment. However, another study found that glucose had no direct excitatory effect on DMN neurons. The NTS neurons transmit information of local glucose availability as well as peripheral glucose metabolic signals received from the vagal afferents toward hypothalamic structures, including the PVN, via ascending adrenergic and nonadrenergic pathways (59,60).

There is also evidence suggesting that the medullary vagal-regulatory circuits responding to changed blood glucose levels are independent of the higher brain structures. In dogs, decerebration and mid-brain or pontine section could not prevent insulin-hypoglycemia–induced gastric acid secretion, which was profoundly reduced after destruction of the DMN. Rats are able to respond to intestinal neural and hormonal signals and to regulate the size of individual meals when their brainstems are completely transected, severing all connections with the hypothalamus (61,62).

Lately, convincing evidence shows that elevated vagal efferent activity in response to external and internal environmental changes related to energy imbalance are associated with activation of medullary thyrotropin-releasing hormone (TRH) containing raphe–DVC pathways. Beside acute cold exposure, hypothyroidism with altered autonomic activities is associated with elevated TRH gene expression in the Rpa and Rob, and Fos induction in the pro-TRH–containing neurons in these nuclei. These studies indicate that the medullary TRH-containing raphe/PPR-DVC pathways participate in energy deficiency–induced vagal activation (63–65).

Blood Glucose Levels Play Important Roles in the Gastric Disorders and Neuropathy of Diabetes Mellitus

Gastroparesis is a common complication of diabetes (66). Gastric acid secretion is markedly lower and gastric emptying abnormalities occur in approximately 30% to 50% of type I and II diabetic patients (67,68). Although morphologic changes of the vagus nerve in diabetic patients have been identified, many observations indicate that hyperglycemia itself may be responsible for the abnormal GI motility in patients with diabetes mellitus, besides the traditionally attributed irreversible autonomic neuropathy. This is evidenced by the fact that acute hyperglycemia causes a reversible impairment of motility in various regions of the GI tract in both healthy subjects and in diabetic patients and animals. Delay of gastric emptying is observed within 1 week after streptozotocin treatment in rats, when autonomic neuropathy has not been developed. Even changes in blood glucose levels within the normal postprandial range have a significant impact on gastric emptying in both normal subjects and patients with insulin-dependent diabetes (69–72).

Clinically, neuropathy is a common complication of type I and II diabetes mellitus. Based on population studies, neuropathy occurs in 60% to 70% of diabetic patients (73). Subclinical neuropathy is much more common than clinical neuropathy, and can affect both the peripheral and autonomic nervous systems. Autonomic neuropathy can contribute to abnormal function of the GI, genitourinary and cardiovascular systems, which in turn contributes significantly to the morbidity and mortality of
diabetes. The diabetes control and complication trials unequivocally established that hyperglycemia caused by inadequate insulin secretion or action is associated with the incidence of diabetic neuropathy. Thus, intensive treatment of glycemia is associated with a 60% reduction of diabetic neuropathy and can prevent or delay nerve damage. Extensive experimental diabetic peripheral neuropathy investigation has demonstrated that the pathogenesis is multifactorial, involving sequentially occurring and often interrelated metabolic aberrations secondary to hyperglycemia (74,75). These pathogenetic mechanisms include an increased presence of free radicals, perturbed neurotropisms, non-enzymatic glycerations, abnormalities in vasoactive substances, and increased activity of the polyol pathway, which all can lead to axonal degradation and damage. Despite extensive investigation of glycemia on peripheral neuropathy, there have been limited investigations conducted on central autonomic neuropathy.

Brain-Gut Axis in Cancer Cachexia-Anorexia Syndrome

Cancer cachexia is a complex syndrome characterized by anorexia, weight loss, adipose tissue and muscle wasting, and severe malnutrition. This symptom complex is just the opposite of obesity. This syndrome occurs in more than two thirds of patients who die with advanced cancer. In addition, the degree of cachexia is inversely correlated to the survival time of the patients. The onset of cancer cachexia usually implies a poor prognosis. The mechanism of cachexia involves both lipid-mobilizing factors and metabolic abnormalities, such as rapid protein and fat turnover, hypertriacylglycerolemia, lipolysis, and immune changes mediating the pathologic process from the tumor or host-derived chemical factors, including neurotransmitters, such as peptides and cytokines. Several proinflammatory cytokines, including tumor necrosis factor interleukin (IL)-1, IL-6, interferon-gamma, and ciliary neurotropic factors have all been implicated in cachexia (69–76).

The hypothalamic feeding-associated pathways are targets for cytokine action. Cytokines can act directly on the neurons in the lateral hypothalamic area, the ventromedial nucleus, and PVN. Direct cytokine administration into the ventromedial nucleus induces robust anorexia. In addition, plasma free tryptophan is increased as a consequence of rapid protein turnover. Tryptophan can cross the blood-brain barrier and is the precursor of serotonin, and increased serotoninergic activity in the hypothalamus can suppress appetite. Alteration of other neuropeptides and hormones such as neuropeptide Y, leptin, glucagon, insulin, and cortisol may also contribute to the catabolism of peripheral tissue. Current research has shown that cancer cachexia syndrome is multifaceted, and understanding the interaction between peripheral and brain mechanisms is key to the integrative pathophysiology and the development of treatment strategy for this syndrome. In addition, the understanding of the integrative pathophysiology of cancer cachexia will add to our understanding of obesity (76–79).
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CONCLUSION

The brain-gut axis and its interactions are mediated by the autonomic nervous system; the vagal pathways play an important role. CRF and its receptors play a significant role in mediating the effects of stress on GI motor function through the parasympathetic efferent pathway. Antagonists to CRF receptors may be of therapeutic use in the management of IBS. Leptin and CCK play a key role in food intake regulation, and integrate short- and mid-term meal-related input signals into long-term control of energy balance through modulation of postprandial vagal afferent pathways. Among the absorbed nutrients, blood glucose level plays a significant role in signaling the brain-gut axis to induce an efferent response through alterations of vagal activity. Growing evidence supports the concept that altered brain-gut interactions may play a significant role in the manifestation of functional IBS, diabetes mellitus, obesity, and cancer cachexia.

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DISCUSSION

Dr. Gareth Williams: I've got a couple of questions about the Fos technique that is used to illuminate over-excited neurons in the brain. The first thing is if you make rats hypoglycemic, what you see really depends on when you look and certainly if you look after 5 hours of hypoglycemia, you get a completely different pattern. Large numbers of cells are activated out in the lateral hypothalamus. They light up in synchrony with groups of cells down in the NTS, the parabrachial nucleus, and it looks as though the lateral hypothalamic ones are mainly orexin neurons. My other comment is about the streptozotocin diabetic model that you use. Obviously, these animals have a very high blood glucose, but if you're looking at areas of the brain that are all connected with the gut, then we need to remember that these animals are also very hyperphagic. If you open the belly of a streptozotocin diabetic rat, its stomach is about four times its normal size and the gut is markedly hypertrophied: the reason is that these animals eat two to four times as much food as non-diabetic controls. So any abnormality that you see in, say, the dorsal motor nucleus of the vagus or the NTS of a diabetic rat is necessarily a direct effect of high glucose, because there are so many other secondary effects of the diabetic state that could interfere with those parts of the brain.

Dr. Vay Liang W. Go: Your point is well taken, but we were addressing the same issue. When we talk about hyperglycemia insulin-induced, there's a timeframe change we need to work through. Now, in relation to a hyperglycemia or hypoglycemia effect, a glucose clump before sacrificing the animal at different times should be considered. As for a diabetic chronic model, the only model we have used is a streptozotocin model. The question of when blood glucose level becomes abnormal, what happens to hypothalamic nuclei are activated with...
fosstudies. Those are the experiments now going on in our laboratory. As to the question, what happens to the hypothalamic nuclei in diabetic patients who died? I don’t have any information, but there is information regarding changes in peripheral diabetic neuropathy, particularly in patients with gastroparesis.

Dr. Gareth Williams: If I can just pick up on that point: studies have looked at the peripheral vagus nerve and have found abnormalities in diabetes. Histological studies have shown signs of damage that correlate with the severity of the defect in gastric emptying. There are major problems in looking at the brain in any chronic condition, where there have been attempts to treat it. For example, insulin exerts effects on the brain, so your findings could be hard to interpret in diabetic people who’ve been on insulin. The effects of cerebral vascular disease, which is very common in diabetes, also make this potentially complicated.

Dr. Vay Liang W. Go: The microcirculation in micro blood vessels become another issue we need to look at, particularly in relation to nerve morphology and peripheral neuropath. There are a lot of reports in this area, bit some of them are contradictory, and the picture is not complete.

Dr. Roger I. Glass: Dr. Go, you tickled us with the ideas that about two thirds of cancer patients have cachexia, which makes me wonder if there’s a difference between those types of cancer patients who have cachexia and those who don’t, and whether there’s something either physiologic in those two groups of patients, or if there’s some mediator that you can measure that might explain the differences.

Dr. Vay Liang W. Go: Well the cancer cachexia depends upon what tumor you’re looking at. You see this in lung cancer. You see less in breast cancer. You see a little bit less in colon cancer, but there are tumors that are more prone to cancer cachexia and we don’t understand why. The same thing with pancreatic cancer. Before I came, I saw a man with pancreatic cancer who is obese. His disease is terminal, and we don’t see cancer cachexia with him. So we don’t understand which mechanism is working here and the problem is how to dissect, which metabolic event that you want to look at, and which are the mediators that you want to be interested to look at. And so what we are now thinking in ourselves is how can we start cataloging them. Do we want to go back to the old era of tumor marker to look for markers of what we need to look at? This is a very early stage and we are starting to discuss in our center with regard to this area of how to approach it, but I don’t have the answer to it. It’s just a beginning, but I just wanted first to let you know that we need to look at this, but not at the late state, when you have already wasting. We need to look at earlier states before wasting sets in, that we identify some abnormality.

Dr. Gareth Williams: Just going back to the issue of tumor markers and the relationship with wasting. You mentioned two products, the so-called lipid mobilizing factor and the proteolysis-inducing factor. Mike Tisdale and Kenneth Fearon have done a lot of work looking systematically at patients with pancreatic and gut cancer so these substances are present in the urine of patients with these cancers who are wasted but not in cancer patients, who are not wasted. Interestingly, both these proteins are produced by the MAC-16 tumor.

Dr. Vay Liang W. Go: I’m aware of this study. In fact, I have been communicating with him for the last 4 years. The major problem that I look at is that you see the changes at the latter stage of pancreatic cancer, where you have muscle wasting, but I don’t know whether this factor is operating, particularly in this patient I was talking about, who is obese, and yet he is not wasting. The question is, after what time frame will this obese patient start going into muscle wasting, because pancreatic cancer eventually will. The question is when. What triggered that mechanism for them to start wasting? I have no answer to that. I think this is where the research should be going on. George, do you have an answer?
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*Dr. George Bray:* I presume that doubly labeled water studies have been done to measure total daily energy expenditure over an integrated period in these wasting states, both the GI ones and the cancer ones, and I just don't know the data. What do they tell us? Is it what we expect, diet-reduced, meaning that their food-intake’s reduced even more?

*Dr. Vay Liang W. Go:* Well, I did ask Dr. Paul Lee, because I knew that question would come up. Paul Lee was the director of our Stable Isotopes Laboratory at Harbor-UCLA Medical Center. I tried to obtain an answer from him. The short answer is: We don't have any data.

*Dr. Anne Ballinger:* I think that in terms of energy expenditure, there have been lots and lots of studies, which have looked at resting energy expenditure, very few have looked at total energy expenditure and as I showed you, in HIV patients in inflammatory conditions, there's no question that total energy expenditure, which is the important bit of the energy balance equation, is reduced. In cancer patients, in the published literature, as far as I can make out, there's only ever studies measuring resting energy expenditure, not total, and resting energy expenditure doesn't matter. It's what the total is.

*Dr. Vay Liang W. Go:* The total energy expenditure of any particular malignancy at a particular stage of their disease.

*Dr. Margries S. Westerterp:* I will continue on this topic of energy expenditure. In our university, that's the University of Maastricht, there has been a collaboration between the department of human biology studying energy expenditure with double labeled water and pulmonologies and especially lung cancer patients have been studied and yes indeed, they do not show a reduction in resting energy expenditure, but they do show reduction in total energy expenditure, because as soon as they try to do some activity, then it's very difficult for them to reach the right level of activity-induced energy expenditure. So that's reduced and also, because their oxygen availability is very poor, they very quickly feel a level of satiety, so that's that situation.

*Dr. Vay Liang W. Go:* What cancer is this and at what stage of the disease?

*Dr. Margries S. Westerterp:* It's lung cancer patients and it's in any stage of the disease. The situations, they are terminal. Total is reduced but rest is not.

*Dr. Michael J. G. Farthing:* How relevant do you think this debate related to the old models? I think they're probably still valid, the sort of starvation-anorexia-weight-loss model, where essentially you mobilize fat stores, and you just get very thin and you preserve skeletal muscle mass and the sort of infection injury model. I don't think there's a simple model for cancer because you can see patients, they can start out with an uncomplicated, say, cancer of the esophagus and they're a pure starvation model, and then they get complications, have an operation, get infected and septic, perforate and they can go into the other model. And I've certainly seen patients like yours who remain ostensibly obese, but they've lost all their muscle mass, because they can't mobilize their fat, so I'm not sure, I mean I think we're, correct me if I'm wrong, but I think we're simplifying this cancer model. I don't think it is quite as simple, and I think different metabolic mechanisms are all operating at different stages in the disease.

*Dr. Vay Liang W. Go:* I think you're right. But, we really just don't know at this moment what the operating mechanisms are. Although there are a lot of hypotheses, we don't know the real story behind them.