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Nutritional status of dogs with cancer: dietetics evaluation and recommendations

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Francis Kallfelz graduated from the Cornell College of Veterinarian Medicine in 1962 and continued on to receive his Ph.D in physiology in 1966 studying calcium metabolism. Soon after graduating he became a faculty member in the department of Clinical Sciences at the Cornell College of Veterinary Medicine. He served as hospital Director from 1986-1997 and was also intimately involved with the Chartering of the American College of Veterinary Nutrition, which was established in 1988. Francis Kallfelz is presently the James Law Professor of Nutrition in the Department of Clinical Sciences. Though much of his career has been spent researching calcium, phosphorus, magnesium and vitamin D metabolism and absorption, his more recent research interests have been examining protein requirements and the molecular mechanisms of lean body wasting.

Nutrition is not often thought of as a critical issue in cancer management, but can be an important variable that effects quality of life and survival times. In patients with cancer, particularly metastatic disease, it is not a question of curing the patient, but a question of how can the quality of life for the patient be increased. Over the past 20 years there has been a growing literature base concerning the role of certain macronutrients (fats, protein, and carbohydrate) and micronutrients, (vitamins, minerals, fatty acids and amino acids) on neoplastic diseases. Though this area of investigation is still in its infancy, there is increasing evidence that nutritional management of neoplasia can have profound effects on the lives of the animals and owners that are involved in this disease process.

1 - Nutritional assessment of the cancer patient

Though not the focus of this chapter, a patient that presents with anorexia requires immediate attention including administration of enteral, or possibly partial or total parental nutrition **(see chapter 14)**. It is often difficult to determine whether weight loss is due to anorexia, or cancer cachexia. Often in advanced neoplastic diseases there is an element of intermittent anorexia associated with chemotherapeutic treatment of the disease itself.

Clinically, cachexia can be defined as progressive weight loss in the face of apparent adequate caloric intake. This situation may be caused by a variety of mechanisms, but is most commonly thought of as an alteration in the basal metabolic rate resulting in an increased resting energy requirement. However, other factors which are not due to an increase in the metabolic rate may also result in lean body wasting.

Obtaining a good history, a thorough physical examination, personal assessment and patient follow-up is critical in determining the metabolic status of the animal. To differentiate whether a cancer patient is hypermetabolic or if there are other mechanisms causing lean body wasting requires not only assessment of body weight, but also determining body condition score and attempting to subjectively determine whether there has been abnormal lean body wasting in the patient.

A veterinary study suggested that a significant sub-population (27%) of feline cancer patients will develop cachexia *(Baez et al, 2002)*. The percentage of canine cancer patients with cachexia has not yet been determined, but as treatment modalities extend the survival times of canine cancer patients, cachexia may become more prevalent.

When cancer is diagnosed in a dog, the veterinarian generally encounters one of three situations:

1) Neoplasia without nutritional complications
2) Neoplasia with anorexia
3) Neoplasia with cachexia

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In general, anorexia will result in weight loss primarily of adipose tissue, while patients with cachexia will lose nearly equal amounts of skeletal muscle and fat mass.

Sophisticated tools including Dual Energy X-ray Absorptiometry (DEXA) and bioelectrical impedence can be used to assess lean body mass, however, these modalities are not available to most clinicians. Therefore regular measurement of body weight and body scoring are essential when monitoring neoplasia.

When assessing the cancer patient for excessive weight loss and lean body wasting, other diseases that must be ruled out include diabetes mellitus, cardiac disease, renal disease, and hyperthyroidism, since biochemical and hormonal stimulation of weight loss and cachexia may also occur in these diseases as well.

Guidelines that have been reported in studies of human cancer patients help to define abnormal weight loss and aid the definition of the cachectic response *(Inui, 2002)* **(Tables 1 & 2)**.

Table 1 - Features of starvation/ anorexia versus cachexia

	Anorexia	Cachexia
Energy intake	⇩	⇧/⇨
Energy expenditure	⇩	⇧/⇨
Body fat	⇩	⇩
Skeletal muscle mass	⇨	⇩

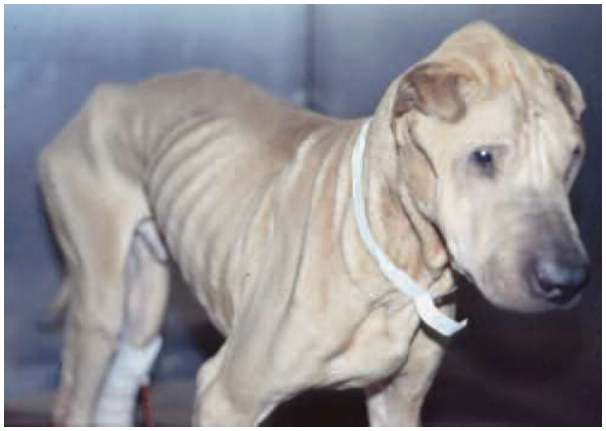
Table 2 - Guidelines to determine whether cachexia is a component of weight loss

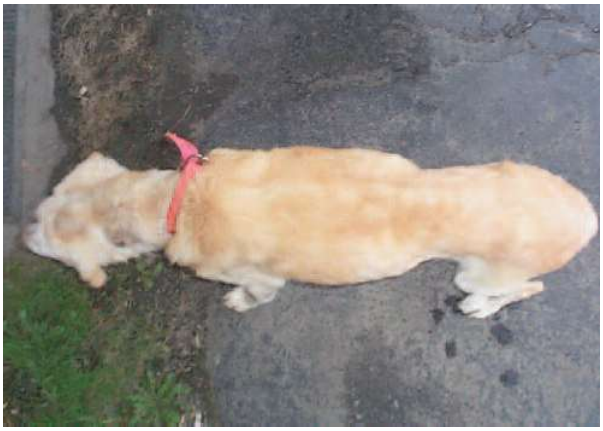
Nutritional Status	Change in body weight	Time interval
Healthy Adult	2%	1 month
Healthy Adult	3.5%	3 months
Suspect Cachexia	**5%**	**6 months**
Definite Cachexia	**> 10%**	**< 6 months**

Close scrutiny of scapular, hindlimb, and masticatory musculature is routinely necessary is cachexia is suspected *(Baez et al, 2002)*. Bony prominences such as the glenoid tuberosity, the spine of the scapula, the tuber ischii, greater trochanter of the femur and the sagittal crest of the skull become more evident in a short period of time.

Examination of the gluteal musculature and paralumbar muscles which lead to prominence of the ileal crest and vertebral spines are also easily useful for assessing lean body wasting **(Figure 1)**. Similar to body condition scoring (BCS) for obesity, there is a muscle condition scoring (MCS) system in development. This tool should be available for clinicians in the near future to help define cachexia and abnormal lean body wasting in dogs.

FIGURE 1 - CLINICAL CANCER CACHEXIA





Emaciated appearance due to inappropriate lean body wasting. Note the prominent ribs, hips, vertebrae and sagittal crest as well as the loss of hindlimb and pectoral musculature

THE TWO MAJOR NUTRITIONAL GOALS THAT NEED TO BE EQUALLY ADDRESSED IN A CANCER PATIENT ARE:

1) Inhibiting tumor growth

2) Preventing or managing cachexia

2 - The role of nutrition in cancer and cachexia

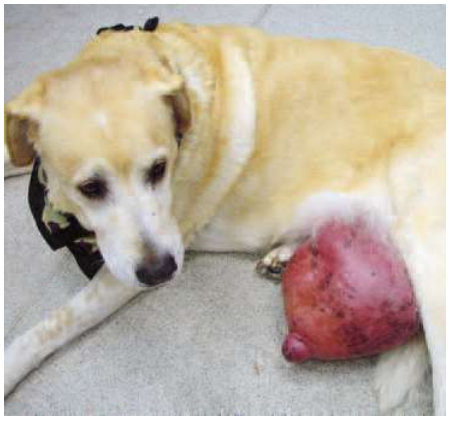
In some cases the demise of the patient with neoplasia is not due to the neoplasia itself, but to the overwhelming loss of body condition. Understanding these processes is important for appropriate nutritional intervention.

► Nutritional epidemiology of cancer in veterinary medicine

The role of nutrition in cancer prevention has become the subject of tremendous research in human medicine because of the variability in the human diet, and the awareness that certain dietary regimens may decrease the relative risk of neoplasia. This may also be true for companion animals, although most veterinary patients are receiving a more balanced diet than most humans. There have been three epidemiologic studies in dogs examining dietary and body conformation risk factors for mammary neoplasia. The results of these studies reported that the fat content of the diet had no significant relationship to the incidence of neoplasia, yet obesity did increase the relative risk of mammary carcinoma *(Sonnenshein et al, 1991)*.

Interestingly, one study showed that as the protein concentration of the diet increased, the relative risk of mammary neoplasia decreased, while a second study reported an increased relative risk of neoplasia in bitches fed raw meat as the primary source of caloric intake *(Shofer et al, 1989; Perez-Alenza et al, 1998)*. When interpreting the results from these studies, it can be deduced that

as the protein concentration in the dog food increases, the quality of the food is often better. Conversely, raw meat based diets are usually nutritionally unbalanced. Therefore, as the overall nutrient balance of the feed decreases, the incidence of neoplasia may increase. Hence, in veterinary patients it may be ideal to feed well balanced diets that comply with nutritional (National Research Council, NRC) guidelines for feeding dogs, when attempting to decrease the prevalence of certain neoplasias.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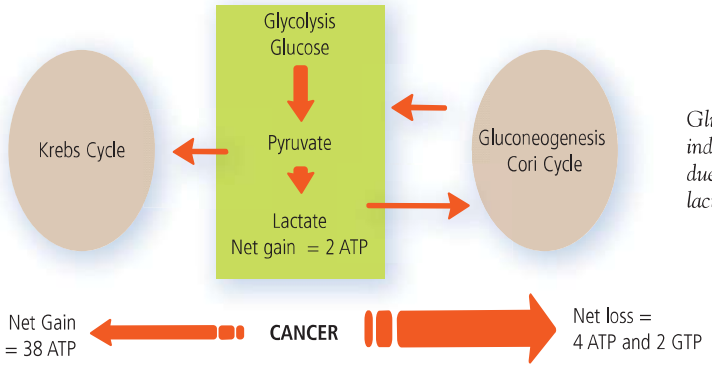
Many approaches have been taken over the past 40 years to influence neoplastic growth through nutritional modification.

► Energy requirements and neoplasia metabolism

Understanding the metabolism of neoplastic cell growth is essential to understanding nutritional intervention in cancer.

In general, neoplastic cells have higher rate of anaerobic energy metabolism than normal cells, therefore they rely more heavily on glucose, i.e. an up-regulation of the glycolytic pathway. This up-regulation of glycolysis leads to an accumulation of pyruvate which is rapidly converted to lactate, thereby resulting in a mild lactic acidosis, which has been documented in canine cancer patients *(Vail et al, 1990; Olgivie et al, 1997)*. Once lactate has been liberated from the neoplastic cell into the bloodstream it will be taken up by the liver, converted back into glucose, and may return to the neoplastic cell to undergo glycolysis, similar to the Cori Cycle *(Olgivie & Vail, 1990; Howard & Senior, 1999)* **(Figure 2)**. During this process of converting glucose into lactate there has been a gain of 2 ATP from glycolysis in the cancer cell, yet the conversion of lactate back into glucose in the hepatic cell requires 4 ATP and 2 GTP yielding a net loss of 2 ATP.

FIGURE 2 - GLUCOSE METABOLISM (CORI CYCLE)



Glucose metabolism during neoplasia indicating futile cycling and energy loss due to resynthesis of glucose from lactate in the Cori cycle.

Additionally, it has been shown that the humoral release of certain cytokines from inflammatory tissue around the neoplasia or from the neoplasia itself leads to uncoupling of oxidative phosphorylation in mitochondria, which may result in reduced ATP production *(Giordano et al, 2003)*.

Certain cytokines may also down-regulate endothelial lipoprotein lipase activity causing fatty acid and triglyceride accumulation in the bloodstream and prevent the storage of fatty acids within adipocytes. Together these changes may result in alterations in serum lipid profiles and hypertriglyderidemia which have been observed in dogs with lymphoma *(Olgivie et al, 1994)*.

To supply adequate energy for the futile cycling of various systems, and in an attempt to alter the dependency of neoplastic processes on anaerobic glycolysis, alterations in dietary levels of the energy providing substrates (protein, fat and carbohydrate) are often made in an attempt to slow progression of disease and thus increase survival time *(Argiles et al, 2003)*.

A major risk factor for cancer cachexia is the increase in energy requirements due to activation of proteolytic systems.

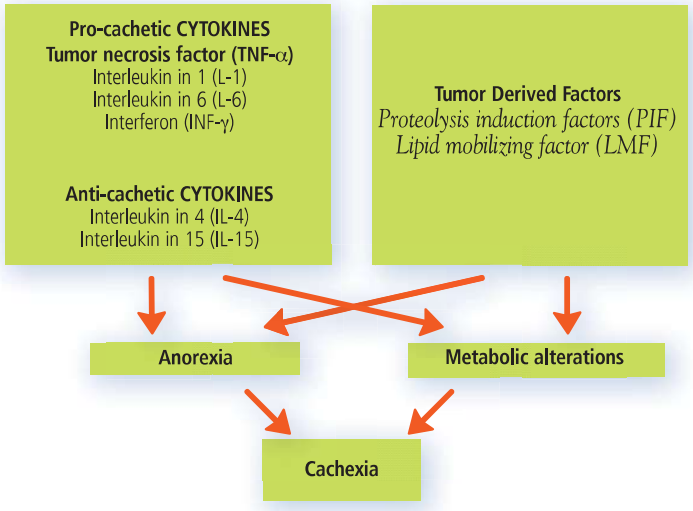
► Cancer cachexia

For many years it was thought that all patients with cancer cachexia had elevated resting metabolic rates due to the increased metabolism in cancerous tissue. However, many studies in human, and now veterinary medicine have shown that the resting metabolic rate after removal of tumors does not change. Furthermore, the resting metabolic rate can be extremely variable, and is often not correlated with the cachectic syndrome *(Vail et al, 1990; Olgivie et al, 1997; Argiules et al, 2003)*. Until recently it was thought that excessive lean body wasting was due to increased degradation of amino acids to support cancer growth, and without adequate intake the body would catabolize skeletal muscle to meet these demands.

Over the past ten years the role of various proteolytic systems (capthesins, calpains and ubiquitin/proteasome) involved in skeletal muscle atrophy associated with cancer cachexia have been studied. The ubiquitin/proteasome system has recently received a lot of attention as this system is up-regulated in cancer cachexia and other diseases associated with lean body wasting *(Baracos, 2000; Inui, 2002; Argiules et al, 2003)*. This is a complex system that marks a protein for degradation and then shuffles the tagged protein through a large multi-subunit protease called the proteasome. The process requires ATP, and may play a role in increasing the ATP consumption observed in neoplasia.

Though speculative, it is thought that the amino acids liberated from this process may be either used for energy production or lost in the urine. Many factors (i.e cytokines) have been implicated in the up-regulation of this system in cancer cachexia. Many of these factors are secreted into the blood stream by the primary or metastatic neoplastic tissue. Some of the more important factors include Tumor Necrosis Factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and a newly identified factor called Proteolysis Inducing Factor (PIF). PIF may be the most important factor involved in cancer cachexia *(Argiules et al, 2003; Baracos, 2000)* **(Figure 3)**.

FIGURE 3 - HUMORAL AND TUMOR DERIVED FACTORS ASSOCIATED WITH ANOREXIA AND CACHEXIA IN CANCER



A lipid mobilizing factor may be secreted by the tumor cells which induces an increase in the cytoplasmatic activity of the lipoprotein lipase in the adipocytes, exacerbating the loss of fat (Hirai et al, 1998; Tisdale, 2001).

3 - Nutritional considerations for cancer and cachexia

► Energy sources

Carbohydrate is often the most abundant energy source found in companion animal diets, particularly dry type canine diets. Since neoplastic tissue thrives on glucose as its primary energy substrate, the strategy is to force the neoplasia to use other substrates which may help in decreasing cell proliferation. During cachexia it may be important to provide extra dietary protein to help attenuate the cachectic process. Therefore, choosing a diet high in fat and protein with low carbohydrate may be helpful. Many premium dry and canned products, in particular specialty foods for active or stressed canines, may be used. Most of these products contain higher quality and quantities of protein and fat as compared to adult maintenance diets.

When changing commercial food, the guaranteed analysis for protein and fat content must be examined. Good guidelines are at least 35% protein and at least 25% fat on a dry matter basis for dogs. The guaranteed analysis can be used to estimate what percentage of protein, fat and carbohydrate are in the chosen food but it should be converted to a dry matter basis **(Table 3)**. Canned foods are often around 70-75% water, therefore the "as fed" percentages of protein and fat listed in the guaranteed analysis are much lower than in dry foods, but when examined for protein, fat and caloric content based on dry matter, they can actually be better than extruded products.

Contraindications for feeding such a diet include dogs and cats with congenital or acquired hypertriglyceridemia, a history of pancreatitis, or chronic renal disease.

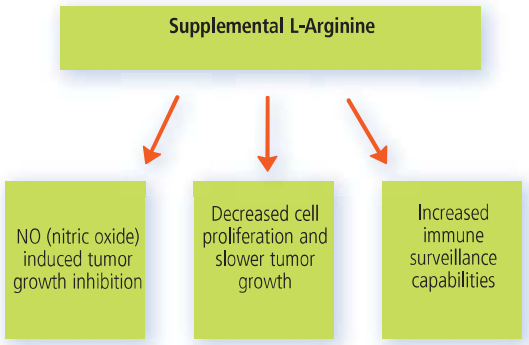
TABLE 3 - COMPARATIVE NUTRITIONAL ANALYSES OF DRY MATTER FROM GUARANTEED ANALYSIS OF DRY OR WET FOOD

dry food	canned food
1) Guaranteed Analysis: Not Less than 32% protein Not Less than 24% fat Not More than 10% moisture Not More than 3% fiber Not More than 7% ash	**1) Guaranteed Analysis:** Not Less than 12% protein Not Less than 10 % fat Not More than 72% moisture Not More than 2% ash Not More than 1% fiber
2) Add all percentages together 32 + 24 + 10 + 3 + 7 = 76%	**2.) Add all percentages together** 12 + 10 + 72 + 2 + 1 = 97%
3) 100 – 76 = 24 % **carbohydrate**	3) 100 – 97 = 3% **carbohydrate**
4) 100 – 10 (% moisture)/100 = 0.90 **DM**	4) 100 – 72 (% moisture)/100 = 0.28 **DM**
Protein: 32/0.9 = 35.5 %/DM **Fat:** 24/0.9 = 27.0%/DM **Fiber:** 3/0.9 = 3.3 %/DM **Ash:** 7/0.9 = 7.7 %/DM **Carbohydrate:** 24/0.9 = 26.5 %/DM	**Protein:** 12/0.28 = 42.0%/DM **Fat:** 10/0.28 = 36.0%/DM **Fiber:** 1/0.28 = 3.5%/DM **Ash:** 2/0.28 = 7.5%/DM **Carbohydrate:** 3/0.28 = 11.0%/DM

► Amino acids and fatty acids

It has been well documented that dietary amino acid alterations may be beneficial as an intervention to retard tumor growth in animal models *(Mills et al, 1998; Epner et al, 2002)*. Further developments in this area will likely lead to a better understanding of how manipulating amino acid metabolism can retard tumor progression and aid in quality of life and survival time of the patient with neoplasia.

FIGURE 4 - THE POTENTIAL ROLE OF ARGININE IN CANCER



Supplementing the arginine concentration in the diet to at least 2% of the amino acids may prove beneficial in dogs with cancer (Olgivie et al, 2000).

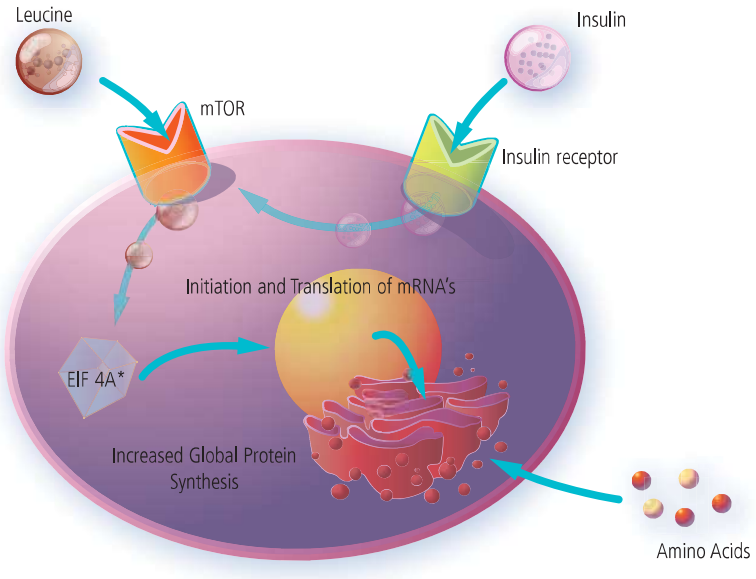
Increased dietary **arginine** has been shown to slow tumor progression in a number of animal models *(Burns et al, 1984; Milner et al, 1979; Robinson et al, 1999)*. This effect may be either due to the ability of arginine to form nitric oxide through NO synthase activity in neoplastic cells leading to retarded cell division, and/or its ability to increase cellular immune surveillance properties *(Reynolds et al, 1990; Robinson et al, 1999)*. The exact mechanism has yet to be elucidated, but providing up to 2% of dietary proteins as arginine may be beneficial to the canine cancer patient *(Olgivie et al, 2000)* **(Figure 4).**

Glutamine may also have suppressive effects on tumorigenesis. Glutamine appears to have a profound immuno-stimulatory role, which leads to greater whole body immunomodulation, and this immunomodulatory function may reduce tumor or metastasis growth rates *(Souba, 1993; Kaufmann et al, 2003)*. Glutamine has also been shown to improve gastrointestinal function and may be considered as a potential GI nutrient to optimize enterocyte function *(Souba, 1993)*. However, glutamine in foods appears to be very labile, particularly if they are exposed to excessive temperatures or in liquid format. After absorption, glutamine is rapidly transaminated by the liver, therefore its efficacy in pet foods for long term clinical cases of neoplasia is uncertain *(Bergana et al, 2000)*.

Branched Chain Amino Acids (BCAA - isoleucine, leucine, valine) are increasingly used as a supplement in critically ill patients due to the potential benefits cited in human literature. The use of BCAA's as anti-tumorigenic amino acids has been debated *(Danner & Priest, 1983; Blomgren et al, 1986; Saito et al, 2001)*, but it is likely that dietary supplementation with certain BCAA's (leucine) may be beneficial in conjunction with other amino acids like arginine in retarding tumor growth *(Wakshlag et al, 2004)*.

FIGURE 5 - PROPOSED ACTIONS OF LEUCINE ON SKELETAL MUSCLE PROTEIN SYNTHESIS

(Anthony et al, 2001 ; Kadawaki & Kanazawa, 2003)



**eukaryotic initiation factor 4A*
Compared with other amino acids, leucine may alter the balance towards anabolism and away from catabolism.

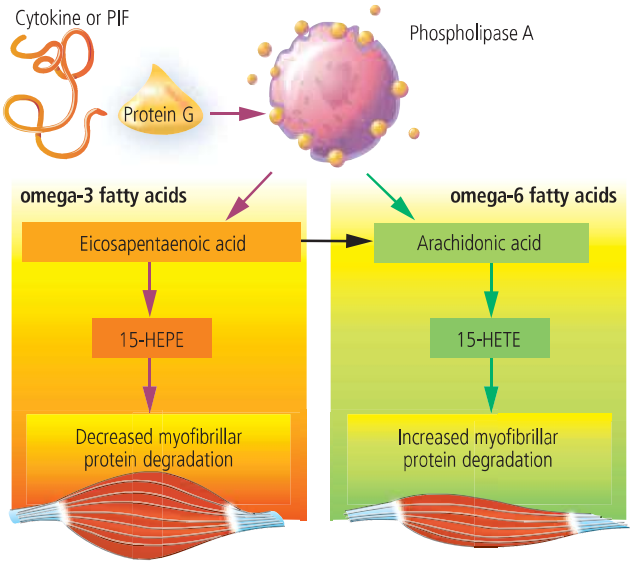
Interestingly, recent literature has demonstrated the beneficial effects of BCAAs for their anti-proteolytic effects during cachexia by increasing lean body mass and preventing excessive lean body wasting in cancer patients. Leucine, as a single amino acid supplement, has been shown to have profound effects of increasing protein synthesis in skeletal muscle when compared to dietary increases of other amino acids, shifting the balance towards anabolism rather than catabolism *(Kadawaki & Kanazawa, 2003; Anthony et al, 2001)* **(Figure 5)**.

Recent clinical studies in humans have revealed increased survival times, improved nitrogen balance, and increased quality of life when diets supplemented with up to 12 grams of BCAAs were fed daily *(Ventrucci et al, 2001; Hiroshige et al, 2001; Inui, 2002; Gomes-Marcondes et al, 2003)*. Though there is no literature in veterinary medicine to support the use of BCAA's, experimental diets with up to 5% of dry matter as BCAAs or the addition of 3% leucine have been used without adverse effects in rodent models. Therefore a safe non-toxic dose for veterinary patients may be approximately 100-200 mg/kg.

► Fatty acids

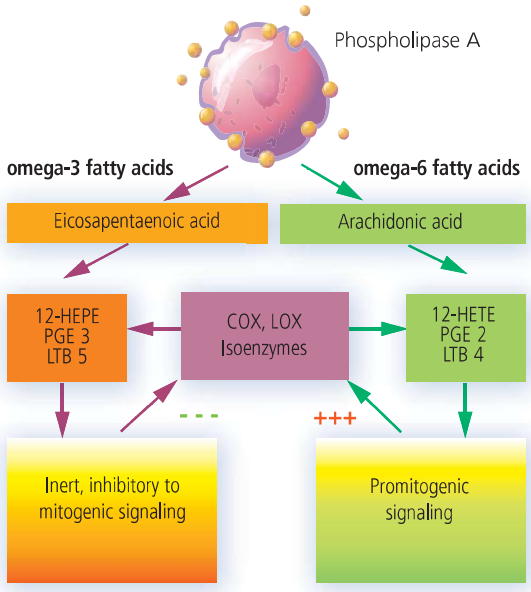
Increased intake of omega-3 fatty acids has shown strong correlation with remission and survival times, and decreased growth rate of carcinomas in animal models *(Thomson et al, 1996; Olgivie et al, 2000; Togni et al, 2003)*. In addition, human clinical studies have shown positive effects of omega-3 fatty acids supplementation on body weight, quality of life, disease free intervals and survival times in cancer cachexia patients. These changes may also be true for canine cancer patients *(Olgivie et al, 2000; Wigmore et al, 2000; Barber et al, 2001; Fearon et al, 2003)* **(Figure 6)**.

FIGURE 6 - PROPOSED ACTIONS OF OMEGA 3 VERSUS 6 FATTY ACIDS ON SKELETAL MUSCLE DEGRADATION



Omega-3 fatty acid supplementation, in particular eicosapentaenoic acid (EPA), has been shown to decrease 15-hydroxytetraenoic acid (15-HETES) concentration thereby suppressing proteolytic activity (i.e. proteasome activity) in skeletal muscle in a model of cancer cachexia (Belezario et al, 1991; Smith et al, 1999).

FIGURE 7 - PROPOSED ACTIONS OF OMEGA 3 VERSUS 6 FATTY ACIDS ON TUMOR CELL PROLIFERATION



EPA slows tumor growth by decreasing the production of promitogenic agents from arachidonic acid.

EPA and DHA can have a profound negative effect on cachexia. Furthermore, they may also attenuate tumor growth through their ability to decrease arachidonic acid metabolism by preventing the promitogenic production of PGE2 in neoplastic cells *(Yuri et al, 2003)* **(Figure 7)**. Fish oils (eg. Menhaden oil) are the richest source of the omega-3 fatty acids EPA and DHA **(Table 4)** and have been shown to be useful in ameliorating cachexia in human clinical trials *(Wigmore et al, 2000; Fearon et al, 2003)*. Some "premium" dog foods are supplemented with omega 3 fatty acids to achieve a 10:1-5:1 ratio of omega 6 to omega 3 fatty acids. The addition of fish oil can significantly alter the omega 6 to 3 ratio beyond what is already found in most pet foods *(Olgivie et al, 2000)*. Though not detrimental to most patients, ratios lower than 1:1 have been associated with increased clotting times and decreased vitamin E concentrations within cellular membranes *(Valk et al, 2000; Hendriks et al, 2002)*.

Only one canine clinical study has been performed with the use of fish oil at a ratio of 0.3:1 and the results showed increased survival times and disease free intervals in dogs with lymphoma, with no discernable side effects *(Olgivie et al, 2000)*. The clinical evaluation of fish oil supplementation in multiple other neoplastic conditions is presently underway and unpublished data suggest that fish oil may be promising for the management of several neoplastic conditions.

TABLE 4 - AVERAGE QUALITATIVE AND QUANTITATIVE COMPOSITION OF DIFFERENT SOURCES OF UNSATURATED FATTY ACIDS

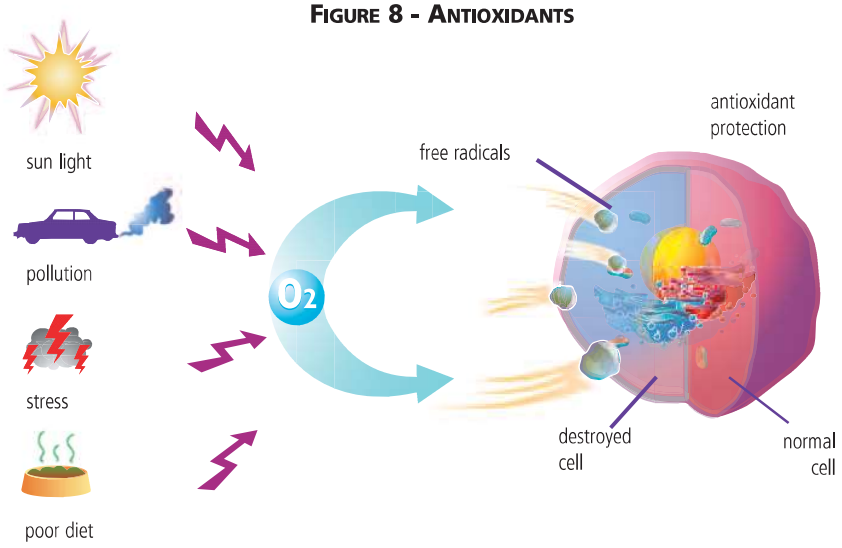
Fatty acids (% dry matter)	Soya oil	Flax seed oil	Rapeseed oil	Poultry fat	Fish oil
Linoleic acid (ω 6 precursor)	54	18	17	17	0,5
α-Linolenic (ω 3 precursor)	8	**51**	9	2,5	1,5
EPA + DHA	< 1	< 1	< 1	< 1	**20**
ratio ω6/ω3	6	0,35	1,8	9	0,15

► Vitamins and minerals

Supplemental feeding of common dietary antioxidants such as β-carotene, retinoids and vitamins C and E have all been associated with decreased risk of carcinogenesis in animal models and in epidemiological cohort studies. Selenium is the only mineral with similar anti-carcinogenic effects. The standing hypothesis is that many of these compounds, except for retinoids, act primarily as antioxidants to decrease cell damage **(Figure 8)**, in particular DNA damage, thus lowering the incidences of functional mutations in DNA resulting in lower incidences of cancer.

Many of these vitamins and minerals are present in adequate concentrations in most dog feeds, and their usefulness in neoplasia once already diagnosed, are largely undetermined. There are multiple human epidemiologic longevity and relative risk studies in progress, using many of these potential anti-carcinogenic agents. However, to date the indiscriminate use of these antioxidants as supplements cannot be supported in veterinary medicine because of the very different dietary patterns and metabolism of these substances in veterinary as compared to human patients.

FIGURE 8 - ANTIOXIDANTS



Antioxidants help the organism combat the destructive effects of free radicals, which are unstable elements continuously produced by the organism. The role of antioxidants constitutes one of the dominant themes in current medical research, particularly in the prevention or treatment of certain cancers.

β-Carotene, and other natural carotenoids and polyphenol compounds have been linked to cancer prevention through their ability to scavenge free radicals within cells in vitro *(Duthie et al, 2003; Cooper, 2004)*. β-carotene has been one of the most widely studied antioxidants in cancer prevention due to its potent antioxidant capabilities. Studies in humans predisposed to neoplasia (lung cancer) have shown that β-carotene supplementation may actually increase the relative risk of neoplasia *(Bendich, 2004; Russell, 2004)*. Considering these recent findings supplemental β-carotene in human medicine has evolved into a cautionary tale of micro-nutrient supplementation.

Sources of carotenoids, (β-carotene, lutein, lycopene, xanthene), generally found in red, green, yellow and

orange colored fruits and vegetables, are receiving significant attention because of their beneficial effects in specific cancers *(Wu et al, 2004; Murtaugh et al, 2004)*. However, their benefit in companion animals is confounded by the fact that carotenoids are absorbed differently in dogs than in humans. Dogs have a far better capacity to cleave β-carotene into retinal than humans, and absorb very little intact β-carotene *(Baskin et al, 2000)*. In light of these findings safety and efficacy data is needed in veterinary medicine before recommendations can be made for supplementing cancer patients with these potentially beneficial antioxidants.

Vitamins C and E are both potent antioxidants which have been shown in human clinical trials to reduce the risk of carcinogenesis *(Henson et al, 1991; Slung et al, 2003; Virtamo et al, 2003)*. Much like β-carotene, these antioxidants have been proven to be preventative rather than therapeutic. Vitamin C (ascorbic acid) has been associated with augmenting the effects of certain chemotherapeutic agents such as vincristine *(Osmak et al, 1997)*. While ascorbic acid supplements may help in some cases of drug resistant chemotherapy, it has also been argued that their use may have tumor promoting effects for some neoplasias, and anti-neoplastic activities for others *(Seifried et al, 2003; Lee et al, 2003)*. No controlled studies have been performed to assess its efficacy in the veterinary patient. Ascorbic acid is synthesized in the dog therefore the relative risk of neoplasia due to deficiency over the lifetime of the animal is not an known. Vitamin E, on the other hand, is required in the diet and further investigation into its efficacy as an anti-neoplastic agent is warranted.

Retinoids (Retinoic acid and retinoic acid derivatives) have been extensively used in the treatment of acute promyelocytic leukemias, and have been associated with increased remission rates in human mammary cancer *(Paik et al, 2003; Altucci et al, 2004)*. They attach to nuclear receptors initiating transcription of genes, promoting cellular differentiation or apoptosis of neoplastic cells. These findings have lead to the use of natural and synthetic retinoid derivatives in the treatment of human cancer. In time such approaches may cross over to veterinary medicine as experimental clinical data is collected regarding efficacy of these retinoids in various neoplastic conditions in animals. Considering the highly potent effects of retinoids, such as retinoic acid which is a known teratogen, and due to toxic effects, e.g cervical spondylosis in cats, as well as anorexia and clotting disorders, recommendations cannot be made at this time for their use in the small animal cancer therapy *(Hayes, 1982)*.

Selenium is the only mineral known to have anti-tumorigenic and preventative properties. There is conclusive evidence that higher serum selenium concentrations are associated with lower incidences of skin, lung and prostate carcinomas in humans *(Duffield-Lillico et al, 2003; Reid et al, 2002; Nelson* et *al, 1999; Clark et al, 1996)*. These actions are thought to be separate from the antioxidant properties of selenium via its role in glutathione peroxidase.

The AAFCO dog food nutrient profile recommended concentration of selenium is met in most commercial pet foods, but the NRC recommendation has recently tripled, therefore the selenium intake of many companion animals may be low normal or deficient. In light of this, and the human clinical studies showing that selenium supplementation has the greatest effects in reducing the relative risk of cancer in those people with low normal serum selenium concentrations *(Clark et al, 1996; Nelson et al, 1999; Reid et al, 2002; Duffield-Lillico et al, 2003)*, it may be wise to supplement (2-4 µg/kg BW/day) animals with a history of neoplasia or a predisposition to develop cancer. At this conservative recommended dose the risks for toxicity are minimal and such supplementation will likely ensure adequate selenium intake.

Overall, when using specific nutrients pharmacologically one may be able to retard tumor growth, enhance quality of life and ameliorate body condition to a certain extent. Yet, it can be difficult to address the specific needs for each neoplastic condition due to the complex nature of cancer, and the various nutrient compositions of the variety of feeds that are available. To properly

TABLE 5 - RECOMMENDED DOSAGES FOR NUTRITIONAL INTERVENTION IN CANCER

Supplement	Condition	Canine Dose
Arginine	Cancer & Cachexia	2% of Dry Matter
Fish oil (EPA-DHA)	Cancer & Cachexia	1:1- 0.5:1 ratio of 6 to 3*
Branch chain amino acids	Cachexia	100-150 mg/kg
Selenium	Cancer	2-4 µg/kg

** It is essential to know either or both the omega-3 fatty acid, omega-6 fatty acid content in dry matter to properly formulate the diet at the desired ratio.*

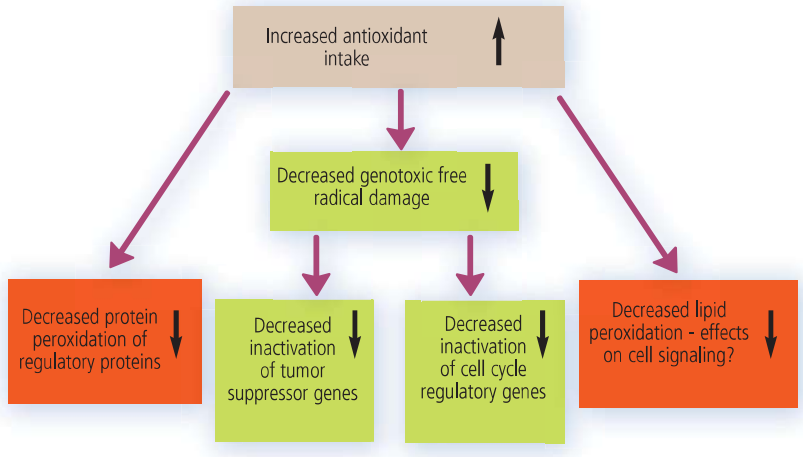
address these nutritional issues, the practitioner needs to know the food consumption and the dry matter content of various nutrients in the given feed, before an effort to alter ratios or total intake of many of the aforementioned nutrients can be made. **Table 5** provides some guidelines for nutritional intervention that should be beneficial in most aggressive neoplastic conditions and can be used once the practitioner has calculated contents of various nutrients in the given food.

4 - Nutritional intervention during cancer treatment

In recent years there has been a significant increase in the use of antioxidants in pet foods, which has hypothetically been associated with less free radical damage in cells throughout the body. This antioxidant supplementation has been associated with amelioration of a variety of different disease processes **(Figure 9)**.

Though these approaches to cancer prevention may be beneficial in theory, once the veterinary patient has been diagnosed with cancer and is undergoing chemotherapy or radiation therapy, use of various antioxidants may actually be contraindicated. If antioxidants are used to prevent free radical damage, and a chemical or radiation treatment has been initiated, the higher levels of cytosolic or membrane bound antioxidant may actually provide a survival advantage to cancer cells. Therefore, it has been recommended by many veterinary oncologists that pets not be given these antioxidant supplements during such treatment. This hypothesis is very controversial, and has yet to be proven. Since the veterinary patient is usually already ingesting sufficient amounts of the essential antioxidants, supplementation may not be necessary *(Virtamo et al, 2003; Prasad, 2004)*.

FIGURE 9 - ANTIOXIDANTS AND CANCER PREVENTION



Massive antioxidant supplementation may be contra-indicated during chemotherapy or radiation therapy, as antioxidant supplementation may facilitate the survival of cancer cells.

On the other hand, many other ingredients and nutrients such as fish oil and arginine, are unlikely to be detrimental. Indeed, supplementation with fish oil has been associated with better radiation therapy recovery and less inflammation to surrounding tissue. Studies in animal models have also suggested that the increase in long chain polyunsaturated fatty acids in cell membranes resulting from fish oil supplementation may actually provide more highly reactive fatty acids for lipid peroxidation during radiation therapy, thus promoting cell death in the neoplastic tissue *(Colas et al, 2004)*.

Conclusion

Clinical veterinary studies have shown that a number of metabolic anomalies produced in human and rodent cancer models are also found in dogs. The nutritional approach to cancer used in human medicine could therefore be adapted to veterinary medicine to influence the progression of the cancer.

Frequently asked questions: Nutrition of dogs with cancer

Q	A
If my dog refuses to eat a new food can I give fish oil on top of the present feed?	Fish oil can be added to regular grocery store brand dog food, but it is ideal to know how much omega-3 fatty acids is already present in the food. A typical beagle, eating a typical grocery store brand food will eat about 6 grams of omega 6 fatty acids a day and only 100 mg of omega-3 fatty acids, so to get to a 1:1 ratio, you would need about 6 grams of omega-3 fatty acids from fish oil. Remember that only 30% of fish oil are omega-3 fatty acids, so you have to triple the fish oil given, thus 18 grams or just over a tablespoon is needed each day.
My dog doesn't like the fish oil. Can I give another source of omega-3 fatty acids?	Flax-seed oil is rich in linolenic acid, a EPA-DHA precursor. It may prove interesting but its clinical efficiency has not been demonstrated with respect to cancer. Another alternative is to feed descented fish oil or lemon flavored fish oil.
If an owner wants to use various antioxidants, which are recommended, and when should they be given if radiation or chemotherapy treatment has been initiated?	The antioxidants that are likely to be safest are those that have the most clinical and cell biological research behind them. Often vitamin E and vitamin C come to mind. Recent research on thiol antioxidants like lipoic acid and the glutathione precursor s-adenosyl-methionine, both of which have few to no known side effects, maybe of interest. If owners feel strongly about using these antioxidants, it is ideal to use them as directed by the manufacturers, and using veterinary formulated products is often safer than using human formulations. If dogs are receiving chemotherapy/radiation treatments then removing all supplemental antioxidants one week before treatment and continuing them again one week after the treatment protocol has been terminated is likely to be the safest approach at this time.
Some owners feel that changing their animal to a "holistic" or "homemade" diet would provide some benefit during cancer, is this a wise approach?	Often owners find diets on the internet that have been designed for canine cancer patients and will implement them, hoping they will prolong survival or cure the neoplasia. More often than not, there are gross imbalances in vitamins and minerals in these diets. It is ideal to have a veterinary nutritionist intervene in these cases and analyze the proposed diet to ensure that there are no gross imbalances.
Often in the anorexia/cachexia syndrome it becomes difficult to implement the diet changes needed, and a diet with lower caloric density may be the diet of choice by the patient? What should the owner do?	In those cases it easier to let the patient choose their feed and attempt to supplement fat and protein sources to increase the caloric density and protein content of the meal. Remember during anorexia/cachexia some caloric intake though not optimal for the disease is better than no caloric intake at all.

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EXAMPLES OF HOME-PREPARED THE TREATMENT OF

Example 1

COMPOSITION
(1000 g diet)

Quark, fresh cheese, 40% fat ..... 415 g
Acid curd cheese * ..... 150 g
Whole egg ..... 120 g
Cow's milk, UHT ..... 120 g
Potato, cooked, with skin ..... 150 g
Honey ..... 20 g
Wheat bran ..... 5 g
Rapeseed oil ..... 20 g

**40% fat grasses on dry matter*

Add a well-balanced mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 28% dry matter and 72% water		
	% dry matter	g/1000 kcal
Protein	40	78
Fat	31	59
Available carbohydrate	21	41
Fiber	2	3

INDICATIVE RATIONING			
Energy value (metabolizable energy): 1465 kcal/1000 g of diet prepared 5150 kcal/1000 g DM			
Dog's weight (kg)	Daily amount (g)*	Dog's weight (kg)	Daily amount (g)*
2	150	45	1540
4	250	50	1670
6	340	55	1790
10	500	60	1910
15	680	65	2030
20	840	70	2150
25	990	75	2260
30	1140	80	2370
35	1280	85	2480
40	1410	90	2590

Key Points

- **High energy density to** favor the amelioration of the body condition and of palatability
- **Maintaining a high protein-calorie ratio despite the high fat content** to combat muscle atrophy
- **Highly digestible ingredients** to maximize the nutritional benefit for the dog

**The fractioning of the daily amount over two or three meals is recommended to favor good digestion.*

DIETS ADAPTED TO CANCER CACHEXIA

Example 2

COMPOSITION
(1000 g diet)

Beef, minced meat, 10% fat ..... 500 g
Cow's milk, UHT ..... 130 g
Whole egg ..... 75 g
Potato, cooked, with skin ..... 255 g
Wheat bran ..... 20 g
Rapeseed oil ..... 20 g

Add a well-balanced mineral and vitamin supplement.

INDICATIVE RATIONING			
Energy value (metabolizable energy): 1445 kcal/1000 g of diet prepared 4870 kcal/1000 g DM			
Dog's weight (kg)	Daily amount (g)*	Dog's weight (kg)	Daily amount (g)*
2	150	45	1560
4	250	50	1690
6	340	55	1820
10	510	60	1940
15	690	65	2060
20	850	70	2180
25	1010	75	2290
30	1150	80	2410
35	1290	85	2520
40	1430	90	2630

ANALYSIS		
The diet prepared in this way contains 30% dry matter and 70% water		
	% dry matter	g/1000 kcal
Protein	40	83
Fat	29	60
Available carbohydrate	17	35
Fiber	4	9

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

© Paula

Cancerous conditions are relatively common in giant breeds, especially osteosarcoma.

Key Points
to remember in:

Nutritional management of dogs with cancer

- The preferred energy sources are fat and protein, at the expense of carbohydrate, which is highly valued by cancer cells. The main principles of formulation are the same as diets that meet the requirements of sporting and working dogs.
- **Fat** helps to increase the energy concentration of the food, which is necessary in anorectic or cachexic patients.
- Enriching the **long-chain omega 3 fatty acid** (EPA-DHA) content in the food helps the dog benefit from the anti-neoplastic properties of EPA-DHA.
- **A high-protein diet** helps combat muscle wasting during cancer cachexia. The amino acids that play an important role in slowing the progression of the tumor, include:
  - **arginine**, which favors nitric oxide production
  - **glutamine**, which has immune-modulating actions
  - **branched chain amino acids** (e.g. leucine, isoleucine and valine), which help combat cachexia.
- **Antioxidant supplementation** (e.g. vitamins E and C, β-carotene, polyphenols, selenium) is of major interest in preventing cancer. However, based on our knowledge at this time, antioxidant supplementation should be avoided during chemotherapy or radiation therapy so that the efficacies of these therapies are not compromised.
- **The palatability of the food** is key in anorexic and cachectic dogs.

Focus on:

BRANCHED CHAIN AMINO ACIDS

Among the essential amino acids, leucine, isoleucine and valine constitute a category of their own called the branched chain amino acids (BCAA's). The dog is incapable of synthesizing adequate amounts of these three amino acids, so dietary intake is needed to meet daily requirements. The concentration of these three amino acids in the blood is very dependent on dietary intake.

Valine, leucine and isoleucine represent at least one third of the essential amino acids constituting muscle proteins and are the only amino acids that are initially degraded by muscles. These three amino acids are unique among the essential amino acids because they are able to undergo reversible transamination to enrich the organism's nitrogen pool.

Valine, leucine and isoleucine are able to stimulate the synthesis of proteins and slow protein degradation in muscles. This property has been specifically attributed to leucine, as it proves as effective as a mixture of the three BCAA's.

In rats, stimulation of protein synthesis by leucine follows a dose-response type curve. This stimulation is produced at very low leucine concentrations, identical to those observed in the blood just before a meal. In older rats, much higher leucine concentrations are needed to obtain maximum stimulation *(INRA, 2002)*. The sensitivity to leucine intake is therefore reduced. This loss of sensitivity may explain the absence of increased muscle protein synthesis after meals in aging subjects.

Leucine
Isoleucine
Valine + α-ketoglutarate → glutamate + α-ketoisocaproate
α-keto β methylvalerate
α-ketoisovalerate

EXAMPLES OF BRANCHED CHAIN AMINO ACID LEVELS IN SELECTED RAW INGREDIENTS USED IN DOG FOODS

(Source: Royal Canin internal data)

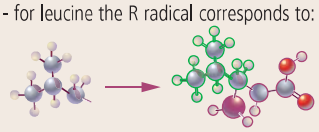
% of the protein of the food	leucine	isoleucine	valine	total BCAA's
Poultry protein	6.5	3.5	4.3	14.3
Corn gluten	14.7	3.6	4.2	22.5
Corn	13.0	3.9	5.1	22.0
Barley	7.0	3.8	5.3	16.1
Rice	7.7	4.1	5.6	17.4

Corn proteins are particularly high in leucine.

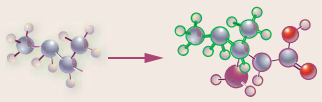
CHEMICAL FORMULA OF BRANCHED CHAIN AMINO ACIDS

The general structure of amino acids is:

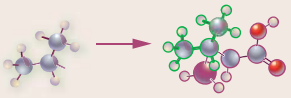
- for leucine the R radical corresponds to:

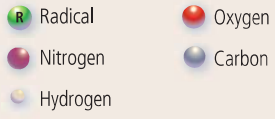


- for isoleucine the R radical corresponds to:



- for valine the R radical corresponds to:





Reference

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