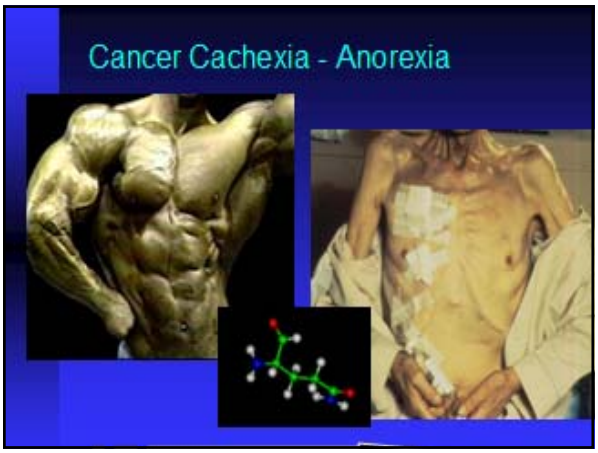
CANCER CACHEXIA

- " A wasting syndrome characterized by loss of muscle and fat caused by an aberrant host response to a wide variety of chronic illnesses. Anorexia usually accompanies cachexia, and is caused by related mediators acting upon the hypothalamus."

MacDonald et al
JACS, July 2003



Negativity – cancer nutrition

- Lack of past success
  - alimentation trials
  - counselling
  - therapeutic failures

  (cyproheptadine, pentoxyfylline, hydrazine)
- Qualified success
  - (corticosteroids, megestrol)

Negativity – cancer nutrition

- False Dichotomy

Tumour Growth vs Symptom Control

- Skewed Research

Do we think it's important?

- ASCO 2005 - 4119 presentations
- Nutrition - 15
- Gemcitabine - 106

ASCO STATEMENT
JCO16: MAY 1998

- "ONCOLOGISTS MUST LEARN TO RECOGNIZE AND RESPOND TO THAT TRANSITION POINT IN A PATIENT'S CARE WHEN DISEASE ORIENTED ANTICANCER THERAPY MUST GIVE WAY TO SYMPTOM ORIENTED PALLIATIVE THERAPY"

Canadian Institutes of Health Research Cancer Institute

Palliative care aims to improve the life of patients and families through early identification and impeccable management of suffering associated with cancer, and emphasis on the positive aspects of life inclusive of physical, psychosocial and spiritual sources. Palliative care is an exercise in prevention — prevention of suffering through prioritizing the diagnosis and skillful care of sources of distress throughout the course of cancer and for the family during the bereavement period. It is not simply an end of life concept separate from other aspects of cancer research and control.

Cancer Cachexia - Anorexia

Anorexia-cachexia

PERIPHERAL

- Inflammation
  - cytokines, eicosanoids
- Hypercatabolism
  - dysautonomia
- Hypogonadism
- Oxidative Stress
- Genetic Predisposition
- Tumour Factors

CENTRAL

Hypothalamus

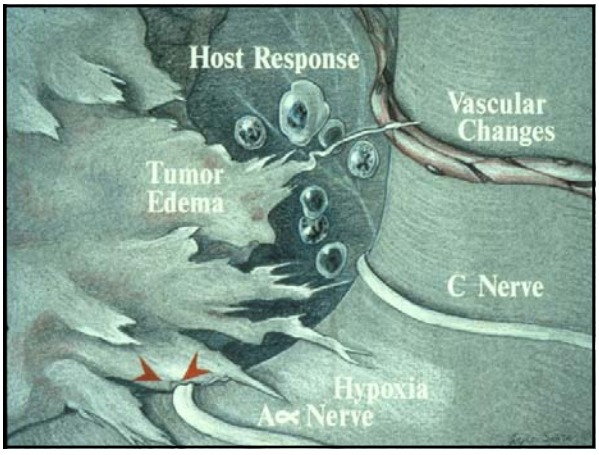
Cerebral influence

appetite

PROTEOLYSIS INDUCING FACTOR

- Glycoprotein
- Induces proteolysis, not anorexia
- Does not cause anorexia
- Present in : serum — MAC 16 mice
  urine — cancer patients with weight loss
- Activates Prostaglandin E_2
- Attenuated by EPA (omega-3 fatty acid)

(Tisdale)



Advancing Cancers

Infiltrating → TAM TIL

Growth Factors
Angiogenesis
Proteases – matrix

↓ Tumour Immunity
Th2 ↑ Th1 ↓

We suggest that the inflammatory cells and cytokines found in tumours are more likely to contribute to tumour growth, progression and immunosuppression than they are to mount an effective host anti-tumour response… some types of inflammation may provide 'the fuel that feeds the flames'.

Balkwill, Mantovani. *Lancet*. February 17, 2001

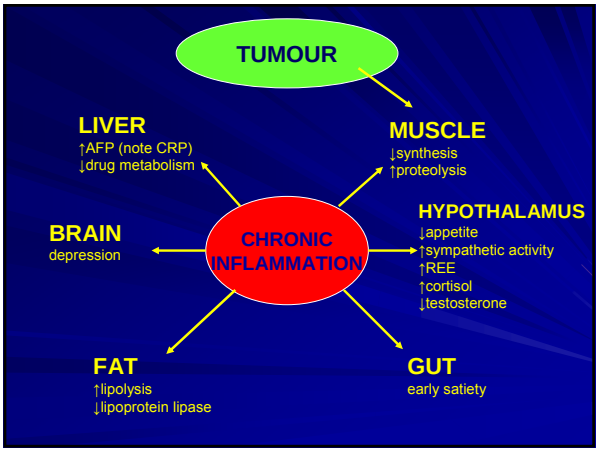
Metabolic Changes in Tumor Related Weight Loss

- ↑Anaerobic Glycolysis
- Insulin Resistance
- Diminished Lipogenesis
- Lipolysis
- Protein Catabolism
- Decreased Muscle Protein Synthesis
- ↑Acute Phase Protein Response - CRP
- ↑Pro-Inflammatory Cytokines

'A Wound That Doesn't Heal'

- Wound Infection
  - Organise cellular response
  - Suppress when resolved
- Tumours
  - Organise cellular response
  - Suppression cues lost
  - Chronic Inflammation
    - Support tumour growth
      - ✓ Growth factors
      - ✓ Angiogenesis
      - ✓ Symptoms – cachexia

Balkwill, Lin, others



Lung Cancer – 1ST Presentation

- C-reactive Protein – 80↑
- Survival -- < 10 mgm/L -- 11 months
  (median) -- >100mgm/L -- 3 months
- Correlations -- weight loss
  fatigue
  poor performance status
  ↓ albumin and hemoglobin

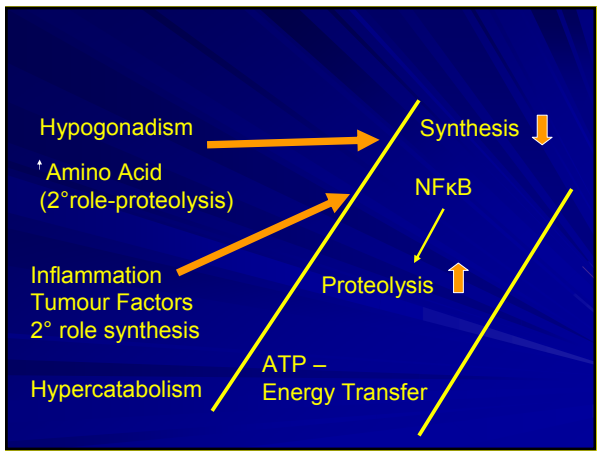
Scott et al *BCJ* 2002 87-264

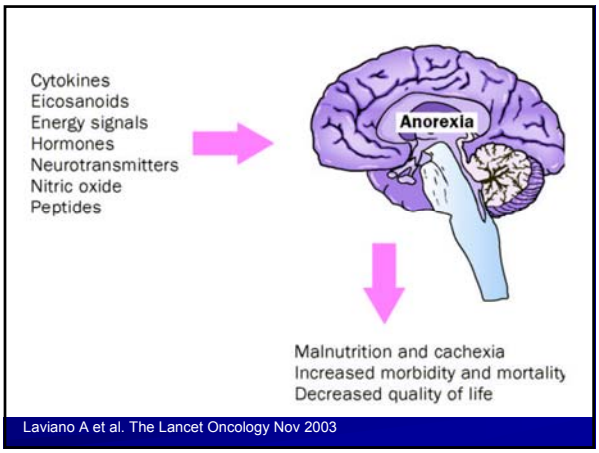
Cancer Inflammation - Chemotherapy

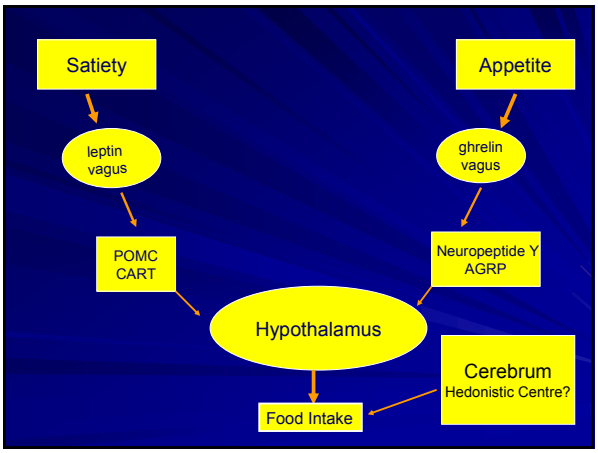
Pharmacokinetics
- ↓ cytochrome P450
  docetaxel, vinorelbine

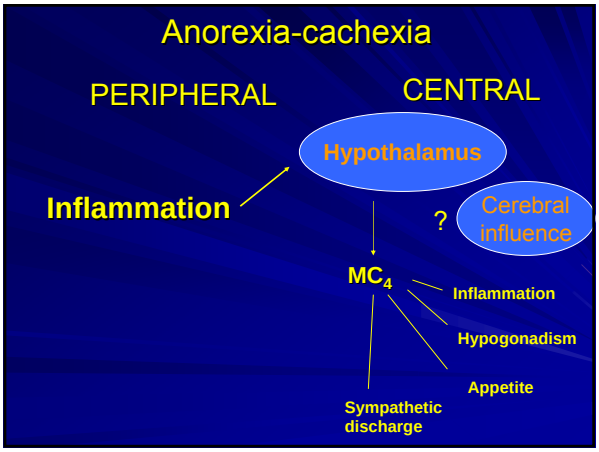
Pharmacodynamics
- Acute phase proteins
  ↑ binding?
- Cytokines
  receptor interference?
  2nd messenger interference?
  (platinum, interleukin 2)

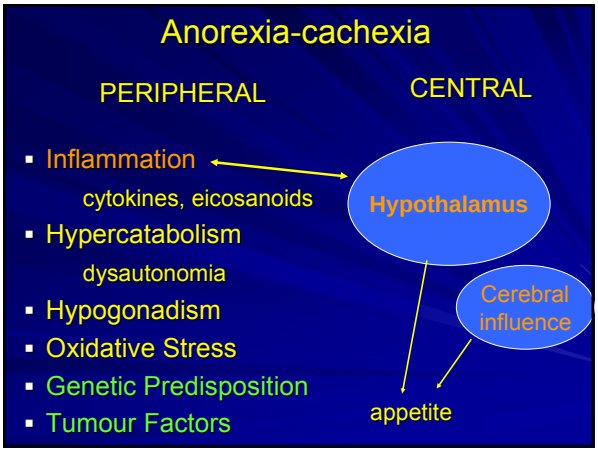
Slaviero et al *Lancet Oncology April 2003 224*











Upon this gifted age, in its dark hour,
Rains from the sky a meteoric shower
Of facts…they lie unquestioned, uncombined.
Wisdom enough to leech us of our ill
Is daily spun, but there exists no loom
To weave it into fabric.

Edna St Vincent Millay

WHO Definition Palliative Care — 2002

Palliative care is an approach which improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Cachexia – Early Rx

Informed Opinion
Clinical Trials
- Time from diagnosis
- Appetite loss

Correlation
- Inflammation
- Cachexia

Cachexia
- Early – Atrophy – fibres intact
- Late - Apoptosis – fibres disappear

CANCER NUTRITION – REHABILITATION PROGRAMME

- Objectives

➢ To provide an assessment and therapeutic clinical programme for patients with cancer and early identified anorexia-cachexia, fatigue and functional loss.

➢ To create a centre of excellence for the conduct of research on cancer induced anorexia-cachexia and fatigue.

Basic Assessment Package

- Paper and Pencil
  - PG-SGA
  - ESAS
- Blood
  - C-reactive protein
  - Testosterone
- Diet History
  - Detail Problems → Depression, Constipation

Screen – Referral - CNR

Albumin	<	35gm/L
CRP	>	50
Weight Loss	>	5% in 6 months
Fatigue	>	6 ESAS
Anorexia	>	judgment
Function	>	judgment

Mechanisms of secondary cachexia

- Impaired oral intake
  - cognitive impairment, delirium
  - depression, fatigue
  - pain, dyspnoea, other uncontrolled symptoms
  - stomatitis, taste alteration
  - dry mouth
  - dysphagia, odynophagia
  - gastric stasis
  - bowel obstruction
  - nausea & Vomiting
  - severe constipation

Anorexia-cachexia general approach

1. Correct other symptoms
   mouth care, anxiety, pain , constipation
2. Gastric Atony
   prokenetics
3. Review patient – family goals
4. Nutritional counselling
   dietitian, print dietary guide, internet

Muscles Need

- Blood Supply
  - oxygen ….. Anemia
  - nutrients ….. Amino acid delivery
- Energy Supply … ↓ ATP Hypercatabolism
- Protein Synthesis … ↓ Anabolic factors
- Balanced Proteolysis … ↑ Ubiquitin ligases
- Exercise ….. Inanition Spiral
- Neuromuscular Junction …. ???

General Pharmacotherapy

➢ **MUSCLE**
- ❑ Amino Acids
- ❑ Omega 3's
- ❑ Vitamins (C, E, B, zinc)

APPETITE STIMULATION
- ❑ Megestrol – corticosteroids
  short-term

Eicosapentaenoic acid (EPA)

- EPA, an omega-3 polyunsaturated fatty acid found in deep sea oily fish (e.g. salmon, sardines, tuna, mackerel), has been shown to:
  - ↓ pro-inflammatory cytokine production[1] ↓ level/activity of proteolysis-inducing factor[2]
  - possess anti-cachectic properties[3]
  - slow tumour growth[3]
  - increase survival

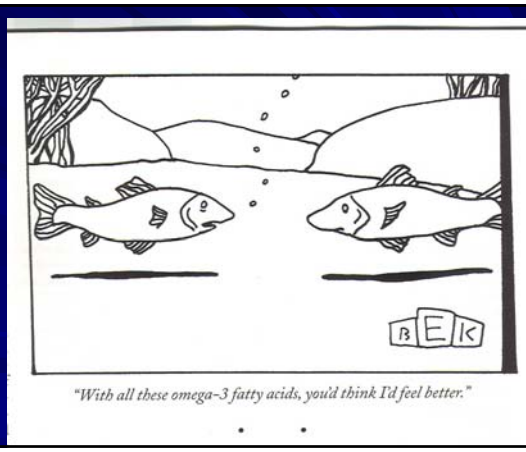
EPA in combination with protein and calories may counteract the causes of cancer cachexia resulting in weight gain and (partial) restoration of body mass

NCI – SC18 megestrol vs EPA

- End Points

	meg	comb	EPA
10% weight gain	18%	11%	6%
Appetite	NS (range 40% - 69%)		
Survival	NS		
Life Quality	NS		

Jatoi et al .JCO;22(12):2469-76



"With all these omega-3 fatty acids, you'd think I'd feel better."

General Pharmacotherapy

- **MUSCLE**
  - Amino Acids
  - Omega 3's
  - Vitamins (C, E, B, zinc)
- **APPETITE STIMULATION**
  - Megestrol – corticosteroids short-term

Rehabilitation - Exercise

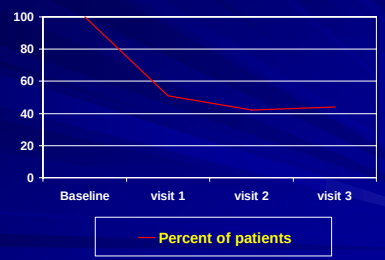
- Reduce cancer incidence
- Increase NK activity
- Increase QOL and fitness, decrease fatigue
- Geriatric literature
  Clear consensus – increased function
- Fatigue therapy

Exercise – patient motivation

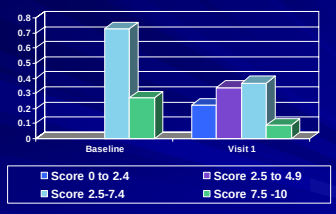
1. Personal Control --Empowerment
2. Do 'something normal'
3. Belief – exercise helps response toxicity

ASCO – Roubenoff & Tattersall 2002

Weight stabilization in patients who reported loss at baseline



Change in the QoL from the baseline in those who reported poor (≥5) QoL at the baseline

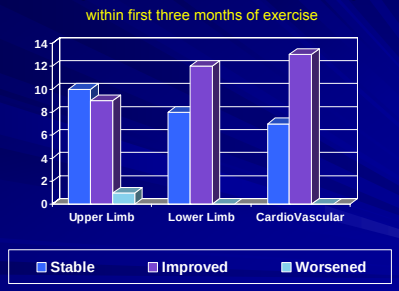


P<0.05 (Wilcoxon Signed Rank test) when compared to baseline

Levels of Training (112 patients)

- 43% trained at a high level
  - **2-3 X per wk, progressive cardiovascular & resistance exercises**
- 10% trained at a moderate level
  - **1-2 X per wk, low level cardiovascular & resistance exercises**
- 47% trained at a low level
  - **1-2 times per month, home care, theraband.**

Functional Improvement in pts with High Level of Training



Progressive Training Limitations

- Cardiovascular: 93%
  - High resting HR
  - Low HR reserves
  - Autonomic insufficiency
- Neurological symptoms:3%
- Dyspnea: 2%
- Bone metastases: 2%

Research on CAA: McGill Studies

Completed – Ongoing - In Planning

- Identification of some causative factors
  - Translational Research at McGill Cancer Centre
- Potential benefit of muscle sustaining therapies
  - Omega-3 fatty acids *Study completed*
  - ACE Inhibitors *Study inaugurated June 2003*
  - Amino Acids *Ongoing*
  - Creatine *NCI(C) – Mayo NCCTG - fall*
- Role of Exercise-Rehabilitation
- NET Grant – PI V Baracos Univ of Alberta

Potential Clinical Trials

- Cardioctive agents – ACE inhibitors
- Beta 2 agonists
- Cytokine inhibitors
- Ghrelin
- Hypothalamic mediators – MC4 antagonists
- Myostatin inhibitors

Logical pragmatic trial

Amino Acid Anabolic Agent Anti-inflammatory ? COX 2 EPA	vs	Amino Acid Anti-imflammatory Anabolic Agent

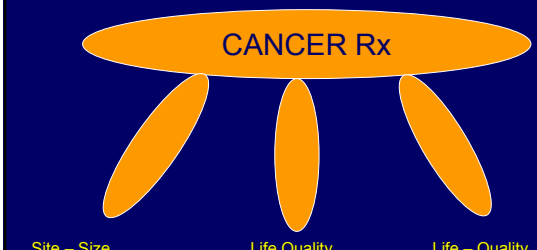
Role of Exercise

New Platform Considerations

- Address Hypogonadism
- Creatine Study
- NSAIDS
- Control Anemia

Cachexia – Developing Countries

- Specific Counselling (print)
- Vitamins
- Amino Acids
- Omega 3's
- Exercise



Priorities?

Life Quality – Life Prolongation