Oral vs. Intravenous Vitamin C

Optimizing the Use of Vitamin C in the Care of Cancer Patients

Cancer is a word, not a sentence.
- John Diamond

Ron Hunninghake, MD
Chief Medical Officer
The Olive W. Garvey Center for Healing Arts

My Objectives

- Redefine Orthomolecular Oncology
- Introduce The Riordan Approach
- Clarify How Vitamin C Fights Cancer
  - IVC as a Biological Response Modifier
  - The Pro-oxidant Effect of IVC – Redox Cycling
  - The Antiangiogenesis Effect of IVC
- Discuss ‘Ortho-dosing’ of Vitamin C
- Illustrate Objectives with Two Case Studies

The Doctor (1891)

Sir Samuel Luke Fildes
- one of the best known of all late-Victorian paintings (partly because reproductions hung in many doctors’ offices)
- now in the National Gallery of British Art
  (Image courtesy of Wikipedia)
- depicts a pensive physician watching a gravely ill child
- inspired by the death of Sir Fildes’ own son

What message was Sir Fildes trying to convey with this painting?

The compassion of the physician
The hopeless feelings of the family
The medical helplessness of that time period
The devastation of life-threatening disease

Clinical Oncology Paradigms

<table>
<thead>
<tr>
<th>Conventional</th>
<th>??????</th>
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</thead>
<tbody>
<tr>
<td>Treat the Disease</td>
<td></td>
</tr>
<tr>
<td>Determine Grade and Stage of Tumor</td>
<td></td>
</tr>
<tr>
<td>Kill Cancer Cells</td>
<td></td>
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<tr>
<td>More Oxidative Stress</td>
<td></td>
</tr>
<tr>
<td>Quantity of Survival</td>
<td></td>
</tr>
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Ronald Hunninghake, MD

Allopathic Oncology

- ‘Relating to or being a system of medicine that aims to combat disease by using remedies (as drugs or surgery) which produce effects that are different from those of the disease being treated.’ – Webster’s
- ‘The Silver Bullet’ mentality
  – the latest chemotherapeutic “breakthrough”
  – the newest and hottest technology…i.e. “the cyberknife”
  – the cancer surgery that is or will be the “standard of care”
- DANGER: the broader clinical context of the patient’s illness is lost in the rush to implement “the therapy”

Orthomolecular Oncology

<table>
<thead>
<tr>
<th>Allo-pathic</th>
<th>Ortho-pathic</th>
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<tbody>
<tr>
<td>Treat the Disease</td>
<td>Care for the Patient</td>
</tr>
<tr>
<td>Determine Grade and Stage of Tumor</td>
<td>Search for and Correct Underlying Causes</td>
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<tr>
<td>Kill Cancer Cells</td>
<td>Strengthen Healthy Cells</td>
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<tr>
<td>More Oxidative Stress</td>
<td>Lessen Oxidative Stress</td>
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<td>Quantity of Survival</td>
<td>Quality of Life</td>
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</table>

“The Brightspot for Health
www.brightspot.org
Dr. Hugh’s Impossible Dream

“We don’t treat cancer here.
We treat patients who have cancer.”
-Dr. Hugh Riordan
1932-2005

The Riordan Approach

<table>
<thead>
<tr>
<th>The Riordan Approach</th>
<th>Ortho-pathic</th>
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<tr>
<td>Riordan Approach</td>
<td>Ortho-pathic</td>
</tr>
<tr>
<td>Doctor-Co-learner Relationship</td>
<td>Identify the Causes</td>
</tr>
<tr>
<td>Characterize (&amp; Correct) Biochemical Individuality</td>
<td>Care for the Whole Person</td>
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<tr>
<td>Food as Medicine</td>
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<tr>
<td>Cultivate Healthy Reserves</td>
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</tr>
<tr>
<td>Healing Power of Nature</td>
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Greek ‘Orthos’ defined…

<table>
<thead>
<tr>
<th>Orthos</th>
<th>Modern Usage</th>
<th>Defined…</th>
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<tbody>
<tr>
<td>Right</td>
<td>orthogonal</td>
<td>a ‘right’ angle</td>
</tr>
<tr>
<td>Correct</td>
<td>orthodontics</td>
<td>correct the bite</td>
</tr>
<tr>
<td>Straight</td>
<td>orthopedist</td>
<td>straighten the fracture</td>
</tr>
<tr>
<td>True</td>
<td>orthodox</td>
<td>a true, correct belief</td>
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<tr>
<td>Akin to</td>
<td>orthochromatic</td>
<td>Colors akin to nature</td>
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<td>Right</td>
<td>orthomolecular</td>
<td>The right molecule</td>
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<td>Summation</td>
<td>orthopathic</td>
<td>_____ approach to illness</td>
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Orthomolecular Medicine
Bridges Allopathic and Alternative

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<td>Ortho-dosing</td>
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<td>Ortho-natural</td>
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First Cancer Case at The Center*

- George Williams, friend and patient of Dr. Hugh
- 1980 – Adenocarcinoma of right kidney
- Underwent nephrectomy → mets to lung, liver
- IVC 30 grams twice weekly…felt well
- After 15 months of therapy, mets were gone
- 14 yrs later, at age 84, George died of CHF
*J Orthomol Med 1990; 5:5-7

IVC – a ‘Natural’ Silver Bullet?

- IVC therapy for cancer is in danger of being viewed as a natural “silver bullet”
- We best NOT FORGET the unique “birthing ground” of IVC in our quest for scientific proof of its therapeutic efficacy
- Ideally, the emerging field of orthomolecular oncology can serve to COMPLETE and HEAL the field of conventional, allopathic oncology

MedicNews: Other Cancers
Re-Assessment Urged for Intravenous Vitamin C and Cancer*
Published: March 27, 2006
- acceptable for CME
*Sebastian J. Padayatty, et al
“Intravenously administered vitamin C as cancer therapy: three cases” CMAJ 2006;174(7):937-42.

Orthomolecular Oncology – the difference between soft & hard

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Ronald Hunninghake, MD

Riordan Approach to Cancer
• Apply all aspects of the Riordan Approach, plus...
  * Use the right dose of vitamin C - “ortho-dosing”
  1. biological response modifier
  2. nontoxic chemotherapeutic agent
  3. natural antiangiogenesis treatment
• The Art & Science of Orthomolecular Oncology
  ‘Spontaneous Remission Induction’

Orthomolecular Oncology Pioneers
• James Lind
• Albert Szent-Gyorgyi
• Irwin Stone
• Abram Hoffer
• Linus Pauling
• Fredrick Klenner
• Lendon Smith
• Claus Jungeblut
• William McCormick
• Ewan Cameron
• Robert Cathcart
• Hugh Riordan
  RECNAC Research Team

Key RECNAC Research Finding

Validation of RECNAC’s Pioneering Work
Sept. 20, 2005 – National Institutes of Health
“Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues”
– Proceedings of National Academy of Science
– Chen, Espey, Krishna, Mitchell, Corpe, Buettner, Shacter, Levine
  Sept 20; 102: 13604, 2005

Ascorbic Acid
Vitamin C Acting as an Anti-oxidant

The importance of ortho-dosing the IVC regimen
Oral vs. Intravenous Vitamin C
Ronald Hunninghake, MD

**Dehydroascorbic Acid**
Oxidized Vitamin C (DHA) Is Not Reabsorbed

Two ferric ions are reduced to the ferrous state

*Dehydroascorbic Acid*  
2Fe^3+ \rightarrow 2Fe^2+ AA^{2e^-} DHA^*

\[ \text{kidneys} \]

*Misguided Sloan Kettering Study*

**The Pro-oxidant Effect of Vitamin C**  
in the Presence of Iron and Oxygen

Fe^3+ + 2O_2 e^- + 2H^+ \rightarrow 2Fe^2+ H_2O_2

\[ \text{kidneys} \]

**Fenton’s Reaction**  
Ferrous Iron is Oxidized Back to Ferric State

Fe^3+ \rightarrow Fe^2+ \text{OH}^* \text{HO}^*\text{H}_2\text{O}_2

**Redox Cycling with IVC**

Fe^3+ \rightarrow Fe^2+ \text{OH}^* \text{OH}^*\text{H}_2\text{O}_2\rightarrow \text{DHA}_{AA}^{2e^-}

\[ \text{kidneys} \]

**Water Wheel Analogy – Vitamin C Generating a Pro-oxidant**

AA \rightarrow OH^*  
Redox Cycling requires ortho-dosing of Vitamin C

National Institutes of Health  
May 14, 2007

“Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo”

– Proceedings of National Academy of Science

Chen, Espey, Krishna, Mitchell, Corpe, Buettner, Shacter, Levine

May 14, 2007 | vol. 104 | no. 21 | 8749-8754
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The Riordan IVC Protocol
Intravenous Ascorbate (IVC) as a Chemotherapeutic and Biologic Response Modifier

- BCRI: Bio-Communication Research Institute
- Introduction
- Treatment rationale and biological response
- Inclusion criteria and candidates
- Precautions and side effects
- Administration of IVC
- Concurrent Therapy
- Conclusions

IVC Relieves the Classic Picture of Scurvy in Cancer Patients.

- The Unrecognized Symptoms of Scurvy
  - Tired and listless
  - Sallow skin color with easy bruising
  - Poor appetite and poor sleep
  - Low threshold for pain
- IVC relieves the scurvy of cancer rapidly

IVC – A Biological Response Modifier

- relieves scurvy
- boosts immunity
- stimulate collagen formation
- inhibits hyaluronidase
- induces apoptosis
- antiangiogenic

BCRI Anti-angiogenesis Research*
Dr. Judah Folkman
The first to investigate angiogenesis in cancer in the early 1980’s
Angiogenesis means “new blood vessel growth”
Tumor cells produce growth factors
Most important → VEGF

Reference: Anti-angiogenic Effect of High Doses of Ascorbic Acid
Mikirova, Ichim, Riordan; J Transl Med. 2008; 6: 50. published 9-12-08

VEGF – Vascular Endothelial Growth Factor

1. VEGF causes cellular proliferation
   - stimulates mature endothelial cells
   - recruits bone marrow endothelial stem cells to the tumor site
2. VEGF stimulates secretion of MMPs
   - proteinases that break down extracellular matrix
   - allow new blood vessel growth toward tumor

Angiogenesis: New Blood Vessel Growth

Tumor cells produce...

VEGF
Vascular Endothelial Growth Factor
a tumor angiogenesis cytokine

1. stimulates proliferation of mature endothelial cells
2. endothelial stem cells are recruited from the bone marrow

Blood Vessel
Mature endothelial cells
Endothelial stem cells
Tumor Nodule
**Oral vs. Intravenous Vitamin C**
Ronald Hunninghake, MD

### New Endothelial Cell Actions

- Endothelial cells produce MMPs that digest collagen.
- Endothelial cells produce nitric oxide.
  1. angiogenesis regulator
  2. stimulates formation of integrins
  3. act as “grapple hooks” for migration and adhesion of endothelial cells through extracellular matrix.

### Blood Vessel Tumor Nodule

**NO**

**Tumor Angiogenesis**
Effect of Tumor Conditioned Medium (TCM) on Angiogenesis

**Control**

**TCM**

### VEGF Feedback Loops

- **Positive local feedback**
  - New blood vessel growth brings more nutrients to the tumor cells.
  - As the tumor cell population grows, more VEGF is made.
- **Negative distant feedback**
  - Tumor cells also make **angiojstatin and endostatin**
  - These cytokines inhibit angiogenesis at sites of metastasis.

### Beware of “I think we got it all!”

- Resection of primary tumors results in sudden vascularization and growth of mets!
- This is due to loss of feedback inhibition from angiostatin and endostatin.
- Mets are free to stimulate angiogenesis.

### Angiogenesis Inhibitors

**FDA Approved**
- Avastin – Antibody to VEGF
  - Increased survival by 5 months in colorectal, GI perforation, wound rupture, high BP, kidney, heart

**Clinical Trials**
- Thalidomide – Blocks migration (Nitric Oxide effects)
- Nonvastat – Multi-functional (from Shark Cartilage)
- Angiostatin – Multi-functional
- Endostatin – Multi-functional

**Natural**
- Foods
  - Pomegranate juice, Red wine.
- Extracts
  - Green Tea, Horse Chestnut, Butcher’s broom
- Nutrients
  - Lipoic acid, vitamin A and D – 8 Vitamin C

**Vitamin C and Angiogenesis**

Cell Types studied by BCRI
- HUVEC (umbilical cord)
  - “Mature” endothelial cells from umbilical cords.
  - Grown in the presence of growth factors and heparin.
  - Form “Tubules” on Matrigel extracellular matrix material.
- Endothelial Progenitor Cells (EPC) are adult stem cells
  - Isolated from human peripheral blood mononuclear cells.
  - Grown on fibronectin with EGF and VEGF supplemented growth medium.
  - Form “Tubules” on extraMatrigel cellular matrix material.
**Vitamin C and Angiogenesis**

**Cell Type Characterization**
- Cells have characteristic surface markers.
- Fluorescence-labeled antibodies to these markers can be used to distinguish cell types.

**Endothelial Cell Markers**
- HUVEC (mature umbilical)
  - CD31
  - CD145
  - VEGFR-2
  - HLA-ABC
- EPC (adult stem cells)
  - CD34
  - VEGF-R2
  - CD31
  - CD105
  - CD90
  - Negative for CD133

**Assays Used to Study Vitamin C and Angiogenesis**

**Angiogenesis Assays**
- Matrigel “Tubule” formation.
- Aorta ring assay.
- Cell migration assays.
- Matrigel plug in vivo assay.

**Cellular Function Assays**
- Nitric Oxide (NO) production rates.
- ATP production rates.

**Vitamin C and Angiogenesis**

**Ascorbate and Tubule Formation**

**Aortic Ring Model**
Effect of Ascorbate (15 mM) on Vessel Sprouts

**Matrigel Plug Assay**
- Insert Matrigel plug under skin
- Control → untreated
- Treated: 400 mg/kg ascorbate
- Remove plug
- Detect and quantify vessel growth in histological sections

**Results of Three Experiments**

- Expt 1: 58%
- Expt 2: 55%
- Expt 3: 70%

**Endothelial Migration Assay**
- Grow Cells
- Scrape a Gap
- Measure Re-growth
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Vitamin C and Angiogenesis
Effects of Ascorbate on Endothelial Cells:
- Slight Decrease in ATP Production
- Decreases VE-adenin Expression and Nitric Oxide Production.

Summary of the Effect of IVC-Dosages of Vit. C on Angiogenesis
Vitamin C inhibits endothelial cell functions key to angiogenesis
- proliferation
- migration
- nitrous oxide production
without affecting viability of endothelial cells.

IV Ortho-dosing required for…
IVC Antiangiogenesis Effect
? IVC Redox generation of the hydroxyl radical ?
?? Biological Response Modification ??
??? Vitamin C Redox Synergy ???
What about Oral Ortho-dosing?

The Hoffer Cancer Regimen
In 1978, Dr. Abram Hoffer started a 15-year test of an ORAL ortho-dosing vitamin C redox regimen on 134 advanced cancer patients:
- Vitamin C – 12,000 mg (as high as 40,000 mg)
- Beta carotene – 30,000 IU
- B complex – B100
- Selenium – 600 mcg
- Vitamin E succinate – 300 IU
- Zinc – 60 mg

Mean Survival (mos.) of Cancer Pts. with Hoffer’s Regimen*

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>With Vitamins</th>
<th>Without Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>70</td>
<td>3.7</td>
</tr>
<tr>
<td>Uterus</td>
<td>99</td>
<td>4.0</td>
</tr>
<tr>
<td>Ovary</td>
<td>16</td>
<td>3.6</td>
</tr>
<tr>
<td>Lung</td>
<td>17</td>
<td>2.0</td>
</tr>
<tr>
<td>Pancreas</td>
<td>40</td>
<td>2.4</td>
</tr>
<tr>
<td>All types</td>
<td>45</td>
<td>2.6</td>
</tr>
</tbody>
</table>

* J of Orthomolecular Med 1990 and 1993

Oral ‘Ortho-dosing’ Redox
1. The frequency and level of dosing of oral C is a critical component of any redox synergy strategy
2. The Riordan IVC Protocol empirically suggests ‘off day’ gram dosing of vitamin C
3. With the addition of ortho-doses of alpha lipoic acid, vitamin K, selenium, and copper, it may be possible to induce hydroxyl formation with an oral C redox synergy strategy
4. Other antioxidants, such as vitamin E succinate, vitamin D₃, Co-Q-10, glutathione, and curcumin, may provide further synergistic benefits
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Redox Cycling – Lipoic Acid

```
\[ \text{Cu}^{2+} \rightarrow \text{OH}^\cdot + \text{H}_2\text{O}_2 \rightarrow \text{OH}^\cdot + \text{LASH} \rightarrow \text{Cu}^{2+} \]
```

Adding alpha lipoic acid to the ascorbic acid in cell culture shifted the dose response curve to the left.

Redox Cycling – Vit. K₃

```
\[ \text{Cu}^{2+} \rightarrow \text{OH}^\cdot + \text{H}_2\text{O}_2 \rightarrow \text{K}_3^{2e^\cdot} \rightarrow \text{DHK}_3 \rightarrow \text{excreted} \]
```

Vitamin K3 for Cancer

- March, 2008 study by Summa Health Systems
  - Apatone* granted orphan drug status by FDA
- A phase I/II study using Apatone at a dose of 5000 mg of vitamin C and 50 mg of vitamin K3
  - 17 subjects with end stage prostate cancer who had failed local treatment
    - "two successive rises in PSA post treatment"
  - Rise in PSA "velocity" decreased in 13/17
  - 15 continued Apatone past 14 months – 1 death
  *Also sold under the name "Prostay"

Reasons to Consider an Oral Ortho-dosing Regimen for Cancer Patients

1. Unavailability of IVC or medical provider of IVC
2. Expense of IVC (especially over the long run)
3. Poor veins/no port-a-cath/oncologist resistance
4. Prevention of “IVC Resistance”
   - maintains “oxidative pressure” between IVC infusions
5. Enhancement of Post-IVC serum C levels
6. Enhanced IVC effectiveness in high grade tumors
7. Long term maintenance strategy after successful IVC therapy and cancer remission

Utilize the Riordan IV-C Protocol
(with the following addendums)

- Ultra low glycemic/high phytonutrient diet
- Ortho-dosing Oral-C on the off-days from IV-C
- Ortho-dosing alpha lipoic acid (100 mg/gr of C)
- Ortho-dosing vitamin K3 (published doses)
- Ortho-dosing selenium (monitor for toxicity)
- Ortho-dosing vitamin D3 (monitor 25-OH-D)
- Ortho-dosing of select antioxidants
  (use published research and ortho-physician’s guidance)
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M.C. – Metastatic Breast Ca

- 61 y.o. WF
- Dx – stage II breast Ca at age 47, 4-positive nodes
  - ER positive, PR negative
  - Breast conserving surgery
  - Tamoxifen for 5 years
  - Letrozole started Nov '03
- Sept. '08 – pulm. nodules probable recurrent metastatic breast cancer
- Thoracic CT on 9-18-08
  - Pleural nodules found
  - 3.6 x 2.8 cm L apical nodule
  - 2.1 x 1.8 cm L ant. seg. Nodule
  - L pleural effusion (small)
- PET scan 9-18-08
  - Confirmatory of above
- MRI 9-18-08
  - No other primary found

M.C. – Appointments and Course

- Sept. 24, 2008 – Dr. GH
- Oct. 9, 2008 – Dr. RK
- Oct. 31, 2008 – Mayo’s
- Nov. 19, 2008 – Dr. GH
- Jan. 2, 2009 – Dr. RH
- Jan. 15, 2009 – Mayo’s
- Jan. 19 – Mar 09 – Mexico
- Mar 3 – Apr 09 – Coleamer
- Apr. 3, 2009 – Dr. RH

Intake & P - The Center
- Reviewed lab workup “poorly differentiated”
- “We have a situation that we cannot cure.”
- Increased IV C dosage to 75 gr 2x/wk
- Adrenal insufficiency – started cortef & oral C redox – 24gr/d
- “Your tumors have tripled in size and are inoperable.”
- Daily IV C, IV-H2O2, IV-EDTA
- Liposomal antioxidants started
  - 1 oz 3x/d = 10 gr C + 1.2 gr GSH etc
  - added R lipoyc acid – 300 mg TID

M.C. – Course of Vit. C Treatments

- 25 IVCs (75 gr. – 2x/wk)
  - Oct 10, ’08 to Jan 14, ’09
  - Jan 19, ’09 to Mar 03, ’09
  - Daily IV C, etc. in Mexico
  - After Mar 03, no further IV C due to loss of home nurse
- Oral Redox (vitamin C)
  - 8 grams 3x/d
  - Dec 11, 2008 – to date
- No bowel intolerance
- Add Liposomal Antioxidants
  - Start – Mar 10, 2009 to date
  - 1 oz 3x/d = total C = 28 gr/d

Post IVC levels
- Cal 127 mg/dl – Oct 6, 08 (15gr.)
- Cal 143 mg/dl – Oct 7, 08 (25gr.)
- Cal 245 mg/dl – Oct 8, 08 (50gr.)
- Cal 288 mg/dl – Oct 10, 08 (75gr.)
- Cal 287 mg/dl – Nov 19, 08 (75gr.)
- Cal 337 mg/dl – Jan 02, 09 (75gr.)

Plasma C levels
- Cal 1.3 mg/dl – Sept 24, 08
- Cal 1.4 mg/dl – Jan 02, 09
- Cal 0.0 mg/dl – Apr 03, 09

R.F. – Metastatic Prostate Cancer

- 81 y.o. WM
- Dx – prostate Ca (in 1996) at age 69
- Abnormal DRE
- PSA – 4.1
- Biopsy – adenocarcinoma
- Well differentiated single focus no Gleason score on path.
- DVT (Feb ’08)

Bone scan (10-22-1998)
- Negative
- Bone scan (07-02-2004)
- Negative
- Pelvic CT (7-25-2007)
  - Mets to R seminal vesel and sacrum
- Bone scan (8-01-2007)
  - 20 areas of radiotracer uptake, including spine, ribs, and large area of S1
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R.F.’s Highest PSA Readings by Year

R.F. – Treatments Through the Years

R.F.’s Clinical Status

• Continues to eat a very low glycemic diet
• Appetite is good (wt. recently up 2 lbs.)
• No pain, sleeps well
• Normal skin color
• With recent addition of 6 gr. vitamin C powder, oral C is up the 18 grams a day, no diarrhea
• May 2nd update:

Take Home Messages

• We can change cancer from a terminal disease to a chronic illness, to an “ortho-remission”
• The allopathic use of IVC is a crucial component of successful cancer therapy… “as an adjunctive Rx”
• The ortho-pathic use of IVC with synergistic ortho-dosing of oral adjunctive nutrients
  – engages the patient as a colearner
  – empowers the colearner to make and sustain dietary, and lifestyle changes to heal/control cancer
  – provides a scientifically proven biological, redox, and antiangiogenic basis for orthomolecular oncologic care

Parting Thoughts

Never go to a doctor whose office plants have died.
- Erma Bombeck

An orgasm a day keeps the doctor away.
- Mae West

126