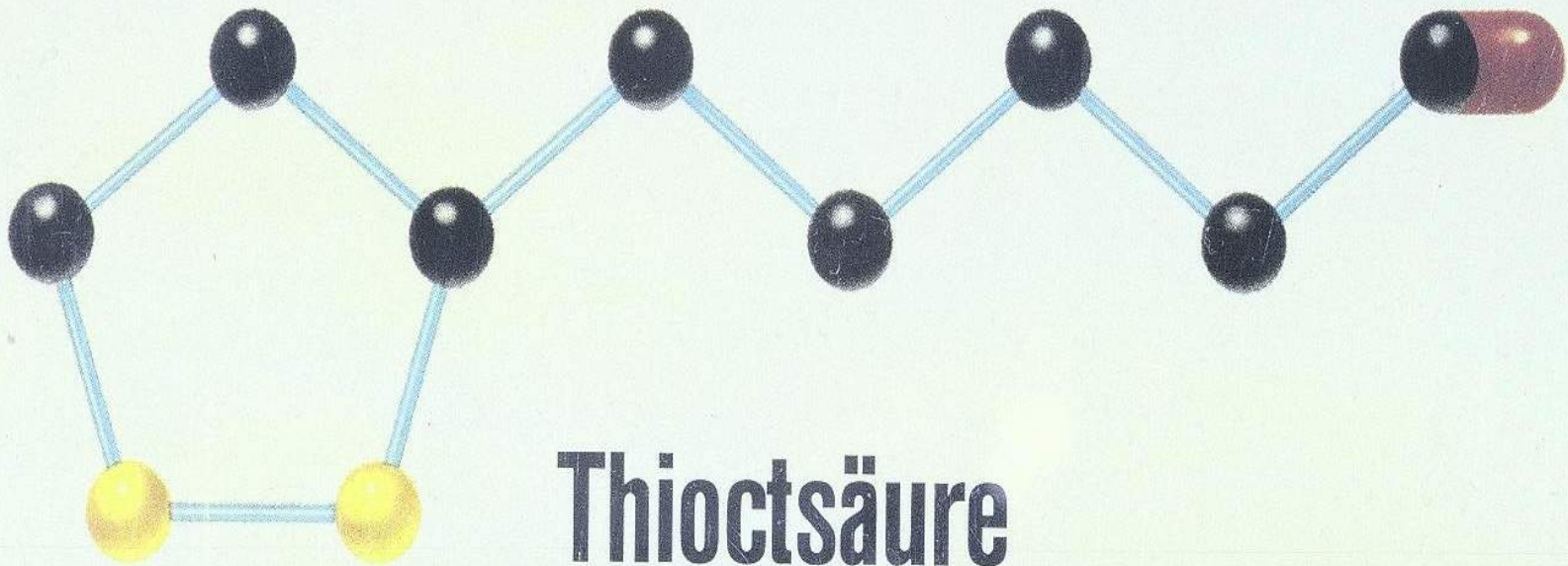


Toronto, 2015

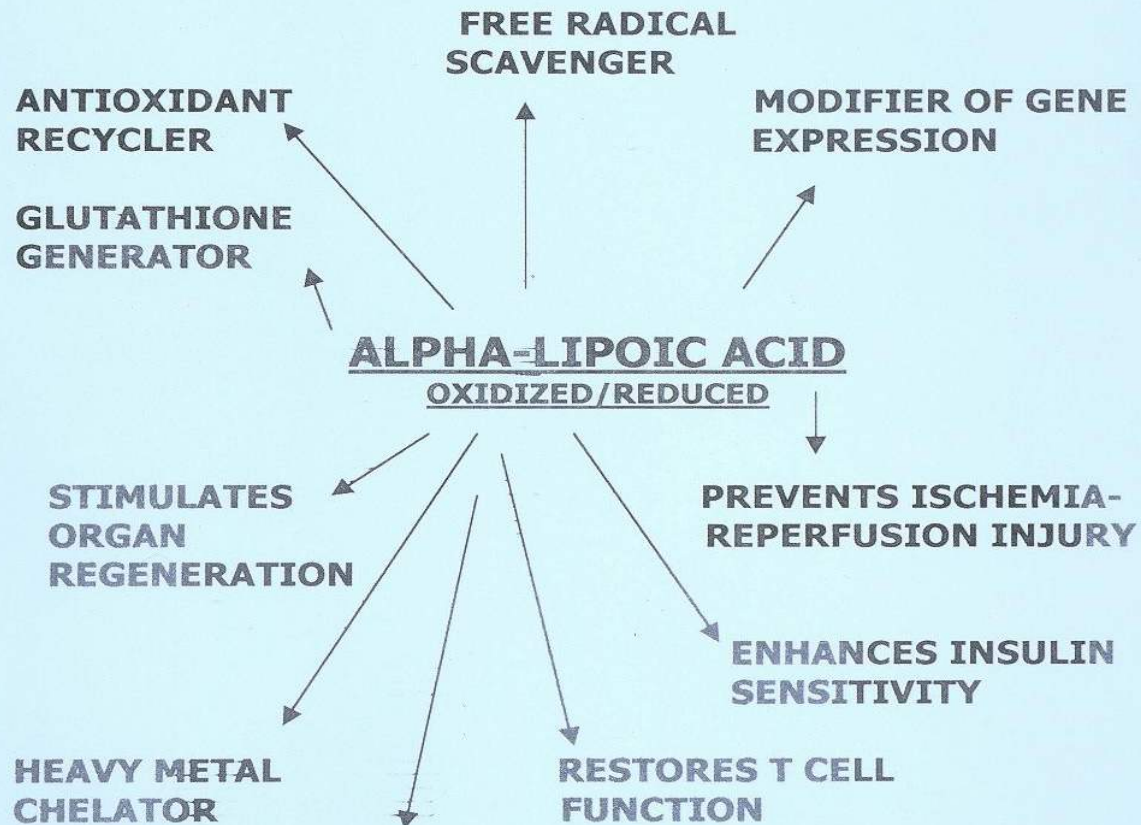
Alpha-Lipoic Acid's Effects on the Mitochondrion
and Human Disease Modification

Burton M. Berkson MD MS PhD
The Integrative Medical Center of NM
Las Cruces, NM 88011



Alpha-lipoic acid, (ALA), Thioctic Acid

ACTIONS OF ALA



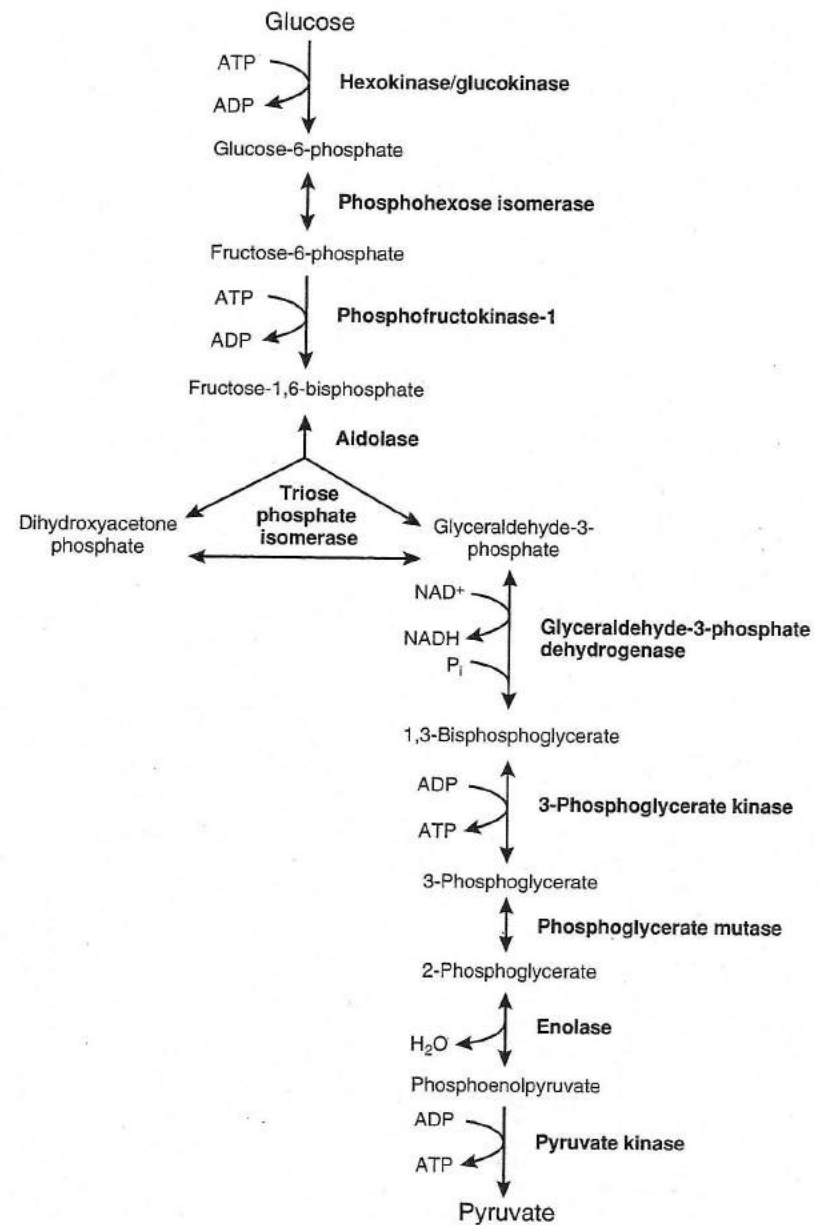
RATE LIMITING FACTOR/ FOOD TO ENERGY

Glycolysis: anaerobic

Occurs in the cytoplasm

Glucose is converted
to pyruvate

Cancer cells typically
just go this far and
convert pyruvate to
lactate even in the
presence of O₂.



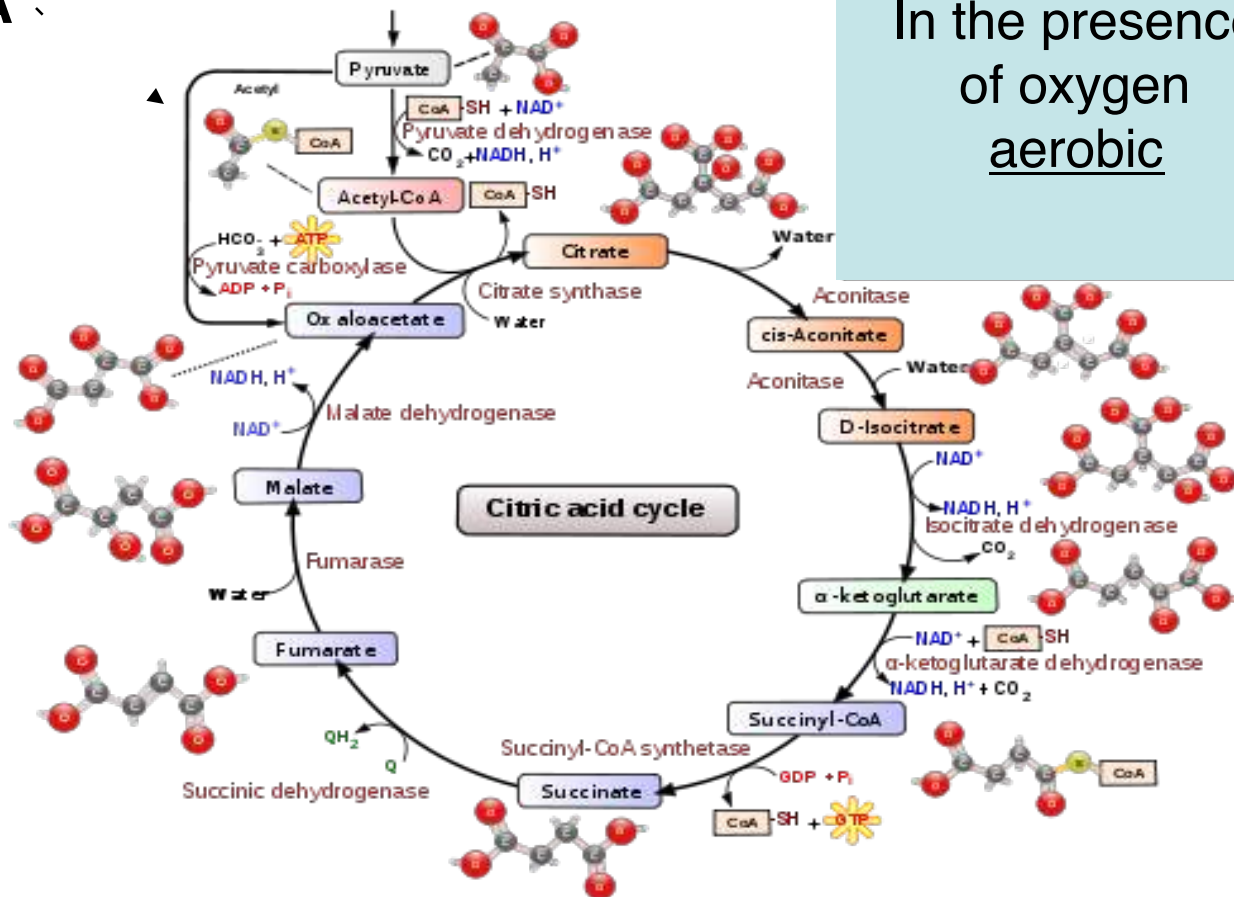
Tricarboxylic acid cycle

Glycolysis
anaerobic

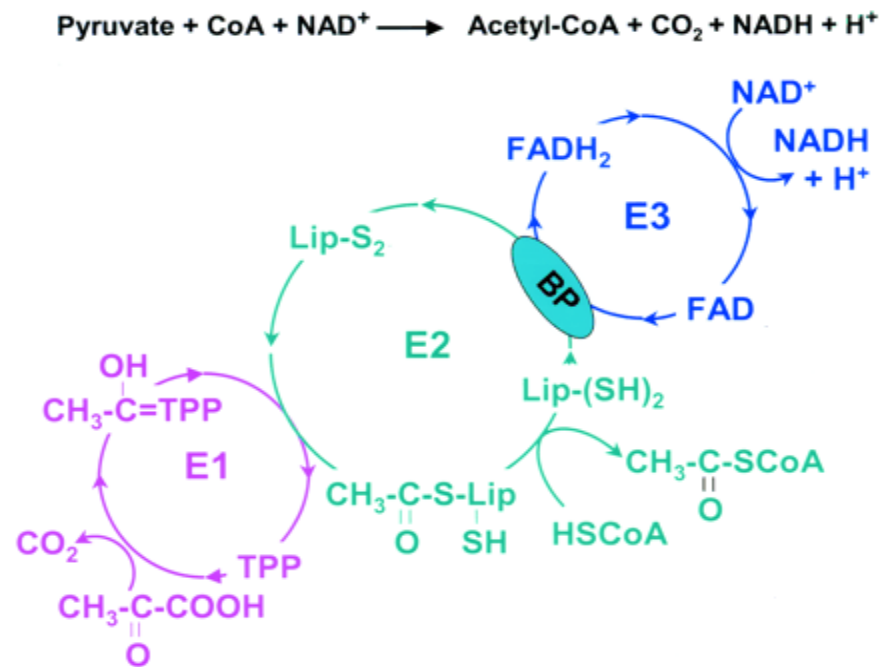
cycle

Occurs in the
mitochondrion
In the presence
of oxygen
aerobic

- ALA



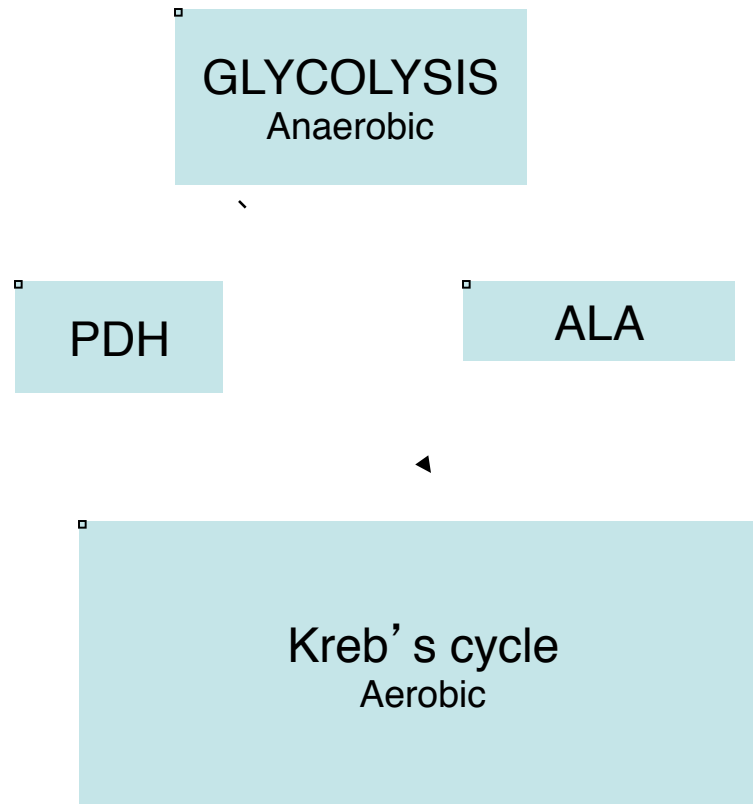
Alpha lipoic acid is fundamental,
for the conversion of food to energy.
It is my hypothesis that ALA is the rate-limiting agent in the
production of energy from food in aerobic cells



Pyruvate Dehydrogenase
Complex

ALA pushes anaerobic cell metabolism into aerobic cell metabolism

ALA accelerates this process and it's more than just a co-factor.



Korotchkina LG, Sidhu S, Patel MS.

Lipoic acid inhibits mammalian pyruvate dehydrogenase kinase.

Free Radic Res. 2004 Oct;38(10):1083-92.

Alpha Lipoic Acid inhibits
Pyruvate Dehydrogenase Kinase (PDK)
PDK inhibits the enzyme that converts
Pyruvate into Acetyl CoA

Pyruvate dehydrogenase
kinase inhibits Pyruvate
Dehydrogenase

More available Pyruvate
Dehydrogenase
results in increased
Pyruvate
being directed into the
Krebs Cycle
over the conversion of
Pyruvate to Lactate

ALPHA-LIPOIC ACID

FATS

CARBS

PROTEINS

Glycolysis

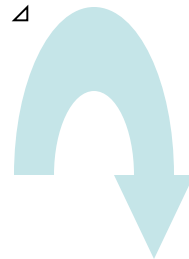
GLYCEROL

► PYRUVATE

Pyruvate Dehydrogenase
Complex PDH

ACETYL CO A

ALPHA-LIPOIC ACID



Since a young person
produces enormous amounts of ALA,

what happens when you feed a Thanksgiving dinner
to a 2 year old child;

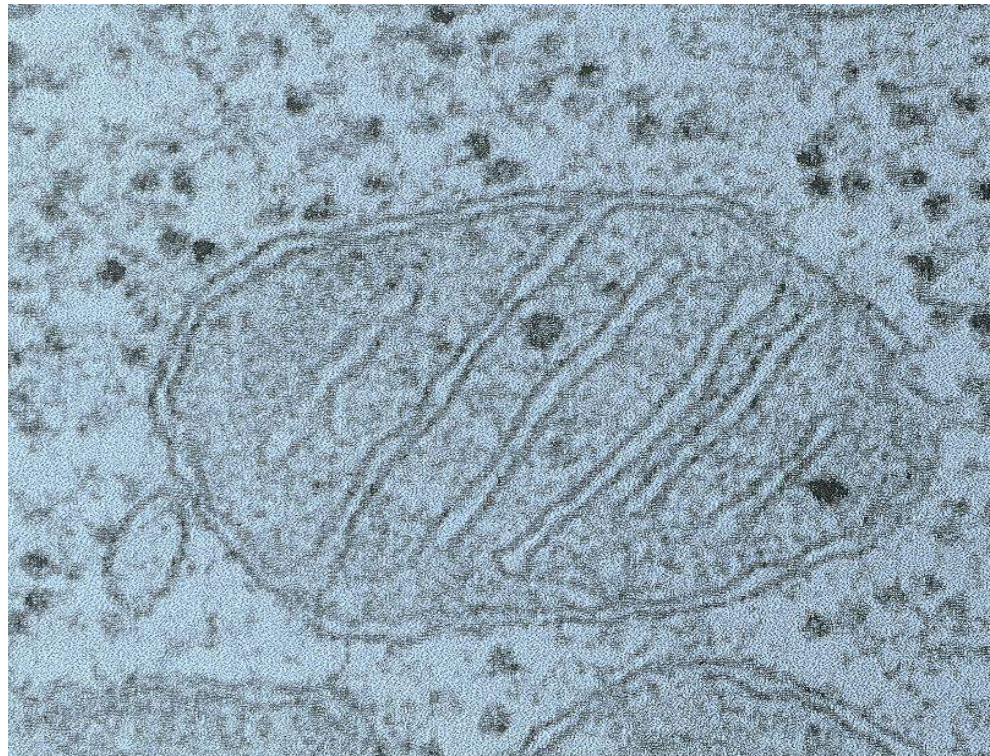
or a 80 year old man?

What if a mitochondrion receives too much ALA?
Lipoic acid LD50 Studies by Drs Vigil and Couch.

Couch RC, Vigil M. et al. A dose escalation toxicity study of
DL-6-8 thioctic acid (lipoic acid) in Rhesus monkeys. 1997.
Poster display. Annual Meeting Society of Toxicology.

- Following these studies I was asked to observe the necropsies and help with the electron microscopy work on the damaged tissues at NMSU.
- I observed extensive necrotic lesions in the liver, kidneys, heart, and the large muscles of the extremities.

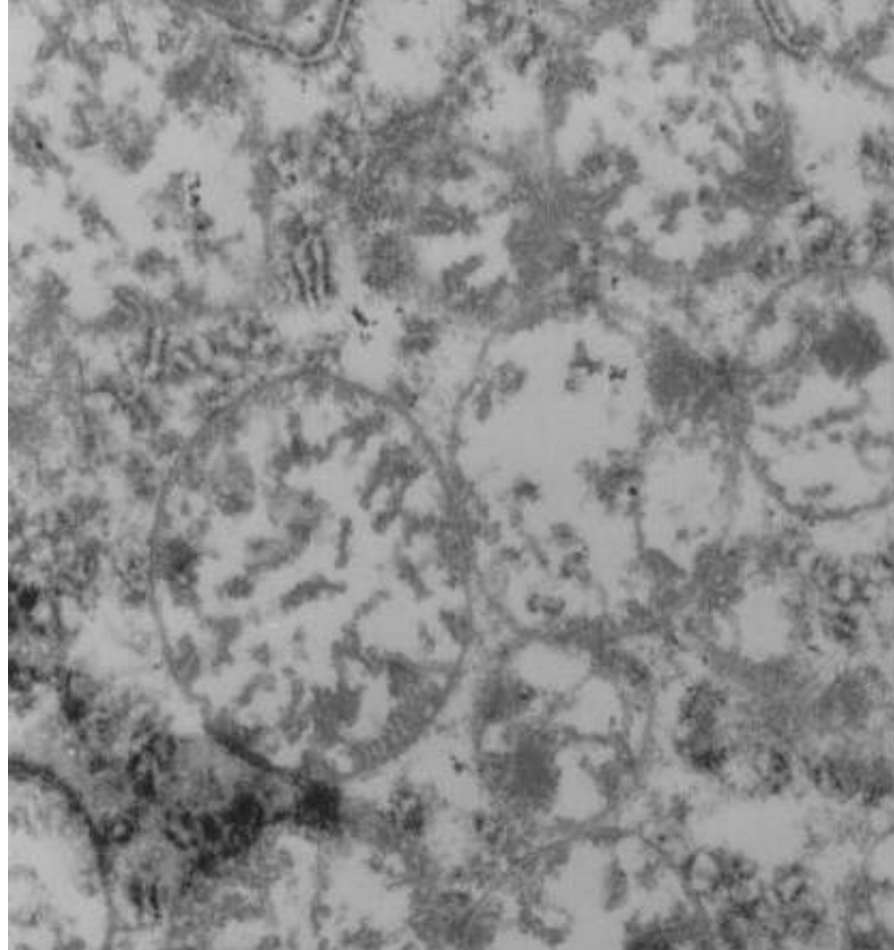
Healthy primate mitochondrion (hepatocyte)



Mitochondria from animals who had received excessively high doses of ALA became extremely edematous, and demonstrated a disruption of all the crucial structures.

These mitochondria did not exhibit the regular double membrane wall structure, but showed a coalescence of these structures with a deliquescence of membranes thus exhibiting a complete disruption of normal ultrastructure.

Primate hepatocyte mitochondria following a LD50
IV lipoic acid dose of
about 90mg/kg



LIVER MITOCHONDRIA SUFFERED SEVERE STRUCTURAL
DAMAGE BY EXTREMELY HIGH DOSES OF INTRAVENOUS
ALPHA LIPOIC ACID

Global Advances in Health and Medicine January,2014, volume 3
number 1

Michael Vigil MD

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Former Associate Professor, Chicago State University

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Associate Research Professor and Veterinary Pathologist Yerkes

Assistant Professor, Department of Pathology and Laboratory Medicine

Emory University School of Medicine

- In reality, much lower doses of IV lipoic acid may cause serious bouts of hypoglycemia and the doctor and nurse must all times watch carefully for possible problems.

With appropriate ALA levels, the mitochondrion functions normally.

If the mitochondrion does not obtain sufficient ALA, it suffers,
and the organism dies.

If the mitochondrion is supplied with excessive amounts of ALA, it accelerates aerobic respiration and the process runs ahead of the other necessary constituents.

The mitochondrion heats up, free radicals accumulate, and its membranous components break down.

Severe damage to the mitochondrion is first seen by gross swelling and then severe damage to the cristae and matrix material.

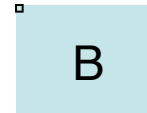
It is interesting to note that therapeutic doses of intravenous ALA helps a liver regenerate but extremely high doses of the same agent causes liver necrosis.

Of course, excessive and unreasonable amounts of any substance given intravenously can be lethal, including water and salt.

Does ALA helps regenerate livers?

1st large scale clinical trial with IV alpha-lipoic acid
at NIH.

(Bartter, Berkson, et. al. 1977-1980)



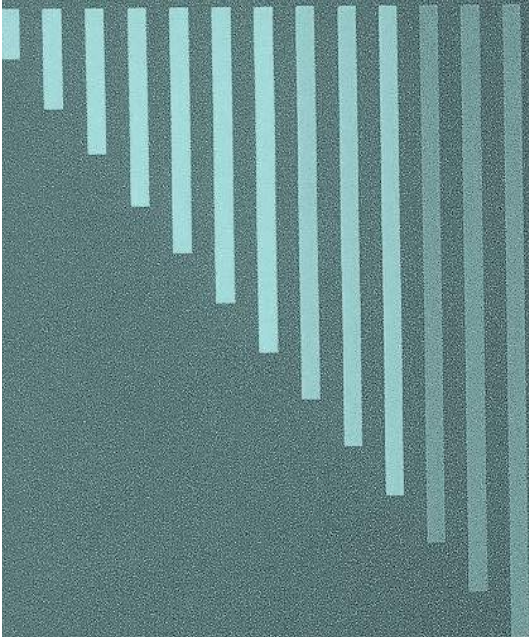


Bartter FC, Barry Rumack, and Berkson B 1978
As visiting scientists at the Max Planck Institute in Heidelberg

We reported in 3 publications that we treated 79 people with acute hepatic necrosis and 75 regenerated their livers with the just the administration of intravenous Alpha-lipoic acid.

I was appointed FDA principal investigator 1983. That lasted 23 years.





THIOCTIC ACID IN THE TREATMENT OF POISONING WITH ALPHA-AMANITIN

Bartter FC, Berkson B, Gallelli P, Hiranaka P 1980, Amanita Toxins and Poisoning, eds Faulstich et al, Verlag Gerhard Witzstrock, Baden-Baden, New York

B

Our first paper.

Should have been titled ALA reverses Acute Hepatic Necrosis

Amanita virosa

Destroying angel



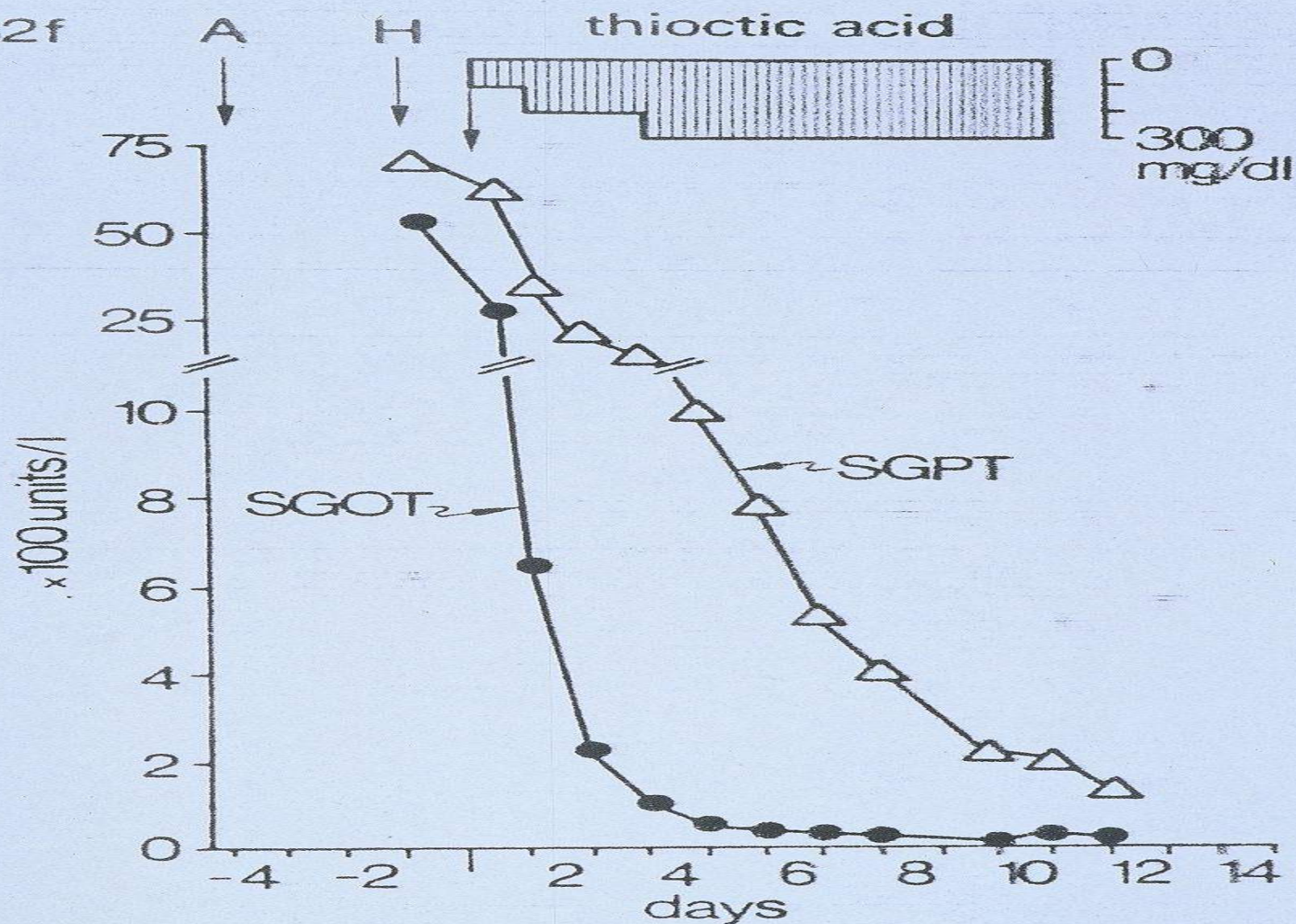


Fig. 2 SGOT and SGPT concentrations before and after the infusion of thioctic acid in an 82-year-old woman who had ingested amanita phalloides. *A* indicates time of Amanita ingestion. *H* indicates day of hospitalization

If IV ALA reverses acute liver disease, will it reverse chronic liver disease, for example hepatitis C?

CIRRHOTIC LIVER



GERMAN JOURNAL OF INTERNAL MEDICINE

ARTICLE

Berkson BM. A conservative triple antioxidant approach to the treatment of hepatitis C. Combination of alpha lipoic acid (thioctic acid), silymarin, and selenium. Med Klin (Munich). 1999 Oct 15;94 Suppl 3:84-9.

I took 3 cirrhotic hepatitis C patients in the process of liver transplant evaluation at University Hospital and administered ALA, silymarin and selenium (inhibition of replication).

The 3 recovered normal liver function within 6 months.

Most important laboratory tests for the evaluation
of liver disease.

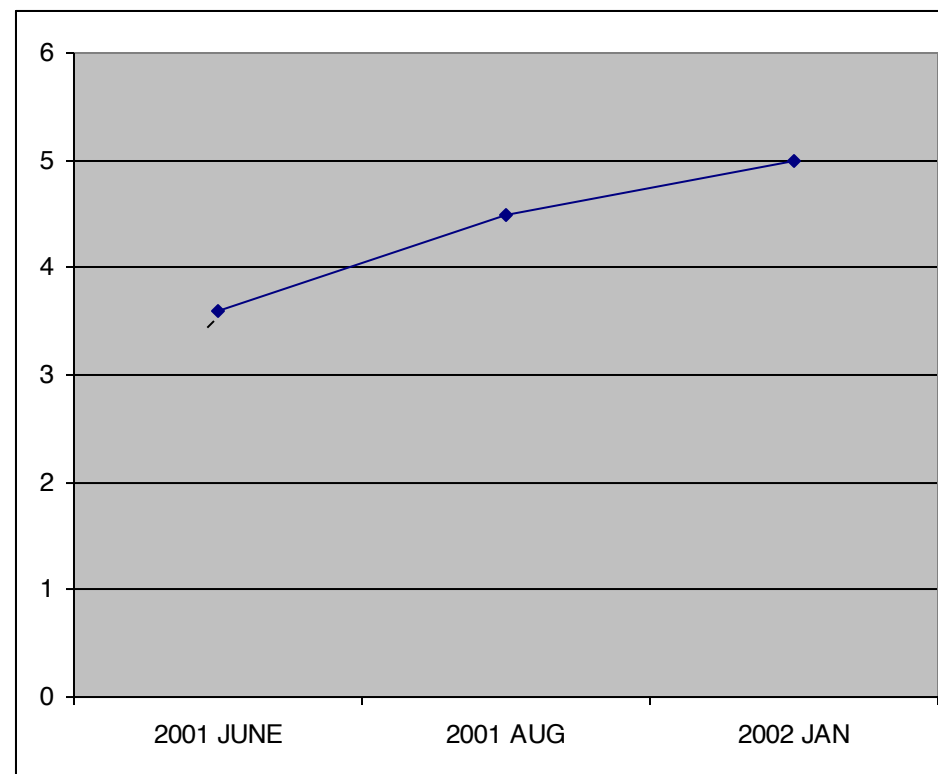
Albumin

Prothrombin Time

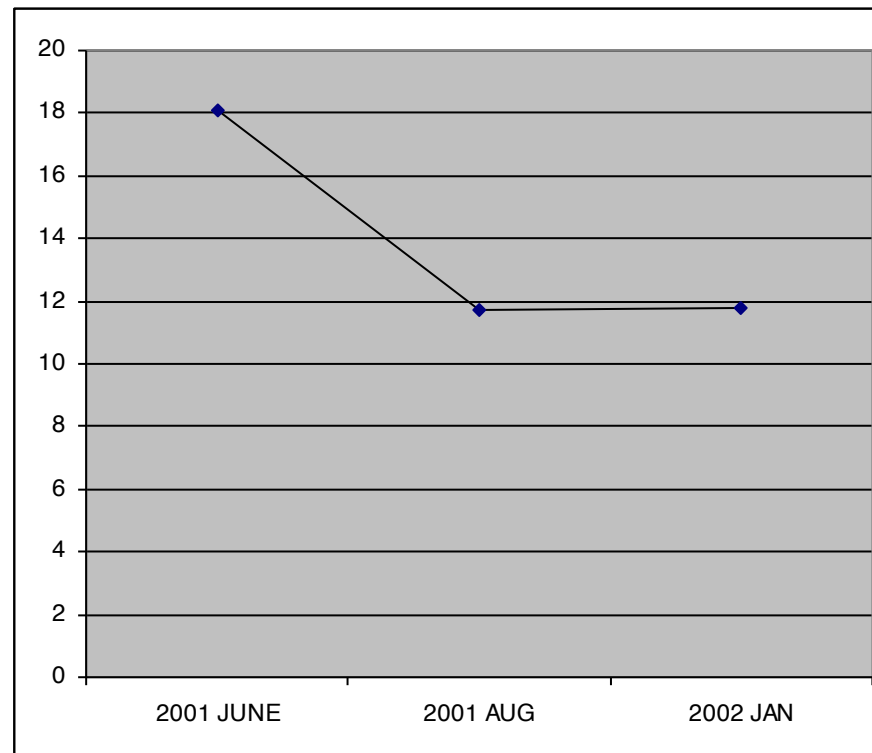
Platelet count

ALT

MR EA (hepatitis C) ALBUMIN LEVELS

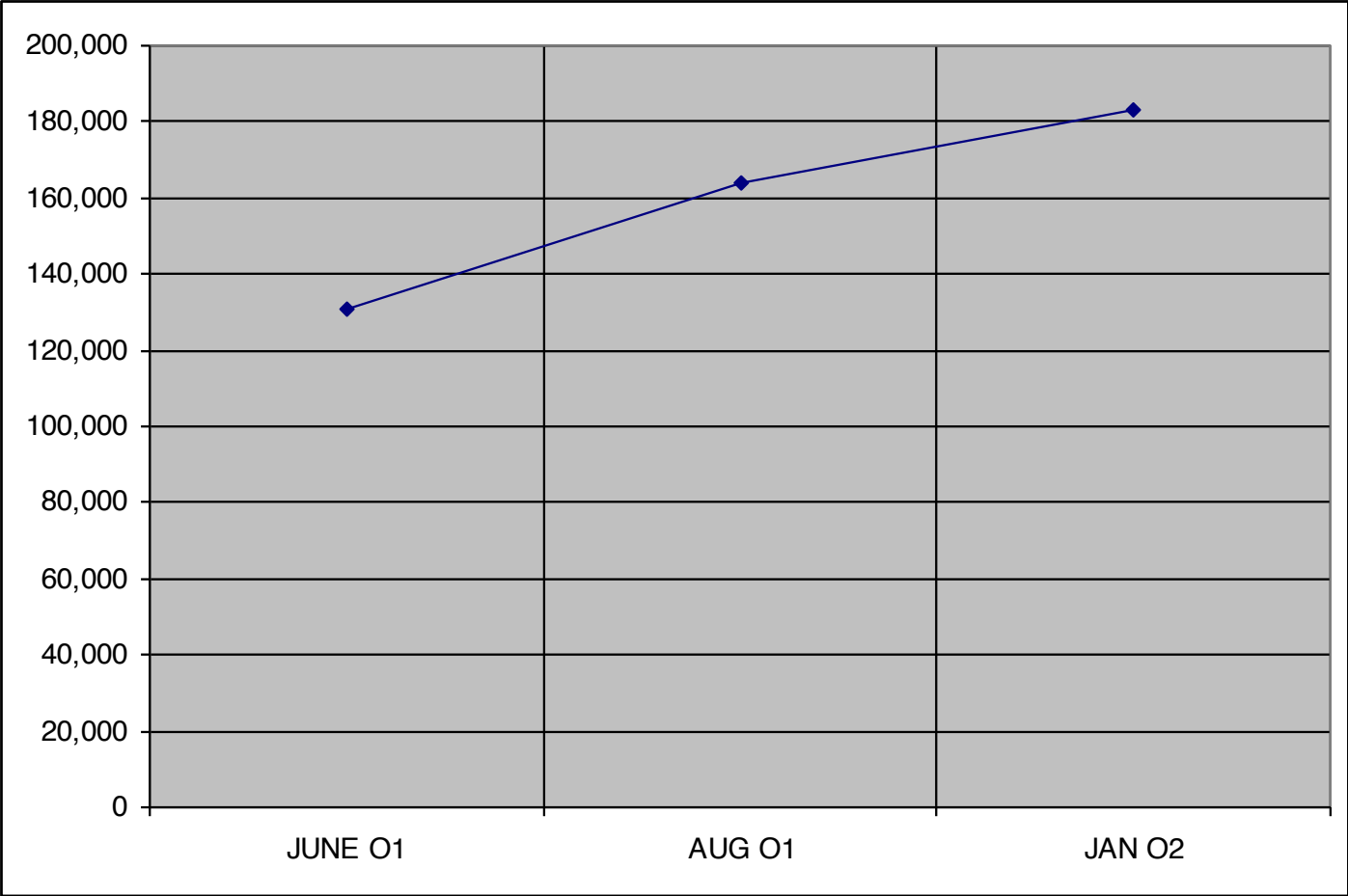


MR EA PROTIMES

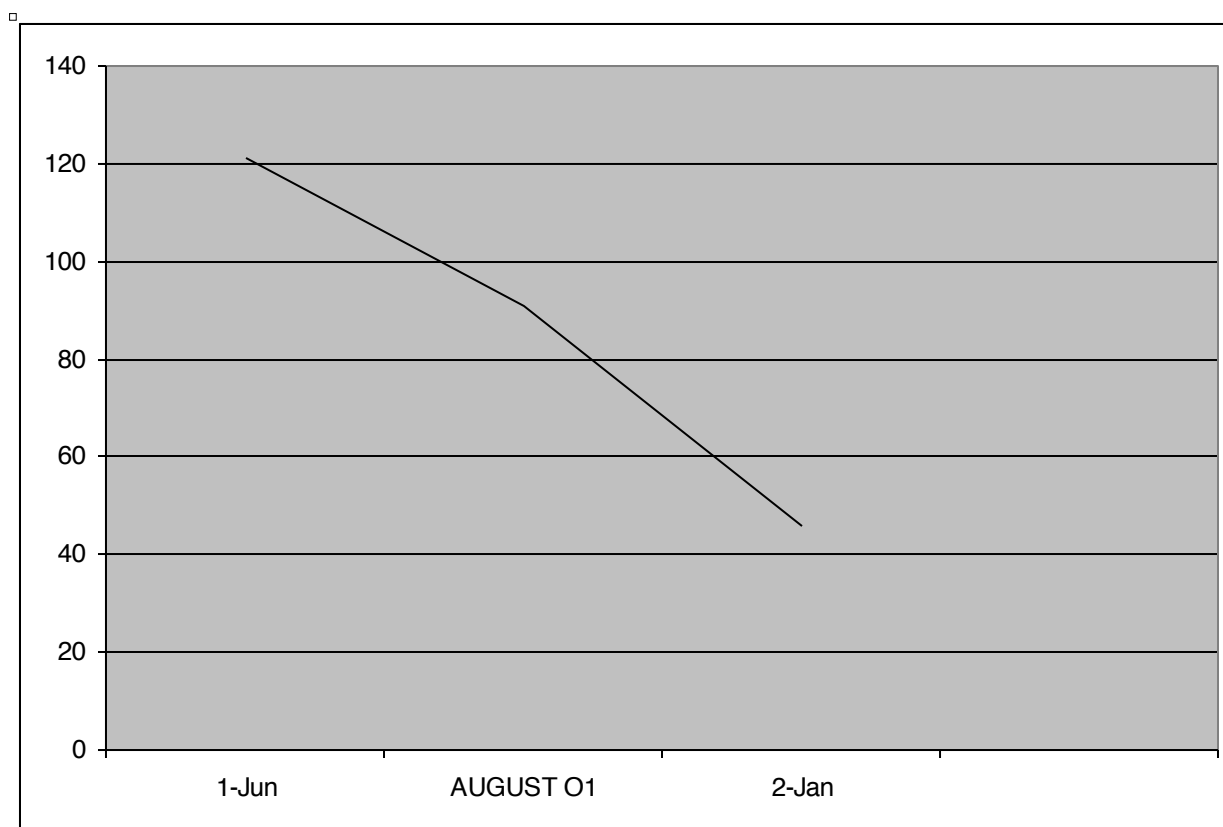


MR. EA-HEPATITIS C SECONDARY TO BLOOD TRANSFUSION

PLATELET COUNT



MR. EA ALT (SGPT) RESULTS



Conclusion of my 1999 paper.

The author offered a more conservative approach to the treatment of hepatitis C, that is exceedingly less expensive. One year of the triple ant-oxidant therapy described in this paper costs less than \$ 3,000, as compared to more than \$ 400,000 a year for liver transplant surgery.

Are there other diseases that ALA might help?

Smith AR, Shenvi SV, Widlansky M, et al. Curr Med Chem. 2004 May;11(9):1135-46.)

Lipoic acid is a potential therapy for chronic diseases associated with oxidative stress.

Most chronic diseases are associated with OS.

Baur, et al., Klin Wochenschr 69 (1991): 722-4.

Alpha lipoic acid has been shown to be an effective inhibitor of human immuno-deficiency virus (HIV-1) replication.

Lipoic Acid prevents ischemia-reperfusion injury

Panigrahi M, Sadguna Y, Shivakumar BR, Kolluri SV, Roy S, Packer L, Ravindranath V. *Brain Res.* 1996;717(1-2): 184-188. -

Alpha-Lipoic acid protects against ischemia reperfusion injury following cerebral ischemia.

Suh JH, Shigeno ET, Morrow JD, et al. Faseb J. 2001;15(3):700-706.

Oxidative stress in the aging rat heart is reversed by supplementation with alpha-lipoic acid.

What about ALA and diabetes?

Jacob S, Henriksen E, Schiemann A. et al.

**Enhancement of glucose disposal in patients with type 2 diabetes
by alpha-lipoic acid.**

Arzneimittel-Forschung 1995, 45(8):872-874.

Henriksen et al. published the first human study to show that ALA increases insulin stimulated glucose movement into the cell, and out of the blood stream, in diabetes.

Singh U, Jialal I Alpha-lipoic acid supplementation and diabetes.

Nutr.Rev. 2008 Nov;66(11):646-57.

**ALA improves insulin sensitivity, reduces oxidative stress,
and improves neuropathy in diabetic patients.**

Jacob S, Ruus P, Hermann R, Tritschler HJ, Maerker E, Renn W, Augustin HJ, Dietze GJ, Rett K. Free Radic Biol Med. 1999;27:309-14.

Administration of alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial.

Tankova T, Cherninkova S, and Koev D.
Treatment for diabetic neuropathy with IV alpha-lipoic acid.
Int J Clin Pract. 2005 Jun;59(6):645-50.

This study demonstrated that alpha-lipoic acid is an effective treatment for peripheral and autonomic diabetic neuropathy and also diabetic neuropathy of the cranial nerves leading to full recovery of the patients.

At the Integrative Medical Center of New Mexico, we treat diabetic neuropathies with IV ALA every day.

What about ALA and cancer?

Cancer cells hate oxygen.

Warburg O. The chemical constitution of respiration ferment. Science. 1928;68:437–443.

Science.68.1767.437.

Thomas Seyfried
Cancer As a Metabolic Disease
(Wiley, 2012)

"All hallmarks of cancer including the Warburg effect can be linked to impaired respiration and energy metabolism," These are "downstream effects of damaged mitochondrial function."

Wenzel U, Nickel A, and Daniel H.

.Alpha-Lipoic acid induces apoptosis in human colon cancer cells by increasing mitochondrial respiration which results in O₂-*-generation.

Apoptosis. 2005 Mar;10(2):359-68

This study provided evidence that ALA and its reduced form can induce cancer cell death by a prooxidant mechanism that is initiated by an increased uptake of oxygen into the mitochondrion.

Shi DY, Liu HL, Stern JS, Yu PZ, Liu SL.
FEBS Lett. 2008 May 28;582(12):1667-71.

Alpha-lipoic acid induces apoptosis and necrosis in
hepatocellular carcinoma cells.

B

Kisurina-Evgen'eva OP, Onishchenko GE.

Alpha-lipoic acid triggers elimination of cells with abnormal nuclei in human carcinoma epidermoid cell line
Tsitologiya. 2010;52(3):225-34.

Alpha-lipoic acid not only triggered apoptosis of carcinoma cells, but it also activated the mechanism of elimination of other cells with abnormal chromosome number.

Zachar Z, Marecek J, Maturo C, et al.
ALA disrupts cancer cell mitochondrial metabolism and is a potent
anticancer agent in vivo
J Mol Med (Berl). 2011 Nov;89(11):1137-48. Epub 2011 Jul 19.

Lipoic Acid causes disruption of tumor metabolism
and this is followed by cell death by multiple,
pathways, including apoptosis and necrosis.

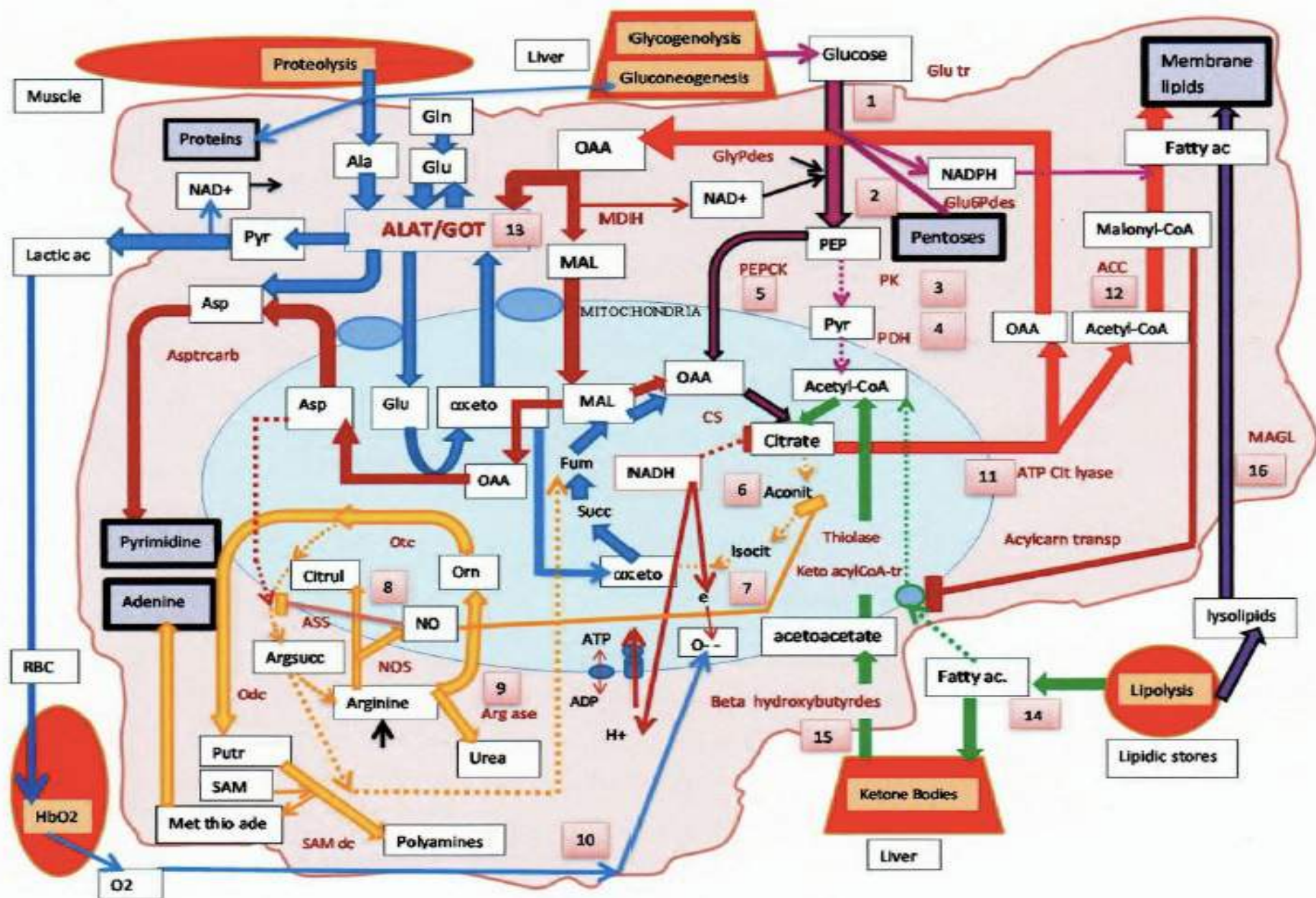
Na MH, Seo EY, Kim WK Nutr Res Pract. 2009 Winter;3(4):265-71.

Alpha-lipoic acid stimulates apoptosis in human breast cancer cells.

and

Choi SY, Yu JH, Kim H. Ann N Y Acad Sci. 2009 Aug;1171:149-55.

Alpha-lipoic acid induces apoptosis of lung cancer cells.



From Cancer metabolic plan from Signaling And Metabolism In Cancer,
Maurice Israël, Cancer Therapy, 2014

Non-Standard Cancer Protocol at IMCNM

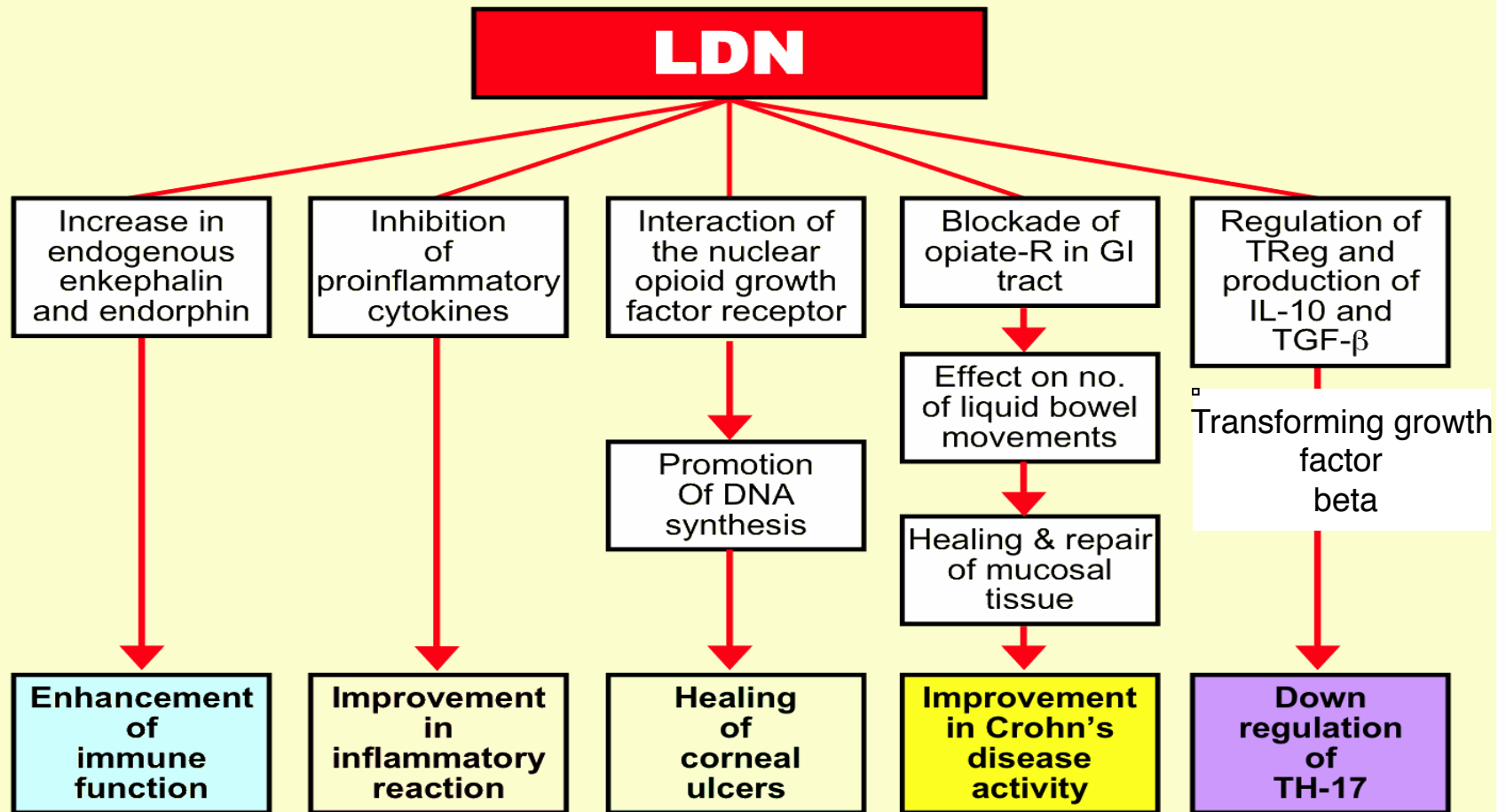
- Intravenous Alpha Lipoic Acid (ALA) (Bartter and Berkson).
- Intravenous Vitamin C.
- Low Dose Naltrexone (LDN) (after Zagon and Bihari.)
- Hydroxycitrate (HCA) (after Schwartz L.).
- Healthy diet and life style.
- Supplements (artemesinin, curcumin, etc)
- Prescription drugs (metformin, xanax, cimetidine, etc.)

Low Dose Naltrexone (LDN)

- 1.5 to 4.5 mg. LDN at hs
- Fools the brain. Not enough endogenous opiates in blood stream.
- In AM, flood of endogenous opiates released.
- At least one of the opiates, **met-enkephalin** binds to cancer cell receptors and promotes apoptosis.

Several papers by Ian Zagon and associates.

MECHANISM OF ACTION OF LDN



From LDN website

➤ Inflammation

T helper 17 cell (Th17) is a type of T helper cells that produce interleukin 17 (IL 17).

These cells produce tissue injury by inflammatory processes Crohn's disease, juvenile diabetes, MS, rheumatoid arthritis, SLE, etc.

Normally, Th17 cells provide epithelial and mucosal anti-microbial immunity by producing interleukin 22, etc. which stimulates epithelial cells to produce inflammatory proteins to kill microbes.

Berkson BM, Rubin DM, and Berkson AJ
Integrative Cancer Therapies
Volume 5, Number 1, March 2006

“The long-term survival of a patient with
pancreatic cancer and metastases to the liver”

We published the first human study
that demonstrated the therapeutic
effects of ALA combined with LDN for
cancer

Berkson BM, Rubin DM, Berkson AJ.
Integr Cancer Ther. 2007 Sep;6(3):293-6.

Reversal of signs and symptoms of a
B-cell lymphoma
in a patient using low-dose naltrexone.
(Patient was on IV ALA for 2 weeks)

Burton M. Berkson, Daniel M. Rubin, and Arthur J. Berkson
Integr Cancer Ther. 2009 Mar;5(1):83-9.

Revisiting the ALA/N (α -Lipoic Acid/Low-Dose
Naltrexone) Protocol for People With Metastatic
Pancreatic Cancer:
A Report of 3 New Cases

Schwartz L, Guais A, Israël M, et al.
Invest New Drugs. 2013 Apr;31(2):256-64. doi: 10.1007/
s10637-012-9849-z. Epub 2012 Jul 14.

Tumor regression with a combination of drugs
interfering with the tumor metabolism: efficacy of
hydroxycitrate, lipoic acid etc.

He added hydroxycitrate to our protocol.

Schwartz L., Buhler L, Icard P, Lincet H, Steyaert J.
Metabolic Treatment of Cancer, Anticancer Research
2014

The metabolic effects of ALA/HCA allows the
reprogramming of cancer cells into oxidative
aerobic metabolism
rather than anaerobic metabolism.

This ultimately should limit the availability of compounds
necessary
for the growth of cancer.

Alpha Lipoic Acid and Hydroxycitrate target at least
two major
Enzymes in the metabolism of glucose.

Pyruvate Dehydrogenase Kinase
and
ATP Citrate Lyase

Hydroxycitric acid (hydroxycitrate)

HCA also inhibits pancreatic alpha-amylase (breaks down starch and glycogen) and intestinal alpha-glucosidase (breaks down starch into glucose), leading to a reduction in carbohydrate metabolism.

Studies of HCA have produced results that indicate a potential for modulation of lipid and carbohydrate metabolism.

Hydroxycitrate (HCA) also inhibits ATP Citrate Lyase
(ACL)
which limits the conversion of cytoplasmic
Citrate into Acetyl CoA available
for the synthesis of Lipids and aerobic carbohydrate
metabolism.

▪ ATP citrate lyase



Jmol

Alpha Lipoic Acid (ALA) inhibits
Pyruvate Dehydrogenase Kinase (PDK)
(the enzyme that stops Pyruvate Dehydrogenase)

More available Pyruvate Dehydrogenase (PDH),
results in the increased Pyruvate
Being directed into the Krebs Cycle
over the conversion of Pyruvate to Lactate

Mrs. MC

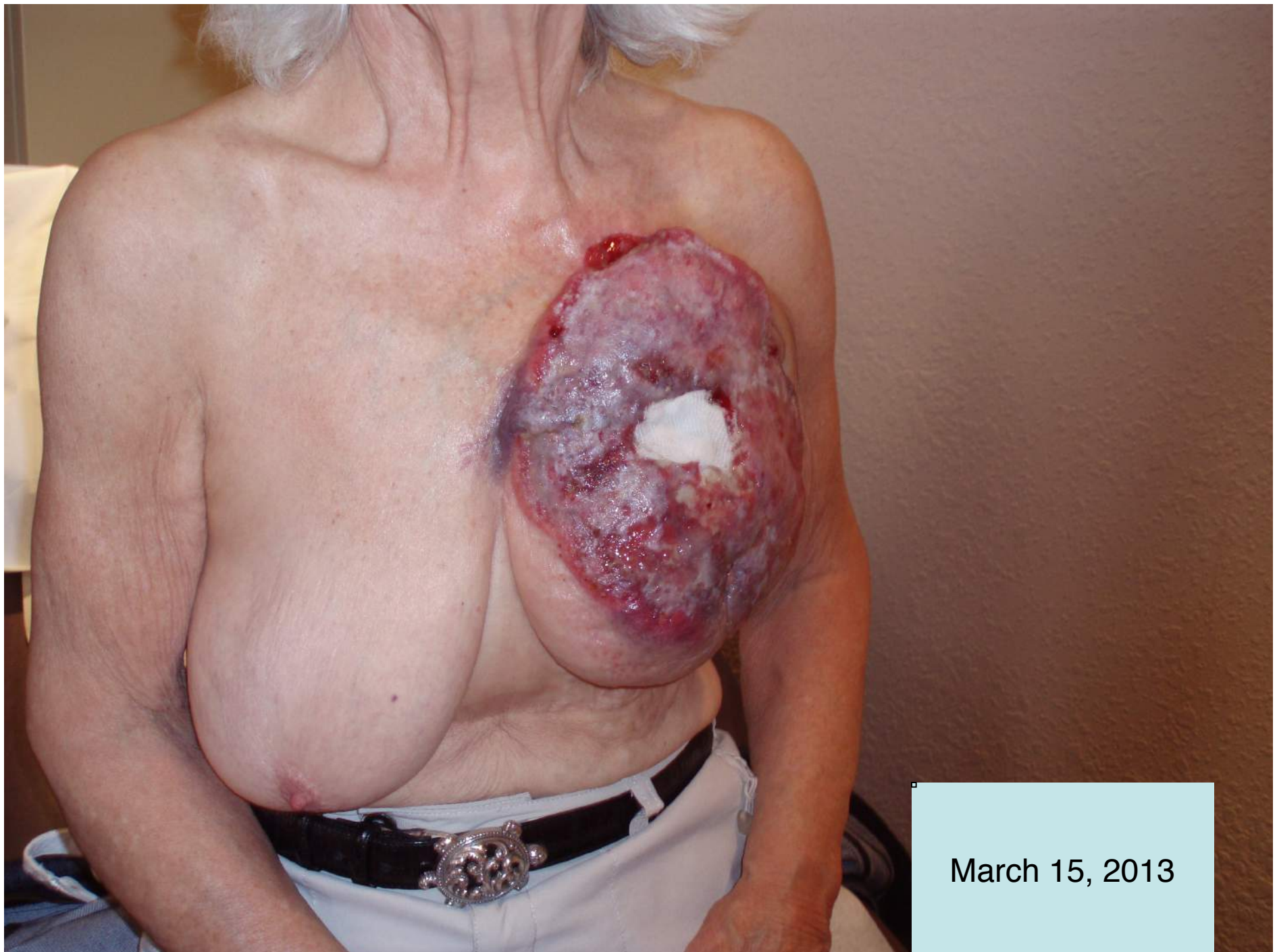
68 yo woman with breast cancer.

Initially refused Surgery, Chemotherapy, and Radiation.

Pathology-Invasive ductal adenocarcinoma Nottingham
grade 2/3, Estrogen +

Progesterone receptor -, pagetoid spread to skin

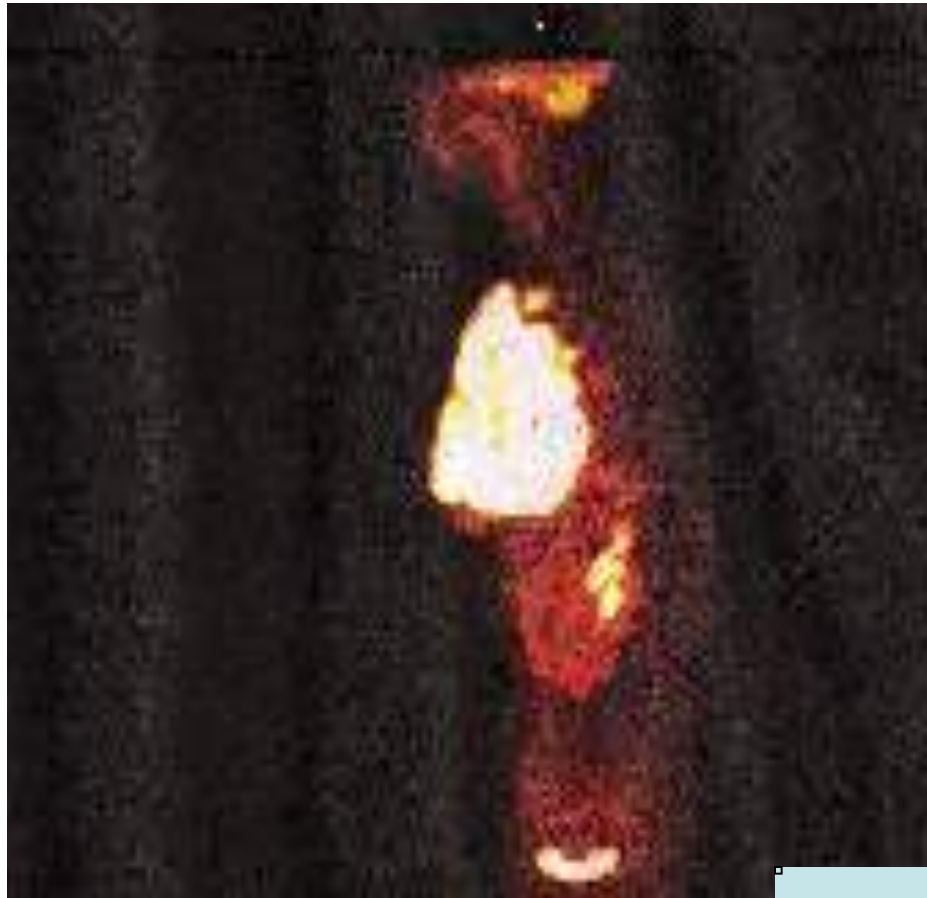
Metastatic to L axilla lymph nodes



March 15, 2013



March 15, 2013



Pet scan
March 20, 2013



Early June, 2013

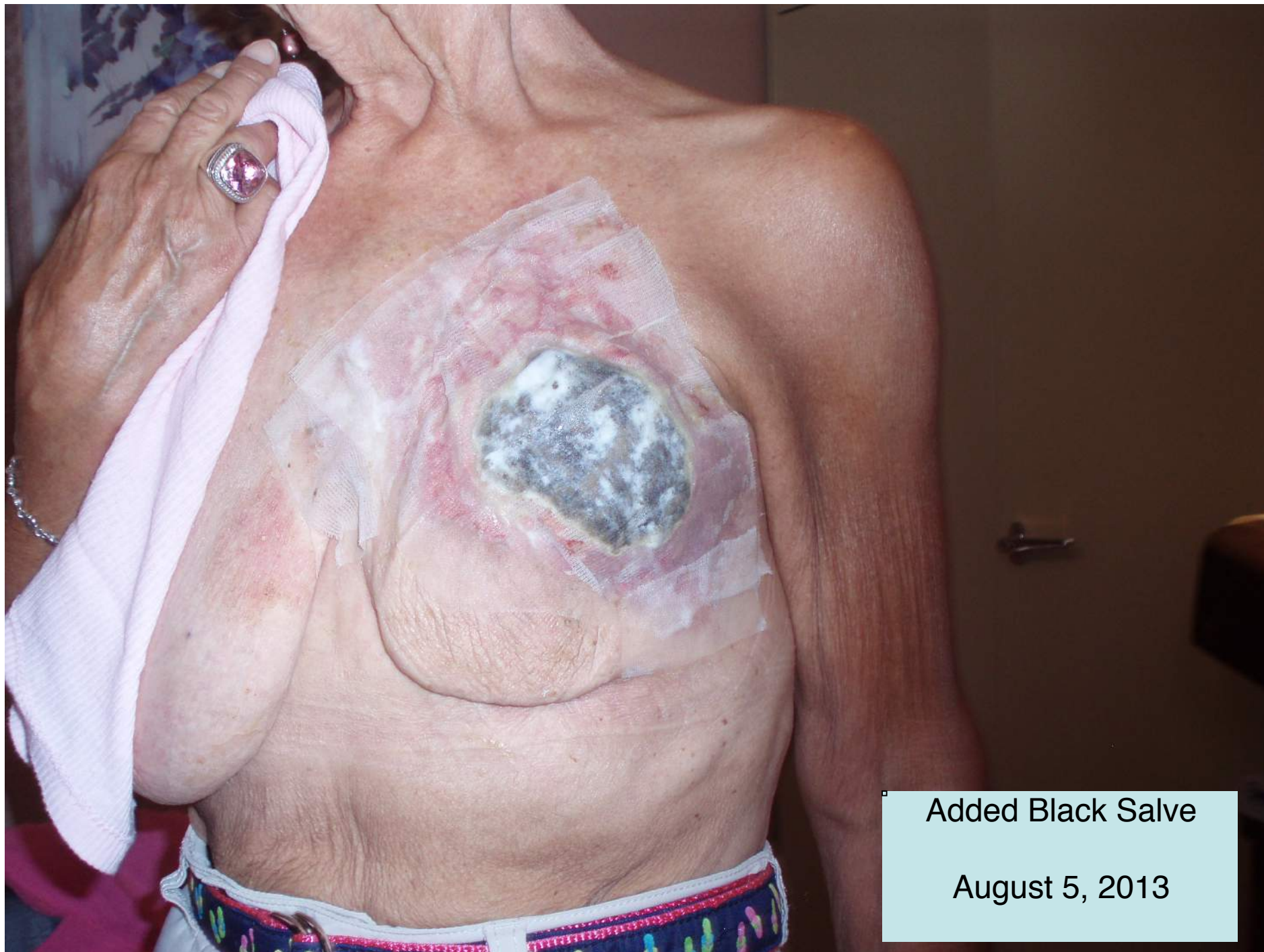
Ca 27.29--60...39
Ca 15.3—27.5...19.6

Visit to oncologist Late June 2013

- I suggested that Mrs. MC see a oncologist. She took my advice and tried taxol and herceptin for less than 3 weeks, became very ill, lost hair etc, and stopped conventional tx.



July, 2013



Added Black Salve

August 5, 2013





August 14, 2013



August 14, 2013

May 14, 2013----September 23, 2013

- Ca 27.29---60---39.5---16---11.5
- Ca 15.3---27.5---19.6---7.3

“The long-term survival of a patient with pancreatic cancer and metastases to the liver”

Berkson BM, Rubin DM, and Berkson AJ
Integrative Cancer Therapies
Volume 5, Number 1, March 2006

Berkson and associates published the first
human study that demonstrated the
therapeutic effects of ALA combined with LDN
for cancer

FIGURE ONE
OCTOBER 8, 2002

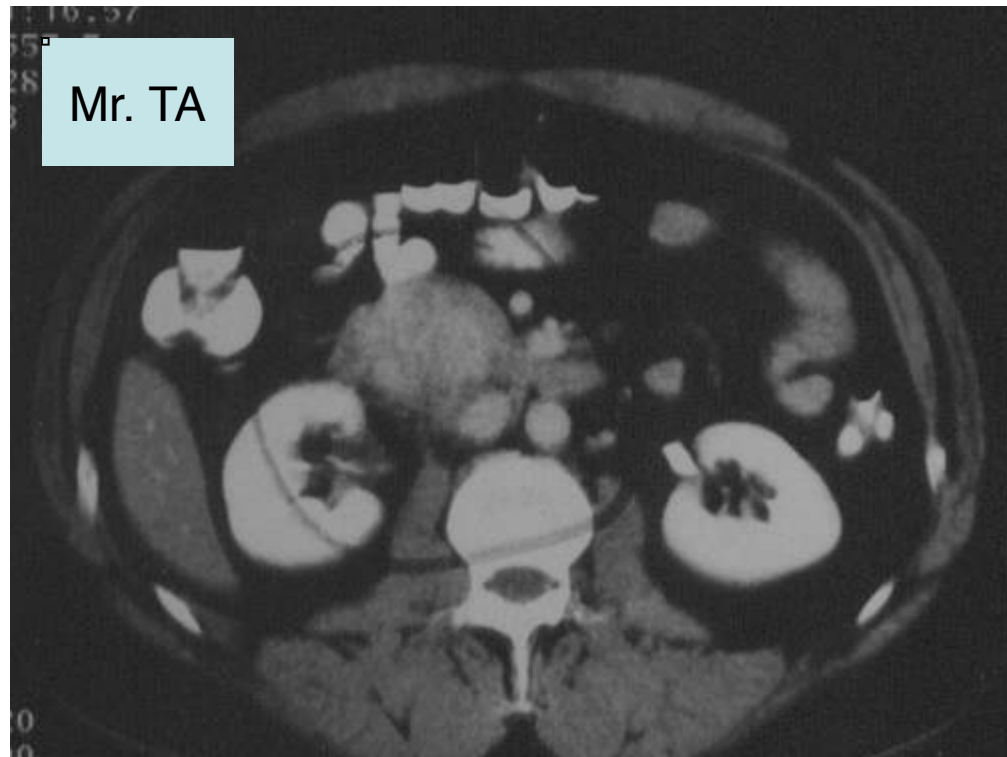


FIGURE 2
OCTOBER 8, 2002



Given no hope by MD Anderson

FIGURE 11
FEBRUARY, 2006

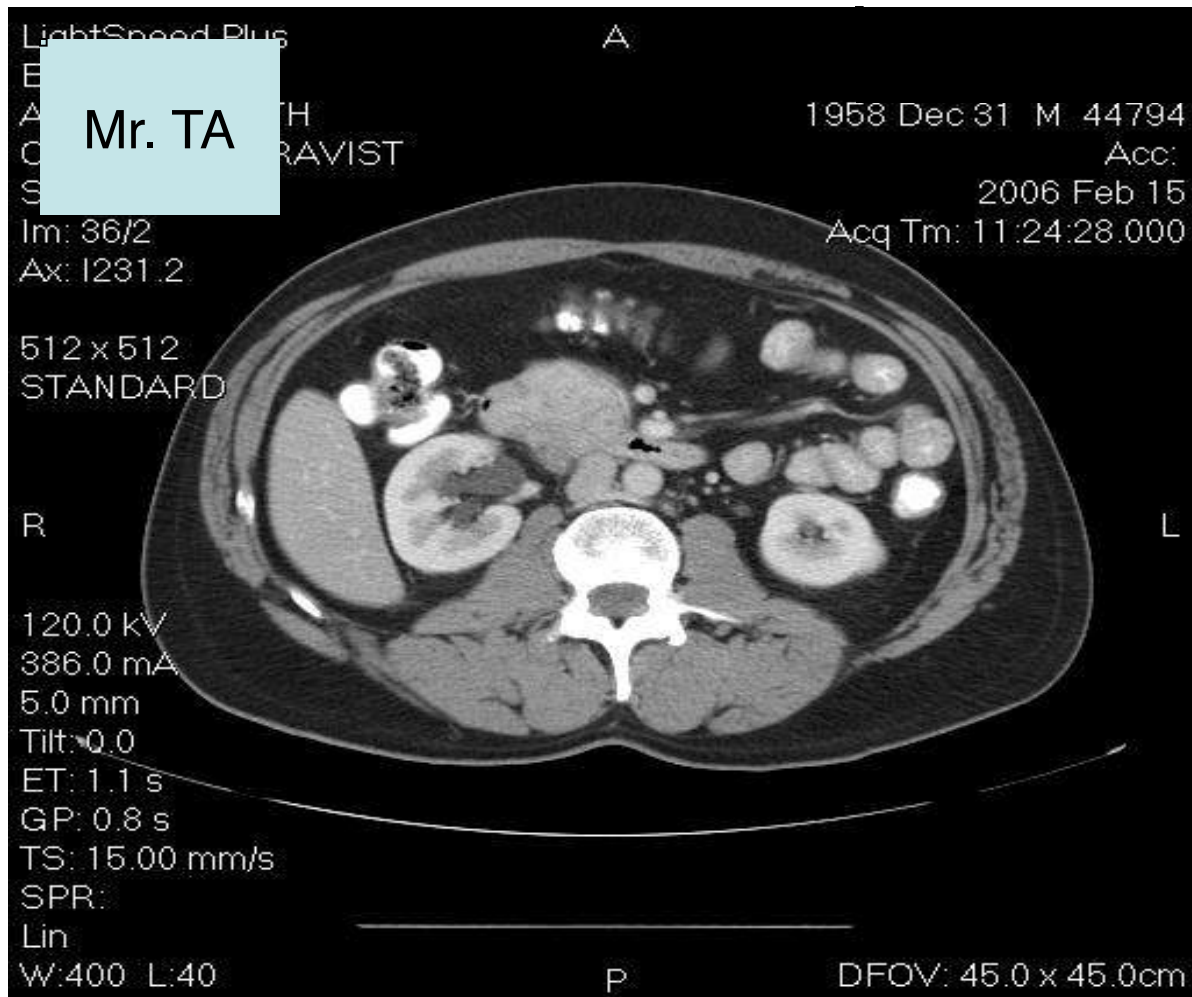


FIGURE 12
FEBRUARY, 2006

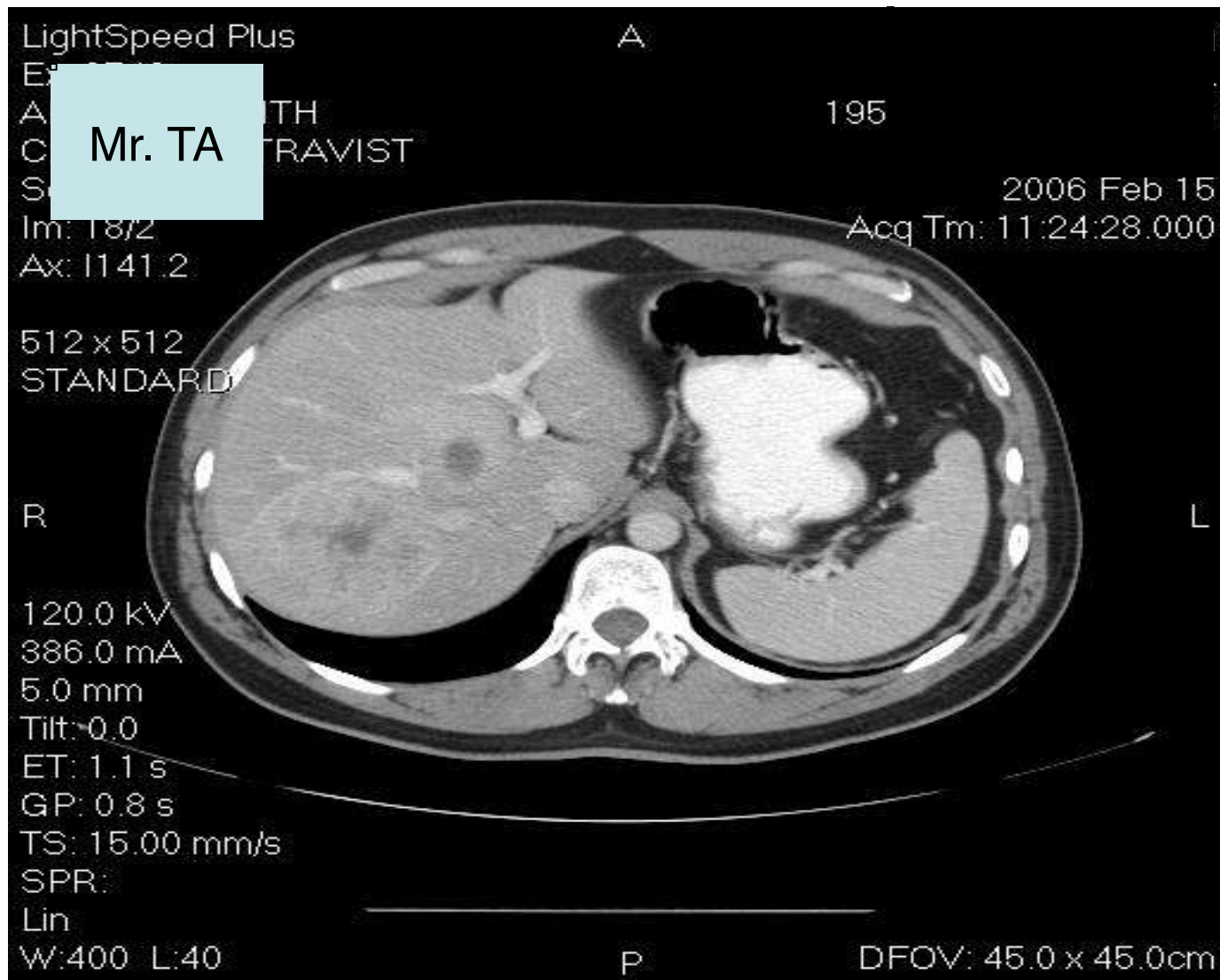


FIGURE 13
AUGUST 2008

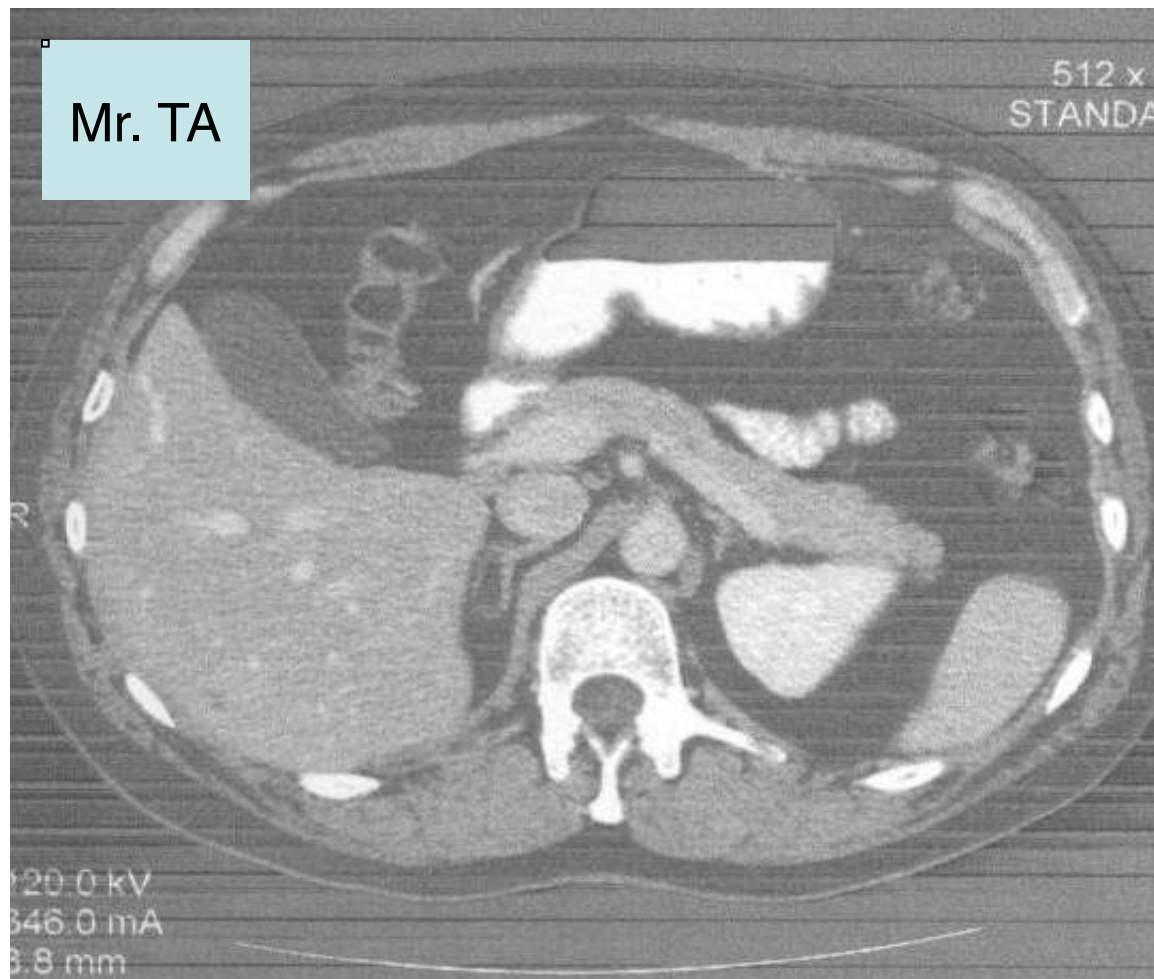


FIGURE 14
AUGUST 2008



Burton M. Berkson, Daniel M. Rubin, and Arthur J. Berkson
Integr Cancer Ther. 2009 Mar;5(1):83-9.

**Revisiting the ALA/N (α -Lipoic Acid/Low-Dose Naltrexone)
Protocol for People With Metastatic
Pancreatic Cancer:
A Report of 3 New Cases**

Adeno-
Carcinoma
Pancreas

Pet Scan
JANUARY 06
Mrs JK



Pet Scan
JUNE 2006
Mrs. JK



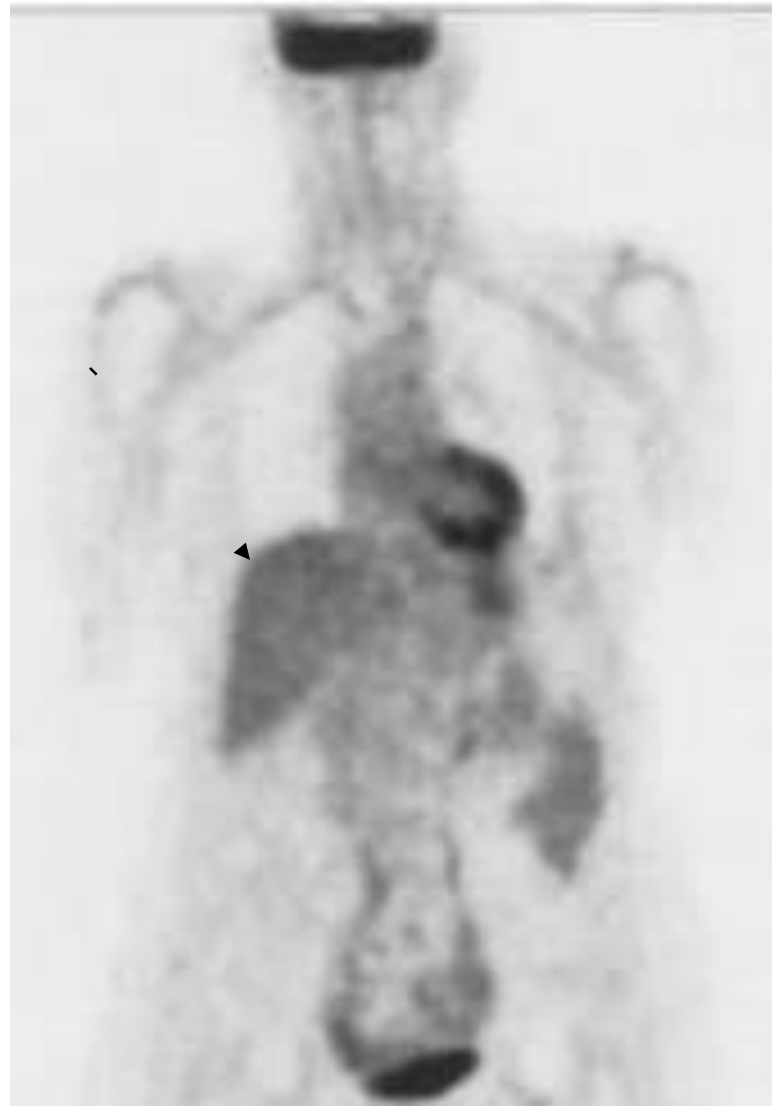
Hepatocellular Carcinoma following
Hepatitis C

Mrs. JAL
60 year old RN

Mrs JAL October 2006



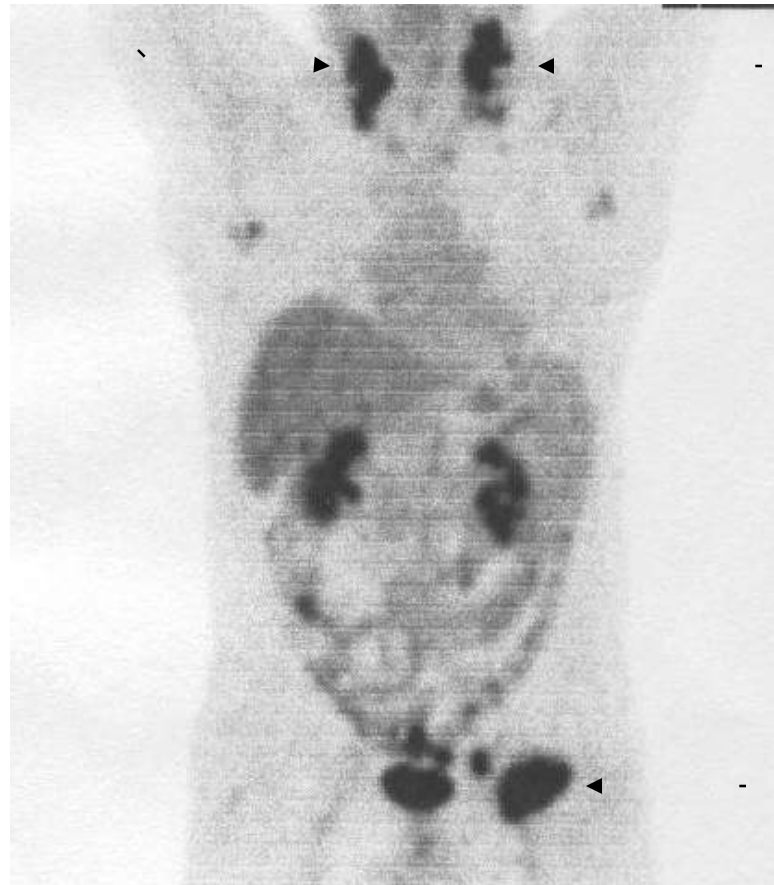
MRS JAL January 2009
28 months later



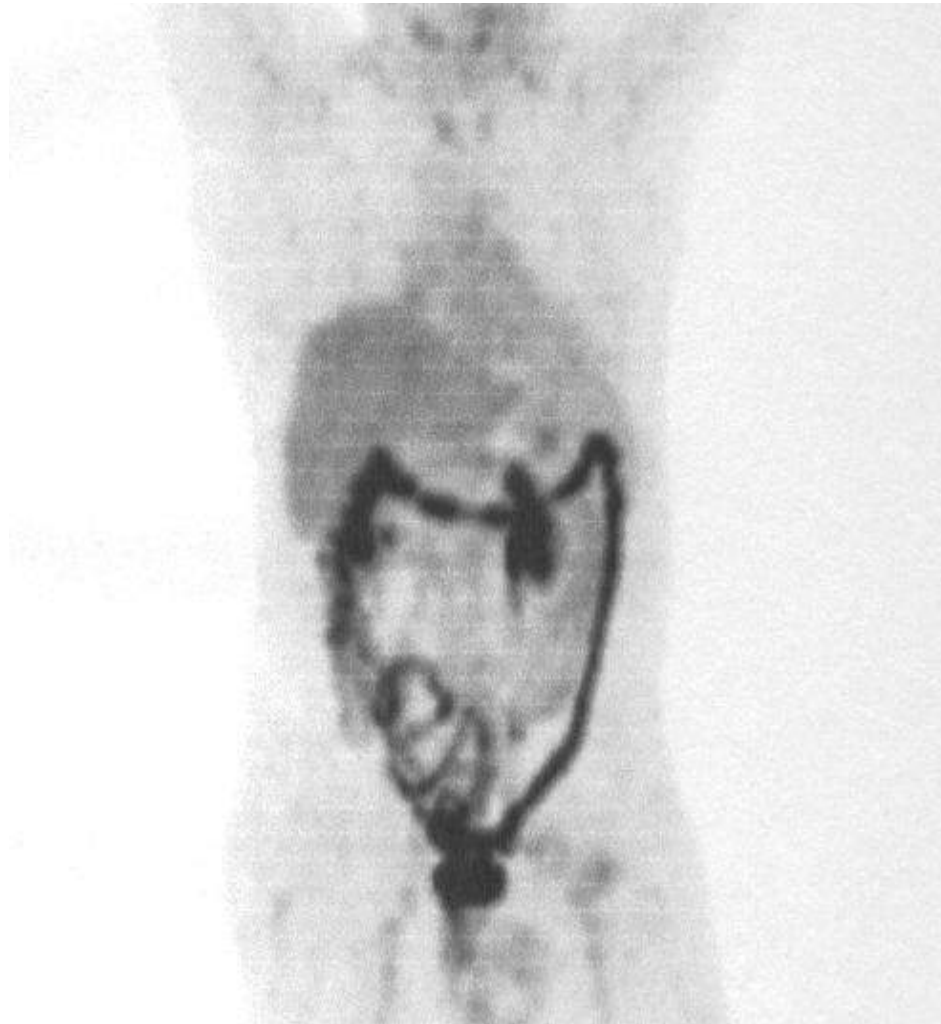
Berkson BM, Rubin DM, Berkson AJ.
Integr Cancer Ther. 2007 Sep;6(3):293-6.

Reversal of signs and symptoms of a B-cell lymphoma
in a patient using low-dose naltrexone.

MR TM
DECEMBER 2005



MR. TM
MAY 2006
6 months later

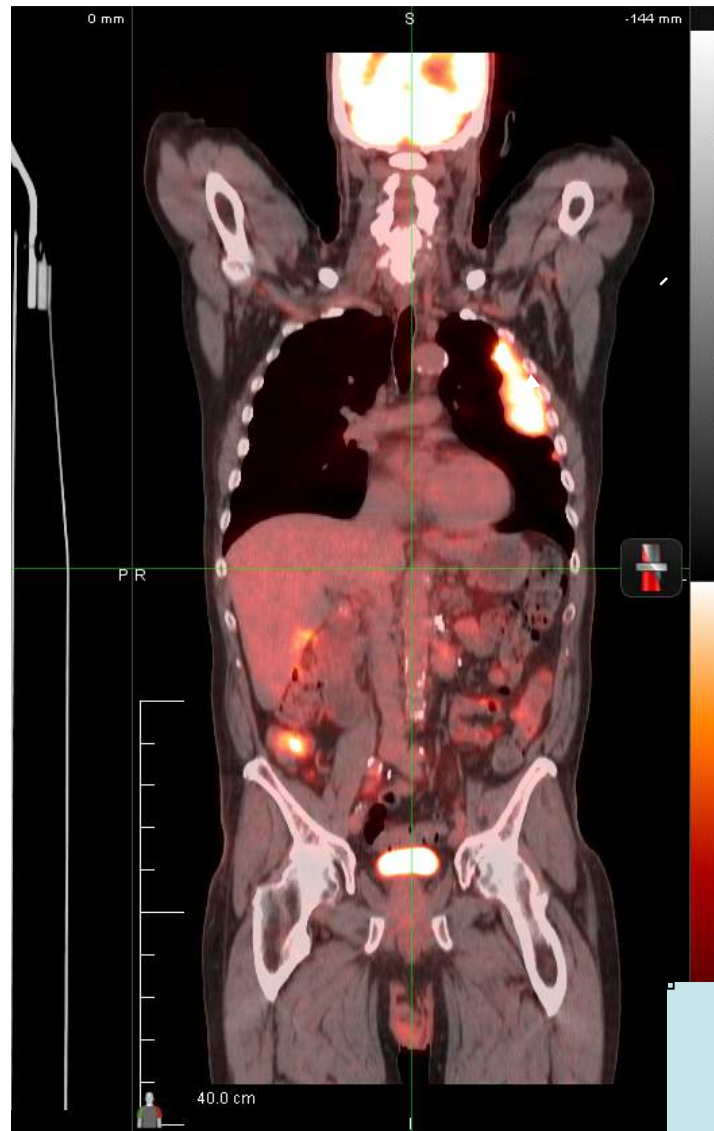


Mr. JT Renal Cell Carcinoma 68 YO male

- Diagnosis June, 2008 Urinating blood.
- CT mass L kidney with possible mets to lung.
- Nephrectomy L. kidney.
- MD Anderson administered biological response modifiers and chemotherapeutics. TS continued To deteriorate. No effect on TS' s RCC.
- TS told to get his affairs in order, no hope for survival June, 2010.
- TS presents to IMCNM August 16, 2010.
- Put on IMCNM protocols.
- March 2015, healthy, working, with no signs of disease.



Mr. JT
August 2010



Mr. JT
January 2011

0 cm

P

2 / 4

.0 cm

Mr.JT
JAN. 2014

Lipoic Acid Plus Low-Dose Naltrexone Reviewed for Cancer Treatment

- **NCI** staff and invited guests listen to **Drs. Berkson and Donahue** discuss their research and treatments on March 19, 2012
- A panel of researchers and clinicians was convened by the National Cancer Institute (NCI) for presentations and a roundtable discussion about “**The State of the Science of Alpha-Lipoic Acid plus Low-Dose Naltrexone for the Treatment of Cancer.**” The meeting was hosted by the Cancer Therapy Evaluation Program (CTEP), both part of the NCI Division of Cancer Treatment and Diagnosis (DCTD). The meeting provided an opportunity for NCI staff and outside experts to review and discuss case reports from **Dr. Burton M. Berkson**, an integrative medicine physician and Ph.D. in Biological Sciences, and Adjunct Professor. Dr. Berkson presented on his experience treating patients with alpha-lipoic acid plus low-dose naltrexone for various cancers and autoimmune diseases. The group also heard from **Dr. Renee N. Donahue**, (Zagon Group) Research Fellow at NCI about her pre-clinical research on the efficacy and proposed mechanism of action of LDN for the treatment of cancer.

The cases being presented today by Dr. Berkson were submitted and given rigorous scientific evaluation under the NCI Best Case Series (BCS) protocol.

The ultimate goal is to identify those integrative medicine interventions that have enough evidence to support NCI-initiated research.

Dr. Berkson reported that a combination of ALA (intravenously and orally) and LDN (orally), along with diet, vitamins, and lifestyle changes caused several cancers to go dormant.

Earlier in his medical career, Dr. Berkson published papers using ALA to repair liver damage in patients from mushroom poisoning and chronic infections with hepatitis C virus.

He also cited a number of research articles in European medical journals showing ALA's beneficial effects on cancer.

Routes of Administration of Alpha Lipoic Acid

- Oral power in capsule.
- Tablet
- Liposomal Alpha Lipoic Acid (phospholipids from soy lecithin)
- Intra Muscular Alpha Lipoic Acid dissolved in Trametamol
- Intravenous Alpha Lipoic Acid dissolved with sodium hydroxide and buffered and delivered in D5W or Normal Saline

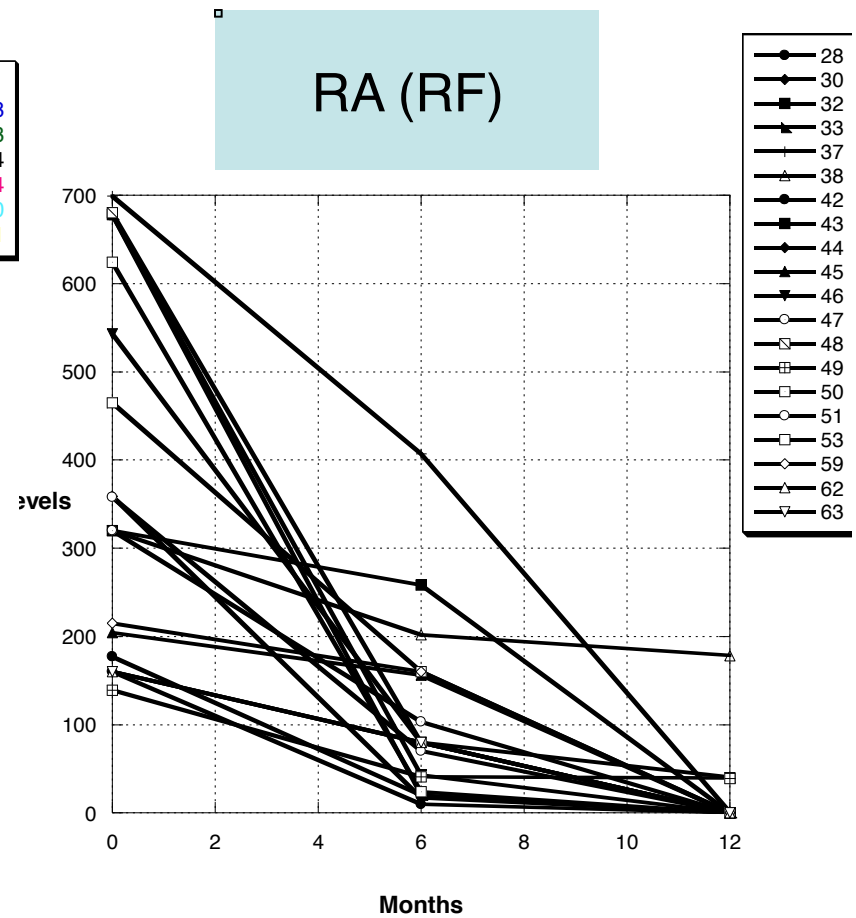
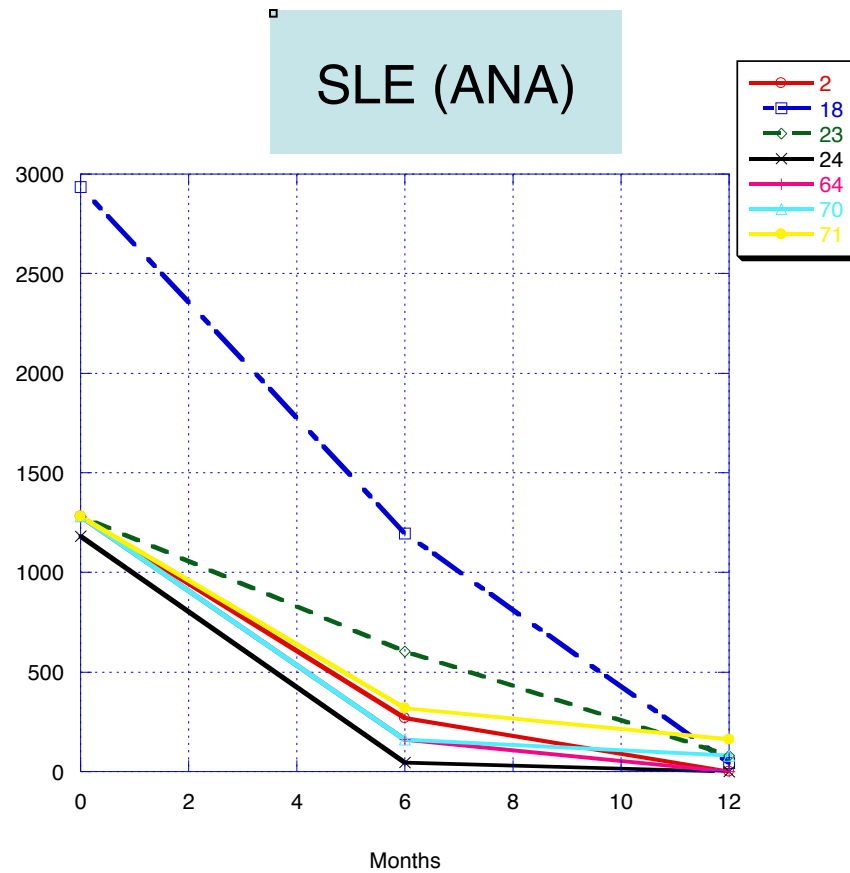
Europe and Asia very interested in Alpha lipoic acid.

Very little interest in the United States.



What about ALA/N for
systemic lupus erythematosus
and
rheumatoid arthritis?

ALA plus LDN for SLE and RA



Summary

ALA is necessary for aerobic cell life.

because ALA is essential for the conversion of pyruvate to acetyl Co A in the mitochondrion.

ALA is the rate-limiting factor for the production of energy from our cells.

ALA inhibits pyruvate dehydrogenase kinase.

ALA forces cells from an anaerobic metabolism into aerobic metabolism.

ALA has many uses in human medicine.

The efficacy, the apparent lack of toxicity, the long clinical track records of this agent in human medicine, all points toward the need for a clinical trial.

Why aren't there any large scale clinical trials? The agent has too many successful indications.

Drug Company Vice President confidential statement following Mayo Clinic positive results treating 1200 plus DM neuropathy patients with IV ALA.

- Diabet Med. 2004 Feb;21(2):114-21.
- **Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid.**
- Ziegler D, Nowak H, Kempler P, Vargha P. Low PA.
- **We want a drug with one indication. ALA has too many indications.**
- Med Klin (Munich).1999 Oct 15;94 Suppl 3:84-9.
- **A conservative triple antioxidant approach to the treatment of hepatitis C. Combination of alpha lipoic acid (thioctic acid), silymarin, and selenium: three case histories.**
- Berkson BM

Companies are working hard to change the alpha lipoic molecule so it can be used as a patented drug and not as useful for so many indications, however, up until now, the corrupted molecules don't work nearly as well as the natural molecule.

Most of the patients that I see have hepatitis C, diabetes complications, SLE, RA, etc.

Patients sign informed consent forms.

Conventional therapies explained carefully with complete objectivity.

Most cancer patients that I see are end stage.

They are told by their oncologist that nothing medically can be done.

This lecture is just my experience and is not an authorization for others to experiment with these protocols.

Books describing my therapies
**Also type in Berkson BM on Google, Google Scholar,
or PubMed**

