

The Metabolic Oncolytic Regimen For Effecting Lysis in Solid Tumors (Revised 2011)

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Background

The original *Metabolic Oncolytic Regimen* is based on the seminal work of former NASA scientist Clarence Cone, Jr., Ph.D. My permutation of the oncolytic approach to treating solid tumors was first published during December 1996. Since that time this species of metabolic therapy has been further refined and modified so as to make achieving oncolysis more probable. This revision (*Revised Metabolic Oncolytic Regimen*) draws on my original body of work with addition of therapeutic agents and measures that complement it.

Acknowledgments

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Summary

The *Revised Metabolic Oncolytic Regimen* is based on an approach to achieving lysis in solid tumors pioneered by Clarence Cone, Jr., Ph.D. (NASA, retired). Dr. Cone's novel therapy, which is reflected in patents granted various versions of same [U.S. patent #s 4,724,230 (1988), 4,724,234 (1988), and 4,935,450 (1990)] essentially involves manipulating various metabolic and biochemical pathways such that tumors produce prodigious quantities of lactic acid. This is achieved using a specific dietary regimen plus various synthetic and natural drugs, e.g., the bioflavonoid quercitin is employed to block export of lactate from the tumor which results in a lethal drop in intratumor pH. [The Cone therapy involves two treatment phases with a resting or nontreatment interval between them].

The principle shortcoming of the Cone therapy lies in the fact that it is hypoxic clusters within certain solid tumors - and not the entire tumor - which synthesizes and exports lactic acid

(Something which came to light after Dr. Cone's original patent application was filed). The Cone therapy is thus very appropriate and quite effective in helping eradicate hypoxic intratumor cell communities. It does not, however, address the lysis of the non-hypoxic regions of solid tumors per se.

The *Revised Metabolic Oncolytic Regimen* is a marriage of Cone's basic hypoxic tumor cell lysing technique with others geared to deal a lethal blow to both hypoxic and non-hypoxic tumor cells. It also incorporates compounds and therapeutic techniques which complement the Cone approach (Most of which were not available and/or widely used when Dr. Cone filed for his patents).

Body of Paper

Fifty percent (50%) or more of solid tumors are characterized by specific genetic and extragenetic (intracellular) features that create a therapeutic "window of opportunity" for effecting oncolysis via the manipulation of various metabolic pathways. A brief review of certain aspects of tumor cell biology is needed to demonstrate this. One of the key players in the genesis of solid tumors is the p53 gene [We all inherit a maternal and paternal copy of this particular regulatory gene]. In normal cells the p53 gene complex is not active. However, when cells incur damage viz exposure to ionizing radiation, toxic agents, etc., the p53 genes switch on and begin synthesizing a protein which typically arrests cell growth (thus allowing time for DNA repair) or activates a cellular self-destruct mechanism called apoptosis. When mutations occur in either the maternal or paternal copy of the p53 gene in a tumor cell - but not both - the cell will produce the p53 protein and, in the increasingly hypoxic environment that accompanies tumor growth, undergoes apoptosis. In essence, the oxygen deficit encourages tumor cell lysis. Unfortunately, tumors circumvent this effect by creating new blood vessels (neovascularization) which provide needed oxygen and nutrients. These vessels are usually very leaky such that blood plasma readily infiltrates intracellular spaces. This process generates intratumor pressures that impede blood flow and thereby reestablishes an oxygen deficit.

This picture is complicated by the tendency of tumors to give rise to cells which possess mutations to both maternal and paternal copies of the p53 gene. These cells do not produce the p53 protein and thus multiply unchecked. They are typically the most aggressive and drug resistant cells in a tumor - and tend to thrive in the most hypoxic regions of same [Those cells able to produce p53 protein die off in the hypoxic intratumor microenvironment. Those lacking functional p53 genes proliferate and thus give rise to clusters of like cells within the tumor].

Given this profile, it follows that the most effective therapeutic approach would be to encourage tumor microenvironment hypoxia via interference with angiogenesis (neovascularization). This will facilitate the lysis of tumor cells that synthesis viable p53 protein.

But what about those tumor cells that do not produce p53 protein? Would not encouraging intratumor hypoxia select for especially aggressive tumor cells? It will indeed. Actually, it adds nothing new to the clinical picture as this selection process is well under way early on in tumorigenesis. As we cannot presently circumvent this process, the principle objective becomes one of introducing therapeutic agents and metabolic challenges that have a selective and lethal effect on hypoxic cells.

As the suppression of the neovascularization or angiogenesis mechanism can be effected in a rather straightforward manner via the introduction of antiangiogenic drugs or natural compounds, e.g. thalidomide, etc., we will focus primarily on the metabolic processes unique to

tumor cells in the grip of profound hypoxia (and how we can effectively exploit same).

The Hypoxic Cells' Dependence on Anaerobic Processes

Tumor cells that lack sufficient oxygen to engage aerobic metabolic pathways typically begin to rely on anaerobic ones to supply needed substrate ([Warburg Effect](#).) These cells convert most of their pyruvate to lactate (and not acetyl Coenzyme A [AcCoA]), which is then excreted from same (1-3). This cellular aberration has several consequences: Only a small percentage (5-6%) of the chemical energy in glucose molecules can be liberated and utilized [Glucose is totally oxidized in normal cells]. As a result, the rate at which tumor cells can generate ATP (from glucose via the Respiratory Chain and Acid Cycle) is limited. To prevent cell lysis due to energy deprivation, malignant cells begin to rely on the mitochondrial B(eta)-oxidation of fatty acids to AcCoA (which can then enter the Citric Acid Cycle) and on the enzymatic transformation of amino acids into metabolically useful compounds (4,5).

The reliance of hypoxic tumor cells on this "alternative" metabolic pathway can be exploited along these lines:

(a) The oxidative catabolism of free fatty acids and amino acids (via the Respiratory Chain and Citric Acid Cycle) might be inhibited in hypoxic cancer cells via the judicious use of agents which inhibit their availability, i.e., partially inhibit hepatic fatty acid synthesis and keep plasma amino acid levels within the normal range, thus decreasing ATP production;

And

(b) The ATP that is produced could be rapidly depleted by (the) use of compounds that stimulate ATPase activity.

The net effect of a. and b. (above) should be rather straightforward:

Hypoxic tumor cells will compensate for this compromised metabolic state of affairs by increasing the rate of intracellular glycolysis. This, too, can be exploited by the introduction of substances that interfere with the shuttling of lactate out of the tumor cell. This will cause a drop in the intracellular pH level that will undermine vital cancer cell metabolic processes (6). Tumor cell lysis is anticipated. What is needed then are therapeutic agents and dietary measures that will:

- Limit the hepatic synthesis of free fatty acids plus inhibit lipolysis elsewhere in the cancer patient's body.
- Keep plasma amino acid levels within the range required to sustain general health [Normal cells will rapidly utilize the amino acids liberated by the catabolism of foods. Excess aminos - typically the end result of metabolic processes stimulated by the stress-induced release of adrenal hormones - will be available for use by cancer cells].
- Interfere with the transport of lactate out of the hypoxic tumor cells.
- Provide sufficient nourishment and caloric intake to meet the metabolic requirements of normal cells without supplying excess fats or protein that will be used to meet the metabolic needs of tumor cells.

The following are compounds that will help achieve the therapeutic objectives delineated above for the p53 protein-producing tumor cells, as well as those which do not synthesize the protein.

Limone

The 10-carbon compound limonene has been shown to inhibit the synthesis of ubiquinone (Coenzyme Q10) in tumor cell mitochondria, thereby reducing the amount of chemical energy produced to meet metabolic needs (7). It also blocks protein prenylation, a process crucial to the synthesis of proteins involved in regulating cell growth and cycling (Coleman *et al*, in press). Lavender (*Lavendula*) oil is rich in limonene as are certain citrus fruit peels used in various herbal medicine traditions.

L-Hydroxycitrate

This compound inhibits ATP citrate lyase, i.e., the cytoplasmic enzyme that cleaves citrate to produce AcCoA and oxalo-acetate (8). Numerous animal studies have shown that L-hydroxycitrate significantly depresses *in vivo* lipogenesis in a dose dependent manner in the liver, adipose tissues, and small intestine (9). This therapeutic activity is of immense clinical value, as tumors release or bring about the release of lipolytic agents which free up fatty acids for the synthesis of new tumor cells (McDevitt et al, 1995).

It should be noted that L-hydroxycitrate, in both animal and human trials, has demonstrated a mild anorexiant effect which might limit its use in patients with tumor-induced anorexia and cachexia (**NOTE: Recent studies indicate that L-hydroxycitrate may not exert any appreciable weight-reducing effects**). However, L-hydroxycitrate's appetite suppressant effects should be offset by the administration of exogenous thyroid hormone [Thyroid is an integral part of the oncolytic regimen]. Update: In recently published clinical trials, L-hydroxycitrate failed to induce significant weight loss. The anorexiant effect would appear a nonissue.

Interestingly, the cachexia commonly associated with malignancy should in many ways be addressed by the *Revised Metabolic Oncolytic Regimen*. In animal studies, insulin has been found to drop during certain stages of tumor formation. The *RMOR* includes use of exogenous insulin - see below (This insures glucose availability to normal cells, as well as increasing cell membrane permeability - which may potentiate the cytotoxicity of various agents used in the *Regimen*); glucose is often converted to fat before being utilized. The *RMOR* introduces L-hydroxycitrate which partially inhibits the conversion of glucose and other sugars derived from dietary carbohydrates to lipids. This glucose is available to provide energy for normal cells, as well as substrate the hypoxic tumor cells will turn into lactate (Which will be at least partially blocked from being shuttled out of the tumor cells by quercetin - see below); while most hepatic glucose processing "plugs into" the Cori Cycle, i.e., glucose from the liver is transported to the muscles where it is converted into pyruvate and back to glucose (Then to lactate - which circulates back to the liver and is converted into pyruvate, then glucose - which leaves the liver and travels back to active muscles, etc.) The *Revised Metabolic Oncolytic Regimen* should appreciably interfere with lactate transport out of not only hypoxic tumor cells, but active muscle tissue as well, thus "throwing a monkey wrench" into the Cori Cycle.

Melatonin

The pineal-synthesized hormone melatonin is a fatty acid transport inhibitor (10). Depriving tumor cells of metabolically useful fatty acids is an important component of the *RMOR*. [It has other oncolytic-promoting actions as well.](#) A slow-release form is recommended as this will

insure a steady supply of exogenous melatonin.

Concentrated Garlic or Insulin i.m.

Concentrated garlic extract or **preferably** exogenously supplied insulin [Isophane - slow release] will elevate the level of circulating (free) insulin in cancer patients (11). This is desirable, as insulin has a pronounced anti-lipolytic effect (12). It also increases cell permeability thus making it easier for chemotherapeutic drugs to have a lethal effect on tumor cells. The physicians who pioneered **Insulin Potentiation Therapy** (Donato Perez Garcia , M.D. , his son Donato Perez Garcia y Bellon, M.D., and grandson Donato Perez Garcia, M.D.) report that the doses of conventional cytotoxic and other antitumor drugs employed to lyse cancer cells is reduced many fold (Go to <http://www.iptq.com/>)

Thyroid

Exogenous thyroid hormone should contribute to the achieve of desired (oncolytic) objectives by: (1) increasing hepatic removal and degradation of cortisol, which brings about plasma reductions of same; and (2) stimulating ATPase activity (so as to "waste" ATP).

The lipolytic activity of thyroid hormone should be offset by the anti-lipolytic effects of insulin and prostaglandin E1.

It should be noted that the diet advocated herein (See **Dietary Guidelines** section below) which closely mirrors the Paleolithic diet or paleodiet ("Stone Age Diet"), has been found to boost thyroid levels in one published study (University Of Illinois At Urbana-Champaign is the original source): <http://www.sciencedaily.com/releases/2001/04/010404080611.htm>

Quercetin

This bioflavonoid interferes with intracellular mechanisms that transport lactate out of cancer cells dependent on anaerobic metabolic processes [Its interaction with the calcium regulatory protein calmodulin appears to have an added antitumor effect (13)]. When lactate shuttling is compromised intracellular pH falls resulting in cell lysis (apoptosis).

The apoptosis-inducing effect of an acidic pH has support from a study showing that alkalization of lovastatin-treated tumor cells abolished the cytotoxicity of the drug (14). Lovastatin's cytotoxicity is linked primarily to its ability to create an acidic intracellular pH. The acidic pH induces the activation of a pH-dependent endonuclease which causes DNA fragmentation. It has been demonstrated that this particular enzyme can be rapidly inactivated by the stimulation of the Na/H antiporter, an acid exporter, with phorbol ester. This strongly implicates an acidic pH and pH-dependent endonuclease in effecting cell lysis (Chen, LC, 1996).

Accordingly, it seems likely that quercetin-induced lactic acidosis in (glycolytic) tumor cells may bring about pH-endonuclease activity that leads to tumor cell die off.

NOTE: Quercetin has been shown to have cytotoxic effects via such mechanisms as: (a) Arrest of cell progression at the G1/S interphase (Two studies indicate blockage at the G2/M interphase); (b) suppression of glycolysis and ATP production; (c) interference with ion pump systems; (d) interference with various signal transduction pathways (Protein kinase C, casein

kinase II, etc.); and (e) inhibits DNA polymerase B and I (15). [Quercetin is also an effective 5-lipoxygenase inhibitor. Recently published studies indicate that arachidonic acid stimulates the growth of several types of cancer viz-a-viz being metabolized through the 5-lipoxygenase pathway into 5-HETE series of eicosataenoids (16)].

Essential Fatty Acids

If dietary omega 3 intake is low (more below under **Fats**): Supplementation with a source of essential fatty acids which, in the context of this cancer treatment approach, should (a) Help provide modest levels of those fatty acids required to maintain general health and; (b) serve as a substrate for the synthesis of various prostaglandins - PGE1 being of immense value because it inhibits lipolysis (17). Emphasis is on a high omega 3 to omega 6 fatty acids intake. The rationale? Archidonate lipoxygenase (LOX) and their metabolites appear to play an integral role in mediating growth factors which support tumor cell proliferation and growth. The LOX pathway may also be a vital component in the regulation of tumor cell survival and apoptosis (18).

Dichloroacetic Acid

Dichloroacetic Acid (DCA) is an analogue of acetic acid in which two of the three hydrogen atoms of the methyl group have been replaced by chlorine atoms. Its oncolytic activity stems from research showing that it reactivates pathways in mitochondria that become dysregulated and dysfunctional due to tumor-related hypoxia, i.e., a switch from mitochondrial oxidative phosphorylation to cytoplasmic glycolysis occurs. (21) This process contributes to cancer cell immortality. Once mitochondrial function has been restored apoptotic programming is activated.

[The Official University of Alberta DCA Website](#)

[New Scientist article on DCA with link to cautionary update](#)

[The DCA Site including a dosage calculator](#)

Bevacizumab (Avastin®)

Bevacizumab is used to treat certain types of colorectal, lung, breast, and kidney cancers and glioblastoma but is being studied in the treatment of other types of cancer. Bevacizumab is a type of antiangiogenesis agent and monoclonal antibody that works by binding to vascular endothelial growth factor (VEGF).

There are a number of other antiangiogenic inhibitors to look at: Interleukin-12, pentosan polysulfate, platelet factor 4, thalidomide, and TNP. Angiostatin and Endostatin produced remarkable results in animal experiments but were disappointing in some clinical studies. Also, [tetrathiomolybdate™](#), a pharmaceutical employed to lower serum and tissue copper levels in persons suffering from Wilson's Disease, has shown promise in effecting angiogenesis in Phase I clinical trials involving patients with metastatic cancer *Clin Cancer Res.*, 2000 Jan; (1):1-10

Also: Garlic raises endogenous nitric oxide levels, which has an antiangiogenic effect. Published research indicates that garlic boosts the activity of NO synthase, but not owed to its high content of arginine or to the phytochemical allicin (22, 23).

Calmative Botanic Formula plus Auto-suggestion, Cognitive Therapy, Biofeedback or other Stress-Attenuating Measures

Cancer patients typically present with substantially elevated serum free fatty acid and amino acid levels. This is due, in part, to cancer treatment (and response) related fears and anxiety. These powerful emotions trigger adrenal hormone release - the physiological effects of which include activation of adipocyte lipase (resulting in mobilization of free fatty acids) and partial inhibition of protein synthesis, i.e., the plasma amino acids which are normally (readily) utilized by nonmalignant cells for protein synthesis are only partially used resulting in an increase in the availability of amino acids to meet tumor cell metabolic needs.

It is vitally important, therefore, to provide the cancer patient with anxiolytic phytomedicines or pharmaceuticals plus supportive psychological therapy (or biofeedback) to minimize fear and anxiety-related stress [Or provide a referral to a qualified psychologist, psychiatrist, or other health care professional who can design a comprehensive stress management program]. Stress can also be attenuated by sexual release in patients interested in and capable of engaging in same. In my own clinical experience (informed by published animal and human trials), an extract of Gotu Kola (*Centella asiatica*), Kava Kava Root (*Piper methysticum*), Valerian Root (*Valeriana officinalis*) or Passion Flower (*Passiflora incarnata*) is usually quite effective. One of the more potent anxiolytic/calmative formulas I have employed in ameliorating stress in cancer patients is a Traditional Chinese drug called the Zizyphus Combination [Suan-Tsao-Jen-Tang]. In a comparative double blind study, the Zizyphus Combination [250 mgs. TID per os] were fully comparable to those of diazepam [2 mgs. TID per os].

There was one crucial difference between the two: When taken at bedtime, the Zizyphus Combination did not leave patients drowsy or otherwise impaired upon rising (24).

DIETARY GUIDELINES

Protein

35% of caloric intake should be in the form of protein (Emphasis on non-plant protein sources. This should be sufficient to maintain nitrogen balance.) NOTE: Patients with kidney disease or other serious health conditions should consult their primary care physician concerning the advisability of consuming high protein meals.

Protein with a high "biologic value", i.e., a mix of all the essential amino acids (plus a high proportion of omega 3 fatty acids. Ideally: A 4:1 ratio of omega 3 to omega 6 fatty acids.) Emphasis: Cold water fish.

Carbohydrates

Approximately 35% of the patient's caloric intake is to come from complex carbohydrates. However, beans, bread, potatoes, and all grains *should be eaten rarely, if at all.* These foods were introduced only recently (Neolithic period) and the emerging consensus among many experts in evolutionary nutrition is that our bodies do not benefit (in the long run) from reliance of such foods.

Raw and steamed vegetables and fruits should comprise the bulk of the patient's carbohydrate

intake.

Fats

Dietary and supplemental forms of fat should provide 20-30% of (daily) calories. Example: A 70 kg. man will require approximately 2,000 calories/day - 400 calories (44 grams - 20% level) of which should come from fats (Primarily omega-3 rich fatty acid sources/supplement).

Caveat: The use of fish oils is contraindicated for patients on blood thinners or who are diabetic.

Caloric and nitrogen intake should be calculated with a mind to meeting the patient's essential metabolic requirements. Allowances must be made, of course, for the increase in metabolic rate wrought by use of exogenous thyroid plus the patient's daily level of physical activity.

Protein or nitrogen (N) requirements to maintain nitrogen balance can be estimated by calculating nitrogen losses:

Total N loss (gm/d) = Nurine + Nstool + Nskin.

Where Nurine = Range of 1.3-1.7 gm/d

Average estimated from urinary urea N (mg/d) x daily urine volume (dl) divided by 0.8.

Nstool = 1-2 gm/d

Nskin = 0.3 gm/d

Normal total N loss = Range of 2.9-5.9 (Mean 4.4) gm/d

Protein estimated as follows:

$N(g) \times 6.5 = \text{Protein (grams)}$

From Internal Medicine, Diagnosis & Therapy (1988-1989). Edited by Jay H. Stein, M.D., Appleton & Lange, pp. 246-7.

The diet should include plenty of potassium-rich foods. High magnesium foods and drinking water are to be eschewed. The rationale is simple: Increases in potassium ion concentration stimulate the secretion of insulin (Desirable in terms of treatment objectives). Magnesium is inhibitory (25).

THE DAILY ONCOLYTIC REGIMEN

AM MEAL

The emphasis should be on fruit and protein. The consumption of fruit after rising is consonant with primate dietary patterns [Patterns virtually all "higher" primates became adapted to over the millennia]. In the case of chimpanzees (*Pan Troglodytes*), our evolutionary siblings (99% identical genome), fruits are consumed early in the morning thereby providing fructose and other sugars needed to replenish fasting serum glucose levels. Interestingly, neuropeptide Y - which stimulates carbohydrate craving - peaks during the early part of the day. This lends support to the view that the general primate metabolic machinery has been conserved

throughout the course of hominoid and hominid evolution. For a detailed exploration of diets that are consonant with our species' evolved nature, peruse [The Paleolithic Prescription](#) (1988) and/or visit the [Paleolithic Diet Page](#). [The Paleo Diet Cookbook](#) will likely come in handy.

Prior to: 250 mgs. L-hydroxycitrate (20 minutes before the meal)

500 mgs. quercetin (See note below)

With: 10-30 drops *Lavendula* oil mixed into fruit juice or water.

After: 2-3 grams concentrated garlic or 5-15 units insulin suspension [Isophane] injected i.m. approximately 30-45 minutes following the A.M. meal. If insulin is used, a glucometer or other method must be employed (by the patient or caregiver) to measure his or her serum glucose level - and monitor same at regular intervals throughout the day. If hypoglycemia occurs, the patient should consume a sucrose rich candy or beverage (26).

1/2 to 1 grain thyroid

Antiangiogenic drug [Dosage depends on the nature of the drug or supplement used, e.g., thalidomide, etc.] and/or DCA (Link to [Dosage Calculator](#).)

[Use DCA with a caffeinated beverage preferably coffee or tea and supplemental thiamine.](#)

NOTE: [The use of high dose DCA and caffeine in brain cancer patients is dangerous!.](#)

Botanic or pharmaceutical calmativ (If needed)

NOTE: As quercetin is very poorly absorbed in the human gut, it is recommended that patients take a more bioavailable form such as water soluble quercetin hydrate or "activated" quercetin [Activated quercetin is a combination of quercetin and Bromelain and magnesium ascorbate. According to literature published by a major "activated" quercetin manufacturer/distributor, Threshold Enterprises Ltd. (Source Naturals brand), various clinical studies have demonstrated that vitamin C improves the absorption of quercetin]. Interestingly, the marriage of ascorbate with quercetin packs its own therapeutic punch. To wit: A quercetin-ascorbate blend inhibited HBT squamous cell carcinoma cells in one study (27).

MID-DAY MEAL

The emphasis should be on complex carbohydrates and protein.

Prior to: 250 mgs. L-hydroxycitrate [20 minutes prior to meal]

500 mgs. quercetin

With: 10-30 drops *Lavendula* oil mixed into fruit juice or water

After: If Isophane insulin was not used in the AM, 2-3 grams concentrated garlic.

1/2 to 1 grain thyroid

Omega-3 fatty acid supplement*

Botanic or pharmaceutical calmativ

Antiangiogenic drug and/or DCA (Link to [Dosage Calculator](#).) [Use DCA with a caffeinated beverage preferably coffee or tea and supplemental thiamine.](#) NOTE: [The use of high dose DCA and caffeine in brain cancer patients is dangerous!](#)

Slow Release Melatonin

PM MEAL

Complex carbohydrates and protein foods are emphasized.

Prior to: 250 mg. L-hydroxycitrate (20 minutes before meal.)

With: 10-30 drops Lavendula oil mixed into water or fruit juice/

After: If Isophane insulin was not used in the A.M., 2-3 grams concentrated garlic.

Omega 3 fatty acid supplement*

* If dietary omega 3 fatty acid intake meets the patient's daily intake level (in grams), there is no need to take an omega 3 fatty acid supplement.

SPECIAL NOTE - For patients who cannot readily obtain sufficient omega-3 fatty acids through the diet: In my experience, patients often find that the most convenient way of getting supplemental fats is to mix and consume omega-3 rich Flaxseed oil with low fat or non-fat cottage cheese or small quantities of reduced fat peanut or soy butter.

Botanic or pharmaceutical calmativ

Antiangiogenic drug or DCA (Link to [Dosage Calculator](#).)

Slow Release Melatonin (Before retiring) – 3 mgs or more.

Low Dose Gamma Radiation Used in Tandem with Lipoxigenase Inhibitors

Low dose targeted radiotherapy (in tumors types with a demonstrated susceptibility to same) coupled with the use of lipoxigenase inhibiting pharmaceuticals or natural substances is in keeping with the cancer pathway compromising thrust of the *RMOR*. This combination was first suggested to the author by *in vitro* research carried out at the Institute of Biophysics in Czechoslovakia (Academy of Sciences of the Czech Republic). Researchers at the Institute found that when human carcinoma HS578T and monoblastoid U937 cell lines were treated with the lipoxigenase inhibitors norhydroguaiaretic (NDGA) and escultein - then exposed to low dose gamma radiation (1GY) - (3H)-thymidine incorporation and cell proliferation was suppressed [NOTE: Quercetin compromises lipoxigenase activities both in vitro and in vivo. The cyclooxygenase inhibitor piroxicam had no effect (28)].

Additional Supporting Evidence: German scientists treated mice with Lewis cell lung cancer with various combinations of i.p. administered collagenase, cyclooxygenase, and lipoxigenase inhibitors plus radiation. The most effective modulation of tumor growth (2.8 - 3.3. fold

increases in tumor growth delay) was seen in animals treated with a combination of monocycline (collagenase inhibitor)/suldinac (cyclooxygenase inhibitor) plus radiation and phenidone (Lipoxygenase inhibitor)/suldinac plus radiation (29).

NDGA ([Nordihydroguaiaretic acid](#)): A General Lipoxygenase Inhibitor and ATP Depleting Agent

NDGA, a chemical compound present in the botanical *Larrea tridentata* (Chaparral) - once widely used in various folk treatments for cancer - has shown efficacy in inducing tumor cell lysis in numerous *in vitro* studies. In one laboratory experiment, NDGA and a 12-LOX selective inhibitor brought about rapid and dose-dependent apoptosis of serum cultured W256 cells (as well as other tumor cell lines including leukemia) (30). In another study, NDGA inhibited an ATP sensitive osmolyte channel in hepatoma cell line HepG2 by virtue of its ability to deplete ATP (31). These properties make NDGA a compound worth further investigation, especially in terms of its efficacy when used in tandem with novel cancer treatment approaches such as the *Metabolic Oncolytic Regimen*.

CAUTIONARY NOTE: Readers and physicians are discouraged from utilizing either *Larrea tridentata* or purified NDGA in conjunction with the *Revised Metabolic Oncolytic Regimen* (or any other cancer treatment). During 1992-4 eighteen cases of hepatotoxicity were reported to the F.D.A. involving Chaparral ingestion. Thirteen cases did show clear evidence of liver toxicity including cholestatic hepatitis (4 persons) with progression to cirrhosis. Two of the thirteen developed fulminate liver failure that required liver transplantation (32).

However, there is a patented nontoxic extract of *Larrea tridentata* [on the market](#) ([U.S. Patent # 6,039,955](#), March 21, 2000). It would be entirely appropriate for cancer patients to use this species of NDGA. The use of lipoxygenase inhibitors and low dose radiation is a relatively new area of medical research and to-date has primarily involved cell cultures. However, the rationale for employing both (where appropriate) is scientifically credible and consonant with extant knowledge of tumor cell biology. As radiotherapy is used quite effectively in the management and even eradication of some solid tumors, patients who elect to undergo the *Revised Metabolic Oncolytic Regimen* - in combination with radiotherapy - would be well advised to discuss the use of a lipoxygenase inhibitor with his/her oncologist.

Admittedly, this is one of the more tenuous components of the *RMOR*. However, as this paper represents a synthesis of what has been utilized in clinical practice - with the hypothetical but promising - I would be remiss not to include it.

Compounds Whose Effects on Various Metabolic Pathways Should Complement the Activity of the Therapeutic Agents Cited Previously

Orange Peel Oil ([Limonene](#) source); [azelaic](#) acid (Evidence indicates it interferes with vital biological processes in tumor cell mitochondria) (33); [Tirapazamine](#) (3-amino-1,2,4-neozotrizine 1,4 dioxide) - a pharmaceutical that is specifically cytotoxic to hypoxic cancer cells (34). Developed by J. Martin Brown et al at Stanford Medical School, tirapazamine has completed [Phase I/ II clinical trials at various centers](#) (1997-Present) typically used in tandem with cisplatin, radiation and other oncolytic agents. The results were encouraging in some forms of cancer; [Amionoglutethimide](#) - an anxiolytic agent viz its ability to lower adrenal levels. Various studies have shown that this drug blocks adrenal steroidogenesis by inhibiting desmolase conversion to pregnenolone (35); phenylacetate phenylacetylglutamine (The end metabolite of this compound is structurally similar to glutamine - a preferred metabolic

substrate in some tumors. It blocks the uptake of glutamine through ASC amino acid transporter) (36). Also: [thrombospondin](#), various metalloproteinase inhibitors and interferons, transforming growth factor beta, and platelet factor 4 (PF4).

Hyperthermia: A Useful Therapeutic Adjunct

Hyperthermia lowers tissue pH and thus should adroitly complement the *Metabolic Oncolytic Regimen* (At least in cases involving relatively superficial solid tumors). Interestingly, quercetin is a hyperthermic sensitizer by virtue of its ability to block lactic acid transport and heat protein synthesis. Normally tumors develop thermoresistance via the production of heat shock protein. Quercetin helps circumvent this process and thus leave the tumor susceptible to hyperthermia therapy [In cervical carcinoma cells, quercetin did not exert cytotoxic effects at normal body temperatures, but did potentiate hyperthermia-induced toxicity at 41 degrees Centigrade (105.8 degrees Fahrenheit) (37)]. If local or regional heating of a tumor is not feasible owed to disseminated malignancy, whole body hyperthermia can be induced. One method which has demonstrated efficacy in a randomized double blind trial at Memorial Sloan Kettering is [Mixed Bacterial Vaccine \(Coley's Toxins\)](#) (38). Another is to employ [whole body hyperthermia technology](#).

Two Novel Theoretical Methods of Inducing Intratumor Hyperthermia

The following are two admittedly very theoretical approaches to inducing intratumor hyperthermia sufficient to affect tumor cell lysis.

1) Ferritin-mediated electromagnetic hyperthermia

In a paper published in the journal *Medical Hypotheses* [(2000) **54**(2), 177-179], the authors suggest that an alternating magnetic field no greater than ~ 100 KHz (kilohertz) should induce heating of intracellular ferritin sufficient to lyse tumor cells without adversely effecting normal tissues and cells. The iron core in ferritin is strongly paramagnetic and thus can be utilized to produce heat via the Brown and Neel effects (respectively). Since ferritin is often found at higher levels in neoplastic cells than normal ones, this makes achieving hyperthermia by way of an externally applied high frequency magnetic field very probable.

Japanese, German, and other researchers have published many papers indicating that intracellular hyperthermia sufficient to achieve cell lysis is possible employing magnetite cationic liposomes and other 'magnetic fluids.' (39,40). The ferritin mediated approach, while different from the aforementioned, retains many features in common and should be explored in the laboratory and in well controlled clinical trials.

A possible permutation to this approach which occurred to the author is this: Introduce magnetotactic bacterial vectors *in vivo* which have been genetically engineered or artificially selected to seek out and bind to specific tumor cell antigens. If achievable, the magnetotactic bacteria might provide sufficient iron once inside tumor cells to make achieving electromagnetic heating more certain.

NOTE: Interestingly, there is published animal studies indicating that hyperthermia used in tandem with glucose administration enhances the tumor lysing impact of the former (41, 42). As the *Revised Metabolic Oncolytic Regimen* is geared, in part, to boost intratumor glucose levels (thus raising the rate of lactate synthesis); the use of the *RMOR* in combination with hyperthermia is logically compelling.

It should be noted that researchers at Jefferson Medical College found that i.v. and i.v. plus oral glucose effectively lowered tumor extracellular pH in 17 non-diabetic cancer patients at Henan Tumor Hospital. These scientists were looking into boosting tumor acidification as a potential thermoradiosensitizer (43).

- 1) 2) While dwelling on the merit of inducing electromagnetic intracellular heating using 'magnetic fluids' and/or ferritin, it occurred to me that **iron and cobalt phthalocyanines** might be exploited to achieve sufficient intracellular hyperthermia to lyse tumor cells.

The [phthalocyanines are being employed in photodynamic oncolytic therapy \(research\)](#) with varying degrees of success. Since these compounds are selectively retained by tumors, resist photochemical and chemical breakdown, are essentially non-toxic, and can be synthesized readily with a neutron-activated nuclide (boron compounds) and as conjugates with epidermal growth factor (thus making tumor cell targeting more contain), they are very attractive to cancer researchers (44).

Setting aside the photodynamic use aspect, there is the electromagnetic heating potential of the iron and cobalt-bearing phthalocyanines (PCs) to consider. As mentioned above (#1), iron is very paramagnetic. Cobalt, while less responsive to a magnetic field than iron, might still be of merit in instances where use of iron might boost tumor growth in micrometastases which are strongly suspected to exist but not confirmable using extant detection technology.

CAUTIONARY NOTE: Copper plays a role in angiogenesis and thus may be contraindicated save as a heroic measure, especially in patients on tetrathiomolybdate (TM).

[Click to access paper by the author that contains MOR measures and ones that complement many of them.](#)

Clinical Efficacy - Cone Metabolic Method

In his patent application, Dr. Clarence D. Cone, Jr., reported that partial to complete oncolysis was achieved in patients with a variety of cancers. Here is a sampling:

Female age 52 Tongue

Male age 57 Throat

Male age 70 Stomach

Female age 47 Cecum

Female age 54 Colon

Male age 45 Breast

Female age 57 Ovary

Female age 60 Uterus

Male age 65 Kidney

Male age 59 Prostate

Male age 49 Pancreas

Male age 49 Lymphoma

Male age 47 Melanoma

Female age 48 Basal Cell (skin)

Male age 66 Leukemia

Male age 50 Bone Sarcoma

Select Case histories:

Female, age 57. Diagnosed with infiltrating ductal cell carcinoma of the breast (Terminal inflammatory stage). Multiple biopsied specimens confirmed diagnosis. Prior treatments: Surgery, radiotherapy (4000 rads), intensive chemotherapy (Mitoxin). Treated using the Cone regimen: By day 20 the tumor was reduced 70%. By day 75 the patient was reported to be in good psychological condition and active while remaining on the regimen (Phase II).

Female, age 54. Diagnosed with advanced colon adenocarcinoma, extensive liver metastases. Confirmed by multiple biopsied specimens and ultrasound scans. Classified as inoperable. Had no standard cancer treatments. By day 16 on the Cone regimen the tumor was reduced by 87.5%. By day 12 of Phase II treatment the tumor was reduced 83.5% [The starting size of the tumor in Phase II was bigger than in Phase I. It is not known whether the tumor grew during the resting interval between treatment phases. Note: There is no resting or non-treatment phase in my version of the Cone metabolic therapy - author].

Male, age 57. Diagnosed with epidermoid carcinoma of the larynx, metastasized to the left neck. Confirmed by multiple biopsied specimens, CT scans and xerograms. No standard cancer treatments undertaken. By day 13 on the regimen the tumor was reduced by 88%. After the resting interval and at the start of Phase II, the tumor grew back to 4 cms. By day 13 the tumor was non-palpable.

Male, age 59. Diagnosed with (moderately differentiated) metastatic adenocarcinoma of the prostate. Confirmed by multiple biopsied specimens, cytoscopy and bone scans. Treated prior to undergoing the Cone regimen with laetrile, vitamin A, oral enzymes, hormone therapy, and surgery (TURP). By Day 22 of Phase I the patient was asymptomatic. At the start of Phase II the prostate was enlarged and very hard. By day fifteen the patient was in excellent condition and asymptomatic. Prostate size was reduced to normal.

Two select but representative cases of patients who utilized the original *Metabolic Oncolytic Regimen*

Male, age 59. Diagnosed with squamous cell carcinoma (4 cm. tumor - lower lobe - left lung. Metastases to the lymph nodes and mediastinum. Diagnosis confirmed by CT scan, biopsied specimens, and endoscopic examination of the tumor. Classified as inoperable and terminal, the patient elected to forego conventional treatment and undergo the *Metabolic Oncolytic Regimen*.

By the 26th day on the Regimen, lymph nodes were no longer palpable and tumor in left lung was 95% obliterated. Patient achieved full remission and is now 7+ years post-diagnosis.

Female, age 38. Diagnosed with oral cancer (squamous cell) with metastases to the larynx and both lungs. Diagnosis confirmed by multiple biopsied specimens. Patient declined surgery, chemo-therapy and radiotherapy, as these offered little but hope of cure. After receiving material on the *Metabolic Oncolytic Regimen*, patient chose to undergo same (Her oncologist agreed to supervise her treatment and monitor her progress or lack thereof). By the 43rd on the *Regimen*, tumors at all sites were reduced an average of 78%. By day 91, no evidence of cancer could be detected by biopsy or CT scan. Patient has been in remission for 10+ years to-date.

Comments

In at least some instances the dramatic responses seen in patients who had standard therapies prior to commencing either the Cone therapy or the original *Metabolic Oncolytic Regimen* are probably due (in large part) to same. What is interesting is that there were good responses, i.e., partial and total remission, in patients who had no standard cancer therapy prior to undergoing the Cone regimen and my permutation (respectively). Better responses are anticipated with the *Revised Metabolic Oncolytic Regimen*.

Concluding Remarks

There were treatment failures on the Cone therapy and among patients on the original *MOR*. This is not unexpected, as no cancer therapy - standard or non-standard - always effects tumor lysis (Partial or complete). Biomedical researchers and research-oriented naturopathic, osteopathic and allopathic physicians are invited to acquaint themselves with and employ this species of metabolic therapy in the treatment of various solid tumors.

Since this is admittedly a **very experimental** approach to effecting oncolysis, it is hoped that the *RMOR* will be used either as an adjunctive measure in tandem with more established oncolytic methods or, in the case of end stage cancer patients, as a heroic measure possibly employed in concert with other promising therapeutic agents or techniques.

I would urge those who use the *RMOR* diligently accrue and freely communicate their findings and observations with me (and any interested researcher or clinician). If the data provided indicates a statistically significant response in one or more types of cancer, i.e., average survival times greater than rates reported of other therapies on such databases as SEERS, etc., justification will exist to pursue funding of a more formal clinical investigation.

REGIMEN BASED ON THE METABOLIC ONCOLYTIC REGIMEN

[Exploiting Hypoxia in Solid Tumors to Achieve Oncolysis \(MED. HYPOTH. Volume 68, Issue 4, 2007, Pages 828-831\)](#)

["Effecting Oncolysis by Depleting Intracellular Glutathione, Boosting Oxidative Stress, and Reducing IGF-1" \(Payne AG, MED. HYPOTH. RES. 1:247-252\).](#)

CLINICAL PROGRAM THAT DRAWS ON THE REVISED METABOLIC ONCOLYTIC REGIMEN IN THE TREATMENT OF CANCER PATIENTS

[Nova Cells Institute of Mexico](#) – NCIM uses elements of the RMOR (above) in tandem with donor granulocyte immunotherapy. [Click to access statement on this.](#)

NCIM also draws from published lines of research such as: [Inhibition of Glycolysis in Cancer Cells: A Novel Strategy to Overcome Drug Resistance Associated with Mitochondrial Respiratory Defect and Hypoxia](#) *Cancer Res* 2005; 65: (2). January 15, 2005

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Dr. Anthony G. Payne is a biomedical theoretician and writer.

Payne's original paper on the *Metabolic Oncolytic Regimen*, which appeared in the Townsend Letter for Doctors (December 1996), earned him 2 medals in medicine and an honorary M.D. degree in recognition of its therapeutic potential [Open International University's 1997 Royal Order of Physicians Gold Medal in Medicine and Scientist of the Year].

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References

1. Racker et al, *Science*, 1981, # 209, pp. 263.
2. Spencer, TL et al, *Biochem. J.* 1976, # 154, pg. 405.
3. Belt JA et al, *Biochem.*, 1979, # 18, pg. 3506.
4. Alberta B et al, Molecular Biology of the Cell 2/e, Garland Publishing, NY. 1989.
5. ibid
6. ibid
7. 'Anticancer Agents in Orange Peel Oil', *Cancer Watch*, June 2, 1993, Vol. 2.
8. Watson J et al, Biol. & Biochem., Vol. # 135, pp. 209-217.
9. Lowenstein JM, 'Effect of (-)-hydroxycitrate on fatty acid synthesis by rat liver in vivo', *J. Biol. Chem.*, 1971; 246(3):629-32
10. Sauer LA, Dauchy RT, and Blask DE. 'A novel mechanism for the regulation of tumor

- growth in vivo: situ'. *Proc. Amer. Assoc. Cancer Res.* 37:224, 1996
11. Bever, BO and Zahand, GR. 'Plants and Oral Hypoglycemic Action', *Qtrly. J. Crude Drug Res.*, 1979, #17, pp. 139-196
 12. Review of Physiological Chemistry, Lange Medical Publications, 1973, 14/e, pg. 489.
 13. 'Quercitin Interacts with Calmodulin, A Calcium Regulatory Protein', *Experimentia*, 1984, 40:184-185.
 14. Perez-Sala D., Callado-Escobar D, and Mollinedo, F. 'Intracellular alkalization suppresses lovastatin-induced apoptosis in HL-60 cells through activation of a pH-dependent endonuclease', *J. Biol. Chem.*, 270:6235-6242, 1995.
 15. Oho, K and Nakane, H. 'Mechanisms of inhibition of various cellular DNA and RNA polymerases by several flavinoids'. *J. Biochem.* 108: 609-661, 1990.
 16. Ghosh J, Meyers CE. *Biochem. Biophys. Res. Commun.*, 1997 June 18, Vol. # 235, pp. 418-423
 17. Review of Physiological Chemistry, op cit, pg.288.
 18. 'Angiogenesis and its inhibitors', *Cancer Watch*, Vol. 3, Nov. 1994, pg. 169.
 19. Tang GD, Honn J., *J. Cell Physiol.*, August 1997, Vol. 172, pp. 155-170.
 20. 'From Ideas To Trials: The Story Behind Lane's Shark Cartilage', *Altern Ther.*, Vol. 1, #5, Nov. 1995, pg. 26
 21. [Sci Transl Med 12 May 2010: Vol. 2, Issue 31, p. 31ra34](#)
 22. Pipili-Synetos E, Skkoula E, Haralabopoulos G, Andriopoulou P, Persisteris P, Maragoudakis ME. 'Evidence that nitric Oxide is an endogenous antiangiogenic mediator', *British J. Pharmacol.*, 1994
 23. Das I, Hirani J and Sooranna S. 'Arginine is not responsible for the activation of nitric oxide synthase by garlic'. *J. Ethnopharmacol.*, 1996 July 26, Vol. # 53, pp. 5-9.
 24. 'Suan-Tsao-Jen-Tang v. Diazepam: A Controlled Double Blind Study in Anxiety', *Internl. J. of Clin. Pharmacol., Ther. & Toxicol.*, 24(12): 6, pp. 49-50, 1986.
 25. Review of Physiological Chemistry, op cit, pg. 443.
 26. [Hypoglycemia - Treatment](#)
 27. Kandaswami C, Perkins E, Solonivk DS, Drzewiecki G, and Middleton, Jr., E, 'Ascorbic acid-enhanced antiproliferative effect of flavinoids on squamous cell carcinoma in vitro', *Anticancer Drugs* 4:91-96, 1993.

28. Hofmanova J, Musilova E, and Kozubik A. 'Suppression of human cancer cell proliferation by lipoxygenase inhibitors and gamma-radiation in vitro', *Gen. Physiol. Biophys.* 15: 317-331, August 1996.
29. Teicher BA, Korbitt TT, Menon K, Holden SA, and Ara G. 'Cyclooxygenase and lipoxygenase inhibitors as modulators of cancer therapies', *Cancer Chemother. Pharmacol.*, 33: 512-522, 1994.
30. Tang DG et al, *J. Cell Physiol.*, Vol. # 172, pp. 155-170, op cit
31. Ballatori N and Wang W, *Amer. J. Physiol.*, May 1997, Vol. # 272, pp. C1429- C1436.
32. Sheik NM, Philen RM and Love LA. 'Chaparral-associated hepatotoxicity', *Arch. Internl. Med.*, 1997 April 28, 157(8); 913-919.
33. Picardo M et al, 'Activity of azelaic acid on cultures of lymphoma and leukemia- derived cell lines, normal resting & stimulated lymphocytes and 3T3 fibroblasts', *Biochem. Pharmacol.*, 1985, 34:1653-1658.
34. Brown JM, 'SR 4233 (Tirapazamine): A new anticancer drug exploiting hypoxia in solid tumours', Review, *Lancet*, 1993: 1163-1170.
35. Coconi G, 'First generation aromatase inhibitors: Amionoglutethimide and testolactone', *Breast Cancer Res. Treatment*, 30: 57-60, 1994.
36. Soltysiak-Ppawluczuk, D and Burzynski, SR, 'Cellular accumulation of antineoplaston A2S1 in human hepatoma cells', *Cancer Lett.*, 107-112, 1995.
37. Pontigi P, Rotella GB, Sabuto A, and Curto FC, 'Hyperthermia in cancer and AIDS: An updated survey', *J. Environ. Toxicol. Oncol.*, 15 (2-4), 89-97, 1996.
38. Johnston, B. 'Clinical effects of Coley's toxin. 1. Controlled study. 2. A seven year study'. *Cancer Chem. Reports* 21:19-68, August 1962.
39. Mitsumori M, Hiraoka M, Shibata T, Okuno Y, Nagata Y, Nishimura Y, Abe M, Hasegawa M, Nagae H, Ebisawa Y, ' Targeted hyperthermia using dextran magnetite complex: a new treatment modality for liver tumors,' *Hepatogastroenterology* 1996 Nov-Dec; 43(12): 1431-7.
40. Yanase M, Shinkai M, Honda H, Wakabayashi T, Yoshida J, Kobayashi T, 'Intracellular hyperthermia for cancer using magnetite cationic liposomes: ex vivo study,' *Jpn J. Cancer Res* Jul;88 (7): 630-2.
41. Akagi K, Aoki Y, Nasu R, Nagata K, Itagaki Y, Sawada S, 'Enhancement of antitumor effects of hyperthermia with glucose administration in murine mammary carcinoma,' *Oncol Res*; 6(3): 593-6 1999.
42. Leeper DB, Engin K, Thistlethwaite AJ, Hitchon HD, Dover JD, Li DJ, Tupchong L, 'Human tumor extracellular pH as a function of blood glucose concentration,' *Int J Radiat Oncol Biol Phys* 1994 March 1;28(4):935-43.

43 Lepper DB, Engin K, Wang JH, Cater JR, Li DJ, 'Effect of i.v. versus combined i.v. plus oral glucose on human tumour extracellular pH for potential sensitization to thermoradiotherapy,' *Int J Hyperthermia* 1998 May-June; 14(3): 257-69.

44 Lutsenko SV, Feldman NB, Finakova GV, Posypanova GA, Severin SE, Skyrabin KG, Kirpichnikov MP, Lukyanets EA, Vorozhtsov GN, 'Targeting phthalocyanines to tumor cells using epidermal growth factor conjugates, ' *Tumour Biol* 1999 Jul-Aug; 20 (4): 218-24.

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