C. Files

FRANK R. WOLF
10TH DISTRICT, VIRGINIA

WASHINGTON OFFICE:
104 CANNON BUILDING
WASHINGTON, DC 20515-4610
(202) 225-5136

CONSTITUENT SERVICES OFFICES:
1651 OLD MEADOW ROAD
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MCLEAN, VA 22102
(703) 734-1500

19 EAST MARKET STREET
LEESBURG, VA 22075
(703) 777-4422
METRO NUMBER
(703) 478-1303

Congress of the United States
House of Representatives
Washington, DC 20515-4610

COMMITTEE ON APPROPRIATIONS
SUBCOMMITTEES:
TRANSPORTATION
TREASURY—POSTAL SERVICE—GENERAL GOVERNMENT
SELECT COMMITTEE ON CHILDREN, YOUTH AND FAMILIES
SELECT COMMITTEE ON HUNGER
COMMISSION ON SECURITY AND COOPERATION IN EUROPE

January 13, 1993

The Honorable James Baker
Chief of Staff
The White House
West Wing, First Floor
1600 Pennsylvania Ave.
Washington, D.C. 20500

Dear Mr. Baker, JIM

I am writing to thank you for your perseverance in helping initiate the planned relocation of the National Science Foundation (NSF).

The contract signing and delivery of the first truck load of NSF equipment to the new site in Arlington last Friday were important signals to taxpayers that no government agency will be permitted to block cost-saving measures.

I appreciated your assistance in a matter that consumed more time than it ever should have, and I salute you for your contribution to its resolution.

Thanks again and best wishes.

Sincerely,

Frank R. Wolf
Member of Congress

FRW:jp

THANK YOU

I wish you + your family the very best. GOD BLESS

To CF

FRANK R. WOLF
10TH DISTRICT, VIRGINIA

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COMMISSION ON SECURITY AND COOPERATION IN EUROPE

January 13, 1993

Mr. Robert B. Zoellick
Deputy Chief of Staff
The White House
West Wing, First Floor
1600 Pennsylvania Ave.
Washington, D.C. 20500

Dear Bob:

I am writing to thank you for your perseverance in helping initiate the planned relocation of the National Science Foundation (NSF).

The contract signing and delivery of the first truck load of NSF equipment to the new site in Arlington last Friday were important signals to taxpayers that no government agency will be permitted to block cost-saving measures.

I appreciated your assistance in a matter that consumed more time than it ever should have, and I salute you for your contribution to its resolution.

Thanks again and best wishes.

Sincerely,

Frank R. Wolf
Member of Congress

FRW:jp

Done
CC to Nick Calio
1/14

Withdrawal/Redaction Sheet
(George Bush Library)

Document No. and Type	Subject/Title of Document	Date	Restriction	Class.
01. Letter	From: Robert B. Zoellick to Ambassador Andreas van Agt Re: Horst Krenzler's letter [redaction of personal information] (1 pp.)	01/14/93	(b)(6)	

Collection:

Record Group: Bush Presidential Records
Office: Chief of Staff to the President, Office of the
Series: Baker, James A. III, Files
Subseries: Chronological Files
WHORM Cat.:
File Location: Chron File: January 1993 [Baker, James A., III, Files]

Date Closed:	6/2/2003	**OA/ID Number:**	93001-001
FOIA/SYS Case #:	2000-0715-F	**Appeal Case #:**	
Re-review Case #:		**Appeal Disposition:**	
P-2/P-5 Review Case #:		**Disposition Date:**	
AR Case #:		**MR Case #:**	
AR Disposition:		**MR Disposition:**	
AR Disposition Date:		**MR Disposition Date:**	

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P-1 National Security Classified Information [(a)(1) of the PRA]
P-2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P-3 Release would violate a Federal statute [(a)(3) of the PRA]
P-4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P-5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
P-6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.

PRM. Removed as a personal record misfile.

Freedom of Information Act - [5 U.S.C. 552(b)]

(b)(1) National security classified information [(b)(1) of the FOIA]
(b)(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
(b)(3) Release would violate a Federal statute [(b)(3) of the FOIA]
(b)(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
(b)(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
(b)(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
(b)(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
(b)(9) Release would disclose geological or geophysical information

THE WHITE HOUSE

WASHINGTON

January 14, 1993

Dear Ambassador:

Thank you for sending me the advance copy of Horst Krenzler's letter. And thank you as well for your kind words.

I, too, have enjoyed our opportunity to work together. We have accomplished a number of important objectives, pushed others closer to completion, and launched many more. I trust, with your ongoing help, that the EC and the U.S. will make even more progress in the future. If you think I can ever be of help on these or other topics in the future, please don't hesitate to contact me; you know that I remain personally committed to strong ties between Europe and the U.S.

Sherry and I look forward to joining you at your dinner for Ambassador Dyvig later this month.

With best regards,

Sincerely,

Bob Zoellick

Robert B. Zoellick
Deputy Chief of Staff

[redacted]

Ambassador Andreas van Agt
Delegation of the Commission
of the European Communities
2100 M Street, N.W. - 7th Floor
Washington, D.C. 20037

DELEGATION OF THE COMMISSION
OF THE EUROPEAN COMMUNITIES

The Head of the Delegation

12 January 1993
358ava/acs

HAND DELIVERY

The Honorable
Robert Zoellick
Deputy Chief of Staff
to the President
The White House
Washington DC 20500

Dear Mr. Zoellick,

I have been requested by Mr Horst Krenzler to forward an advance copy of his letter of 8 January 1993 addressed to you. The original will be forwarded as soon as it is received from Brussels.

I also wish to take advantage of this opportunity to say that I and the Delegation have very much enjoyed working with you over the last few years and wish you every success in your future.

Yours cordially,

Andreas van Agt

Andreas van Agt
Ambassador

2100 M Street NW 7th Floor Washington DC 20037 Telephone: (202) 862-9500 / FAX: (202) 429-1766 / Telex: 64215 EURCOM UW

COMMISSION
OF THE EUROPEAN
COMMUNITIES

Brussels, 08.01.93

000293

DIRECTORATE-GENERAL
EXTERNAL RELATIONS

The director general

Mr Robert Zoellick
Deputy Chief of Staff
The White House
Washington DC
USA

Dear Bob,

Now that your period in office is drawing to a close I thought I would write to say how much I have appreciated working with you over the last four years.

It has been a hectic period, a time of great change, the disappearance of old certainties, and the search for new structures and insights. Your contribution to filling this intellectual gap has been outstanding and both the European continent and the Transatlantic relationship have profited as a result.

I hope very much that the next stage in your career will be as exciting and as rewarding, and that you will stay closely in touch with us whatever you are doing.

With warm personal regards,

Sincerely,

Horst

Horst G Krenzler

Rue de la Loi 200 – B-1049 Brussels – Belgium

Telephone: direct line 299.00.97 exchange 299.11.11 – Telex COMEU B 21877 – Telegraphic address COMEUR Brussels – Telefax 299.02.03

585 MARLIN COURT
REDWOOD CITY CA 94065 12/08/92

Senators Lloyd Bentsen, John Chaffey, Robert Dole, Strom Thurmond, & Richard Lugar, Malcolm Wallop & Others.

Most of us fought in WW II, and we said "never again, as regards genocide; death camps, sealed trains, & murder of women and children. This is what George Shultz said on PBS McNeil-Lehrer tonight.

A strong Republican over the years, I am including Senator Bentsen in this note, because what we are talking about is morality and decency, and not politics.

What we were referring to — when we said "never again" — has been happening in the former Yugoslavia for over a year. And George Bush has proved to be, in retrospect, another Chamberlain — perhaps even worse. Because he had full knowledge of what is going on, and did nothing.

I now regret his absolute failure to lead

in this crisis, as much as the failure of any other President in memory. His inaction sold out every man & woman who died in World War II. Margaret Thatcher and George Shultz are right to advocate strong action, and George Bush is tragically wrong regarding the Yugo-Slavian genocide.

Certainly we were right in the Gulf War. But what happened to the war crimes indictments against Saddam Hussein and his gang for the Kuwait City atrocities and setting fire to the oil fields?

Certainly we are doing the right thing in Somalia. No one can oppose that relief effort, tardy as it may be.

But compared to the organized butchery, torture and terror in Yugoslavia directed by one madman & master demagogue, Slobodan Milosevic, the famine & anarchy in Somalia is pale tea.

Up to this point, George Bush and his foreign policy advisors have betrayed the free world by their cowardice and inaction.

If George Bush cannot summon the will to lead against Miloserić's Nazis, must we wait until January 20th to try to persuade a new President to do the only right and necessary thing? Do we want to see Sarajevo fall and 100,000 people perish — many butchered in the main square — on George Bush's watch?

You and I know that the Somalia operation must be carried to a successful conclusion. But you and I know that it is a TV sideshow, a media event — compared to Yugoslavia.

You and I know that a deadline to Miloserić's gang followed by one stiff bombing raid on his artillery will do more to save "the new world order" than all the Marines in Somalia, even though there would be no TV coverage.

To the argument that we have a full plate — we are overcommitted, remember December 7, 1941. We had a full plate then. But we did not engage Japan, and let Hitler alone to have his way in Europe.

To the argument that the Europeans are cowards — that they have the responsibility — I concur. But you and I know that without a swift kick and firm leadership from America, nothing can be done. After all, are we the leader of the Free World, or are we not?

George Bush's foreign policy has lost its morality and its bearings. George Bush must now be forced to reverse his course on Yugoslavia.

Robert M Prestidge
Lieut USNR 185926

POSTSCRIPT: I have written to the Administration asking for action on 5-25, 6-3, 6-11, 6-26, 7-27, & 9-4. Copies of letters to them available upon request.

R. M. Prestidge
585 Marsh Court
Redwood City CA 94065

USA
29

Robert Goelick
& White House Chief of Staff
White House
Washington DC 20500

Z,

I suggest sending to
Central Files,
no response necessary
OK? V

Co 12/14

12/31/92
585 MARLIN COURT
REDWOOD CITY CA 94065

Robert Zoellick, Acting Chief of Staff
The White House

Dear Mr. Zoellick,

Thank you for your reply several weeks ago to my letter supporting the President (re "Free Trade Forever").

I want to send you and the President the following thought.

Don't let up — the next 20 days are critical. Our commitment to Freedom, Morality, & Democracy demand the President keep fighting for what is right until the last second of his Stewardship. This demand is even more obligatory because of the Naval Officer's "Best Estimate of the Situation".

I must be brutally frank. Evidence indicates based on past performance that the President's successor is a man with a visceral dislike of the military. He has shown that following bold campaign rhetoric — he is a man paralyzed by indecision & conflicting advice. His past indicates that in many ways he seems to be a closet Buchananite — Isolationist.

I believe Slobodan Milosevic and the Russian military understand and read Clinton. The old Slavic proverb — "Codoba Lecendamus

He Kopmeem" - Fine fables will not feed the Nightengale" - those words define him. Milosevic & the Russian right know he is soft and a bluffer.

Therefore, use the 20 days wisely and to the hilt. For the sake of World Peace the following are essential.

(1) Get the No-Fly Zone ineffect.

(2) Get arms to the Bosnians - even if we have to do it alone & shake up the UN.

(3) If at all possible, deliver a hard air blow at Milosevic. There is no need to wait for further negotiation as Bhutros Ghalli is always doing. You & I know that the Serbs are already practicing "quiet ethnic cleansing" in Kosovo.

If President Bush acts - even tho Mr. Clinton may wish to back out, he cannot. Not after all his posturing about taking tougher action against the Serbs!

Play the game hard until the final second. Those last 20 days could save Europe.

Best Regards, Robert M. Bostick Jr. LTUSNRet 18 Sep 26

cc Geo. Bush

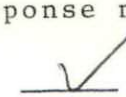
R M Prestridge
585 Marlin Court
Redwood City CA
94065

SAN FRANCISCO CA
31 DEC
1992

Robert Zoellick, Acting Chief of Staff
The White House
Washington DC
20500

Z,

I recommend sending
to Central Files,
no response necessary

ok? 

Co 1/4

C. Files

Frank J. Ball
4 Atlantic Street
Charleston, South Carolina 29401

Mr. James Baker

I'm hope that some of this gets through and helps or intrigues some one of your three.

Frank J. Ball

January 13, 1993

4 Atlantic Street
Charleston, SC 29401

President George Bush
Mr. James Baker
Mrs. Barbara Bush

Dear Mr. President, Mr. Baker, and Mrs. Bush,

Today your staff and Dr. Burton Lee received the enclosed letters dealing with the demonstrated critical importance of correcting magnesium deficiency (little used up to now in this country) to more effectively and quickly control heart, artery, and arrythmia problems. Also discussed was the recently demonstrated oral use of non-toxic gamma-linolenic acid (present in evening primrose oil, human milk and your cells) to effectively reduce or completely control arthritis, other inflammatory problems, and even cancer.

The first page of my letter happened to mention the comment in a letter to interested rheumatologists almost a year ago (at the time of your annual physical) concerning potential future use of oral gamma-linolenic acid for the presidents right hip joint.

Today our newspaper indicated at your annual physical exam you got a clean bill of health; but also got a cortisone shot to relieve arthritis pain in your left hip which sounds like last years minor problem might have worsened some. Almost thirteen years ago in the hospital, I was concerned about the cortisone shots in my shoulders; but was told they might freeze solid. I am not suggesting any similarity between my problem and yours; except that the same approach that worked for me appears generally useful in arthritis. A number of close friends use it to remove small pain problems with their golf swing, etc.

The purpose of this letter is to send the exact same set of letters that I sent to Senator Ernest F. Hollings, when he requested information on the phone over two years ago on the therapeutic use of evening primrose oil to control arthritis; for possible use by the wife of one of his colleagues. I do not know whether or not it was ever tried or found effective.

I very much hope the president does not have any further problems; but still felt it worth while to send on this additional information.

With heartfelt thanks again for your unbelievable twelve year contributions,

Frank J. Ball

FJBkaj

cc: Dr. Burton Lee, III
Dr. James E. Edwards
Senator Ernest F. Hollings
Senator Strom Thurmond
Representative Arthur Ravenel

October 11, 1991

Senator Ernest F. Hollings
Senate Office Building
Washington, D. C.

Dear Fritz,

My sincere apologies for the very long delay in responding to your request made in one of our phone conversations that I send you information on the therapeutic use of evening primrose oil for the control of rheumatoid arthritis. You knew that I had successfully used it over the past decade to stop my earlier severe rheumatoid arthritis problem, and were interested in passing this information on to an important colleague of yours whose wife had developed rheumatoid arthritis.

****

Fritz, right here I am having the typist insert an addendum to the letter that had already been typed.

I had earlier tried to catch Dr. Robert Zurier (now Director of Rheumatology, University of Mass Medical in Worchester) to mention to him that I was recommending in the last paragraph of this letter that if your colleague was interested in trying gamma-linolenic acid to control rheumatoid arthritis that he contact Dr. Zurier. He is both a medical doctor, and a very active research scientist particularly on the effects of the anti-inflammatory cellular hormone, (Prostoglandin E-1) on cells, animals and humans. I had contacted him in late 1980 or early 1981 shortly after I found out that combined evening primrose and Vitamin C seemed to have successfully controlled my rheumatoid arthritis without the daily 12 - 14 aspirins and 6 Motrins that I had to take throughout most of 1980 to lower my pain and improve my ability to move around.

Dr. Zurier has just told me that he had just completed a quite successful double blind study using oral borage oil containing gamma-linolenic acid from Great Britain on 14 rheumatoid arthritic patients and placebo on 13 similar patients. Last week he had reported on this trial at the Joe Hollander Lecture at University of Pennsylvania Medical; and had given a talk on it at Worchester this week. I knew he had this study underway. Had I known the double blind test was completed successfully this would have been a much shorter letter without my earlier letters and Zurier's earlier paper trying to give enough back ground to convince. I'm leaving my letter and attachments as prepared; since you claim to have read through some of my very long medically related letters sent to you off and on over the past 13 years. Note on page three of the attachment from my long August 1979 letter on Vitamin C, hydrazine sulfate, and cancer sent to you that I happened to have picked up and reported on the relationship between Vitamin C and Prostaglandin E-1 formation about six months before I came down with severe rheumatoid arthritis; and about a year before I began taking Vitamin C and evening primrose oil to try and control rheumat oid arthritis. This happens to be described in my December 22, 1980 letter on page 32 of this attachment which was included with my other earlier letters to various medical personnel around the world beginning on attachement page 13.

I am also enclosing a snapshot of Dr. Zurier that might interest your colleague which was taken in Washington at the March 20-23, 1990 Second International Conference on Health Effects of Polyunsaturated Fatty Acids in Seafoods. These are even more

unsaturated fats which produce three-series prostaglandin hormones. I happened to have talked on the phone with Dr. Zurier on the 21st (I paid for the 47 minutes). He mentioned that he was not on the program, but had been invited to come there and give a talk on his studies employing gamma-linolenic acid in rheumatoid arthritis during their session on Rheumatoid Arthritis and Inflammatory Mediators on the 22nd. I fortunately caught a plane in an hour to this interesting session; and now also take a fish oil capsule. This was a mighty long inserted paragraph; but pertinent to one in pain who also has trouble moving about.

****

I have generally been careful in passing on any therapeutic type information picked up in my intensive medical literature studies except to medical scientists, doctors, family contacts, and close friends familiar with my effort and experience. I don't hesitate to say that I take particularly high levels of antioxidants (Vitamin C, E, and beta-carotene) and feel 500 mg. of magnesium as the oxide or chloride is desirable unless you have severe kidney disfunction.

Vitamins, critical minerals, antioxidants and essential fatty acids such as gamma-linolenic acid in evening primrose oil often take months to build up to beneficial levels in the cells of people our age. In the past several years the likelyhood of low body levels, and the benefits of high body levels of such nutients in inhibiting various degenerative diseases during aging have become much clearer. The particular degenerative disease that may bother you most depends on your own genetics, life conditions, and disease exposures.

My own reading and experience indicates to me that I will have to take high levels of authentic evening primrose oil or another gamma-linolenic acid source for the rest of my life to prevent overactivity or uncontrolled division of possibly transformed cells in my joints.

Your colleague knows nothing about me or my experience; and if his wife decided to try evening primrose oil she may not get benefit for several months. Since this makes it unlikely she will try it, I am enclosing some underlined copies of letters I have written to rheumatologists and others about my situation. Also enclosed is a October 1990 paper from Arthritis and Rheumatism by Dr. Robert B. Zurier and others at University of Pennsylvania Medical. His enclosed paper, Alteration of the Celular Fatty Acid Profile and the Production of Eicosanoids in Human Monocytes by Gamma-Linolenic Acid, deals with how oral gamma-linolenic acid that we are supposed to adequately produce in our cells can affect the inflammatory prostaglandins and leukotrienes in animal models. The paper also presents the apparent clinical improvement in 6 of 7 rheumatoid arthritis patients who were given about a gram of gamma-linolenic acid daily in borage oil capsules. I take about two thirds of that daily in evening primrose oil capsules.

I called Dr. Zurier a few months after I fortunately brought my severe rheumatoid artritis under control in 1980 without continued use of drugs using 4 grams daily of evening primrose oil (EFAMOL that I had been able to get from Dr. David Horrobin in Montreal) along with an equal amount of Vitamin C. I now find that I need 7.5 grams of authentic evening primrose oil and take 6 grams of Vitamin C.

Dr. Zurier had been conducting extremely interesting studies on the effects of the cellular hormone, Prostaglandin E - 1, which is produced from the gamma-linolenic acid that is present in our cellular membranes. Our cells usually produce adequate levels of this precursor of our anti-inflammatory cellular hormone, Prostaglandin E-1, by desaturating the linoleic acid present in vegetable oils and plants. Depending on our specific genetics,

extent of cellular aging, and certain retroviral invasions; then different sets of our cells can apparently inadequately produce gamma-linolenic acid which causes localized inflammation as with the joint cells in rheumatoid arthritis.

Whereas I have always used evening primrose oil you will note Dr. Zurier used borage oil which was made available to him when he was on a six month fellowship in London in 1986. He and I were at the London annual meeting of the British Society of Rheumatology in November, 1986, where Doctors JJF Belch and R. R. Sturrock presented the first successful double-blind trial on the use of 6 grams per day of EFAMOL (with and without fish oil) compared to placebo on 49 rheumatoid patients.

Dr. Zurier, now chairman of Rheumatology at the University of Mass. Medical in Worchester, is apparently just about to complete a double blind study on rheumatoid patients using borage.

Dr. David Horrobin is a very widely published Canadian prostaglandin scientist who has been amazingly innovative, perceptive, and dynamic, and seems largely responsible for the therapeutic success in a number of really novel disease trials currently being conducted worldwide. Adequate oral evening primrose oil is used to provide sufficient gamma-linolenic acid, which is the precursor of the inflammatory-inhibiting one-series of prostaglandins. This is proving to be an effective alternative to the almost universal approach of using a host of different drugs (aspirin, ibuprofen, etc., etc.) to progressivly inhibit the conversion of the precursor (arachidonic acid from meats and fish) of our inflammatory two-series prostaglandins. The latter keeps us from bleeding to death when injured; but are the source of an awful lot of pain, thromboses, etc.

Dr. Horrobin recently sent me a copy of the 44 Chapter 600 page book he edited: Omega-6 Essential Fatty Acids: Pathophysiology and Roles in Clinical Medicine. It deals mainly with a very broad range of disease problems where disturbances in the proper distribution of gamma-linolenic acid and other prostaglandin precursors often seem to be a major factor. Since I had already purchased , largely read, and underlined my copy; I'll pass his on to the medical library and hope others read it.

Oral evening primrose oil has been very successful in five double blind trials in England for the control of atopic and infantile eczemas; and now the British Health Service pays for it as EPOGAM in handling this serious problem. One of my brothers had infantile eczema and I can thus truly appreciate what a great benefit this simple cure for that infant malady (that you grow out of) would be for the child and the family

This is getting too complex; and since Dr. Robert Zurier is the most scientifically and clinically active in this country relative to the use of gamma-linolenic acid for rheumatoid arthritis; your colleague might be interested in contacting him.

Sorry it's such a long letter, but my experience is that where there is not yet medical acceptance, people really have to truly understand why they might benefit. This is also needed for them to continue to stay with it when they are later doing fine.

I am leaving tomorrow morning at 6:30 am to attend the American College of Nutrition annual meeting in Clearwater Beach until Monday night. I will then join Mary Lib in New Orleans where our son, Stuart, is an opthamologist at LSU medical. There are also three of our nine grandchildren, all under seven.

All the best,

Cappy

Frank J. Ball

Dr. J. J. F. Belch
Dr. J. Booyens
Dr. David Horrobin
Dr. Carwile Le Roy
Dr. R. D. Sturrock
Dr. Robert B. Zurier

Ps: A letter from David Horrobin indicates EFAMOL will be used this year in a multi-location double-blind placebo study on 500 rheumatoid arthritis patients; but dramatic results are not to be expected for many months.

attachment to Oct. 10th 1991 letter to Senator Ernest F. Hollings (1)

Frank J. Ball
4 Atlantic Street
Charleston, S. C.

PERTINENT INTERRELATIONSHIPS BETWEEN CANCER, RHEUMATOID ARTHRITIS, THE EVENING BLOOMING PRIMROSE AND THE GREEN-LIPPED MUSSEL

(Memory Jogger for Presentation: May 19, 1981)

CANCER TISSUE

Completely different from normal cells in that 60-99% of nutrients are fermented to lactic acid rather than almost total oxygenation to carbon dioxide.

Cancer invasivness promoted by:

1. High continual release of collagenase enzyme by cancer tissue breaks down the external collagen ropes that enmesh near-by cells.
2. The semi-rigid gelled water which binds together adjacent cells and collagen ropes is made fluid by release of hyaluronidase enzyme which can depolymerizes the soluble hyaluronic polymer gell.

Recent evidence indicates cancer tissue is composed of up to 85% activated, but incompetent defensive macrophages (very large white cells). These produce collagenase, hyaluronidase, lactic acid, and toxic superoxide; and could be a major part of the problem.

Recently found that the protective enzyme (SOD) that destroys superoxide was very low or absent in cancer cell mitochondria where nutrients must be oxidized.

Cancer patients exhibit extremely low Vitamin C blood levels and are low in zinc.

Prostaglandin E_2 (PGE2, an inflamatory cellular hormone) runs quite high in cancer patients. Cancer cells appear to lose the capacity to convert polyunsaturated fats to gammalinolenic acid. This precursor of PGE1, appears to be needed to inhibit excessive PGE2 formation.

RHEUMATOID ARTHRITIS JOINTS

Involved joints produce high lactic acid levels which may be one cause of pain.

Joint problems partially involve:

1. Collagenase release attacks the collagen lining of the joint.
2. Detrimental thinning of the jelled joint lubricant by depolymerization of the dissolved hyaluronic polymer gell.

Macrophages activated by injesting uric acid crystals in joints appears to be the cause of gout. High levels of activated macrophages, which live for months are in rheumatoid joints.

Superoxide dismutase (SOD) enzyme from cattle gave reduced inflamation and pain on rheumatoid patients.

Rheumatoid patients run quite low in Vitamin C levels and their blood is often one-third down in zinc and histidine.

Inflamatory PGE2 in the joints is generally acknowledged as the main cause of swelling and pain in rheumatoid arthritis. Pain reducing aspirin and similar drugs inhibit the oxygenation of arachidonic acid which otherwise is converted to the inflammatory PGE2.

Evening Blooming Primrose Seed Oil

Dr. David Horrobin, a leader in prostaglandin research and thinking, showed PGE1 can inhibit PGE2 formation and may correct immune T lynphocyte defects, but its half life is only about a minute and its effectiveness occurs only over a precise ultra low concentration range. He postulated beneficial use of the only available gammalinolenic source (Evening Primrose Oil) to boost continuous PGE1 formation in possible treatment of arthritis, scleroderma, cancer, multiple sclerosis, or selected collagen and autoimmune diseases.

Dr. Robert Zurier, Chairman of Rheumatology, Univ. Pennsylvania Medical, demonstrated the ability of PGE1 to reverse the severe symptoms (identical to the arthritic disease, systemic lupus) which are spontaneously generated in the hybrid cross of New Zealand black and white mice (NZB/W). He also showed that the presence of PGE1 could prevent the usual arthritic symptoms developed in mice on injection of Freund's adjuvant.

Horrobin and others showed that at physiological blood concentrations Vitamin C, Vitamin B_6, zinc, histidine and ethyl alcohol selectively promote formation of PGE1 from gammalinolenic acid. There is significant research and medical literature suggesting some benefits from each of the first four of these in rheumatoid arthritis. Vitamin C also appears most important in promoting cancer control.

Vitamin C strongly inhibits collagenase formation, is required for collagen fiber formation, is a necessary cofactor in over 50 enzymes and decomposes toxic superoxide. Promotion of PGE1 formation, however, may constitute a major mode for many of its beneficial actions.

Extract of the Green-Lipped Mussel (Perna Canaliculus)

Last month, on an Australia-New Zealand trip, a freeze dried extract (SEA TONE), which was produced from a local mussel extract was noted to be marketed in drug stores as a food supplement. The 1979 book "Relief from Arthritis - A Safe and Effective Treatment from the Ocean" covering this green-lipped mussel extract gave no convincing evidence, but a reliable physiotherapist there reported observing a surprising beneficial response in two patients taking it.

A computer search of the medical literature turned up no pertinent literature studies on shell fish extract in control of arthritis, but some impressive demonstrations of cancer control in animals using extracts from clams (mercenaria mercenaria). Clams had been selected for evaluation as they were found surprisingly free of any cancer growth. Clinical studies were not conducted, but experiments on various cancer cells and oral use in various animal cancer studies seem to show quite encouraging efficacy.

6. P. W. A. Mansell and N. R. DiLuzio have reported encouraging clinical results in the chapter "The In Vivo Destruction of Human Tumor by Glucan Activated Macrophages", in Book 3, pages 227-243.

7. White blood cells are activated and emit chemiluminesence presumably because of superoxide radical release; when intact yeast cell wall (zymosan) is added and picked up (B. M. Babior, Book 1, pages 277-281). Zymosan from which DiLuzio extracts the active Glucan has been known to be active against implanted solid animal tumors since 1940; and a number of animal studies have been conducted with it.

Activated but Unsuccessful Macrophages in Diseases of the Joints (?)

1) Macrophages are remarkable defenders when properly armed and supplied; since they can multiply as needed, consume large quantities of bacteria, consume dead cells, kill and then consume cancer cells larger than themselves, excrete chemicals that slow down the division of other cells, etc. If they are activated; and are not able under the existing body situation (such as low blood ascorbic acid) to complete their job and return to the resting state; then macrophages seem to continually release superoxide radicals from their membrane and secrete collagenases. This should result in inflamation, breakdown of the lubricating hyaluronic acid polymers, (J. M. McCord, Science 185, 529 (1974)) and decomposition of adjacent body collagen. In essence, as may be happening in cancer, the inadequate macrophage could become a major source of a continuing disease problem.

2) In gout the macrophages quite clearly phagocytize the sodium urate crystals that sometimes precipitate from our blood when high levels of protein are consumed. This happens because humans long ago lost the capability to convert their relatively insoluble uric acid to soluble allantoin, like other animals do (Book 9, pages 1647-1660). Since the macrophage wasn't designed to handle sodium urate crystals it doesn't quickly complete the job and apparently keeps excreting inflammatory products. When this occurs in a joint (and it is evident in microscopic pictures) then the superoxide radicals that would be continually released should contribute to a break down of the lubrication (water - hyaluronic acid jell) and the constantly released collagenase should and does attack the collagen lining of the joint. It is not surprising that pain should be acute.

3) In tuberculosis, as mentioned earlier (page 18), the white cells can phagocytize the tuberculosis bacillus, but they cannot completely kill it off. Their constant attempt seems to account for the internal formation of tubercles in the lung.

4) Off and on browsing through the various arthritis sections in my copy of Book 9 and the later Book 8 during vacation, left the strong impression that releases from variously activated, but "inadequate" macrophages could be a major factor in the unattractive aspects of a number of arthritis and similar type diseases. Pain problems apparently occur from an inflamatory release of "toxins" into the synovial fluid of the joints. One "toxin" seems to be superoxide, probably from "inadequate" white cells in the joints, since injection

of a soluble superoxide dismutase enzyme (Orgotein) from the red cells of cattle reduces inflammation and joint pain in horses and dogs. This enzyme is reported to be nontoxic, nonallergic, and to give quite encouraging results in clinical trials controlling inflammatory and thus pain problems in animals and man (Book 1, pages 516-549). We will thus presumably be hearing a lot more of it in the future.

5) Sufficient ascorbic acid in our plasma will also get rid of inflammatory superoxide radicals as they oxidize ascorbic to dehydroascorbic acid. Ascorbic also energizes macrophages, turns off the attack of released collagenase on joint linings, and promotes decomposition of any inflammatory histamine.

6) Dropping of ascorbic acid levels (page 16) with aging could be one large cause of the "normal" degenerative joint response to aging. Adequately higher ascorbic and other vitamin levels, it seems, should slowly reverse collagen degeneration and bone distortions in the active joints.

Macrophages in Human Cancer

1. Just before mailing this letter, a Cancerline computer search was made to try and determine if human cancer tissue exhibited cellular contents of macrophages near the high values found in the induced and implanted rat tumors.

2. Although induced and implanted rat tumor tissue contained from 2 to 68% macrophages, it was still an open question to what extent human tumor tissue contained macrophages. The human immune system has seemed relatively ineffective against human cancer when it has reached the size at which it is usually detectable. This could be because the macrophage wasn't attracted to the tumor or it wasn't very viable in the human tumor.

3. Three pertinent recent papers were found, which in total seem most encouraging; and also give the answer why it wasn't realized that human cancer tissue can actually be composed of a high percentage of macrophages.

4. The paper, "Mononuclear Cell Content of Human Solid Tumors", by E. M. Hersh, et. al. (Med. Pediatr. Oncol 2, 1-9 (1976) assessed 28 primary and 17 metastatic solid human tumors for cancer and mononuclear type cell content by light microscopy and lymphocyte stimulation to blasto-genesis. On average there were about 13.5% lymphocytes and this dropped to 5% in the metastatic tumor tissue. What appeared to be macrophages only constituted about 1% of the solid tumor tissue cells. The Lymphocytes, however, are attracted to the solid tumor in substantial numbers and they exhibited a 96% viability. Very few macrophages could be detected by optical microscopy; and their identification was not certain.

5. The paper "The Significance of the Macrophage Content of Human Tumors" by C. L. Gauci, was found in the Swiss book "Lymphocytes, Macrophages, and Cancer (1976)" edited by G. Mathe, I. Florentine and M. C. Simmler. Using the same immunological technique of Robert Evans on page 9 to detect macrophages, Gauci first evaluated a rat benzopyrene-induced sarcoma (HSBPA) and a rat

Vitamin C and immunity: an assessment of the evidence

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Clin. exp. Immunol. (1978), 32, 370–379

SUMMARY

The high concentration of ascorbate in leucocytes and its rapid expenditure during infection and phagocytosis suggests a role for the vitamin in the immune process. Evidence published to date shows an involvement in the migration and phagocytosis by macrophages and leucocytes, as well as the induction and expression of delayed hypersensitivity. Its effect on antibody production and complement levels is controversial but probably minimal. This study suggests there is room for further investigation into the effect of ascorbate on immunity, particularly with defined populations, but cautions the use of megadose therapy.

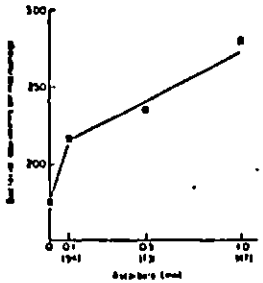

Fig. 1. Phagocytic activity of peritoneal macrophages after incubation with media supplemented with ascorbate. Monolayer cultures of mouse peritoneal macrophages were incubated for 20 hr with the concentration of ascorbate shown. Media containing fresh ascorbate was then added and after 1 hr these shaken to phagocytose heat-killed radiolabelled *Pseudomonas aeruginosa* was measured. Results are the mean of three cultures and show the amount of radioactivity, in bacterial equivalents, accumulated after 2 hr incubation in media containing 10^8 – 10^9 bacteria per ml. Details of the method used have been published [Thomas, Holt & Keast, 1978]. Some cell death occurred during the incubation and the percentage viability of the cultures is shown in parentheses.

Vitamin C Regulation of Prostaglandin E1 Hormone Formation

While looking for the latest information on macrophages in human cancer, I looked into the August 1979 issue of Medical Hypotheses, and found (p. 849-58) an article by D. F. Horrobin, et. al., entitled THE REGULATION OF PROSTAGLANDIN E1 FORMATION: A CANDIATE FOR ONE OF THE FUNDAMENTAL MECHANISMS INVOLVED IN THE ACTIONS OF VITAMIN C. Dr. Horrobin is at the Clinical Research Institute of Montreal and wrote the book, Prostoglandins: Physiology, Pharmacology and Clinical Significance (1978). He reviewed in this paper as indicated in the abstract below the potential significance of his recent publication (Prostaglandins Med. 3: 129-37, 1979) which showed that ascorbic acid enhances the formation of prostaglandin hormones, such as PEG1.

ABSTRACT

Vitamin C stimulates the formation of PGE1 in human platelets. The effect occurs over the physiologically relevant range of concentrations. PGE1 is required for T lymphocyte function and plays a major part in the regulation of immune responses. PGE1 is also important in the regulation of collagen and ground substance metabolism, in cholesterol metabolism and in regulation of responsiveness to insulin. It is proposed that defective formation of PGE1 could account for many of the features of scurvy and for many of the reported therapeutic effects of vitamin C. If correct, vitamin C will be of value only in conjunction with an adequate supply of dihomogammalinolenic acid, the precursor of PGE1. Essential fatty acids, pyridoxine and zinc are

Since the conversion of linoleic acid to dihomogamma linolenic acid also involves oxygenation with lipoxygenases (Book 2, pages 29-79; Mats Hamberg, et. al., "Fatty Acid and Steroid Metabolism") it seems possible that ascorbic may also be beneficial in that conversion

Since both the lymphocytes and macrophages seem the most important defensive white blood cells in resisting cancer, this additional information indicates how the low ascorbic acid levels found in cancer patients might damage their immune capability.

As it is not certain how many macrophages there are in a cancer; it seems propitious to try both high levels of ascorbic acid, and to improve the odds and quality of life by use of hydrazine sulfate. Hopefully, stimulation of macrophage division through use of glucan or other non-toxic polysaccharides will develop as still another natural approach to stimulate our immune system to control cancer.

With sincere admiration for your effort, courage, and progress in fighting back this scourge!

Most sincerely,

Frank

Frank J. Ball

CC:
Dr. G. G. Allan
Dr. J. A. Austin
Dr. B. M. Babior
Dr. Prioleau Ball
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Also to distribution of July 14,1978 letter to Dr. H.B. Gregorie

Medical Hypotheses 5:849-858, 1979

THE REGULATION OF PROSTAGLANDIN E1 FORMATION: A CANDIDATE FOR ONE OF THE FUNDAMENTAL MECHANISMS INVOLVED IN THE ACTIONS OF VITAMIN C.

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ABSTRACT

Vitamin C stimulates the formation of PGE1 in human platelets. The effect occurs over the physiologically relevant range of concentrations. PGE1 is required for T lymphocyte function and plays a major part in the regulation of immune responses. PGE1 is also important in the regulation of collagen and ground substance metabolism, in cholesterol metabolism and in regulation of responsiveness to insulin. It is proposed that defective formation of PGE1 could account for many of the features of scurvy and for many of the reported therapeutic effects of vitamin C. If correct, vitamin C will be of value only in conjunction with an adequate supply of dihomogammalinolenic acid, the precursor of PGE1. Essential fatty acids, pyridoxine and zinc are all required to achieve this.

INTRODUCTION

Although the clinical features of vitamin C deficiency are well known, there is still no fully convincing explanation of its actions at the cellular level. This lack of understanding of a fundamental biochemical mechanism may have contributed to resistance to the use of vitamin C as a therapeutic agent even though there is relatively good evidence of its value in a number of situations. We have recently discovered that over a physiological range of concentrations vitamin C enhances the conversion of dihomogammalinolenic acid (DGLA) to prostaglandins (PGs), particularly PGE1, in human platelets (1). We suggest that this mechanism can account for many of the known actions of vitamin C and reveals that therapeutic results are to be expected only if adequate supplies of DGLA are available.

By far the best documented effects of vitamin C are those on collagen and ground substance and on resistance to infections. Severe vitamin C deficiency in humans and other species which cannot manufacture it themselves leads to a widespread disruption of collagen, susceptibility to a variety of infections, weakness, depression, elevated cholesterol levels, resistance to

Medical Hypotheses 6: 469-86, 1980

THE REVERSIBILITY OF CANCER: THE RELEVANCE OF CYCLIC AMP, CALCIUM, ESSENTIAL FATTY ACIDS AND PROSTAGLANDIN E1.

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ABSTRACT

Transformed cells in culture can be normalised (made to undergo reverse transformation) by exposure to cyclic AMP, prostaglandin (PG) E1 and certain drugs. One of these drugs, thioproline, has been successfully used in treating human cancer. All cancer cells have a number of common characteristics: they exhibit aerobic glycolysis, they fail to show feedback regulation of cholesterol biosynthesis, they do not regulate cytoplasmic calcium levels normally and they produce excessive amounts of 2 series PGs. It has been known since 1975 that transformed cells cannot make PGE1 because of loss of the delta-6-desaturase enzyme which converts linoleic acid to gamma-linolenic acid. There is evidence that PGE1 acting in concert with thromboxane A2 has effects which make it able to reverse all the metabolic abnormalities common to all cancer cells. It is therefore argued that loss of the ability to make PGE1 and/or thromboxane A2 may be the critical step in malignant change in many forms of cancer. Restoration of normal PGE1 synthesis by providing gamma-linolenic or dihomogammalinolenic acids which will by-pass the blocked desaturase, should be of value in normalising malignant cells and reversing cancer growth. Since this approach is completely non-toxic it is here seriously suggested that it might be used as a first step in treatment of those cancers where current evidence suggests that delay in the administration of orthodox treatment is unlikely to affect prognosis.

INTRODUCTION

Cancer therapy is dominated by the idea that treatment must aim at destruction of cancer cells. The goal is to exploit some difference between the cancer cells and the normal cells which will allow the cancerous ones to be selectively destroyed. The selectivity of current chemotherapy and radiation therapy, such as it is, depends on the idea that the already damaged regulatory functions of cancer cells can be totally disrupted more easily than those of normal cells. Since the purpose of these treatments is to produce damage it is not surprising that they harm normal cells. It is thus not surprising that most cancer therapeutic agents are themselves carcinogens and vice versa. It is the thesis of this paper that a more rational aim in cancer would be the normalisation of cancer cells by techniques which

(5)

ALTERATION OF THE CELLULAR FATTY ACID PROFILE AND THE PRODUCTION OF EICOSANOIDS IN HUMAN MONOCYTES BY GAMMA-LINOLENIC ACID

SALLY PULLMAN-MOOAR, MICHAEL LAPOSATA, DIANA LEM, RALPH T. HOLMAN, LAWRENCE J. LEVENTHAL, DEBORAH DEMARCO, and ROBERT B. ZURIER

We administered borage seed oil (9 capsules/day) for 12 weeks to 7 normal controls and to 7 patients with active rheumatoid arthritis. The therapy provided 1.1 gm/day of γ-linolenic acid (GLA). GLA administration resulted in increased proportions of its first metabolite, dihomo-γ-linolenic acid (DGLA), in circulating mononuclear cells. The ratios of DGLA to arachidonic acid and DGLA to stearic acid increased significantly in these cells. Significant reductions in prostaglandin E_2, leukotriene B_4, and leukotriene C_4 produced by stimulated monocytes were seen after 12 weeks of GLA supplementation. The antiinflammatory effects of GLA administration observed in animal models, and the apparent clinical improvement experienced by 6 of 7 rheumatoid arthritis patients given borage seed oil in this open, uncontrolled study may be due in part to reduced generation of arachidonic acid oxygenation products.

Arachidonic acid (20:4 n6) is the major fatty acid substrate for cyclooxygenase and lipoxygenases in cell membranes of people who eat standard western diets. Oxygenation of arachidonic acid leads to production of mediators of inflammation such as prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4). One approach to modulation of eicosanoid production is supplementation with alternative dietary fatty acid substrates for these enzymes in an effort to generate a unique eicosanoid profile with different biologic effects. The ω3 (n3) fatty acids eicosapentaenoic acid (EPA) (20:5 n3) and docosahexaenoic acid (22:6 n3), which are prominent in fish oil lipids, inhibit formation of cyclooxygenase products derived from arachidonate (1). Diets enriched in fish oil also reduce the amount of LTB_4 generated via the 5-lipoxygenase pathway in stimulated polymorphonuclear leukocytes (PMN) and monocytes, suppress LTB_4-induced PMN chemotaxis and adherence to endothelial cells (2), reduce generation of platelet-activating factor by monocytes (3), and reduce production of interleukin-1 (IL-1) and tumor necrosis factor by peripheral blood monocytes (PBM) (4). Fish oil supplements have therefore been used in attempts to suppress inflammation in experimental models (5–7) and in patients with rheumatoid arthritis (RA) (3,8–10).

Less attention has been paid to certain plant seed oils, notably those extracted from seeds of the evening primrose and borage plants, which contain relatively large amounts of γ-linolenic acid (GLA) (18:3 n6). GLA is converted to dihomo-γ-linolenic acid (DGLA) (20:3 n6), the fatty acid precursor of the

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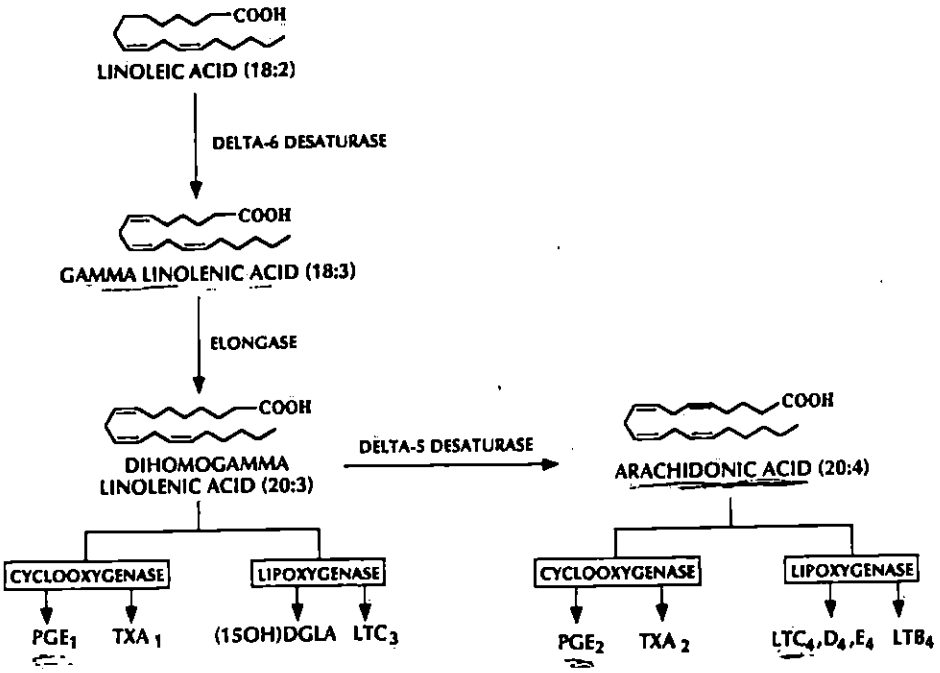

Figure 1. Metabolic pathway of ω-6 (n6) fatty acids. PGE_1 = prostaglandin E_1; TXA_1 = thromboxane A_1; (15OH)DGLA = 15-hydroxy dihomo-γ-linolenic acid; LTC_3 = leukotriene C_3.

monoenoic prostaglandins (e.g., PGE_1) (Figure 1). DGLA can also compete with arachidonate for oxidative enzymes, thereby reducing production of arachidonate-derived cyclooxygenase products (11). In addition, DGLA cannot be converted to an LTB compound (12); it is converted via 15-lipoxygenase to 15-hydroxy DGLA, which has the capacity to inhibit 5- and 12-lipoxygenase activities (13). Therefore, DGLA should have antiinflammatory actions due to its capacity to reduce synthesis of oxygenation products of arachidonic acid, which are mediators of inflammation. GLA dietary enrichment does in fact suppress acute and chronic inflammation as well as joint tissue injury in several experimental animal models (14–17). In animals treated with evening primrose or borage seed oils, cells from inflammatory exudate are enriched in GLA and its elongated product DGLA, exudate PGE_2 and LTB_4 concentrations are reduced (15,16), and leukocyte effector functions (chemotaxis, lysosomal enzyme release) are suppressed (14). Thus, the n6 fatty acids GLA and DGLA may have biologic effects analogous to those of the more extensively studied n3 fatty acids.

We therefore evaluated selected effects of borage seed oil administration on peripheral blood cells from normal controls and from patients with RA. The present effort was made to determine whether the potential antiinflammatory effects of GLA administration would be reflected in biochemical responses. The results of this study indicate that GLA administration increases the proportion of DGLA in circulating cells and reduces PGE_2, LTB_4, and LTC_4 production by PBM stimulated in vitro.

PATIENTS AND METHODS

Study design. The study, designed to evaluate the effects of borage seed oil administration on selected in vitro biochemical responses of normal controls and patients with RA, was approved by the University of Pennsylvania Committee on Human Experimentation. Seven patients (2 men and 5 women) with an age range of 26–45 years and a disease duration of 6 months to 5 years were selected for study. The 7 patients and 7 normal controls gave informed consent, and all finished the entire 12-week study. Patients had class II or class III RA according to the criteria of Steinbrocker et al (18) and met the American Rheumatism Association criteria for definite or classic RA (19). RA patients had active disease as defined by the presence of at least 3 of the following: 3 or more swollen joints, 6 or more tender joints, morning stiffness of at least 45 minutes duration, and a Westergren erythrocyte sedimentation rate (ESR) of at least 28 mm/hour.

Patients were treated with nonsteroidal antiinflammatory drugs (NSAIDs) and analgesics, and could be taking up to 10 mg prednisone/day. Patients were not receiving any

other drug, except that 2 were taking oral contraceptives. No patient had been treated with slow-acting antirheumatic drugs during the previous 6 months. No attempts were made by the examining physician to alter diet or reduce medication during the 12-week period. Patients were free to reduce the NSAID dosage if they felt better, and to reduce the prednisone dosage after consultation with the physician. Before borage seed oil treatment began, and at weeks 6 and 12 of therapy, patients were assessed with a complete blood count including differential leukocyte count, platelet count, ESR, and for levels of liver enzymes, serum creatinine, cholesterol, and triglycerides. Fertile women were also given a pregnancy test.

Normal controls were also seen at 0, 6, and 12 weeks, and laboratory studies were done at those times. Patient evaluation included duration of morning stiffness, 50-foot walk time, grip strength, number of times sleep was interrupted each night, patient assessment of disease activity on a visual 0–10 scale (0 = absent and 10 = very severe), change in medication, and joint examination. Activity of joint disease (joint score) was recorded as the sum of swelling, tenderness, and warmth (1 point for each) for all involved joints. Each patient was interviewed and examined by the same physician-investigator.

The 14 participants took 9 capsules of borage seed oil (provided by John Williams; Bio-Oil Research, Ltd., Nantwich, Cheshire, UK) daily for 12 weeks. The fatty acid profile of borage seed oil is 47% linoleic acid, 23.6% GLA, 15.1% oleic acid, and 14% saturated fatty acids (palmitic and stearic). Each capsule contained 0.5 gm of oil and 118 mg of GLA; the oil supplementation provided 40.5 kcal/day. Cells from controls and RA patients exhibited similar enrichment with DGLA and similar changes in eicosanoid production. Thus, controls and RA patients are presented as 1 group for purposes of the biochemical studies.

Individuals are identified by the same number in each table. Patients 1–7 represent the 7 RA patients, and subjects 8–14 represent the 7 healthy controls. Treatment of RA patients was as follows: patients 1 and 2 were receiving an analgesic (acetaminophen), patients 3, 4, and 5 were receiving an NSAID only, and patients 6 and 7 were receiving an NSAID plus prednisone (5 mg/day and 6 mg/day, respectively).

Isolation and activation of peripheral blood mononuclear cells (PBMC) and PBM. Leukocytes were harvested from heparinized venous blood (20), diluted 1:1 with calcium- and magnesium-poor sterile phosphate buffered saline, and fractionated with Ficoll-Hypaque to separate mononuclear from polymorphonuclear cells. PBM were obtained by adherence to gelatin-coated flasks (21). Nonadherent cells were washed off the flasks, and PBM were removed from the flasks with 5 m*M* EDTA. A cell pellet was obtained by centrifugation. Cells were resuspended in RPMI 1640 with 10% fetal calf serum, 0.1% penicillin/streptomycin, and plated at a concentration of 10^6 PBM/ml. Cell viability determined by trypan blue exclusion was routinely >90%. Stains for nonspecific esterase indicated that preparations contained >90–95% PBM. In some studies, samples of mononuclear cells (PBMC = monocytes + lymphocytes) were obtained before monocyte adherence.

PBM (1×10^6 in a volume of 1 ml) were allowed to adhere to 24-well flat-bottom tissue culture plates (16-mm wells; Linbro, Fischer Scientific, Pittsburgh, PA) for 1 hour before addition of 500 μg of heat-aggregated human IgG. Indomethacin (10^{-6} *M*) was added to selected wells at the same time. After incubation at 37°C for 19.5 hours in an atmosphere of 5% CO_2, calcium ionophore A23187 (5 μg/ml) was added to the remaining untreated PBM for 30 minutes. After 20 hours, supernatants were removed from PBM cultures, centrifuged to remove cellular debris, and stored at −70°C. Cell viability evaluated by trypan blue exclusion after the 20-hour incubation was >90%.

PGE measurements. Total PGE was measured by radioimmunoassay (RIA) (22) using an antibody (Advanced Magnetics, Cambridge, MA) that does not discriminate between PGE_1 and PGE_2 (100% crossover), and dextran-coated charcoal was used to separate free PGE from bound PGE. The sensitivity of the assay is ~30 pg, and the intraassay variation is <10%. ^{3}H-labeled PGE_2 was obtained from New England Nuclear (Boston, MA).

Leukotriene measurements. LTB_4 and LTC_4 were measured by RIA with the Amersham (Arlington Heights, IL) ^{3}H assay system.

Preparation and analysis of fatty acid methyl esters. Samples for fatty acid analysis were stored under nitrogen in 1 ml of an aqueous solution at −70°C until studied. Lipids from each sample were extracted according to the procedure of Cohen et al (23), and the fatty acids were methylated using boron trifluoride in methanol (Applied Bioscience, Paterson, NJ). The mixture of fatty acid methyl esters (FAME) was analyzed by gas-liquid chromatography using a 180-cm packed column of 10% SP 2330 on chromosorb W (Supelco, Bellafonte, PA) and a temperature program from 150°C to 250°C increasing 10°C/minute, in a Varian (Palo Alto, CA) 3700 instrument equipped with a flame ionization detector. Peaks were identified by comparing retention times of the FAME to known reference standards (Nu Check Prep, Elysian, MN). The area under each peak was calculated using a Hewlett-Packard (McMinnville, OR) 3390A integrator; the percentage of each FAME was calculated by dividing the individual peak area by the total area under all the peaks.

In some studies, the composition of phospholipid fatty acids was determined. Lipid extracts were applied to silica gel thin-layer plates and developed in 30–60°C petroleum ether:diethyl ether:acetic acid (80:20:1 volume/volume/volume). Chromatograms were sprayed with 0.1% 2,7-dichlorofluorescein solution and exposed to ultraviolet light. The lipid classes appear as distinct bands. Phospholipid bands were scraped from the plates and transesterified at 75°C for 1–1.5 hours. Gas chromatographic analysis of phospholipid fatty acids was carried out on a 50m × 0.25-mm bonded fused silica capillary 007 FFAP column (Quadrex, New Haven, CT). The column temperature was 180–220°C, increasing at 2°C/minute (held constant at 8 minutes). Helium was used as the carrier gas at a flow rate of 1.44 ml/minute.

RESULTS

Fatty acid composition of cellular lipids. The administered GLA was readily converted to DGLA,

Table 1. Effect of γ-linolenic acid (GLA) administration on peripheral blood monocyte (PBM) dihomo-γ-linolenic acid (DGLA) in rheumatoid arthritis patients and controls

Subject	Treatment*	% DGLA† Pre-GLA	% DGLA† 12 weeks	% increase‡
Patient				
2	Analgesic	1.1	2.2	100
3	NSAID	1.5	1.6	6
4	NSAID	1.8	3.1	72
6	NSAID + 5 mg prednisone/day	1.2	1.9	58
7	NSAID + 10 mg prednisone/day	1.6	2.0	25
Control				
8		2.3	6.2	170
9		1.2	2.4	100
10		1.0	1.9	90

* NSAID = nonsteroidal antiinflammatory drug.
† Values are the percent of total PBM fatty acids accounted for by DGLA.
‡ $P = 0.01$ for all 8 subjects, by Wilcoxon 2-tailed signed rank test. A significant increase in DGLA did not relate to the pre-GLA value ($r = 0.15$, $P = 0.78$, by Spearman's rank correlation).

since this fatty acid was increased substantially in PBM after 12 weeks of daily borage seed oil administration. Very little GLA was found in PBM lipids, presumably due to rapid conversion to DGLA. Arachidonic acid proportions either did not change or increased marginally, and were not statistically significant (data not shown).

DGLA proportions in PBM from 5 RA patients and 3 healthy controls were assessed before administration of borage seed oil and after 12 weeks of GLA supplementation. Taking the group as a whole, PBM DGLA proportions increased significantly over the 12-week period ($P = 0.01$ by Wilcoxon 2-tailed signed rank test), regardless of the initial (before GLA administration) DGLA value (not significant using Spearman's rank correlation) (Table 1).

Table 2. Effect of γ-linolenic acid (GLA) administration on peripheral blood mononuclear cell (PBMC) phospholipid dihomo-γ-linolenic acid (DGLA) in 3 healthy controls

Control subject	Phospholipid DGLA (μg/10 × 10^6 PBMC) Pre-GLA	12 weeks*
12	0.19	0.53
13	0.65	1.35
14	0.48	1.02

* $P < 0.05$ for the group, by Student's t-test.

Table 3. Effect of γ-linolenic acid (GLA) administration on prostaglandin E (PGE) production by peripheral blood monocytes (PBM) from rheumatoid arthritis patients and controls*

Subject	Treatment	PGE (ng/10^6 PBM) Pre-GLA	PGE (ng/10^6 PBM) 12 weeks	% decrease†
Patient				
1	Analgesic	14.2	3.1	78.2
5	NSAID	4.1	0.83	79.8
Control				
8		2.5	1.3	48.0
9		26.0	11.0	57.7
10		4.0	2.0	50.0

* PBM were stimulated with 500 μg of heat-aggregated human IgG. NSAID = nonsteroidal antiinflammatory drug.
† $P = 0.05$ for all 5 subjects, by Wilcoxon 2-tailed signed rank test.

Phospholipid fatty acid levels were determined in PBMC from 3 healthy controls (subjects 12–14) given borage seed oil (1.1 gm/day GLA). The results (Table 2) indicate a 2–3-fold increase in phospholipid DGLA (μg/10 × 10^6 cells) after 12 weeks of borage seed oil administration.

PGE, LTB_4, and LTC_4 production by PBM. PBM generation of the cyclooxygenase pathway product PGE and the 5-lipoxygenase pathway products LTB_4 and LTC_4 was determined before and after 12 weeks of borage seed oil administration. Significant reductions in PGE production by IgG-stimulated PBM were observed in all 3 normal subjects studied and in the 2 RA patients studied (Table 3). Cells incubated with $10^{-6}M$ indomethacin did not produce measurable PGE. Cells from 2 other RA patients who were treated with NSAIDs produced <1.5 ng PGE/10^6 PBM when stimulated with IgG (data not shown), and changes in PGE production were not discerned after 12 weeks of GLA administration. Substantial reductions in LTB_4

Table 4. Effect of γ-linolenic acid (GLA) administration on leukotriene B_4 (LTB_4) and LTC_4 production by stimulated peripheral blood monocytes (PBM) from 4 healthy controls*

Control subject	LTB_4 (ng/10^6 PBM) Pre-GLA	LTB_4 (ng/10^6 PBM) 12 weeks	% decrease	LTC_4 (ng/10^6 PBM) Pre-GLA	LTC_4 (ng/10^6 PBM) 12 weeks	% decrease
8	61.2	23.4†	61.8	8.3	3.5‡	57.8
9	36.3	15.0	58.7	7.9	4.8	39.2
10	57.7	4.2	92.7	6.5	2.6	60.0
11	160.0	49.0	69.4	14.0	5.4	61.4

* PBM (2×10^6) were stimulated with calcium ionophore A23187 (5 μg/ml).
† $P = 0.05$, by Student's paired t-test.
‡ $P = 0.02$, by Student's paired t-test.

Table 5. Effect of γ-linolenic acid (GLA) administration on clinical parameters in rheumatoid arthritis patients*

	Pre-GLA	12 weeks
Joint score	32.1	15.4
Sleep interruptions/night	5	0.25
Morning stiffness time (minutes)	113.4	49.2
50-foot walk time (seconds)	17.6	13.6
Patient assessment of disease activity	6.3	2.2

* Joint score is the sum of swelling, tenderness, and warmth scores (1 point for each) for all involved joints. Patient assessment of disease activity was graded on a scale of 0–10 (see Patients and Methods). Values are the mean for 7 patients.

and LTC_4 by PBM stimulated with calcium ionophore A23187 were seen in all 4 control subjects studied (Table 4).

Clinical response of RA patients. Clinical evaluation of patients with RA was done before and after 12 weeks of borage seed oil treatment. There was no placebo control group in this pilot study. No adverse effects were noted, other than softening of stools and an occasional sensation of bloatedness. Administration of 1.1 gm GLA (9 capsules/day of borage seed oil) to 7 RA patients for 12 weeks in an open, uncontrolled study design resulted in apparent clinical improvement in 6 patients (Table 5). Clinically relevant improvements in sleep patterns, joint scores, morning stiffness, and the patients' overall assessment of disease activity were observed after 12 weeks of treatment. Changes were not seen in 50-foot walk time, grip strength, complete blood count, platelet count, ESR, or blood chemistry at 12 weeks compared with those obtained during the pretreatment period.

Quantification of individual patient responses for joint score and morning stiffness is shown in Table 6. Patient 6 experienced no measurable change in clinical status. Taken as a group, the improvement in joint score was not significant using the Wilcoxon 2-tailed signed rank test or Student's paired *t*-test ($P = 0.06$). However, using Spearman's rank correlation, there was a significant positive correlation in the percent improvement in joint score compared with the initial degree of severity ($r = 0.79$, $P = 0.04$). Thus, the patients with the worst joint scores received the most benefit from the therapy. Clearly, reduction in joint score was *clinically* relevant in 5 of 7 patients. The improvement in morning stiffness was statistically significant ($P = 0.03$ by Wilcoxon 2-tailed signed rank test), and, in this small group, did not correlate with the severity of morning stiffness at the beginning of the trial. Again, it is clear that 5 of 7 patients had clinically relevant relief of morning stiffness.

The subjective impression of the principal clinical examiner (SP-M) was that in general, patients experienced a mild flare in disease activity ~4–8 weeks after discontinuation of GLA. The joint score in patient 1, which was 10 after 12 weeks of GLA administration (Table 6), increased to 36, 8 weeks after GLA supplementation was stopped. He was then given an additional course of 1.1 gm/day of GLA in borage seed oil. After 8 weeks of GLA therapy the joint score decreased to 4. Disease activity was not quantified in a formal manner in the other patients after the borage seed oil administration was stopped.

DISCUSSION

Administration of 4.5 gm/day (9 capsules) of plant (borage) seed oil containing 1.1 gm of GLA to 7

Table 6. Effect of γ-linolenic acid (GLA) administration on joint score and morning stiffness in 7 rheumatoid arthritis patients*

Patient	Treatment	Joint score			Morning stiffness (minutes)		
		Pre-GLA	12 weeks	% improvement†	Pre-GLA	12 weeks	% improvement‡
1	Analgesic	74	10	86.5	60	15	75.0
2	Analgesic	23	13	43.5	60	5	92.7
3	NSAID	43	20	53.5	10	10	0.0
4	NSAID	40	11	72.5	90	60	33.0
5	NSAID	5	6	−20.0	120	20	83.3
6	NSAID + 5 mg prednisone	8	10	−25.0	10	0	100.0
7	NSAID + 10 mg prednisone	42	28	33.3	480	180	62.5

* See Table 5 for definition of joint score. NSAID = nonsteroidal antiinflammatory drug.
† $r = 0.79$, $P = 0.04$ for the group, by Spearman's rank correlation.
‡ $P = 0.03$ for the group, by Wilcoxon 2-tailed signed rank test.

RA patients and 7 healthy subjects for 12 weeks was not associated with significant adverse effects, and produced changes in certain biochemical responses of peripheral blood leukocytes. GLA treatment also appeared to be associated with clinical improvement in 6 of 7 patients with active RA who received the borage seed oil in an open manner without placebo control.

Significant increases in total and phospholipid DGLA were seen in PBM and PBMC, respectively, from subjects taking GLA for 12 weeks. In addition, significant increases were observed in the DGLA: arachidonic acid and the DGLA: stearic acid ratios in 7 subjects after 12 weeks of GLA, compared with pre-GLA values ($P < 0.05$ by Student's paired t-test) (data not shown). Stearic acid is a major saturated fatty acid in the cell membrane, and remains at a relatively fixed concentration. Thus, the DGLA:stearic acid ratio reflects changes in the polyunsaturated fatty acid:saturated fatty acid ratio by addition of the novel polyunsaturated fatty acid DGLA. The DGLA:arachidonic acid ratio reflects the potential capacity of DGLA to compete with arachidonic acid for oxidative enzymes.

Administration of GLA for 12 weeks does in fact reduce production by stimulated PBM of LTB_4 and LTC_4, both of which are mediators of inflammation (24). A 6-week course of borage seed oil resulted in a modest reduction of LTB_4 production by stimulated PMN, and did not influence superoxide anion generation or lysosomal enzyme release by these cells (data not shown). It is possible that long-term administration of higher doses of GLA would influence PMN secretory function to a greater degree. PMN functions are influenced after 6 weeks, but not after 3 weeks, of fish oil administration (2). The delayed response suggests an effect of GLA on stem cells.

PGE production by stimulated PBM is also reduced significantly by borage seed oil supplementation. The RIA measures total PGE, but it is likely that most, if not all, of the PGE is PGE_2. When PGE_1 and PGE_2 in supernatants from stimulated PBM were separated by high performance liquid chromatography and the samples were measured by RIA, PGE_1 was not detected (data not shown). It is possible that small increases in PGE_1 production do occur in vivo, but that the PGE is rapidly metabolized. Perhaps measurement of PGE_1 production by larger numbers of cells will be necessary. Increases in PGE_1 production by platelets were seen after ingestion of DGLA by human volunteers (11), and addition of DGLA to human synovial cells in vitro leads to a marked reduction in PGE_2 synthesis and a substantial increase in PGE_1 production by these cells (25). PGE_1 and PGE_2 do have different biologic activities. For example, PGE_1 inhibits aggregation of human platelets in vitro whereas PGE_2 has no effect (26), and PGE_1 causes relaxation of uterine muscle arterioles whereas PGE_2 causes contraction of these arterioles. In addition, PGE_1 is far more effective than PGE_2 in increasing cyclic AMP in human synovial cells (25,27). Similar differences in activity of fatty acid precursors for these PGE have been noted. Arachidonic acid is a well-known inducer of platelet aggregation, whereas DGLA inhibits platelet aggregation in humans and rats in vivo and in vitro (28).

Although changes in eicosanoid production due to alteration of fatty acid intake form the basis of the current hypothesis for the antiinflammatory effects of this type of treatment, it is unlikely that all effects of the increased cellular DGLA are due to conversion of the fatty acids to eicosanoids. For example, altered fatty acid ratios might influence membrane fluidity, receptor expression, and enzyme activities (29). Indeed, we have shown (30,31) that DGLA suppresses in vitro mitogen-induced IL-2 production by human PBMC and growth of IL-2–dependent human T lymphocytes by mechanisms that are independent of PGE production.

Enrichment of DGLA in cells by virtue of GLA administration (540 mg/day) given in primrose seed oil has been shown in a placebo-controlled study to reduce pain and the need for NSAIDs in patients with RA (32). Other investigators, using similar doses of GLA in primrose oil, report minimal (33) or no (34) benefits. The pilot clinical trial presented here suggests that a higher dose of GLA (1.1 gm/day) may be able to suppress joint tissue inflammation in RA patients.

In the studies designed to determine the effects of fish oil supplements on cell function and on the course of RA (2,3,8,9), healthy volunteers and patients ingested 2.4–3.6 gm/day of EPA. Thus, EPA represents a much higher proportion of the total dietary fatty acids than in studies using primrose or borage seed oils, in which the GLA administration is ~0.5–1 gm/day. In addition, the fish oil studies provide the eicosanoid precursor (EPA) directly, whereas the plant seed oils provide a precursor (GLA) to the eicosanoid precursor (DGLA). Nonetheless, the percent reductions in cellular PGE and LTB_4 induced by GLA administration (Tables 3 and 4) are similar to those observed after fish oil ingestion (2,8).

Anecdotes from preliminary, short-term, or uncontrolled studies are suspect, but they do encourage

further study of the role of fatty acids in cell function. It is not known whether the novel fatty acids themselves (GLA and DGLA), their metabolites (prostaglandins and related compounds, and longer chain fatty acids), or both, are responsible for the results presented here. Pursuit of the answer will not be trivial. It will also be important to determine whether drugs that inhibit cyclooxygenase activity interfere with or enhance the effects of prostaglandin precursor fatty acids. Potential adverse effects of fatty acid administration cannot be dismissed, but to date, none of any consequence have come to our attention. The accumulated experimental evidence of the effects of GLA and DGLA in animal models and in vitro systems, the demonstrated capacity of GLA administration to reduce PBM PGE_2 and LTB_4 production, and the results of the short-term, uncontrolled trial with 7 RA patients suggest that more extensive double-blind, placebo-controlled clinical trials of GLA administration in RA patients should be undertaken.

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attachment to Oct. 10th 1991 letter to Senator Hollings
(cont.)

(13)

4 Atlantic Street
Charleston, SC 29401

January 23, 1989

Dr. E. Carwile LeRoy, Director of Rheumatology
Medical University of South Carolina, Charleston, SC
Dr. Robert B. Zurier, Chief of Rheumatology
University of Pennsylvania, Philadelphia, PA
Dr. J. Booyens
Medical University of Southern Africa, Pretoria,
South Africa
Dr. R.D. Sturrock
Dr. J.J.F. Belch
Center for Rheumatic Diseases, Glasgow University Medical, Scotland

Dear Doctors LeRoy, Zurier, Booyens, Belch and Sturrock:

Last week I wrote quite a long letter to a British author and scientist, Dr. James E. Lovelock, about his significant innovative contributions that analyzed and interpreted the progressive interaction of the earth's living organisms which apparently have so beneficially influenced our atmosphere, oceans and temperatures over the past 3 1/2 billion years. In the last paragraph of the enclosed letter, I told him about the 1988 Annals of Rheumatic Disease paper by Doctors Belch and Sturrock that covered a successful, 18-month double blind study using 6 g per day of oral evening primrose oil (EFAMOL) with 9% gamma-linolenic acid to control rheumatoid arthritis, and about my satisfactory use of EFAMOL for the same purpose since late 1980.

Since I sent copies of the above letter to Doctors Belch and Sturrock and as Doctors LeRoy, Zurier and Booyens were contacted in the early months of 1988, when I developed the first rheumatoid arthritis relapse since one in the summer of 1984, a letter detailing this second relapse and its resolution seemed useful.

Both of these relapses progressively developed over about a six week period with no realized changes and while taking the usual levels of evening primrose oil (EFAMOL), ascorbate, vitamins and minerals that seemed since the end of 1980 to have so successfully corrected my previous severe rheumatoid arthritis problems, that had been only partially held in check throughout 1980 by 12 Ecotrins and 4-6 Motrins per day.

As discussed in the enclosed July 12, 1984 letter to Dr. Zurier, I felt based on literature findings that an added 13 g of dry lecithin that I had been taking daily for a month, might have been the cause of my first real relapse since 1980. I had been taking this 13 g lecithin since attending (with Dr. Zurier) the George Washington University Symposium, Prostaglandins and Leukotrienes '84, a little over a month before then.

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The normal about 1 part phospholipid to 10 parts fat in the intestine aids emulsification and enzymatic splitting of fats to adsorbable fatty acids. My 13 g lecithin (phospholipid) and 2 g fat (EFAMOL) ratio apparently could have prevented lipase splitting of the EFAMOL and thus inhibited adsorption of my necessary gamma-linolenic acid during that month. This could thus have been a factor in the severely increased inflammation that developed throughout that month and the subsequent two weeks by which time I had developed a large hard left knee supra-patellar bursa. When I dropped by and showed the swollen knee and bursa to Dr. LeRoy, he recommended tapping into the bursa to reduce pressure unless 12 aspirins reduced it very quickly, which 12 Ecotrin fortunately did. After two months on 12 Ecotrin and 2 Advils I succeeded in dropping the Advil and in a total of 3 1/2 months the Ecotrin, without stimulating an almost immediate (day or two) swelling of the joints. This 3 1/2 months time was about the amount of time it took me before I could completely drop the 12 Ecotrin and 4 Motrin that I took along with 2-3 g EFAMOL, 4 g ascorbate, vitamins and minerals in the latter half of 1980.

Throughout 1985, 1986 and 1987, I have had very little if any problem with my rheumatoid arthritis, while constantly using only the EFAMOL, vitamins and minerals. Over this period I did find a progressive need to about double the EFAMOL from 2-3 g per day to about 5 g per day. Throughout I noted initial morning knuckle stiffness; but it cleared up in minutes while walking, bicycling, hand shaking, etc. were O.K.; but no tennis.

Beginning in January 1988, joint tenderness slowly began increasing; and the knees progressively increased in swelling through February, despite an increase to 6 g EFAMOL, with no evident reason or change that I could think of then. When I stopped by to see Dr. LeRoy and sat next to him at a concert in late February, he suggested returning to conventional therapy; but I didn't want to.

About that time I came to the realization on reading the literature that the timing and increased amount (700 mg) of magnesium that I was taking as its oxide in the morning with EFAMOL, vitamins and minerals, and no breakfast could have been precipitating hydrolyzed gamma-linolenic acid (from the EFAMOL) as its magnesium salts in the intestine; and thus inhibiting necessary adsorption. I thus shifted the magnesium oxide intake to the evening. My continually mounting interest in magnesium supplementation is indicated in the enclosed September 24, 1986 response on magnesium to Dr. LeRoy; and the enclosed "Memory Jogger" from my January 1988 Medical University talk on Chronic Dietary Magnesium Deficiency and Cardiovascular Death.

My knees however, got very rapidly worse in a week or two with supra-patella bursars appearing above both knees which completely filled each cupped hand with fingers touching. Twelve Ecotrins and two Advils significantly softened and reduced these bursas; but my stomach bothered me so much that in a week I decided to try and see if DMSO would work.

I had tried DMSO in the first half of 1980 when I came down with severe arthritis since I had attended and had the book on the 1967 New York Academy of Science symposium, Biological Actions of Dimethyl Sulfoxide. I had a patent at that time on production of dimethyl sulfide; and it was during this DMSO meeting that the FDA totally shut down any activity on DMSO for about 15 years.

With this background, I thus swabbed DMSO on me in 1980 at the levels used in that book, but it had no affect on my arthritis. The extensive pre-1967 studies had indicated DMSO only worked on about two-thirds of the arthritis patients; so I decided I was in the one third and left it alone. Fortunately, later in 1980 I first tried evening primrose oil on my arthritis and it worked.

I tried DMSO again in March 1988 because I was in real trouble and had since seen that DMSO increased the synthesis of Prostaglandin E-1 from gamma-linolenic acid in a paper, Role of Dimethyl Sulfoxide in Prostaglandin-Thromboxane and Platelet Systems after Cerebral Ischemia, by J.D. de la Torre in my copy of the New York Academy of Science 1983, Vol. 411, Biological Actions and Medical Applications of Dimethyl Sulfoxide, that he also edited. Since my experience with DMSO described below, I very much enjoyed meeting Dr. de la Torre this past summer at the George Washington University symposium, Biological Advances in Aging '88, and told him of my experience in using DMSO on arthritis. His data on using DMSO to control oxidative attack associated with trauma; seem so impressive, I would assume it would be widely used in time.

I thus bought 16 oz. (472 ml) and later a second bottle of "99.9% DMSO" distributed by DMSO, Inc. for my trial from a shelf for pets or animals. A friend whose M.D. had prescribed DMSO for a non-arthritis problem of hers, had told me she bought her DMSO there instead of much more expensively at the drug store, with her M.D.'s knowledge.

I stopped the Ecotrin and Advil for a day; and by the next morning the inflammation in the hands, knees, bursas, and feet was very much worse. Swabbing my knees, hands, and feet was started; but on the first day I found it necessary to wet down my skin from the toes up to the bottom of my ribs twice in the day (avoiding the genital and anal areas) to be effective on the pain and most importantly the inflammation. But it was decidedly effective in bringing down the inflammation and bursa swelling. The medical literature on DMSO speaks of it being effective in reducing pain; but not having an effect on inflammation, and that its effectiveness stops as soon as you cease using it.

Several minutes after swabbing with DMSO there was a quite strong and unpleasant tingling sensation in the wetted skin which lasted 10-20 minutes while it was being all absorbed into the skin.

A continual somewhat unpleasant to others breath odor (dimethyl sulfide) lasted throughout the four weeks that I applied the approximately 25 ml per day of DMSO to my skin, using up about a bottle and a half of DMSO.

The effectiveness of that level of DMSO on my arthritis was fairly similar (without stomach problems) to the 12 Ecotrins and 2 Advils per day. That is, the ability to walk and use stairs was very limited, you couldn't pick up a baby, and there was low level pain in the joints. There were no other evident side effects; but it interested me that during that month the blue veins all above, below and on my ankles that had been increasing for perhaps 30 years progressively largely disappeared. Over the past nine months; however, they have returned some.

DMSO was still sufficiently unpleasant and unattractive that after one month I stopped it; and within a day, strong inflammation and pain returned with swelling of the bursars. I immediately took 12 Ecotrins and 2 Advils per day which controlled the situation; but after a quite unpleasant week with my stomach I decided to try very high levels (18 g) of EFAMOL in hopes that would work.

In early January 1988, before attending a cancer conference at the Medical University in Tucson, Arizona, I had phoned Dr. J. Booyens at MEDUNSA in Pretoria, South Africa for an update on his and Dr. Van der Merwe's extremely encouraging studies using high levels of EFAMOL for control of human cancer. In 1983 I had corresponded with him about his in vitro studies demonstrating the effectiveness of gamma-linolenic acid in controlling various cancer cell lines; and subsequent studies that showed remarkable effectiveness of 9-18 g EFAMOL and 8 g of ascorbic acid on terminal patients with primary liver cancer. I had also met Dr. Booyens and Dr. I.E. Katzeff from Johannesburg at the Prostaglandins and Leukotrienes '84 conference in Washington. He now was in semi-retirement; but told me they had just published in the Brit. J. Clin. Pract. 41: 907-915 (1987), a paper, Oral Gamma-Linolenic Acid in 21 Patients with Untreatable Malignancy by C.F. Van der Merwe, J. Booyens and I.E. Katzeff, which confirmed and extended their earlier quite encouraging reports.

I decided to try 18 g of EFAMOL per day because in the paper just above a cancer patient with malignant mesothelioma and another with cerebral astrocytoma had both taken 18 g EFAMOL per day for over three years and were still improving, Dr. David Horrobin of EFAMOL research was in Europe, so I called Dr. Booyens in South Africa; and he confirmed that no detrimental or unexpected side effects had arisen from long term use of this high EFAMOL level.

The EFAMOL was thus increased from 6 g to 18 g per day in early April while continuing my usual 6 g of ascorbic acid as the calcium salt (Bronson Pharmaceutical) and the usual vitamin and mineral supplements with the magnesium at night. Within about a week I progressively completely stopped the 12 Ecotrins and 2 Advils that I had been taking for the previous week and was very pleased that my situation did not get worse. The 18 g level of EFAMOL was continued for a month with generally improving capabilities and quality of life. That level was dropped to 12 g for a month with no deterioration and then to 8 g for a month. By then I felt as well as I had during the three previous very satisfactory years. Now 6 grams of EFAMOL; however is too little for me, and I have stabilized at 7 1/2 g (15 capsules of EFAMOL). I also take in the morning my ascorbate, 800 I.U. of Vitamin E and 30 mg of beta-carotene along with one Ultra-Max 42 (a powerful vitamin and mineral supplement that doesn't have Vitamin C and E) and then take 400 mg of magnesium at night.

I discussed my experience in using high levels of EFAMOL with Dr. Zurier during the first week in May; and he very kindly sent me a collection of most interesting but still confidential reports being submitted for publication.

In the 1984 and 1988 relapses it was interesting to note that in addition to the swelling of joints and around the knees, spurs that had progressively grown out in 1980 on the two fingers and on a foot joint; which had subsequently disappeared; grew back totally and very quickly in these relapses. Fortunately they have gone back down again since the one on my foot hurt in walking. The two supra-patellar bursas went down to half size or less fairly quickly; but took more than three months to completely disappear.

With 9% gamma-linolenic acid in the 18 g, 7.5 g or 4 g of EFAMOL, I am likely taking two to ten times our reported intake as carnivores of about 150-200 mg of arachidonic acid. It's therefore, not surprising that there would be a shift in the PGE1/PGE2 or PGE1/TXA2 ratios and a reduction in leukotrienes or other two-series inflammatory products. It has been more surprising to me that there hasn't been some detrimental effects of this gamma-linolenic precursor of the "one-series" prostaglandins during the extensive use and testing of EFAMOL over the past ten years.

When you're really in trouble one is willing to try almost anything, as is certainly evident in cancer chemotherapy; and in people where conventional arthritis therapy is still inadequate. It is thus mighty satisfying when problems don't arise.

I remember Dr. I.J. Zeitlin, from the same university as Drs. Belch and Sturrock, who conducted research at the Medical University in Charleston for some months in 1984; who I met when we both attended the Kinins '84 international symposium in Savannah. He used the opposite approach to what I was doing to control his difficulty controllable psoriatic arthritis. He had totally given up all meats, fish, etc. that contained any arachidonic acid; and this worked for him. That is certainly a less risky approach; but a tough one that not many would accept unless the alternatives were worse. I gave him some information on the gamma-linolenic approach; but he left soon afterwards.

In General Nutrition's catalogue they now advertise not only Oil of Evening Primrose (EFAMOL) but Black Currant Oil and Borage GLA oil, which along with human milk have been known for some time to contain high levels of gamma-linolenic acid. These are cheaper sources; as are other brands of evening primrose oil; but I'll stick with EFAMOL. Reports on the efficiency of this general approach of Dr. David Horrobin in various directions are really mounting in the medical literature; but acceptance is slower than seems indicated.

I happen to have heard this year from a number of people away from Charleston that I knew professionally or otherwise before retirement, who had asked about and decided to do what I did when they found out about my improvement. They called me this year since Bronson Pharmaceutical early this year stopped carrying EFAMOL; because the FDA had questioned why they were carrying evening primrose oil (apparently their first complaint from the FDA in 27 years). I told the callers that the FDA had stopped General Nutrition's 1200 stores from carrying EFAMOL for most of a year, because two stores suggested in print possible therapeutic value, but they again carried it as did various health food stores, but suggested they be sure it was EFAMOL they bought.

The most interesting call was from an executive of a chemical company in the South who happened to have had arthritis and visited in my last month before retirement in early 1984. He apparently took down exactly what I was taking at that time; and then did the same with apparently very satisfactory results. He said his mother also had severe arthritis for 15 years; and she then tried what he did and got over her arthritis. He reported his sister, who couldn't raise her right arm, then did the same and that problem was also corrected. A manager, with an arthritis problem, who worked with him took the same to prove it wouldn't work on him, but it did. He said since he had had obvious arthritis (and had corrected it); that in the four years since he had seen me between 20 and 30 people with arthritis had done what he had done and usually with success. He then sent me a large box of candy, my only material thank you ever.

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This has thus been another one of my very long letters, but at least they're pretty far apart. I took it as an opportunity to discuss what seems to me a generally successful (thank God!) experience of holding in check for most of eight years what had been and still seems to be a severely inflammatory capability in my joints and earlier elsewhere.

If you get to the end, many thanks for your patience, and hope you may glean some points of interest.

All the best,

Frank J. Ball

cc: Dr. J.D. de la Torre
Dr. Martin Eastwood
Dr. C.F. Hazelwood
Dr. David Horrobin
Dr. James E. Lovelock
Dr. I.E. Katzeff
Dr. C.F. Van der Merve
Dr. I.J. Zeitlin

(Typed copy of handwritten letter)

October 8, 1986

Dr. E. Carwile LeRoy, Director
Division of Rheumatology & Immunology
Medical University of South Carolina
Charleston, SC 29425

Dear Carwile:

Thank you for your kind comments about my August letters relating to magnesium deficiency, and your request to point you "directly to the data implicating same in Raynaud's" My comment in this section, Vasospasm Caused by Magnesium deficiency in Arteries to the Heart and Brain, dealt with the many papers of Dr. Burton Altura which demonstrated all arteries are constricted by magnesium deficiency; and that cardiac and cerebral arteries are particularly susceptible to vasospasm. The sentence in that section which included Raynaud's disease was almost totally lifted from Dr. Altura's sentence: "During the past decade, considerable experimental and clinical data have appeared which indicate that vasospasm plays an important role in Raynaud's disease, classical migraine, transient ischemic attacks, stroke, head injuries, pre-eclampsia, eclampsia, angina, and sudden-death IHD" This was on page 261 in the enclosed paper by B. M. and B. T. Altura, New Perspectives on the Role of Magnesium in Pathophysiology of the Cardiovascular System (Magnesium 4, 245-71 (1985)). They then suggested that as magnesium can alleviate and relax constricted cerebral and coronary blood vessels in experimental studies it should be extended to other vasospastic phenomena.

I personally am not familiar with any literature where oral magnesium therapy or testing to correct the widely spread problem of Raynaud's disease in fingers, etc. is presented; but it seems a simple, non-toxic procedure which could well prove beneficial. There is a pertinent paper by M. J. Halpern et al in Lisbon Medical University which demonstrated the cessation of peripheral vascular spasms (Raynaud type) in 9 out of 10 patients taking 3 g. per day of oral magnesium lactate for 16 weeks. This paper, Therapeutic Effect of a Magnesium salt in Patients Suffering from Mitral Valve Prolapse and Latent Tetany, was published in Magnesium 4, 283-90 (1985) and is enclosed. Doctors Halpern and J. Durlach are co-editors of Magnesium Deficiency, Physiopathology and Treatment Implications (1985).

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Another enclosed paper from December 15, 1985 Cancer, p. 2765-70 by N. J. Vogelsang et al (University of Minnesota Medical) clearly related hypomagnesemia induced by certain chemotherapeutic drugs with the development of Raynaud's phenomenon in their treated patients. Cis-platinum, first used about 1980, induced hypomagnesemia through dose related renal damage which results in constant subsequent urinary leakage of magnesium.

Dr. Vogelsang, who is now at the University of Chicago, gave a talk at the 2nd Annual Magnesium Conference in Washington. I hadn't gotten your letter and didn't talk with him; but his comments were largely in the paper above. He did state that 75% of his patients with less than 1.0 m.e. Mg per liter of plasma had Raynauds, while 22% between 1.0-1.3, and none when above 1.4, which is the lower limit of normal. Usually the undamaged kidney keeps blood magnesium relatively constant even though cell magnesium may drop and cause vasospasm.

In 22 patients two years after treatment with cis-platinum, 19 had hypomagnesemia; and their median plasma magnesium was 1.08 m.e. While 70% are cancer free there were serious other vascular problems such as five prior cardiovascular fatalities. Magnesium supplementation was allowed, but not yet recommended; and it is difficult to bring up and sustain magnesium in these patients. He thought its use may have prevented the epileptic seizures reported by others with this drug.

Evening Primrose Oil Double Blind Treatment of Raynaud's

My September 24 letter discussing the very successful double blind trial employing gamma-linolenic acid in evening primrose oil (EFAMOL) to control rheumatoid arthritis was sent you before I got your letter requesting the above information on Raynaud's and magnesium.

You thus should be interested in the enclosed paper by J. J. F. Belch et al (Thrombosis and Hemotosis 54; 490-94 (1985)) covering a successful 8 week double blind trial on Raynaud's using 12 capsules of EFAMOL per day which was the same level used in the rheumatoid arthritis trial. J. J. F. Belch, A. O'Dowd, and C. D. Forbes from the Centre for Rheumatic Disease, Royal Infirmary, Glasgow were common authors on both these double blind trials.

Following a combined computer search on Raynaud's and prostaglandins last September fifteen 1983-85 papers were copied and studied which seemed to clearly show that intravenous PGE1 or prostacyclin given continuously for several days were quite effective; and the benefits could continue for several weeks. As these prostaglandins also improved the deformability of the stiff red cells found in Raynauds, it seemed likely the PGE1 producible from adequate gamma-linolenic acid in EFAMOL should prove right beneficial; and the double blind now clearly substantiates this. I've really missed my lightning-blasted computer, but as prices are beginning to drop for Christmas hope to have another one soon.

Dr. David Horrobins ideas and review related to Scleroderma and Sjogren's (Medical Hypotheses 14, 233-47 (1984)) and Dr. Jill Belch's on red cell deformability in systemic sclerosis and Raynaud's (Prostaglandins, Leukotrienes and Medicine 17, 1-9 (1985) present keen insight and data as to the interactions of fatty acids, prostaglandins, and cellular derangements. Your excellent chapter on Scleroderma and Dr. Robert Zurier's on Mediators of Inflammation in the 1985 Rheumatoid Arthritis: Etiology, Diagnosis, Management prompted my purchase when it came out; and it seems a quite useful contribution to this field. In a phone call from Dr. Zurier last week we discussed the double blind trials; and I am sending him my description to you and the August letters before he goes to Europe on a sabbatical on November 1.

Most sincerely,

Frank Ball

CC: B. M. Altura
J. J. F. Belch
P. C. Gages
M. J. Halpern
D. F. Horrobin
W. M. Newberry
R. D. Zurier

(22)

(Typed copy of handwritten letter)

September 24, 1986

Dr. E. Carwile LeRoy, Director
Division of Rheumatology and Immunology
Medical University of South Carolina
Charleston, SC 29425

Dear Carwile:

I know your time is committed following your trip to Europe, but this information obtained at the American College of Nutrition meeting in Washington last week should interest you. I saw an abstract from the Abstract Book of the 6th International Conference on Prostaglandins (Florence, June 1986) which covered a most successful double blind study at Glasgow University Medical School demonstrating the apparent efficiency of gamma-linolenic acid in evening primrose oil or eicosapentaenoic acid in fish oil in therapeutic replacement of NSAID drugs in rheumatoid arthritis. These acids as you know are the respective precursors of the "one-series" and "three-series" prostaglandins. The authors were D. Andsell, J. J. F. Belch, L. Curan, M. McLean, A. O. Dowd and C. P. Forbes.

Double blind results were presented on 34 patients on NSAID drugs, who took 12 half-gram capsules of placebo, EFAMOL (evening primrose oil with 9% gamma-linolenic acid), or EFAMOL marine (fish oil with 18% eicosapentaenoic acid and 12% docosahexaenoic acid) for one year. During the first three months both their usual levels of NSAID drugs and the 12 blind capsules were taken each day, while in the following months the NSAID was progressively withdrawn as long as patient pain, etc. was not increased.

During the second period of 9 months, 18 of the 34 patients showed sufficient improvement to enable them to substantially reduce or stop the NSAID while continuing to take their 12 blind capsules per day.

During an additional six months the 12 daily capsules were all changed to placebo; but this was only known by the physicians. During this period 16 of the 18 patients who had substantially reduced or stopped NSAID therapy had to be restored to their full dose of NSAID.

When the code was broken after 18 months it was found:

1. Of the 12 patients who received placebo, only 1 reduced or stopped his NSAID during the second period, and he did not relapse during the final period. Possibly he did not need the NSAID from the beginning.

2. Of the 11 who were on EFAMOL, 9 were able to reduce or stop their NSAID in the second 9 month period; but 8 of these relapsed in the final six month period on placebo; and required NSAID.

3. Of the 11 on EFAMOL Marine, 8 were able to reduce or stop their NSAID in the 9 month stage, but all 8 relapsed and required NSAID in the final 6 month period on placebo.

Thus, 17 of the 22 patients taking polyunsaturated fatty oils which would have contained either 540 mg of gamma-linolenic acid or 1080 mg of eicosapentaenoic acid daily showed sufficient improvement to permit substantial reduction or cessation of NSAID therapy; yet 16 of the 17 relapsed during the final all placebo phase, which they did not realize existed. This would indicate only one did not need NSAID therapy when not taking these levels of "one series" and "three series" prostaglandin precursors (not influenceable by cellular delta-6 desaturase deficiency). A statistical $p < 0.005$ was shown.

Their final abstract sentence stated "These results are dramatic and open up a completely new line of treatment in rheumatoid arthritis." I heard a paper is being given at British Rheumatology meeting or published in its journal in November. I don't know which. Twenty-six additional patients had not completed the 18 months in June.

In your July 20, 1981 letter to me you expressed an interest in a controlled study of evening primrose oil in classical rheumatoid arthritis, if funding could be obtained. It would seem the fairly definitive and statistically very strong Glasgow study could strongly back additional clinical study in this country since the widely used NSAID drugs decidedly bother the stomach and don't stop joint deterioration. The negative interpretation in the Denmark study by T. M. Hansen et al covered in my letter to you of September 18, 1983 where 8 capsules of EFAMOL and no NSAID were tested double blind for 3 months would have been a decided deterrent to a new study over here; but the Glasgow should supersede this.

I am also enclosing a letter from Dr. Marcus Newberry relating to my interests in the past year; and conceivable future grant proposals and funding in that area. It would seem that timing of a possible clinical grant proposal and funding related to rheumatoid arthritis could be more critical if you were interested in it; before other rheumatologists over here become interested.

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Both the procedure and results in this trial are very similar to what we did and observed beginning back in 1980. They used 50% more EFAMOL throughout the 12 month double blind than I ever used; but we both used combined NSAID and EFAMOL throughout the first three months; and then tried to reduce NSAID in subsequent months. I actually tried to reduce the 12 aspirins by one-third twice in the first three months; but immediately had to go back to 12 aspirins.

I don't know, of course, how far or how fast they reduced the NSAID; but based on my experience and of acquaintances about the country, the cuts can be deep and rapid after 3 to 4 months on EFAMOL; but it probably depends on how long and how serious. After 3 1/2 months as you may remember, I dropped the aspirin to zero over one week at 4-6 EFAMOL and have continued the same since then. Twice pain problems arose when the gamma-linolenic acid was inadvertently stopped for over a week; but subsided after a week or two of proper replacement.

The one really serious relapse in six years occurred when based on discussions at Prostaglandins and Leukotrienes '84 I took oral soybean lecithin for a month. Over the month and the subsequent two weeks pain and swelling developed, particularly in my knees, which you examined, recommended 12 aspirins, and possible fluid tapping. While the aspirins brought down the swelling some, walking was seriously limited for three months, despite increased EFAMOL; but then the 12 aspirins were dropped without problem and I've been okay since. Literature research indicated my morning ratio of lecithin (13 g) and fat (EFAMOL 2 g) could have seriously inhibited digestive splitting and absorption of the gamma-linolenic acid from the oral evening primrose oil during this month.

Enclosed is an annotated 1986 Bibliography on evening primrose oil and a brochure on the EFAMOL organization. If I can be of further assistance do not hesitate to call.

Most sincerely,

Frank Ball

FB/kmk
cc: Dr. Marcus Newberry
Enclosure

(Note: As discussed in a later letter, the EFAMOL Marine is not fish oil, but preponderantly evening primrose oil with some fish oil.)

(25)

(Typed copy of handwritten letter)

December 28, 1984

Dr. Robert B. Zurier
Chief
Rheumatology Section
School of Medicine
University of Pennsylvania

Dear Dr. Zurier:

I never did write you that I no longer have to use aspirin and Advil to control the relatively severe renewal of my rheumatoid arthritis described in my letter of July 15, 1984. During the two months following the letter it took 12 aspirin (timed-release) and 4 Advils per day to control inflammation and swelling; and my walking was limited to two to four blocks. When I dropped the Advil and one-third of the aspirin at the end of the first month, painful and heated swelling required complete return in two days. At the end of the second month the Advil was successfully dropped; but then trial with 8 aspirins within three to four days gave pain and swelling, and I increased back to 12 aspirins with about three days required before the pain subsided. After about three and a half months; however, the 12 aspirins were successfully dropped over a week without developing pain or inflammation and no more aspirin or Advil have been taken since and I seem generally okay.

During this period on aspirin and Advil, I increased my evening primrose oil (EFAMOL) from the prior 2 g per day to 3 g, in hopes of more quickly restoring the gamma-linolenic acid, which I believed had likely been prevented from adsorption for a month by the very high rate of lecithin to EFAMOL taken every morning that month when my arthritis progressively increased. I am now taking 2 g of EFAMOL along with 4 g of calcium ascorbate and added multi-vitamin-minerals.

In a phone conversation last month, Dr. I.E. Katzeff in Johannesburg asked why I used only 2-3 g of EFAMOL since they find 6 g per day most effective. Initially 4 1/2 years ago I took 4 g per day; but lowered to the 1-3 g level because of an initial increase in pain and lack of experience. They apparently note increased pain at 6 g per day; but find it worthwhile to achieve earlier and better results.

All the best in 1985,

Frank

cc: E. Carwile LeRoy
I.E. Katzeff
D.F. Horrobin

(26)

(Typed copy of handwritten letter)

July 15, 1984

Dr. Robert B. Zurier
Chief
Rheumatology Section
Department of Medicine
University of Pennsylvania
Philadelphia, PA

Dear Dr. Zurier:

You have no idea what a pleasure it was to finally meet you at the Prostaglandins and Leukotrienes '84 Symposium on May 10 in Washington. I tremendously appreciated the various long telephone calls since 1980 discussing your pioneering animal studies on the effects of Prostaglandin E1 on arthritis and lupus-type problems; and my attempt to successfully use the Prostaglandin E1 precursor in evening primrose oil to control my rheumatoid arthritis. There was true satisfaction from your comments on my health; and the opportunity to discuss means to maximize conversion of the gamma-linolenic acid in evening primrose oil to Prostaglandin E1 and thereby raise cyclic-AMP finally to hopefully dampen the inflammation of synovial cells.

This meeting in Washington was exactly three and one half years after I completely stopped taking the previous 12 aspirins (Ecotrin) and 6 Motrins that had marginally handled my rheumatoid arthritis that began in February, 1980. My satisfaction over the years from the use of 2 g of evening primrose oil (EFAMOL) in combination with therapeutic levels of Vitamins C, E, B-complex, zinc and selenium was described in detail in the letters to Doctors Eastwood (12/22/80) and Hazlewood (1/27/83) sent you previously.

My only relapses were for periods of a week or two--February, 1981 and again in June, 1982. The 1981 experience occurred when I ran out of EFAMOL which was being sent to me from overseas; and within a week very evident muscle and wrist swelling required 12 aspirins to take down. A phone call to you at the time brought out that General Nutrition now carried EFAMOL, which I got in Charleston and quickly was able again to drop the aspirin. In June, 1982 I purchased and took VITAMIN SPECIALTIES evening primrose oil with an identical analysis to EFAMOL; but within about a week my hands and particularly my feet bothered me enough to shift back during the following week with satisfaction shortly. In October 1982 an analysis on the VITAMIN SPECIALTIES primrose oil indicated that it contained no gamma-linolenic acid; which prompted the enclosed October 22, 1984 letter to the president of VITAMIN SPECIALTIES.

I have gone into the above background since a third and much more unpleasant slip-back occurred during the two months since seeing you in Washington. During the last half of May and the first half of June, arthritic unpleasantness developed slowly, but substantially in some of my joints. This time, however, it was first evident and most painful in the knees with the feet next and very little trouble from the hands. Finally it became a real problem for me to walk up to three blocks before things started improving again, when I took high levels of aspirin and Advil. No stress or psychological problems had arisen; and I was otherwise very happy in my retirement over the past five months.

I personally am convinced I likely and mistakenly brought this situation on myself; but am afraid it may take a while to get the stirred up macrophages or whatever to die off without attracting more. Based on some literature findings in the past week or two, I now feel this unpleasant arthritis bout may have again been brought on because of inadvertent removal of gamma-linolenic acid from my joints, which probably contain immortalized synovial cells with a gamma-linolenic deficiency.

Before and while traveling to Washington I had been reading a personal copy of an interesting and provocative 1983 book, PHOSPHOLIPIDS AND ATHEROSCLEROSIS, with most chapters by Europeans. One Washington evening I got to briefly talk with Olaf Adam (Medizina Polik; Munich) who wrote the book chapter "Relationship Between Linoleic Acid Intakes, Plasma Phospholipids, and Prostaglandin Formation in Man" but did not realize he wrote it at the time. This book further convinced me of the potential benefit of an increased oral intake of soybean lecithin for most older people's vascular and cardiac systems. Around the same time I had talked with a couple of people who had been taking a palatable granular form of soybean lecithin (flavored with cinnamon and apple) from General Nutrition. I thus added an individual sealed server packet (13 g) with enough milk to wet it to my usual breakfast of orange juice, coffee, vitamins, minerals, and 2 g evening primrose oil. At that time my thinking was that this innocuous food substance seemed a useful source of choline, inositol, polyunsaturated fatty acids for my blood vessels and brain with no thought of arthritis.

After taking the lecithin for about a week, I noted some feeling in my joints; and this increased in the second and third weeks with increased focus on the knees and then feet. The problem wasn't large and I wasn't concerned since during the early months of using evening primrose oil in 1980 I noted increased and somewhat controllable pain with increasing levels of evening primrose oil. It seemed to me to be more on the outside of the joint back then; and anyway, things ended up really great. I thus decided to ride this out for the fourth week and then quit the lecithin. Unfortunately the pain has continued or increased for a couple of weeks more.

Based upon further reading I've come to the conclusion the high ratio of phospholipid (lecithin) to evening primrose fatty oil (13 g to 2 g) which I had been taking in the morning could have seriously interfered with the lipase digestive hydrolysis (J.S. Patton and M.C. Carey: Am. J. of Physiol. 241G, 328-36 (1981); and also that excessive phospholipid ratios could seriously retard adsorption (A.J. Rampone and L.R. Lang: Biochin, Biophys. Acta. 486: 500-510 (1977)) of gamma-linolenic acid. I thus doubled my evening primrose oil and Vitamin E and seemed to have gotten some benefit in pain in the knee and ankle and decided softening of what I had thought was a 2-3 inch badly swollen tendon above my left knee.

I went by to see Dr. Carwile LeRoy early this week and he said the "swollen tendon" was a supra patella bursa from water pressure in the knee; and to take 12 aspirins or he would have to tap it if it swelled further again. The aspirin along with high primrose and "E" have reduced the knee swelling and foot unpleasantness; and sure hope the gamma-linolenic works again okay; because my stomach sure doesn't like adequate levels of aspirin or other NSAIDS.

Apparently lecithin in bile markedly assists the bile acids in emulsifying dietary fat (which contains 1 lecithin to 40 fat). This is increased to 1 lecithin to 10 fat from biliary lecithin which emulsifies just fine; and is right for fat hydrolysis. Lecithin itself, however, is slowly hydrolyzed by lipases compared to fat, and fat hydrolysis can be markedly reduced by excessive lecithin ratios. Excessive unhydrolyzed lecithin can also, in excessive quantities, coat intestinal cells and inhibit fatty acid adsorption.

Sorry for such a long Sunday letter. My wife and I are flying off tomorrow to visit our son in Seattle (will visit Peter Simkin who earlier worked on zinc and arthritis), and sons in Juneau, Alaska and in Houston for next two weeks.

I will send a copy of this to Carwile LeRoy who keeps surprisingly up to date in his scientific reading for a Department Chairman. I had to pry the Ciba Foundation--BIOLOGY OF VITAMIN E--from him, and he had already gone over the abstracts of the Washington meeting. I have found personal copies of that book and TOCOPHEROL, OXYGEN AND BIOMEMBRANES (1978) to be most important reference stock.

Frank J. Ball

Just numbered the pages and see they are seven so hope you find value in some of it; but my wife says I have verbal diarrhea and it's probably too true!

cc: E.C. LeRoy

(29)

4 Atlantic Street
Charleston, S. C. 29401
January 27, 1983

Dr. Carlton F. Hazelwood
Professor of Physiology and Pediatrics
Director of Graduate Studies, Department of Physiology
Baylor College of Medicine
Houston, Texas 77030

Dear Carlton:

Many thanks for the kind remarks in your letter and the request for the generic name of the vegetable oil that contains gammalinolenic acid and the source of fine crystalline ascorbic acid products. It was a true pleasure to visit you in Houston and hear of your significant progress in nuclear magnetic resonance assessment of normal and cancer tissue; and to see examples of your NMR scan imaging. Your 1978 phone call and fat packet of papers and draft reports related to cell associated water was certainly a major factor in sustaining my early interest in the metabolic aspects of cancer.

With reference to your consideration of using combined ascorbic acid and evening primrose oil (which contains 8% gammalinolenic acid) for possible control of arthritic problems that you believe arose after measles at 29; it seems like a wise and justified try to me. Dr. David Horrobin's papers and contacts indicate genetic defects or viral invasion can cause loss or partial loss of a cell's delta-6-desaturase enzymatic capability. The cell's ability to convert polyunsaturated fat (linoleic acid) to gammalinolenic acid is thereby seriously impaired. Since gammalinolenic acid is the precursor of the "1" series of prostaglandins (cellular hormones), any cells so damaged will be deficient in "1" series prostaglandins. The cells may then excessively produce the inflammatory "2" series of prostaglandins from arachidonic acid as this acid is readily available in the lecithin of cells. The December 1980 letter on the back of the enclosed May 1981 "memory jogger" was given out at an informal talk in my home covering certain relationships between cancer, rheumatoid arthritis, and gammalinolenic acid. That letter discussed a sustained and severe arthritic problem which came on in the month following an acute throat infection on a trip in January 1980. This was diagnosed and treated throughout the year as seronegative rheumatoid arthritis, with twelve coated aspirin and six Motrin being just tolerated by the stomach. I was fortunately also permitted to try innocuous other approaches in the medical literature that made the most metabolic sense, as is covered in the letter. I finally arranged to have evening primrose oil sent to me from Canada as "vegetable oil for experimental purposes"; and when 4 grams per day of this first increased the pain some, its potential to have an effect seemed provocative. Before I succeeded in getting the evening primrose oil, I tried to increase the linoleic and linolenic acid content of my lecithin by dieting at around 500 calories per day for a couple of weeks and then subsequently eating lots of walnuts, which are high in linoleic and (alpha) linolenic acids. During this period for phychosomatic or other reasons, I was able to lower my Motrin without swelling up the joints. I still could not take the aspirin down any, still could not drive; and continued spending only about a half day at work with 5-15 minutes of each hour at work lying down.

When I started taking the evening primrose oil at about 2-3 grams per day, I was already taking a couple of grams of ascorbic acid, a super B complex, 800 I.U. units of Vitamin E, 25 mg. of zinc, and a gram of histidine. I did not observe any marked change in the joints but tried periodically to take the aspirin

down by one third for a day or so, but would observe substantial swelling of the joints in the hands and pain in the feet. What really intrigued me; however, was that after two or three weeks, I found I had lengthened my stay at work to where I was full-time, was not periodically lying down there, and this has been so ever since. I have noticed in the medical literature that the ATP level in muscle tissue of rheumatoids can be down one-third; and feel that might be a reason why there is such a low level of energy.

After about three and a half months on evening primrose oil, when I tried to take down the twelve aspirin, I got all the way to zero over a four-day period without swelling of the joints and with little increase in discomfort. I have never taken aspirin since then, except about three to four months later when the evening primrose ran out; and the next shipment was not in. After two to three days I had to go back up to 12 aspirins to stop swelling and pain, whereas I had not expected this. It had seemed possible to me that the several months required by gold, penicillamine, and now possibly by gammalinolenic (to rheumatoid improvement in the joints) might be the time it takes for superoxide excreting macrophages in the joints (who live for months) to progressively die off without new ones being attracted. If this is so, they weren't all gone at that time, but when I again took the three grams per day of the new evening primrose, the aspirin was dropped with no trouble.

Last summer after months on two grams of evening primrose per day (160 mg of gammalinolenic acid), I once again inadventently went without gammalinolenic acid without realizing it, as covered in the enclosed letter to the president of Vitamin Specialties, Inc. This time I took a lower priced "evening primrose oil" with the identical analysis on the bottle. After about a week enough apparent discomfort arose in my hands and feet to make me change back to the EFAMOL brand, which I had gotten earlier from Canada and was now available in the states at GNC (General Nutrition Corp.) in most shopping malls. Since a couple of months later analysis indicated there was no gammalinolenic acid in the Vitamin Specialty brand, my joint problem had apparently continued to improve as I had only progressive discomfort and pain and no swelling during that week.

All of the above are just anectdotal comments on possibly the first try on seronegative rheumatoid arthritis in this country. Vastly more pertinent and significant are a series of papers sent to me by Dr. David Horrobin in December that were published around the world in the last two months and strikingly support the validity, importance, and potential for control of gammalinolenic acid deficiency-dependency in critically important diseases. As professor of both physiology and pediatrics, you will appreciate the practical significance to many children of the paper, "Oral Evening Primrose Oil Improves Atopic Eczema" by S. Wright and J. L. Burton, published in the November 20 "LANCET"; and a draft of the supporting paper, "Reduced Levels of Prostaglandin Precursors in the Blood of Atopic Patients: Defective Delta-6-Desaturase Function as a Biochemical Basis for Atopy" by M. S. Manku, D. F. Horrobin, S. Wright, and J. L. Burton, which I understand just published in the December issue of PROSTAGLANDINS, LEUKOTRIENES, AND MEDICINE. These enclosed papers include a successful double blind trial in Bristol, England, on 99 atopic eczema patients; and strongly underpin Dr. Horrobin's brilliant predictions on the likely, broad clinical significance of possible gammalinolenic acid deficiency in various important diseases and the potential of reversing the clinical problem by use of oral evening primrose oil.

Four really mind-boggling papers were published in the two issues of the South African Medical Journal (comparable to JAMA) in October from three different medical schools. These papers following up on Dr. Horrobin's ingenious predictions, present seemingly critical in vitro experiments that produce convincing evidence that malignancy in a mouse melanoma cell line, human oesophagal carcinoma cell line, and human liver carcinoma cell line were all gammalinolenic acid deficiency-dependent. Cancer cell growths were dramatically reduced in the presence of gammalinolenic acid while normal cell lines were not affected. The final conclusion stated "We are of the opinion that, in view of the known safety of (gammalinolenic acid) in human beings, prompt investigation of (gammalinolenic acid) administration in human cancer patients should be a high priority."

More specific to your own health interest was some most encouraging raw data from a European clinical study on the successful use of evening primrose oil at 2, 4, and 6 grams per day on scleroderma patients, which was made understandable by pertinent fundamental cellular data.

While in Houston, I picked up from the Jesse Jones Library and enjoyed your Cell-Associated Water and Dr. Ronald Pethig's Dielectric and Electronic Properties of Biological Materials. Looking through those 1979 books and my own copy of Physiochemocal State of Ions and Water in Living Tissues and Model Systems, 1973, that you edited, surely reconvinces me that you and your colleagues' maverik explanations based on structured water will turn out to be the main cause for cellular sodium/potassium ratios, rather than the "sodium pump theory." I am sending you these two books to return to the library (due back Feb. 11); since I am certain you will find Dr. Pethig's book of high interest, if you haven't read it.

Once again many thanks for fitting me in at 8:00 AM for such a long time; and for the opportunity to meet your delightful wife, and your competent NMR associate, Joe Forster. If you do have joint pains (you surely didn't look it) then based upon my experience and a number of others who have tried it on osteoarthritis; there seems worthwhile odds for benefits from a couple of grams of ascorbic, and a couple of grams of GNC evening primrose oil per day. I also recommended and take a controlled release Super B, 800 I.U. of Vitamin E, and 25-50 mg of zinc. Don't expect results right away. Some seem to take a couple of months to really improve and some may quit with no improvement, but yesterday there was an extremely pleased grocery owner after just two weeks. The fine crystalline ascorbic acid comes from Bronson Pharmaceutical, 4526 Rinetti Lane, LaCanada, California 91011. I am enclosing a catalogue, as they seem the cheapest and most comprehensive source of most Vitamins.

Best of luck to yourself and your research programs,

Frank

Frank J. Ball

P.S.
I was quite pleased to see the provocative clinical and NMR data on malignant breast cell lines in the Cell-Associated Water chapter by your co-worker, Paula T. Beall. It brought back to mind my 1978 rough plots of some of your collected NMR data in a number of different normal, benign, and cancerous tissues with normal breast having the lowest T_1, but very high when malignant. Incidentally, I am also enclosing an excellent, comprehensive, and well-referenced Technical Information Bulletin on EFAMOL that I got from Dr. Horrobin.

cc: Dr. David Horrobin Dr. Jan Van Eys Dr. Bruce D. Ball

4 Atlantic Street
Charleston, SC 29401
December 22, 1980

(32)

Dr. Martin Eastwood
Wolfson Gastrointestinal Laboratories
Western General Hospital
Edinburgh, Scotland

Dear Martin:

Had one hell of a year, but informative and finally encouraging. Came down with rheumatoid arthritis in January, following a severe throat infection while on a trip; and was in hospital and at home about six weeks. Spent the rest of the year on 12-16 coated aspirins (Ecotrin) and 6 (2.4g) Motrin with pain mainly in hands, wrists and varied in feet (earlier all over); and in all joints and muscles if tried to lower these. Read about as much in this area and prostaglandins as I did cancer in past two years, and some surprising similarities. Protected collagen and hyaluronic acid in joints, I hoped, with high C and B-complex vitamins; and joints progressively improved over the year. Terribly tired and was 1/2-2/3 time at work until about 3-4 months ago when went to full time. Took on my own, zinc and histidine throughout year, since these seem to be about one third down in blood of rheumatoid patients. Blood sedimentation rate went down progressively from 50 range to normal, but stamina very low and couldn't take down aspirin and Motrin. Tried during summer to convert to higher linoleic in my lecithin using polyunsaturated fats and did get the Motrin down. For the past 3 1/2 months I have been taking 1-6 capsules (0.4g each) a day (in addition to the vitamins, zinc, and histidine) of the seed oil of the evening blooming primrose (Efamol, which I bought in Canada); and which contains about 10% gamma linolenic acid. It comes from England and is called "Naudicell" there. J. N. McCormick and W. A. Neill at Northern General reported encouragment on rheumatology using 2g per day for 3 months, in the Lancet, Sept. 3, 1977, p. 508. I called him but he was on a months vacation and I succeeded in getting in touch with Dr. Robert Horrobin in Montreal, a brilliant doctor who has written extensively in this area as related to prostaglandins; and Dr. Robert Zurier, now head of Rheumatology at University of Pennsylvania Medical, who had worked with Prostaglandin E1 and subsequently with this oil in inhibiting induced arthritis in rats. Horrobin told me McCormick didn't get money for his planned additional tests. Tell him about 3 weeks ago, for the first time, I succeeded over a three-day period in bringing down the aspirin from 12 to 0 and have taken no more aspirin. Never before was I able to bring it down to 8 because of increased swelling and pain in the joints. Horrobin knew of encouragement in Copenhagen and Barcelona on arthritis, but felt not if taking aspirin, Indomethacin, etc. and thus not on rheumatoids. He seemed interested and pleased. Me too!!

The gamma linolenic acid is converted by the cells of the body as needed to Prostaglandin E1 which Horrobin indicates apparently controls the excessive formation of Prostaglandin E2 which is very excessive in rheumatoids and a factor in inflammation. We may run low or out of Prostaglandin E1 in the joints and thus get into this self-generating arthritic problem.

Best of luck in your work in Edinburgh and stop by Charleston again when you get a chance. Haven't written any further letters in cancer area this year except the recent enclosed one to Senator Hollings; and it looks like the hydrazine sulfate and Vitamin C are really demonstrating efficacy and being progressively accepted and understood for cancer control without toxicity.

Sorry so long, but thought you would be interested. With hope!

Merry Christmas.

Frank J. Ball

FJB/dr
Enclosure

January 7, 1993

4 Atlantic Street
Charleston, SC 29401

President George Bush
Mr. James Baker
Mrs. Barbara Bush

The White House
Washington D. C.

Dear Mr. President, Mr. Baker, and Mrs. Bush,

The president spoke in his excellent address to the cadets yesterday about incredible accomplishments; and also mentioned "getting on with the rest of my life."

Correction of Personal Magnesium Deficiencies

After hearing of the presidents atrial fibrillation while flying back from a California symposium on Magnesium in Clinical Practice; a series of letters over the past year and a half persistently attempted to alert the president and his staff as to his critical cardiovascular dangers and their apparent very simple correction. Understandably, I do not yet know if the president and his wife are supplementing with adequate (500 mg) levels of critically needed magnesium or with high levels of natural antioxidants. This final attempt to possibly catch some personal attention seemed merited considering the previous arrythmia warning and your coming personal responsibilities for your own health.

At this juncture it seems quite important that all three of you appreciate the striking protection to your hearts and arteries from increased oral magnesium to correct widespread deficiency; and also to realize that very extensive foreign medical evidence demonstrates marked prompt improvement following heart attacks or arrythmias from prompt adequate intravenous injection of magnesium salts. This is well covered in the enclosed Oct. 29, 1992 letter and attachment to Doctors Burton Lee and James E. Edwards (now president of M.U.S.C. and previously Energy Secretary). Just quickly (half a minute) running your eyes over some of the enclosed underlined abstracts from five Cardiology sessions at this latest European Magnesium Conference is very likely to indicate why this area merits your personal attention and action.

Antioxidants, Evening Primrose Oil, Arthritis and Cancer

Brief contact with Dr. James O. Mason at the International Cancer Conference in Charleston, prompted the enclosed Nov. 3, 1992 letter and attachment to him. That letter covered the first successful U. S. double-blind trial presented earlier that week in Atlanta at the annual rheumatology meeting; which successfully employed the same natural essential fatty acid that had completely controlled my very severe rheumatoid arthritis without drugs since 1980. The last paragraph of the first attached letter copy to interested rheumatologists mentions potential future applicability of this approach to the president's right hip joint. Other attached letter copies deal mainly with provocative similarities between rheumatoid arthritis and cancer; and the apparent effectiveness of high levels of the antioxidant Vitamin C and the gamma-linolenic acid in evening primrose oil in achieving sustained control of both these degenerative diseases.

Dr. James McLaren, Thermonuclear Weapons, and You

You three just returned from Moscow after the all important mutual agreement

to further massively reduce our thermonuclear weapons. President Truman as you know had ordered production of any possible hydrogen bomb in 1950 after the Russians surprised us by exploding their first nuclear fission bomb four years earlier than expected; and during the same week Klaus Fuchs was found to be passing our nuclear secrets to the Russians.

You should thus find interest in the thermonuclear physicist, whose five year control of bone cancer and bone pain with very high levels of Vitamin C was discussed on the last two pages of the James Mason attachment. Based on five years (1980-85) of phone conversations with him he believed in 1947-54 that the "hydrogen bomb" should be based on Lithium-6; and apparently contributed very significantly when the Russians exploded the first transportable thermonuclear bomb in 1953.

Dr. James McLaren (B.S. at Syracuse) obtained his Ph.D in Scotland in 1933 on the separation of Lithium-6 from Lithium-7. He also then helped construct the equipment and beryllium target with which Sir James Chadwick produced and detected the first neutron; and thereby obtained the Nobel Prize.

Our race to quickly isolate bomb quantities of Lithium-6 occured when the August 1953 Russian thermonuclear bomb exploded with 25 times more power than at Hiroshima; and subsquent atmospheric analysis showed it had contained Lithium-6. With Dr. McLaren's background on Lithium-6 isolation and also being an electro-chemist; he apparently was deeply involved in proper utilization of an electochemical counter-force amalgam at the Oak Ridge plant to rapidly isolate the required Lithium-6 from lithium.

This Lithium-6 was then reacted with deuterium gas to form a solid Lithium-6-Deuteride nuclear fusion core. Detonation in one millionth of a second by neutrons from adjacent Uranium-235 fission; produced the massive fusion energy and also sufficient additional neutrons to double again the explosive power by causing fission of a cheap Uranium-238 casing.

This extremely small Lithium-6-Deuteride thermonuclear fusion bomb apparently demonstrated at Bikini in March 1954 half again more explosive power than the sixty-three ton liquid deuterium bomb (cooled to almost absolute zero) that exploded at Einewetok in November 1952; and fifty times greater explosive force than the Russian bomb seven months earlier.

The whole world surely owes Presidents Reagan and Bush incredible gratitude for so quickly and massively rebuilding our military capability and markedly reducing our nuclear danger even if it cost two trillion dollars. Timely, very quick and successful movement at an apparent critical period forty years ago could also merit our thanks and recognition. I remember his comment that the deuterium bomb cost twenty billion and was not usable; while theirs was achieved for fifty million. Of the six who worked together from 1949 to 1952, two had bone cancer, two had leukemia and two were dead.

Why Do We Age

If you are not yet convinced your vital organs need significant increased antioxidants as we age, then please look at the third paragraph of the enclosed Dec. 15, 1992 response to Dr. Peter Greenwald (NCI Director of Cancer Prevention and Control) and the table at the end of the attachment showing how much Vitamin C seems to drop in different vital organs over your life.

With hope that you might see this and find personal benefit or pertinent information, since all of us have benefited so tremendously from your combined twelve year effort.

Most sincerely,

Frank J. Ball

Frank J. Ball

FJBkaj

cc: Dr. James E. Edwards
Dr. Peter Greenwald
Dr. Dr. Burton J. Lee, III
Dr. James O. Mason
Senator Ernest F. Hollings
Senator Strom Thurmond
Representative Arthur Ravenel

PS: January 11, 1993

Since I couldn't get the typist to quite complete corrections on Friday, Monday's Post & Courier write up covering the quite significant progress on ovarian cancer with the natural product Taxol by Dr. William T. Creasmann is enclosed. He spoke to and possibly attracted the 8th International Cancer Conference that Dr. Mason also spoke to in Charleston.

I am not a medical professional, do not know Dr. Creasmann or the medical university oncologists and the enclosed picture with comments was attached to my 26 page 1978 letter on Vitamin C and cancer to indicate my situation.

Enclosed is the 1983 letter to the vice-president on non-toxic control of cancer that I briefly discussed with him in Charleston and a letter to Dr. Jan Van Eys at the same time. I retired a few months later and have been mainly interested in and have pushed the very deterimental effects of deficiencies of magnesium, gamma-linolenic acid and antioxidants in degenerative diseases since there was a much more receptive medical response.

I have since had an old Weimramer dog who weakened and almost quit eating; and was found to have a bladder tumor the size of a grapefruit, not recommended for removal. It turned out his bowel tolerance point for the oral half salt of Vitamin C in his food was about forty grams per day. His quality of life and weight returned to normal and his tumor progressively shrunk until it could no longer be detected by the veterinarian even with x-rays.

In early October my 12 year old English Sheep dog at her annual shots and check up, was reported to have a large mammary tumor, along with arthritis and an operation with subsequent radiation treatments were recommended. I found however that her bowel tolerance for Vitamin C was 32 grams which she has taken daily in her food along with some evening primrose oil since then. Progressive shrinkage of the tumor is evident; and there has been recent need to reduce the Vitamin C level to about half.

cc: Dr. William T. Creasmann
Dr. Samuel Broder, NCI Director
Dr. Jan Van Eys

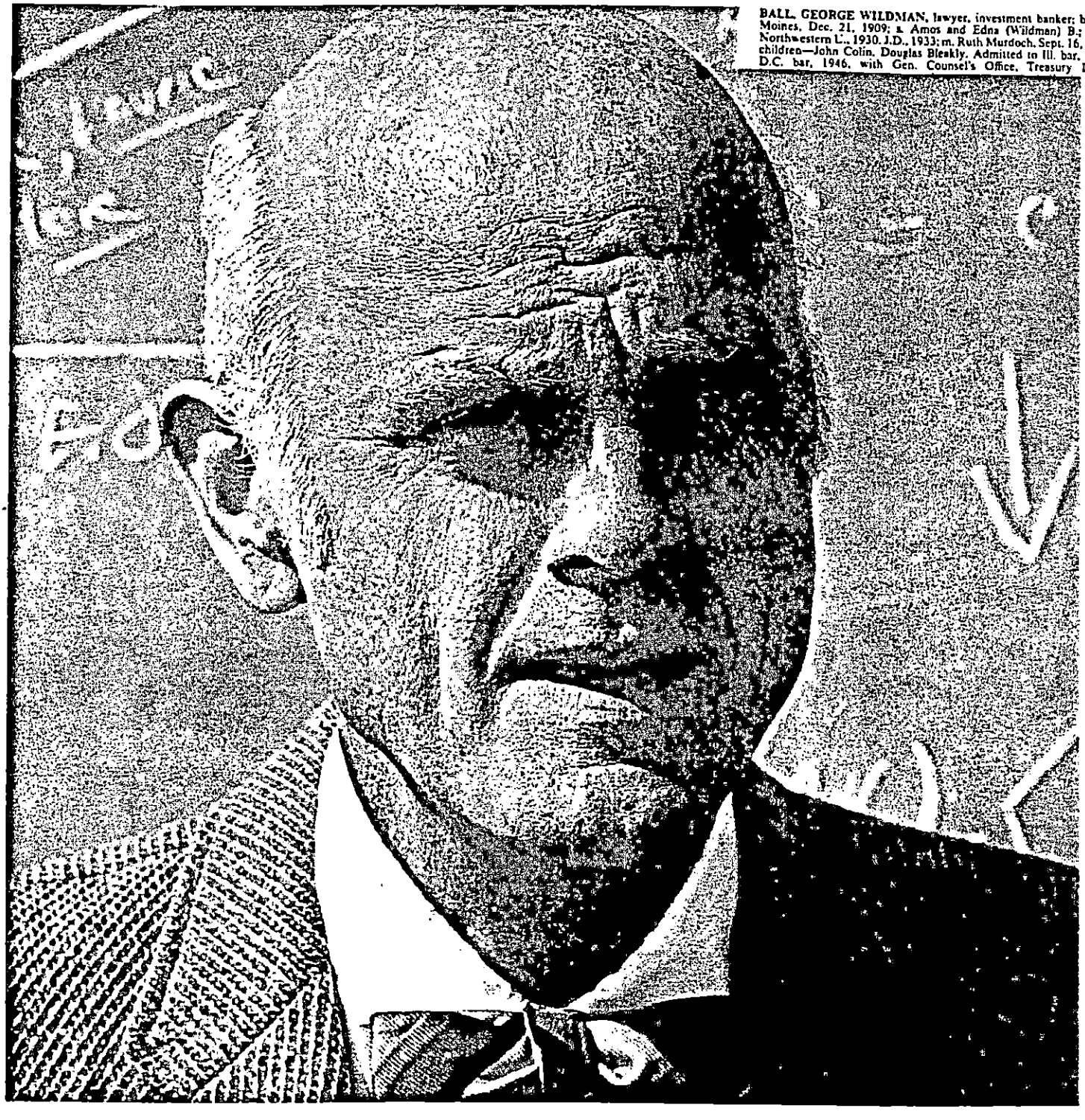
The Westvaco managers pictured on the four cover pages of this report have responsibilities in the key areas of forest resource management, technological research, manufacturing and marketing. Scott Wallinger (front cover), who holds a master of forestry degree from Yale, is manager of our Timberlands Division. Now 36 years old, he assumed responsibility for the management of nearly 1,200,000 acres of Westvaco forestland three years ago. He has been associated with Westvaco for eleven years. Dr. Frank J. Ball (below) has been a research scientist with Westvaco for 31 years. He is now associate corporate research director and director of our Charleston, South Carolina, research center, which concentrates on the development of high technology products that have accounted for the rapid growth of our specialty chemicals business. Now 56 years old, Dr. Ball has a Ph.D. degree from the University of Rochester.

WHO'S WHO IN THE WORLD

(1978-79)

BALL, FRANK JERVEY, chemist; b. Charleston, S.C., Jan. 29, 1919; s. John Coming and Annie Arden (Jervey) B.; B.S., U. of South, 1941; Ph.D., U. Rochester, 1944; m. Mary Elizabeth Furtwangler, Feb. 16, 1950; children—Frank Jervey, Stuart Furtwangler, Bruce Devon, Steven Moultrie. Research chemist Westvaco Corp., Charleston Research Center, 1944-46, group leader, 1946-53, dir., 1953-75, asso. corp. research dir., 1975—; dir. Tyrone Research Lab., 1958-60. Pres., Empire State Paper Research Assos., 1970—. Mem. Am. Chem. Soc., T.A.P.P.I., Charleston C. of C. (chmn. higher edn. com. 1969-74), Phi Beta Kappa, Sigma Xi, Omicron Delta Kappa. Episcopalian. Clubs: South Carolina Soc., St. Cecilia Soc., Carolina Yacht. Contbr. articles profl. jours. Patentee in field. Home: 4 Atlantic St Charleston SC 29401 Office: PO Box 5207 North Charleston SC 29406

BALL, GEORGE WILDMAN, lawyer, investment banker; b. Des Moines, Dec. 21, 1909; s. Amos and Edna (Wildman) B.; B.A., Northwestern U., 1930, J.D., 1933; m. Ruth Murdoch, Sept. 16, 1932; children—John Colin, Douglas Bleakly. Admitted to Ill. bar, 1934, D.C. bar, 1946, with Gen. Counsel's Office, Treasury Dept.,



October 29, 1992

Dr. Burton J. Lee, III, Physician to the President
Dr. James E. Edwards, President, Medical University of South Carolina
Dr. Peter C. Gazes, Distinguished University Professor of Cardiology, M.U.S.C.
Dr. James F. Spann, Director, Department of Cardiology, M.U.S.C.

Dear Doctors Lee, Edwards, Gazes, and Spann,

During the past year and a half you four have been exposed to continuing letters and literature emphasizing the wide-scale critical dangers of arrythmias and heart attacks caused by inadequate maintenance of our cellular magnesium. Diet-induced, stress-induced and running-induced magnesium deficiencies occur particularly in the heart, cardiovascular and cerebrovascular arteries and specific concern was expressed throughout this period because of the potential dangers from President Bush's very high stress levels and his arrythmia warning.

Doctors Edwards, Gazes, and Spann and their M.U.S.C. colleagues had been repeatedly written and contacted over the previous five years; as clinical evidence became progressively more impressive on 1) our serious chronic cellular magnesium deficiencies brought about largely by industrial preparation of foodstuffs, 2) the progressive resulting cardiovascular health problems and 3) the demonstrated major beniefit from intravenous magnesium supplementation in various cardiovascular crisis without detrimental side effects.

I came close to attending the IVth European Congress on Magnesium in Geissen, Germany last month; but couldn't finally get past the $ 1,650 plane ticket. Dr. Sighart Golf, Conference Chairman, however fortunately very kindly just sent me all of the 129-Magnesium abstracts. The 27 enclosed underlined abstracts from the five Cardiology Sessions decidedly merit perusal by all cardiologists; and by those of us who want to avoid, put off, or control deadly heart attacks. Just running your eyes over the titles would seem to suggest personal supplementation to lower chronic deficiency; since your likely intake appears to be half that desired.

Extensive intravenous magnesium supplementation in both heart attacks and arrythmias may begin in 1993 following completion of the 18 month Fourth International Study of Infarct Survival (ISIS-4) which ends in December; and which my Dec. 5, 1991 letter tried to get M.U.S.C. to join.

This week's November Harvard Heart Letter comment More on Magnesium (enclosed) covers the recent Lancet paper by K. L. Wood et al on a five year double-blind trial using 1776 mg of intravenous magnesium or placebo on 2316 randomized patients with suspect acute myocardial infarction. The magnesium group evidenced both a 28 day mortality reduction of 24% and a left ventricular failure reduction of 25% that were independent of thrombolytic or antiplatelet therapy and with no detrimental side effects. The ISIS-4 trial finishing in December uses 2000 mg of intravenous magnesium on half of the perhaps 40-50,000 randomized, double-blind acute myocardial infarction patients on hospital arrival; with end points at the first month and the end of the trial.

Enclosed are four underlined abstracts dealing with magnesium and the heart from the October American College of Nutrition annual meeting in San Diego; which had one day mainly on magnesium, zinc and selenium. Incidentally, two weeks earlier I also attended most of the excellent week-long Intensive Review In Emergency Medicine in

Charleston. The first talk on Monday by Dr. Bruce Usher covered Emergency Management of Myocardial Infarction; that prompted a final question on possible magnesium use, which he surprisingly referred to me. Several other questions on magnesium use were asked at this conference but with no answers. Dr. Robert Leman's quite interesting, late Friday afternoon talk on Emergency Management of Ventricular Tchycardia mentioned my presence; and that 2-4 grams of intravenous magnesium sulfate was now a good drug to use in certain acute heart problems. He later commented in his talk that where bradycardia converted to ventricular tachycardia this problem was magnesium responsive as were torsades de pointes arrythmias.

The Magnesium abstract in the STRESS session, Noradrenergic Activity in Panic Disorder: The Effect of Magnesium Salt Administration, that happened to be copied with the last of the 27 Cardiovascular Abstracts; seems another quite pertinent indication of the importance of adequate magnesium and clinical amelioration. Hopefully such encouraging abstracts and trials will accelerate acceptance of both daily magnesium supplementation to correct our wide-spread diet-induced, stress-induced and genetic magnesium deficiencies; and the intravenous use of magnesium in arrythmia and cardiovascular crises.

Most sincerely,

Frank J. Ball

Frank J. Ball

P.S. Enclosed is my August 1992 response and the July 29 New York Times story sent to me about Dr. Curtis Hames' long term efforts to demonstrate that the very much higher stroke death rate across the South (highest in South Carolina) was because eons ago, selenium was largely washed out of our soil (as was magnesium). Low soil level cellular selenium (reduced antioxidant capability) and low level cellular magnesium (reduced metabolic, enzymatic, synthetic and energy capabilities) thus certainly must be avoided. The amount of the readily absorbed magnesium in drinking water at various locations in industrial countries becomes critical and decidedly relates to cardiovascular death; because industrially prepared foodstuffs are so very low in magnesium.

cc: President George Bush,
Mrs. Barabara Bush,
Vice-president Dan Quayle
James Baker
John Sununu
Secretary for Health Loius W. Sullivan
Assistant Secretary for Health James O. Mason
Senator Ernest Hollings
Senator Strom Thurmond
Representative Arthur Ravenel
Dr. Curtis Holmes
Dr. Robert B. Zurier
Dr. Sighart Golf

M.U.S.C. Personnel

J. C. Allen
M. E. Assey
J. C. Ballenger
W. H. Barnwell
B. A. Carabello
J. A. Colwell
F. A. Crawford, Jr.
A. J. Crumbley
R. H. Gadsen
L. M. Haddad
H. G. Hempling
E. L. Hogan
J. E. Keil
R. B. Leman
E. C. LeRoy
W. M. Newberry
W. M. Simpson
C. P. Summerall, III
B. W. Usher
F. Tecklenburgh
W. C. Worthington

clinical basis. Severity of coronary sclerosis was quantified according to the Kaltenbach' score and patients were divided into 4 groups (I. mild CHD, n=20; II. medium CHD, n=22; III. severe CHD, n=22; IV. very severe CHD, n=9). Leftventricular ejection fraction was used to evaluate pump function. Furthermore we assessed the influence of digitalis or diuretic therapy and also of the presence of arterial hypertension or myocardial infarction. For statistical analysis we used Student 's t-test and Mann and Whitney's u-test . Magnesium content of erythrocytes decreases significantly with rising severity of coronary sclerosis (I.- 2, 55 SEM 0.24; II.2, 44 SEM 0.30; III.- 2,40 SEM 0.24; IV.- 2, 00 SEM 0,44) . There was no significant difference between patients with normal or impaired pump function. Considering the presence of hypertension or myocardial infarction, we could not find any difference. The results were not influenced by digitalis or diuretic treatment. Plasma magnesium did not show any difference in all cases. The decrease of erythrocyte magnesium in patients with coronary heart disease is a phenomenon which is primarily related to severity of coronary sclerosis and which does not depend on digitalisation, diuretic therapy, myocardial infarction or arterial hypertension.

13 **Magnesium and Hypertension**

Wester, P.O
Internal Medicine, University of Umeå, Sweden

In experimental work magnesium (Mg) has been established to be an important regulator of vascular tone and in some studies hypertension has developed in Mg deficient rats. The evidence from epidimiological studies of a role for Mg in the development of human hypertension is inconsistent. Dietary intake of Mg and also Mg in serum are reported to be inversely related to blood pressure (BP) in several investigations but urinary Mg excretion is unrelated to BP in most studies. A BP fall in relation to i.v. Mg infusion is often observed. The results of peroral Mg substitution to hypertensive patients are inconsistent. Peroral Mg added in physiological doses to hypertensive patients seems not to affect BP unless the patients have a Mg deficiency which often is the case after several years of diuretic treatment. However, the administration of Mg in pharmacological doses seems to lower BP dose dependently without any uncomfortable side-effects. The pathophysiological background may involve several mechanisms such as interference with the sodium, potassium, pump function, the calcium transport mechanisms, the renin-angiotensin-aldosteron system and also the prostacyclin and inositol metabolism.

14 **The Dose-Dependent Reduction in Blood Pressure through Administration of Magnesium - A Double Blind Placebo Controlled Crossover Study**

L. Widman, P. O. Wester, B. Stegmayr
Internal Medicine, University of Umeå, Sweden

Seventeen patients with a diastolic blood pressure over 90 mm Hg were recruited from a running health screening programme to a double blind crossover study with 15 mmol Mg 2+/day (Emegsan)® for three weeks, followed by a 30 mmol Mg2+/day for another three weeks with 40 mmol Mg2+/day for a final three weeks. A significant decrease in the mean systolic blood pressure was recorded from 154±10.7 mm Hg to 146±16.9 mm Hg (p=0.031) and the mean diastolic blood pressure decreased from 100.2±4.2 mm Hg to 92±6.6 mm Hg (P=0.0001).

15 **Influence of vascular endothelium on Mg-induced relaxation in isolated aorta from DOCA-Salt hypertensive rats.**

P. Laurant, A. Berthelot
Laboratoire de Physiologie Pharmacie, Faculté de Médecine et de Pharmacie, Place St Jacques, 25030 BESANCON Cedex, France

Few investigations have been focused about the relationships between extracellular Mg (Mg e.c.) and endothelium in arterial hypertension. The present study was designed to determine whether increasing Mg e.c. leads to endothelium-dependent relaxation in noradrenaline-precontracted isolated aorta from 12 weeks-old deoxycorticosterone acetate salt (0.9% NaCl) hypertensive (DOCA) (n = 10) and normotensive (NT) (n = 10) Sprague-Dawley rats.
Mg-induced relaxation was lesser in intact aorta from DOCA as compared to NT rats with increased IC_{50} value to Mg (1.22 ± 0.19 vs 0.12 ± 0.01 mM, P < 0.001). Removal of endothelium depressed the Mg-induced relaxation in aorta from both DOCA (IC_{50}: 2.33 ± 0.26 vs 1.22 ± 0.19 mM; P < 0.01) and NT rats (IC_{50}: 1.00 ± O.23 vs O.12 ± O.01 mM , P < O.01). The same observation was made in presence of L-NAME (inhibitor of endothelial NO biosynthesis) (IC_{50}: 0.52 ± 0.11 vs O.11 ± 0.01 mM, P < 0.01 in NT rats; IC_{50} : 3.87 ± 0.51 vS 1.09 ± 0.15 mM, P < 0.001 in DOCA rats). However the Mg-induced relaxation following contraction with noradrenaline was significantly less in intact aorta treated with L-NAME or in aorta with disrupted endothelium from DOCA rats than those from NT rats. It is concluded that Mg-induced vasorelaxation on noradrenaline precontracted aorta can be mediated by endothelium-dependent mechanism implicating NO. The influence of NO on the impaired Mg-induced relaxa-

tion is more pronounced in aorta from DOCA rats. These differences could be related to the impaired endothelial function from hypertensive rats which seems ameliorate by Mg e.c.

Influence of a Magnesium Supplementation on Serum Lipids and blood Pressure.

K. Kisters, C. Kaiff, K. H. Rahn, W. Zidek
Med. Univ. Poli . nik. 4400 Münster, Albert-Schweitzer-Str. 33, Germany

The effect of an oral Mg^{++} supplementation on serum lipids in patients with hyperlipidemia of Frederickson type IV and IIb and on blood pressure was examined. In 65 patients with normal renal function, on cholesterol-poor and calorie restricted diet, blood pressure, serum cholesterol, triglyceride, HDL- and LDL-cholesterol as well as plasma and intracellular magnesium concentrations were measured before and 4 weeks after therapy. 35 patients received 500 mg Mg^{++} daily additionally. The results show that a Mg^{++} supplementation in addition to the usual dietary measures is beneficial with regard to serum triglycerides (values, means±SD, decreased from 197, 57±47.12 to 163,80±40,73, $p<0,05$), but exerts no positive effect on blood pressure and serum cholesterol. Furthermore intracellular magnesium concentration increased significantly under Mg^{++} supplementation (values, means± SD, increased from 1 ,73±0,23 to 1,90±0.19 mmol/1, $p<O,05$) .
This study has shown that a peroral magnesium therapy can alter blood lipid composition and therefore be of use in reducing atherogenic risk factors, but further investigations, especially with regard to a long-term Mg^{++} therapy, still remain to be settled.

16 **Reduction of Blood Pressure with Oral Magnesium Supplementation in Women with Mild to Moderate Hypertesion**

J.C.M. Witteman (1), D.E. Grobbee (1), F.H.M. Derkx (2), R. Bouillon (3), A.M. de Bruijn (1), A Hofman (1).
(1) Department of Epidemiology & Biostatistics,
(2) Department of Internal Medicine I, Erasmus University Rotterdam, The Netherlands.
(3) Laboratory of Experimental Medicine and Endocrinology, Catholic University of Leuven, Belgium.

486 mg-Mg In a double-blind controlled trial, 91 middle-aged and elderly women with mild to moderate hypertension who were not on anti-hypertensive medication were randomly assigned to treatment with magnesium aspartate-HCl (20 mmol magnesium per day) or placebo for 6 months. Magnesium aspartate-HCl in the given dose was well-tolerated and was not associated with an increased frequency of diarrhoea compared to placebo. At the end of the study, systolic blood pressure had fallen by 2.7 mmHg (95% confidence interval -1.2 to 6.7) and diastolic blood pressure by 3.4 mmHg (1.3 to 5.6) more in the magnesium group than in the placebo group. The presence of a low plasma renin or a high plasma parathyroid hormone level at baseline enlarged the effect on systolic but not on diastolic blood pressure. Urinary magnesium excretion significantly increased in the magnesium compared to the placebo group. No changes were seen in other biochemical parameters. The findings suggest that oral magnesium supplementation with magnesium aspartate-HCL may be a safe and effective measure for lowering blood pressure in subjects with mild to moderate hypertension, who are not receiving anti-hypertensive treatment.

17 **The role of Magnesium in Glucose Intolerance and Insulin Resistance in Patients with Essential Hypertension**

K. Sebeková, V. Spustová, R. Dzúrik
Dept. Clin. Pharmacol; Inst. Prev. Clin. Medicine; Bratislava, CSFR

Decreased free erythrocyte magnesium (fErMg) concentrations associate with and even appear to be a common cause of both essential hypertension and glucose intolerance and/or insulin resistance (GI/IR). The prevalence of GI in patients with essential hypertension (n=98) could be predicted (95% confidence limits) to 26-35%, and rose even to 39-59% if both GI/IR were considered. The parameters characterizing Mg metabolism [Mg-S, Mg-U, total (atomic absorption spectrophotometry), fErMg (31P NMR spectroscopy) and bound Mg (calculated) were studied in 25 patients with essential hypertension during standard oral glucose tolerance test (oGTT) under basal conditions and aftr i.v. load of 2 g Mg sulfate. It was found that GI/IR was significantly more frequently associated with low fErMg>200, chi2, $p<0,001$. No difference was found in other parameters of Mg metabolism, therefore the shift of fErMg towards the bound fraction seemed to result from its increased intracellular binding. I.v. Mg load prior to oGTT improved GI/IR in patients with low fErMg, and 3/7 patients completely normalized their glucose tolerance. It is concluded, that low fErMg associates with GI/IR, and both improve after acute i.v. Mg load.

18 **Magnesium Reduces Mortality in Acute Myocardial Infarction Patients Unsuitable for Thrombolytic Therapy**

M.Shechter, H.Hod, E.Kaplinsky, B.Rabinowitz.
Heart Institute, Sheba Medical Center Tel-Hashomer and Tel-Aviv University, Israel.

The effects of intravenous magnesium (Mg) were evaluated in 181 pts with acute myocardial infarction (AMI) unsuitable for thrombolytic therapy, in a randomized, double-blind placbo controlled study. Gr I, 98 pts received 48-hour Mg infusion while 83 pts, Group II, received isotanic glucose as placebo. In-hospital mortality was significantly reduced in Gr I pts compared to Gr II [2 pts (2.2%) vs 12 pts (15%), p<0.021]. Thirty per cent of pts (51/181) were > 70 years old (range: 71-86, mean 77±4): 24 pts from Gr I (subgroup A) and 27 pts from Gr II (subgroup B). Analysis of multiple factors showed good randomization.

Results	Gr I N = 98 N (%)	SubGroup A N = 24 N (%)	Gr II N = 83 N (%)	SubGroup B N = 27 N (%)
Major arrhythmias	21(21)	11(46)	34(41)	19(70)
Conduction disturbances	8 (8)	5(20)	12(14)	5(19)
Heart failure	15(15)	5(20)	18(22)	10(37)
Mortality	2 (2)	2 (8)	12(14)	6(22)

No significant side effects were seen during the trial. We found that intravenous Mg is an effective alternative therapy in AMI pts unsuitable for thrombolysis and is associated with reduced in-hospital mortality, possibly by reduction in major arrhythmias and in incidence of heart failure. These effects are particularly seen in patients > 70.

19 **Leicester Intravenous Magnesium Intervention Trial (LIMIT-2): A Double Blind Study of the Use of Magnesium Sulphate in Suspected Acute Myocardial Infarction.**

Woods, K.L., Fletcher, S., Roffe, C., Haider, Y.
Department of Pharmacology and Therapeutics, University of Leicester, Coronary Care Unit, Leicester Royal Infirmary, Leicester, England

Magnesium salts have been reported to protect myocardial tissue in experimental model of ischaemia and reperfusion. Several small clinical trials in suspected acute myocardial infarction have suggested thatearly mortality can be reduced by intravenous magnesium salts in the acute phase, but none have been of sufficient size to be conclusive. The Leicester Intravenous Magnesium Trial (LIMIT-2), a double blind, placebo controlled study was undertaken randomising 2316 patients with suspect acute myocardial infarction. Patients recieved either intravenous magnesium sulphate (8 mmol over 5 min followed by 65 mmol over 24 h) or physiological saline. This protocol was designed to double serum magnsium on admission to the coronary care unit in order to maximize benefit of treatment.

1774 mg · mg

The primary outcome of interest was 28 days mortality, by intention to treat, which is not susceptible to bias providing good randomization and high follow up was acheived. These criteria were met. The result showed, on analysis of morality from all causes, a reduction of 24% in the magnesium group (95% confidence interval 1. 43%). The overall morality in the magnesium group was 7.8% and 10.3% in the placebogroup (2p = 0.009). The two groups were well matched in all aspects. Myocardial infarction was confirmed in 65% in both groups with similar cardiac enzyme elevations. No differences were found between the groups in antiarrhythmia treatments, heart block, direct-current cardioversion or temporary pacing.

Side effects of magnesium treatment were transient flushing, related to the speed of injection of the loding bolus and an increased incidence of sinus bradycardia (2p = 0.02). Experience in a large and representive group of patients has shown that is a simple and safe treatment, which can be generally used for suspected myocardial infarction. The efficacy of magnesium sulphate in reducing early morality of myocardial infarction is comparable to, but independent of, that of thrombolytic therapy or antiplatelet therapy.

20 **Die Ermittlung der therapeutischen Wirksamkeit von Magnesiumadipat bei Patienten mit einem akuten Myokardinfarkt**

Th. Hildebrandt, R. Thiele, K. Winnelfeld und H. Dawczinski
Universität Jena, Germany

In eine placebokontrollierte Doppelblindstudie wurden 51 Patienten mit einem akuten Myokardinfarkt (34 Männer und 17 Frauen von 49 bis 80 Jahren) über einen Zeitraum von 1/4 Jahr integriert. Von diesen Patienten erhielten 25 (49%) täglich 2 x 150 mg Magnesiumadipat (Verumgruppe) der Firma APOGEPHA Arzneimittel GmbH Dresden und 26 Patienten (51%) ein entsprechendes Placebopräparat (Placebogruppe) per os. Die mittels Atomabsorptionsspektrophotometrie am 1., 2., 3. und 20. Tag sowie nach 1/4 Jahr gemessenen Magnesiumkonzentrationen im Serum, im Vollblut und im Erythrozyten zeigten bei Patienten der Verumgruppe ein gutes Resorptionsverhalten des Präparates. Dabei ließen sich bei diesen Patienten im Vergleich zu denen der Placebogruppe insgesamt deutlich

den. Dem Präparat Magnesiumadipat käme generell bei Herzinfarktpatienten bereits in der vorgenommenen Dosierung eine kardioprotektive Funktion zu.

21 **Plasma Mg, Zn and Cu in Acute Myocardial Infarction (AMI)**

C. Zeana, Z. Chirulescu, A. Suciu, R. Pirvulescu, C. Carseli, C.C. Zeana
Medical Clinic, Emergency Hospital (1, 5, 6) and Medical Clinic Colentina Hospital (2, 3, 4), Bucharest, Romania.

150 AMI cases were studied in comparison with a control lot of 50 healthy individuals. Magnesemia was repeatedly determined using Merck kits in 50 patients not receiving Mg supplements. Zn and Cu plasmatic levels were determined by atomic absorbtion spectrophotometry and ceruloplasmin level was determined enzymatically in all 150 pts. In AMI, a lowering of Mg was registered especially within the first week of infarction: 0.76 ± 0.09 versus 0.92 ± 0.06 mmol/l. In the same time Zn level went down from 96.56 ± 15.96 to 85.02 ± 47.34 µg/dl. Cu raised from 100.22 ± 15.96 to 161.3 ± 61.14 µg/dl. The Cu/Zn ratio which is close to 1 in normal people grows up to 2.5 in AMI (greatest values about 6) and becomes normalised during convalescence. The Cu/Zn ratio has not only a diagnostic but also a prognostic value.
The serum ceruloplasmin level goes down to approximatively half of the normal level in some cases, becoming normalised during the next 3 to 4 days and then tends to overtake the normal level. Plasma ceruloplasmin in control lot: 26 ± 1.2 mg/dl. Ceruloplasmin in plasma within the first 3 days: 16±4.05 mg/dl, AMI lot.

CARDIOLOGY V

22 **Oral Potassium/Magnesium Therapy in chronic stable ventricular ectopy.**

K. Glänzer and D. Stolberg
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Potassium and magnesium supplements are effective in cardiac arrythmias in acute myocardial infarction and in definitivly magnesium-depleted states. The antiarrhythmic effect of magnesium and/or potassium supplements in chronic stable ventricular ectopy is still controversial. Methods: We investigated in this open, not blinded pilot study the antiarrhythmic effects of potassium/magnesium aspartate (Trommcardin Forte 2 tabl tid) in patients on benign ventricular arrhythmias in a total of 13 patients (mean age 48.8 years). Other antiarrhythmics drugs were not allowed. All patients suffered from ventricular premature ectopic beats since many weeks or years. Exclusion criteria: known malignant ventricular tachycardia, ventricular fibrillation and other states of successful cardiopulmonary resuscitation. Two 24-h-ECGs were recorded in two consecutive days before and after 14 days of treatment with magnesium/potassium aspartate. Statistical evaluation of the data was done by Wilcoxon- Rank- sum- test. Results: Mean serum potassium and magnesium values remained unchanged during treatment. The frequency of ventricular ectopic beats was reduced in almost all patients, but due to the large mean variation the difference was not statistically significant. All patients noted a marked relief of their complaints under therapy. Conclusions: Magnesium/potassium supplements may be useful in patients with PVC's. Therefore larger, controlled studies should be carried out to prove these preliminary results. Since there is no risc in therapy, harmless ventricular ectopy should be treated with Mg/K- supplements before treatment with conventional Class I and II antiarrhytmics.

23 **Möglichkeiten und Grenzen des Einsatzes von Kalium und Magnesium bei Erkrankungen des Kreislaufes Ein Überblick**

W. Zidek
Medizinische Fakultät Poliklinik Münster

Die Wirkungen von Kalium- und Magnesiumionen auf die Kreislaufregulation sind sowohl aus experimentellen Untersuchungen als auch aus klinischen Beobachtungen gut bekannt. Sowohl Kalium als auch Magnesium wirken vasodilatierend. Die gefässerweiternde Wirkung von Kaliumsalzen wurde bereits 1929 in Untersuchungen an essentiellen Hypertonikern nachgewiesen und seither mehrfach bestätigt. Der Mechanismus der vasodilatierenden Kaliumwirkung besteht möglicherweise in einer Stimulation der Natrium-Kalium-Pumpe. Dieser Vorgang führt zu einer Senkung des intrazellulären Natrium und zu einer Zunahme des intrazellulären Kalium. Die Abnahme des intrazellulären Natrium in der Gefässmuskelzelle führt zu einem verminderten Calciumeinstrom über den Natrium-Calcium-Austausch. Durch die verminderte Calciumaufnahme nimmt auch die cytoplasmatische freie Calciumkonzentration in der glatten Muskelzelle ab. Dies dürfte ein wesentlicher Mechanismus der vasodilaterierenden Kaliumwirkung sein. Hinsichtlich des Magnesium ist die vasodilatierende Wirkung vor allem bei Patienten mit Präeklampsie klinisch bekannt. Im Vergleich dazu ist die blutdrucksenkende Wirkung bei essentiellen Hypertonikern wesentlich geringer ausgeprägt. Die Mechanismen der Magnesiumwirkung auf das Gefässsystem können unter anderem in einem der Calciumwirkung entgegengesetzten Effekt auf das kontraktile System der glatten Muskelzellen liegen. Ferner ist bekannt, dass bei hoher extrazellulärer Magnesiumkonzentration vermehrt Calcium aus den Zellen

ausgeschleust wird. Da Magnesium auch ein notwendiger Kofaktor der Natrium-Kalium-ATPase ist kann auch ein Mechanismus wie oben für das Kalium dargestellt für die Vasodilatation eine Rolle spielen.

24 **The Role of Potassium and Magnesium on Cardiac Glycoside Toxicity in the Human Myocardium**

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Electrolyte alterations may be due to the pathophysiological conditions seen in the heart failure state and due to the complications of drug therapy with diuretics, ACE inhibitors and cardiac glycosides. Several studies have documented lower Mg^{2+}-levels in patients with heart failure. Mg^{2+} is essential for maintainance of intracellular K^+. In patients with low Mg^{2+}-levels, the treatment of heart failure with cardiac glycosides is complicated by an increased incidence of arrhythmias. In addition to extracardiac actions, Mg^{2+} may also have direct effects on the myocardium. We studied the influence of Mg^{2+} (1-3 mM) on contractility and on force-frequency-relationship (FFR) as well as on the positive inotropic (PIE) and toxic effects (TOE) of ouabain (OUA) on electrically driven human right auricular trabeculae (AUT, aortocoronary bypass operation, nonfailing, no cardiac glycoside treatment, n = 16, age = 60.1 ± 1.7 years). The maximal PIE of OUA (+5.9±0.9 mN, 1 mM Mg^{2+}) was preserved after increasing Mg^{2+} (+5.8±0.9 mN, 2 mM Mg^{2+}). Time until TOE occurred after OUA was significantly ($p<0.05$) longer with higher Mg^{2+}-levels. In AUT the force of contraction increased with increasing frequency (0.5-3 Hz) of stimulation (2 Hz: 146±8% basal). The FFR becomes negative after elevation of extracellular Ca^{2+}. Mg^{2+} was effective to restore the normal FFR in the presence of enhanced Ca^{2+}-concentrations (2.4 mM Ca^{2+}, 2 mM Mg^{2+}; 2 Hz: 145 ± 16% basal). Mg^{2+} increased concentration-dependently the affinity of ^{3}H-ouabain to its receptor ($p<0.05$).
In conclusion: (1) Mg^{2+} acts directly on human myocardium to diminish OUA-induced toxicity but preserves the maximal PIE of OUA; (2) the antagonistic action of Mg^{2+} is not due to a reduced receptor-binding, but may be due to an alteration of the sensitivity to intracellular Ca^{2+}-changes. Therefore, when treating congestive heart failure, one must take care to prevent depletion of electrolytes or to replete K^+ and Mg^{2+} in deficiency states.

25 **The Influence of Aspartate Anions on Contraction of Isolated Myocytes**

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External Ca^{2+} and Mg^{2+} have opposite effects on the contractile force of the heart muscle (Ca/Mg-antagonism). But only little is known about the influence of the anions applied together with Mg^{2+}. Thus the aim of this investigation was to test the effect of aspartate-anions in combination with Mg^{2+} on contraction of isolated ventricular myocytes of the Guinea pig. Shortening of isolated cells was measured optically in an inverted microscope. Increasing of external $MgCl_2$ decreases shortening in a dose dependent way (from 120% at O mM $MgCl_2$ to 25% at 20 mM). The influence of external $MgCl_2$ is especially pronounced in the physiologically relevant concentration range. The negative inotropic effect of $MgCl_2$ is superimposeable to that of $MgSO_4$. But if Cl^- is exchanged for DL-hydrogenaspartate (MgAsp), the negative inotropic effect of Mg^{2+} is largely suppressed in the concentration range between O and 5 mM. Only at concentrations higher than 5 mM a negative inotropic effect can be recorded. To suppress shortening by about 30 % 15 mM Mg-Asp are necessary but only 5 mM $MgCl_2$. The difference between $MgCl_2$ and Mg-Asp can be explained by a positive inotropic effect of DL-aspartate itself. In the case of ß-stimulation the negative inotropic power of Mg-Asp exceeds that of $MgCl_2$ by a factor of two i.e. 5 mM Mg-Asp have a stronger suppressing effect than 10 mM $MgCl_2$. In isolated ventricular cells stimulated with adrenaline application of 5 mM Mg-Asp result in an effect comparable to 10 -15 nM propanolol. Thus exchanging the Cl^- for aspartate-anions transforms a Ca^{2+}-antagonistic substance to one with ß-antagonistic force at low concentrations and Ca^{2+}-antagonistic force at high concentrations.

26 **Parenteral Application of Magnesium and Potassium as an Adjuvant Treatment-Possible Clinical Approaches**

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There are various reasons for the lack of intracellular potassium and magnesium in patients treated in intensive care unit. Acute myocardial hypoxaemia or myocardial infarction are followed by a loss of both cations. States of cardiopulmonary resuscitation and hypoxic metabolism are often accompanied by a dcreasing serum potassium level, especially after substitution of sodium bicarbonates. In the diuretic therapy of chronic heart failure substitution of potassium is usual, while the depletion of magnesium often remains unregarded. The benefit of magnesium is already well known in the treatment of "torsade de pointes", a special form of ventricular tachycardia. Clinical experience shows, that parenteral application of potassium and magnesium improves the effect of antiarrhythmic drug also in other forms of ventricular and supraventricular arrythmia, especially when a deficit must be taken into consideration. So in one of the reported cases defibrillation of a patient with ventricular tachycardia was not successful until

500 mg of potassium/magnesium aspartates were administered intravenously. In other patients with atrial fibrillation a stable sinus rhythm could be achieved after magnesium/potassium-aspartate was added to the standard therapy with digoxin, verapamil and quinidine.

27 **Mg-Deficiency and the Effects of Mg-Protection of the Heart, a Problem of Quantative Evaluation**

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It is frequently assumed that Mg deficiency induces several morphological damage of heart muscle. On the other hand it is likewise supposed that Mg protects the heart against catecholamine and other damage. Such effect should never be denied. However, reports may be of minor significance or even risky if there is no quantative evaluation. For such efforts stereological techniques have been developed years ago. Using such methods it comes out that all morphological damage of heart muscle is modest in comparison to biochemical alterations and possible acute disturbances in excitation. Because Mg deficiency is highly critical, when catecholamines are applied, it is not improbable that some of the morphological effect might be caused rather by an additional stress than by the Mg deficiency per se. Likewise, even so-called infarct-like, isoprenaline inducible necroses consist in the rule only of some volume percent of heart muscle, where repeated lower doses are more effective than one mighty injection. The necrosing effects of Mg in experiments is not very impressive. Functional aspects may be more important than histological effects. In addition, it should be pointed out that a quantative experimental evaluation of the pathological anatomy of ß-sympathomimetics could help to avoid such long term side effects of antiasthmatics that were noticed recently in some countries.

STRESS

Noradrenergetic Activity in Panic Disorder:The Effect of,Magnesium Salt Administration

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Dept. of Neurology III, Neurological Institute "C. Nondino", University of Pavia, ITALY.

Panic disorder (PD) is a syndrome characterized by unexpected and unprovoked attacks of psychic and somatic anxiety symptoms. Althougb the exact pathogenesis of PD is unknown, the existence of an unbalanced noradrenergic activity has been suggested. On the other hand, panic attacks can easily occur in patients suffering from neuronal hyperexcitability syndrome (NHS), the so-called "spasmophilia", whose pathogenesis may be related to a primitive magnesium (Mg) deficiency. Thus, a clinical (and pathogenetic?) overlapping of these two pathologies could be hypothesized. In this study we evaluated the influence of magnesium administration on the noradrenergic activity in 10 patients suffering from PD. For this purpose, we measured the plasma levels of Norepinephrine (NE) in response to a Cold Pressor Test (CPT): immersion of one hand in ice-cold water for 5 minutes) and to the infusion of sodium lactate (Lactate Test, LT), highly effective in inducing a panic attack in PD sufferers. The same tests were performed in a group of 10 age-matched healthy controls. In the PD patients, the tests were repeated after a two-month treatment with Mg pidolate (4.5 g/die per os): they were also studied from a neurophysioloqical point of view by evaluating the basal and after-treatment skin conductance response (SCR), used as an additional index of autonomic excitability.

As regards CPT, PD patients showed significantly higher NE levels than controls in basal conditions (m+/-sem: 210+/-30 vs 131+/-18 pg/ml; p<O.05), a reduced response to the stimulation and the absence of a recovery phase. The LT had no effect on the controls, whereas it induced a panic attack in 9 out of 10 patients, with a significant rise in NE levels, that maximized at the 20th minute of lactate infusion (O' vs +20': 217+/-42 vs 328+/-48 pg/ml: p<O.OOl). Mg therapy determined a normalization of the NE response to the CPT and a decreased noradrenergic response to LT, although the lactate infusion induced a new panick attack in the same 9 patients. Moreover, the treatment induced a significant increase of the SCR threshold (2.4+/-O.5 vs 4.0+/-0.9 mA; p<O.05). The treatment was able to significantly reduce the number of spontaneous panic attacks per month (10.6+/-2.9 VS 5.2+/-1.8; p<O.05).

These data, while confirmEing the existence of a noradrenergic hyperactivity, show a dysregulation of the sympathetic stress response in PAD patients: they also suggest that Mg pidolate may play a role in correcting this dysfunction determining, at the same time, a clinical amelioration.

American College of Nutrition Cardiology, San Diego

PLENARY SESSION II, SATURDAY

Abstract 36

MAGNESIUM, MYOCARDIAL INFARCTION AND ARRHYTHMIAS. *Brodsky M.A.* Cardiac Arrythmia Service. University of California, Irvine, College of Medicine, Orange, CA 92668 USA.

Magnesium (Mg) is the fourth most abundant cation in the human body and the second most abundant cation in intracellular fluids. It has an important role in the activation of many enzyme systems. Mg deficiency is estimated to occur in 20–80% of the population. Yet Mg is commonly ignored by clinicians because its level is not usually measured: its deficiency is not always revealed: the association of its deficiency to pathology is not always obvious; and its use in research and clinical situations is not commonly promoted.

Mg has an important role in cardiovascular pathophysiology. The development of experimental atherosclerosis is potentiated by magnesium deficiency through many different mechanisms. The level of Mg is also related to coronary vascular tone, and hypomagnesemia has been associated with clinically significant angina secondary to coronary vasospasm. In the setting of acute ischemia and/or myocardial infarction, magnesium therapy has been shown to reduce the incidence of life-threatening ventricular tachyarrhythmia. Seven separate trials evaluated 1301 patients and, taken in total, documented a 55% reduction in the odds of death in the group given Mg therapy. The principal mechanism of action was through a reduction in the incidence of ventricular tachyarrhythmia. Mg has both primary and secondary electrophysiologic action. By itself Mg delays AV nodal conduction and decreases early afterdepolarization and triggered activity. It interacts with potassium ions and may allow for repletion of hypokalemia with secondary benefits in reducing arrhythmia. Intravenous Mg was initially reported to have antiarrhythmic action in 1943. Since then multiple reports have detailed its efficacy in supraventricular tachycardia, atrial fibrillation, ventricular premature depolarizations, both monomorphic and polymorphic ventricular tachycardia and ventricular fibrillation. It has also been beneficial in treating arrhythmia related to digitalis toxicity and coronary artery spasm.

In conclusion, Mg is an important component in cardiovascular pathophysiology. Recognition of its therapeutic potential should help reduce morbidity and mortality associated with cardiovascular disease.

PLENARY SESSION II, SATURDAY

Abstract 39

LOW MAGNESIUM: A COMMON DENOMINATOR IN PATHOLOGIC PROCESSES IN DIABETES MELLITUS, CARDIOVASCULAR DISEASE AND ECLAMPSIA. *Seelig MS*, Altura BT, Resnick LM, Handwerker SM, Altura BM. Community and Preventive Med, NY Med Coll, Valhalla, NY and Nutrition, Sch of PH, Univ of N Carolina, Chapel Hill, NC; SUNY, Bklyn, NY, Cornell Univ NY Hosp, NY, NY, Booth Mem Med Ctr, Flushing, NY USA.

Microcirculatory disorders of diabetes mellitus (DM)—a disease that when poorly controlled was early identified with Mg loss—have characteristics in common with those of experimental Mg deficiency. Low blood Mg (in concert with high Ca) increases platelet aggregability and blood coagulation—which have been implicated in the pathogenesis of DM, myocardial infarction (MI) and eclampsia. Low serum Mg, though present at phases of the disorders in many cases, is an unreliable index of Mg deficiency. Low ionized Mg in erythrocytes (determined by utilizing nonmagnetic resonance) is present in all, as well as in hypertension (HT) unrelated to DM or toxemias of pregnancy. Using a new ion-selective electrode specific for the Mg ion, we have found that low levels of the biologically active ionized Mg is present in whole blood, as well as in plasma and serum, of patients with HT, with or without DM, of patients scheduled for open-heart surgery, and of preeclamptic patients. Recent studies by others have shown that there is also endothelial damage in DM, and in cardiac and preeclampsic patients. Low Mg concentration influences endothelial integrity and its production of prostacyclin (PGI)—the vasodilating, antiaggregating prostanoid, mediating its activity, and increases release of thromboxane (TXA)—the vasoconstricting, platelet aggregating prostanoid. Other endothelial derivatives (endothelium-derived relaxing factor (EDRF), endothelin, and fibronectin may also be affected by Mg. Low Mg favors a high TXA/PGI ratio. It is suggested that imbalance of the prostanoids and that of the other endothelial derivatives may be linked to the low Mg reported in these diseases. With the new Mg ion-selective electrode, which uses a neutral carrier-based membrane to provide readings in 60–90 seconds, it will be possible to resolve the problem of laboratory diagnosis of Mg deficiency. With growing recognition of the roles of the endothelial factors, this should improve understanding of the vulnerability of diabetics to HT and other vasospastic and structural arterial diseases, and to cardiomyopathy and MI and other thromboembolic conditions, as well as to preeclampsia.

POSTER SESSION II, SATURDAY

Abstract 40

ADVERSE STRESS REACTIONS IN MAGNESIUM DEFICIENCY: PREVENTIVE AND THERAPEUTIC IMPLICATIONS. *Seelig MS.* Community and Preventive Medicine, New York Medical College, Valhalla, NY; Department of Nutrition, School of Public Health, University of North Carolina, Chapel Hill, NC USA.

Stress hormones (catecholamines and corticosteroids) that evoke responses allowing for increased survival in life-threatening situations, can increase the risk of sudden cardiac death (SCD) in the presence of Mg deficiency. They mediate release and utilization of substrates for production of energy and for improved skeletal and cardiac muscle performance, and mobilize tissue Mg. The resultant (transitory) increase of serum Mg protects against arrhythmias and intravascular coagulation in the short-term. However, plasma Mg at levels exceeding the renal threshold is excreted, and free fatty acids that are released through the lipolytic effect of catecholamines, inactivate Mg. Both stress hormones mobilize bone minerals, with resultant increase in the plasma Ca/Mg ratio, which increases risks of both intravascular coagulation, and arrhythmia. High Ca/Mg ratios also stimulate, and high Mg/Ca ratios suppress catecholamine secretion by the adrenal medulla and by secretory granules at nerve endings and in the myocardium. Low Mg also increases output of mineralocorticoids, which in turn directly enhance urinary excretion of Mg and intensify cardiopathogenicity of both Mg deficiency and catecholamine excess. Furthermore, reduced arterial tissue Mg can lead to coronary constriction—directly and through humoral vasopressors. Reduced myocardial Mg increases vulnerability to cardiac damage. With marginal Mg intakes, athletes undergoing exhausting physical exertion and athletic competition, experiencing stress-induced Mg loss can exhibit impaired performance and endurance, and muscle cramps. Adolescent athletes may be at high risk because they require more Mg for development and growth. Genetic differences in Mg homeostasis may be responsible for differences in susceptibility to pathologic reactions to stress. Mg deficiency and stress mutually enhance one another.

POSTER SESSION II, SATURDAY

Abstract 41

MAGNESIUM STATUS IN PATIENTS WITH CORONARY ARTERY DISEASE ADMITTED TO NEW HANOVER REGIONAL MEDICAL CENTER. *Montano CE.* Seelig CB. Ranney JE. Internal Medicine Training Program, New Hanover Regional Medical Center, Wilmington, NC and the University of North Carolina School of Medicine, Chapel Hill, NC USA.

Retrospective chart review of 98 consecutive patients, admitted with known coronary artery disease (CAD), to New Hanover Regional Medical Center (NHRMC), a 500-bed community teaching hospital (in a low Mg-water area), from January to June 1991, was undertaken to ascertain the behavior of practicing physicians with regard to surveillance for, and treatment of, hypomagnesemia. Patients with creatinine >2.0 mg/dl or with acute myocardial infarction were excluded. Patients averaged 65 years of age. Twenty-six were diabetic, 3 alcoholic; 24 were on digitalis, 22 on diuretics, and 7 on antiarrhythmics. Thirty-nine had arrhythmias (18 ventricular, 26 atrial). Sixty-eight were admitted by cardiology; 34 had cardiac surgical consultation. Nine were admitted for cardiac surgery. Twenty-one were admitted by others. Serum magnesium (Mg) was ordered only for 49 patients (50%). Thirty-nine (79%) were ordered by cardiac surgeons, 8 (16%) by cardiologists), and 2 (4%) by others. All but two were ordered on a routine basis. Nineteen patients (38% of those tested) were hypomagnesemic (<1.8 mg/dl), with an mean of 1.5 mg/dl (SD = 0.5). Potassium level was significantly associated with Mg level. Mean potassium in the hypomagnesemic patients was 3.9 mEq/l; it was 4.4 mEq/l in the normomagnesemic patients ($p < 0.001$). Eleven of the 19 hypomagnesemic patients (57%) received suboptimal treatment, with an average dose of 1.25 g of intravenous MgSO4. The remaining 8 patients received no Mg. Only 3 hypomagnesemic patients (8%) had a second determination. In conclusion, despite the known importance of Mg, it was only rarely determined by physicians at NHRMC. When checked, there was high prevalence of hypomagnesemia (38%). Even when identified, hypomagnesemia was not treated effectively, nor were follow-up determinations requested. In contrast, potassium was checked on admission in 100% of patients with only 4 being found to be mildly hypokalemic (3.3–3.4 mEq/l). Our study indicates that determination of serum Mg should be considered for inclusion in the routine panel of tests ordered for patients admitted to the hospital.

the Effects of Aging in Middle-Aged Women," they were not suggesting that walking can turn back the clock. However, perhaps regular physical activity can make the clock go more slowly. For many who wish to embark on a new exercise program, a walking regimen that will reduce cardiovascular risk may be the best way to start. And once they are walking a couple of miles a day, they may even stop to smell the roses. ❐

Heart Line

More on Magnesium

Evidence regarding the importance of magnesium for cardiovascular health continues to accumulate (see the *Harvard Heart Letter*, August 1991). Seven previous trials involving a total of 1,300 patients with suspected heart attack showed that magnesium supplements reduced the number of deaths. Now, a large study from England has confirmed this finding: when magnesium was given during the early hours after suspected heart attack, survival improved by 24% over the first four weeks.

At the Royal Leicester Infirmary, 2,316 patients admitted to the coronary care unit were randomly assigned to receive either intravenous magnesium or a placebo. Heart attacks were ultimately diagnosed in 65% of the patients. After 28 days the death rate was 10.3% among those receiving the placebo and 7.8% among those given magnesium. This difference indicates that magnesium might lower mortality by about 25 deaths per 1,000 patients treated. Moreover, magnesium therapy reduced the incidence of left ventricular failure — an important predictor of survival and long-term quality of life.

The use of other drugs, such as aspirin or thrombolytic ("clot-busting") agents, did not diminish magnesium's benefits. Although in some cases the magnesium infusions caused side effects, such as flushing of the skin or a slowed heart rate, none of these problems were serious.

Based on this study, magnesium may become routine therapy during heart attacks, especially since the benefits of magnesium infusion are about the same as those afforded by other heart-attack medications (such as aspirin or beta blockers) but with less risk involved. Additional research will be needed to determine the mechanism responsible for magnesium's beneficial effects and how this mineral may interact with other proven therapies in order to target specific patient populations likely to be helped. (Woods KL, et al: Intravenous magnesium sulfate in suspected acute myocardial infarction: Results of the Second Leicester Magnesium Intervention Trial. *Lancet*, June 27, 1992, pp. 1553–1558.)

Smoking After Bypass Surgery

Some cigarette smokers who undergo coronary artery bypass grafting (CABG) refuse to quit after their operation, perhaps believing that the treatment has cured them. However, vein grafts placed during CABG tend to fail more readily if the patient keeps smoking. Now a long-term study has shown that regardless of whether they have undergone CABG, patients with coronary disease who continue to smoke have a higher mortality than their nonsmoking counterparts.

During the 1970s, in a trial called the Coronary Artery Surgery Study, 780 patients with coronary artery disease were randomly assigned to either medications or CABG to relieve their symptoms. After ten years, patients who were initially randomized to medical therapy with the option of later bypass surgery had a somewhat higher survival rate if they quit smoking than if they continued to smoke.

However, after CABG, a large difference was noted in survival rates between quitters and smokers. Those who gave up cigarettes had a ten-year survival rate of 84% compared with 68% for those who continued smoking. In other words, giving up cigarettes after CABG decreased deaths by about half.

Compared with persistent smokers, people who gave up cigarettes were less likely to have angina and more likely to be employed. In addition, they were in better physical condition. Continued smoking is harmful for anyone with coronary disease, but this study emphasizes that people who give up cigarettes after CABG are especially likely to get a new lease on life. (Cavender JB, et al: Effects of smoking on survival and morbidity in patients randomized to medical or surgical therapy in the Coronary Artery Surgery Study: 10 year follow-up. *Journal of the American College of Cardiology*, August 1992, pp. 287–294.)

4 Atlantic Street.
Charleston, SC 29401

November 3, 1992

James O. Mason, M. D., Dr. P. H.; Assistant Secretary for Health
Head of U. S. Public Health Services
U. S. Department of Health and Human Services
200 Independence Avenue, S. W. Room 716-G
Washington, D. C. 20201

Dear Dr. Mason,

I enjoyed very much both hearing your really excellent closing address at the 8th International Symposium on Cancer Research; and briefly meeting you immediately afterwards as we happened to be seated together. I had just mentioned an apparent provocative relationship between cancer and rheumatoid arthritis; and had pulled some letters from my coat pocket when Doctors Layton McCurdy and Peter Fischinger understandably whisked you from the room.

Those attending this conference were certainly as you stated the giants in cancer research around the world; and you indicated your job was to clear the path and help translate their findings into better health for all people. You expressed however, disappointment by the way we use our don't use what we already know.

The local newspaper that day featured Dr. Bruce Ames' previous days talk which had emphasized that peroxidative attacks on DNA were major factors in cancer generation; when one's antioxidant supply or antioxidant capabilities were insufficient to beat back the attack. With Dr. Ames and others very substantial contribution and influence in this area over the past decade, we now realize the truly major health importance of deficient, RDA, or higher levels of antioxidants (particularly Vitamin C, E, beta-carotene and selenium). This now provides such potential for rapid and effective progress in control of cancer and other degenerative diseases, if you and others in public health adequately support this area.

The trials using beta-carotene and other antioxidants against cancer are certainly a good start; but so much more financial support, based on benefit to cost ratios and lack of toxicity, now seem merited.

I am attending the Adjuvant Nutrition in Cancer Treatment conference in Tulsa on Friday and Saturday of this week sponsored by the American College of Nutrition and Cancer Treatment Centers of America (program enclosed). The American College of Nutrition annual meeting in San Diego was also attended the week-end before the rheumatology and your conferences.

On returning to Charleston after attending the American College of Rheumatology meeting in Atlanta, Bruce Ames' newspaper story was noted; and I immediately attended the last afternoon sessions, not realizing until afterwards that it was an invited conference.

My attendance at the Rheumatology Conference that week and my spontaneous move to pass on to you the enclosed underlined stapled letters I had taken to that conference was because twelve years ago I was the first in this county (perhaps the fifth

in the world) to cure very severe rheumatoid arthritis by use of gamma-linolenic acid the precursor of the anti-inflammatory cellular hormone Prostaglandin E-1. On Monday in Atlanta Dr. Robert Zurier, head of Rheumatology at the University of Massachusetts Medical in Worchester, presented the first double-blind trial in this country successfully using gamma-linolenic acid on 37 rheumatoid arthritis patients and his abstract is shown just below.

TREATMENT OF RHEUMATOID ARTHRITIS (RA) WITH GAMMALINOLENIC ACID (GLA). Lawrence J. Leventhal, Eric G. Boyce, Robert B. Zurier. Univ. of PA, Presby. Med. Cent., Phila. Coll. Pharm., Philadelphia, PA. 19104 and Univ. MA, Worcester, MA 01655.

A randomized, double-blind, placebo (Procottonseed oil)-controlled, 24-week trial of GLA (as borage seed oil) treatment of active RA was conducted to determine its clinical efficacy, tolerability and safety. Patients (pts) maintained pre-entry dose of NSAID and/or low dose corticosteroids. No pts took 2nd-line agents within 3 months of entry; 37 pts enrolled (19-GLA, 18-P). Demographic, pre-study treatment, clinical, and laboratory variables for the 2 groups were similar. 5 pts in each group withdrew from the study due to: inefficacy (3-GLA, 2-P), toxicity (1-P), and protocol violations (2-each). No pt went into remission. In intention-to-treat analysis, GLA demonstrated improvement from baseline in platelet count, joint tenderness and swelling scores (p .05). Compared with P, GLA was superior in physician global assessment, pt global pain assessment, joint swelling score and platelet count reduction (p .05). Of the study completers (GLA-14, P-13) GLA demonstrated improvement from baseline in physician global assessment, pt global pain assessment, morning stiffness, and both joint tenderness and swelling counts and scores, and platelet count reduction (p .05). Compared with P, GLA showed improvement in physician global assessment, pt pain assessment, and both tenderness and swelling counts and scores (p .05). No GLA pt. withdrew from the study due to adverse reaction. 1 P pt withdrew due to rash. Adverse effects included soft stools (GLA-2, P-1), constipation (P-1), flatulence (GLA-1) and belching (GLA-1). We conclude that GLA is a safe, well-tolerated and effective treatment for active RA.

EVIDENCE FOR PROFOUND ANTIOXIDANT DEPLETION IN THE SYNOVIAL COMPARTMENT IN RHEUMATOID ARTHRITIS (RA). [1]A.Bal, C.Chaloner, D.Schofield, O.Mel, [1]AR.Thompson, JM.Brogan, [2]JL. Holt. University Departments of [1]Rheumatology & Medicine (Gastroenterology), Royal Infirmary, Manchester, U.K.

Oxidative stress, has been proposed as a pathogenetic mechanism in RA. We have analysed a free radical marker and 4 micronutrient antioxidants in paired samples of synovial fluid (SF) and serum from 11 patients with classical RA (Table). M/M% is the molar ratio of 9 cis-11 trans linoleic acid to the parent 9 cis-12 cis fatty acid, a validated marker of free radical activity. In RA sera, a shortfall in ascorbic acid acid and selenium-conferred anti-oxidant protection is accompanied by enhanced free radical activity, ie oxidative stress prevails. This problem is magnified in their SF by 50% decreases in selenium, α-tocopherol and β-carotene. Thus antioxidant supplementation should ameliorate the inflammation.

Material	M/M(%)	Selenium (uM)	Ascorbic Acid (uM)	α-Tocopherol (uM)	β-carotene (uM)
Control Serum	1.80 (0.80 -3.90)	1.43 (0.76 -2.04)	62 (29-89)	22 (13-34)	180 (71-473)
RA Serum	3.20[a] (2.15 -5.29)	0.93[a] (0.72 -1.27)	23[a] (2.80 -59)	25 16-33	128 (13-417)
RA Synovial Fluid	3.15 (2.14 -6.05	0.46[b] 0.33	31 (<2.80 -55)	12[b] 8.0-20	48[c] (9-205)

Medians with ranges; [a] = $p<0.05$ vs controls; [b] = $p<0.05$ vs RA serum; [c] = $p<0.10$ vs RA serum.

The other rheumatology conference poster abstract shown just above presents really striking evidence of the profound depletion of antioxidants and the enhanced free radical activity found in both the serum and the synovial fluid of rheumatoid arthritis patients. Under such conditions the gamma-linolenic acid produced in synovial and other cells by delta-six desaturation of cellular linoleic acid would be decidedly reduced. This highly unsaturated acid which is precursor of the PGE-1 cellular hormone that inhibits cellular division would also tend to be oxidized and destroyed. As I understand it the cells in these joints (synovium) are not supposed to begin dividing, but do before we run into rheumatoid arthritis problems.

My substantial supplementation for the past decade of gamma-linolenic acid present at 9% levels in authentic evening primrose oil (EFAMOL); plus high levels of ascorbic acid, beta-carotene, Vitamin E and selenium now seems (as discussed in the enclosed letters taken to the rheumatology convention) to make even more sense.

The enclosed 1981 one-page "memory jogger" on my presentation Pertinent Inter-Relationships Between Cancer, Rheumatoid Arthritis, The Evening Blooming Primrose and The Green-lipped Mussel now seem to stand up well. Also relevant is the enclosed Jan. 17, 1985 letter to Doctors Linus Pauling and Ewan Cameron on the five year bone-cancer experience of an atomic scientist, who was a very major contributor as to the time achieved and the very small size of our first real thermonuclear bomb. He controlled his pain and cancer with 24-35 grams of Vitamin C per day throughtout this five year period with the additional use of gamma-linolenic acid in the last two years.

MEDLINE search last week on my home computer turned up 42,177 medical papers on rheumatoid, 4,046 on antioxidant and only 29 combined. These abstracts were printed out (half since 1988) and were very supportive. MEDLINE on cancer turned up 161,915 medical papers; and when combined with antioxidant showed only 115 medical papers.

These abstracts were again printed out with two thirds since 1988 and again extremely supportive. Cardiovascular had 63,379 medical papers and with antioxidant combined again gave only 29 medical papers. Twenty-four of the 29 abstracts were since 1988 and all were since 1984. Heart at 359,662 showed 328 when combined with antioxidant and was not checked further.

There has properly been considerable treatment in the media in the past year on the decidedly beneficial effects of vitamins, antioxidants and magnesium on the heart; and were going to see a lot more because it is right.

Yesterday the New York Academy of Science Vol. 669, Beyond Deficiency, New Views on the Function and Health Effects of Vitamins, was received in a surprisingly short time since I attended that superb conference on Feb. 9-12, 1992. This book largely covers studies around the world on the beneficial use of vitamins and antioxidants at higher than usual (or the RDA level) in this country. It is very up-to-date, pertinent, often surprising and certainly merits serious consideration by public health leaders in our country.

Another serious but little realized health problem in this country has been the chronic detrimental effect of magnesium deficiency on the heart, cardiovascular and cerebrovascular artieries of most of us. The enclosed additional letter written last week to Doctors Lee, Edwards, Gazes, and Spann contains very pertinent information from the latest European Magnesium Conference which may prompt you to consider the need and benefits of personal and hospital magnesium supplementation, if you don't now.

In hopes this too long letter might possibly get through to you and prove of some value in moving toward such simple and inexpensive approaches to improved health.

Most sincerely,

Frank J. Ball

Frank J. Ball

cc: December 15, 1992
Those copied on October 29, 1992 letter to Doctors Burton Lee, James Edwards Peter Gazes and James Spann

Frank J. Ball
4 Atlantic Street
Charleston, S. C.

PERTINENT INTERRELATIONSHIPS BETWEEN CANCER, RHEUMATOID ARTHRITIS, THE EVENING BLOOMING PRIMROSE AND THE GREEN-LIPPED MUSSEL

(Memory Jogger for Presentation: May 19, 1981)

CANCER TISSUE

Completely different from normal cells in that 60-99% of nutrients are fermented to lactic acid rather than almost total oxygenation to carbon dioxide.

Cancer invasiveness promoted by:

1. High continual release of collagenase enzyme by cancer tissue breaks down the external collagen ropes that enmesh near-by cells.
2. The semi-rigid gelled water which binds together adjacent cells and collagen ropes is made fluid by release of hyaluronidase enzyme which can depolymerizes the soluble hyaluronic polymer gell.

Recent evidence indicates cancer tissue is composed of up to 85% activated, but incompetent defensive macrophages (very large white cells). These produce collagenase, hyaluronidase, lactic acid, and toxic superoxide; and could be a major part of the problem.

Recently found that the protective enzyme (SOD) that destroys superoxide was very low or absent in cancer cell mitochondria where nutrients must be oxidized.

Cancer patients exhibit extremely low Vitamin C blood levels and are low in zinc.

Prostaglandin E_2 (PGE2, an inflamatory cellular hormone) runs quite high in cancer patients. Cancer cells appear to lose the capacity to convert polyunsaturated fats to gammalinolenic acid. This precursor of PGE1, appears to be needed to inhibit excessive PGE2 formation.

RHEUMATOID ARTHRITIS JOINTS

Involved joints produce high lactic acid levels which may be one cause of pain.

Joint problems partially involve:

1. Collagenase release attacks the collagen lining of the joint.
2. Detrimental thinning of the jelled joint lubricant by depolymerization of the dissolved hyaluronic polymer gell.

Macrophages activated by injesting uric acid crystals in joints appears to be the cause of gout. High levels of activated macrophages, which live for months are in rheumatoid joints.

Superoxide dismutase (SOD) enzyme from cattle gave reduced inflamation and pain on rheumatoid patients.

Rheumatoid patients run quite low in Vitamin C levels and their blood is often one-third down in zinc and histidine.

Inflamatory PGE2 in the joints is generally acknowledged as the main cause of swelling and pain in rheumatoid arthritis. Pain reducing aspirin and similar drugs inhibit the oxygenation of arachidonic acid which otherwise is converted to the inflammatory PGE2.

Evening Blooming Primrose Seed Oil

Dr. David Horrobin, a leader in prostaglandin research and thinking, showed PGE1 can inhibit PGE2 formation and may correct immune T lymphocyte defects, but its half life is only about a minute and its effectiveness occurs only over a precise ultra low concentration range.. He postulated beneficial use of the only available gammalinolenic source (Evening Primrose Oil) to boost continuous PGE1 formation in possible treatment of arthritis, scleroderma, cancer, multiple sclerosis, or selected collagen and autoimmune diseases.

Dr. Robert Zurier, Chairman of Rheumatology, Univ. Pennsylvania Medical, demonstrated the ability of PGE1 to reverse the severe symptoms (identical to the arthritic disease, systemic lupus) which are spontaneously generated in the hybrid cross of New Zealand black and white mice (NZB/W). He also showed that the presence of PGE1 could prevent the usual arthritic symptoms developed in mice on injection of Freund's adjuvant.

Horrobin and others showed that at physiological blood concentrations Vitamin C, Vitamin B_6, zinc, histidine and ethyl alcohol selectively promote formation of PGE1 from gammalinolenic acid. There is significant research and medical literature suggesting some benefits from each of the first four of these in rheumatoid arthritis. Vitamin C also appears most important in promoting cancer control.

Vitamin C strongly inhibits collagenase formation, is required for collagen fiber formation, is a necessary cofactor in over 50 enzymes and decomposes toxic superoxide. Promotion of PGE1 formation, however, may constitute a major mode for many of its beneficial actions.

Extract of the Green-Lipped Mussel (Perna Canaliculus)

Last month, on an Australia-New Zealand trip, a freeze dried extract (SEA TONE), which was produced from a local mussel extract was noted to be marketed in drug stores as a food supplement. The 1979 book "Relief from Arthritis - A Safe and Effective Treatment from the Ocean" covering this green-lipped mussel extract gave no convincing evidence, but a reliable physiotherapist there reported observing a surprising beneficial response in two patients taking it.

A computer search of the medical literature turned up no pertinent literature studies on shell fish extract in control of arthritis, but some impressive demonstrations of cancer control in animals using extracts from clams (mercenaria mercenaria). Clams had been selected for evaluation as they were found surprisingly free of any cancer growth. Clinical studies were not conducted, but experiments on various cancer cells and oral use in various animal cancer studies seem to show quite encouraging efficacy.

4 Atlantic Street
Charleston, SC 29401

April 29, 1992

Dr. J.J.F. Belch, University Medical School, Dundee, Scotland
Dr. J. Booyens, Semi-retired, MEDUNSA, Pretoria, South Africa
Dr. Wilbur H. Caney, Retired, Vermont and upper South Carolina
Dr. David Horrobin, Efamol Research Institute, Kentville, Nova Scotia
Scotia Pharmaceuticals, Surrey, England
Dr. E. Carwile LeRoy, Medical University of South Carolina, Charleston, SC
Dr. R. D. Sturrock, Center Rheumatic Diseases, Glasgow University Medical, Scotland
Dr. Robert B. Zurier, University of Massachusetts Medical, Worchester, Mass

Dear Doctors Belch, Booyens, Caney, Horrobin, LeRoy, Sturrock and Zurier,

I would like to pass on to you one additional small personal experience that occured this month in my twelth year of completely successful control of severe rheumatoid arthritis using authentic evening primrose oil without other drugs. Results have been very satisfactory over the past three years using 15 gelcaps (7½ g.) per day of evening primrose oil, as discussed in my long Jan. 23rd, 1989 letter sent to you.

That letter was prompted when I successfully controlled the pain and swelling of my 1988 relapse without the usual 12-14 aspirins and 4 Motrins needed throughout 1980; and during the months required to initially build up adequate gamma-linolenic acid products in my membranes during initial control at the end 1980, and also following my first relapse in 1984. As discussed in my 1989 letter; the 1988 gamma-linolenic build up without aspirin or Motrin was achieved by tripling my normal 12 gelcaps of EFAMOL to the 36 used in South Africa by Doctors Booyens and Van der Merwe in their effective control of certain acute cancer patients for a period of three years.

As discussed in the 1989 letter; both the 1984 and 1988 relapses apparently were caused by inadvertent lack of gamma-linolenic acid for about a month during which time my pain, swelling, and locomotion capability returned to the severe 1980 status.

This month I induced in my low back; muscular or joint pain and spasm, which had happened only several times before in my life. This was painful standing, lying down or getting up and decidedly limited activity to prevent spasms. Over several days it progressively worsened in both spasms and pain; and very seriously interfered with sleep. After several days the knuckles on my hands swelled up to the extent observed whenever the 12-14 aspirins were reduced one-third for a day or two throughout 1980, or when reduced in a similar manner during the 1980 and 1984 months while gamma-linolenic products were being built up.

As my back spasms and pain seemed to be detrimentally interacting with my rheumatoid and getting worse; I tripled the level of evening primrose oil after a sleepless night from 15 to 45 gelcaps per day. Fortunately this was very effective in reducing knuckle swelling, pain and spasms within 24 hours. When dropped to the 36 used in the 1988 relapse for the following day, the knuckles went down to almost normal by the next day and back problems were significantly reduced further. With use of 25 to 15 per day the spasms were stopped and my situation has returned to about normal in a week at 20 and will be reduced to 15. In my few previous low back pain and spasms, increasing pain and spasm

wasn't evident; but the serious pain and spasms lasted very much longer despite available drugs.

The last paragraph of the enclosed March 29, 1992 letter to President Bush covered some most encouraging information obtained in the past month on the striking success of one retired doctor, Dr. Wilbur H. Caney, over the past five or more years in helping control arthritis on over 200 personal contacts having arthritis problems in the Southeast, New England, and Bermuda by their use of evening primrose oil, some vitamins and magnesium. His interest had been stimulated by the success first on his wife's arthritis and then on friends and retirement contacts.

My letters to the president and his physician over the past year involved my six year realization that heart arrythmia and heart attack problems can be decidedly caused by stress-induced, diet-induced and running-induced magnesium loss from the heart, cardiovascular and cerebrovascular arteries. The enclosed Feb. 5, 1992 letter to the president and Dr. Burton Lee, his personal physician, also discussed in the middle paragraphs of The Executive Summary; my experience and the recent progress and understanding in the use of gamma-linolenic acid for control of rheumatoid and other arthritis. It was my hope this provocative area might increase the odds of the letter getting through and being considered.

It is thus of possible future interest that our newspaper reported on April 19th during the president's Maine visit that following a vigorous morning walk, he had indicated to reporters that he would feel it in his right hip joint at 2 AM; but had asked at his recent physical if he would eventually have to have the hip replaced, and was told "not for a long time."

Over all these years it has been most impressive that no detrimental side effects have been caused by such extensive and successful use of gamma-linolenic acid in various difficultly handled diseases. It has been a God-send to me for the past decade; and hopefully large numbers with various inflammatory and bone degenerative problems will get to benefit during this decade.

All the best,

Frank J. Ball

FJB:kaj P. S. April 30, 1992

My Feb. 6th and Mar. 29th letters and attachments to the president emphasized recently demonstrated very marked health benefits from high level antioxedent supplements, particularly beta-carotene; thus the even more concise and definitive presentation on this subject in the just received May 5th U.S. News and World Report is enclosed.

4 Atlantic Street
Charleston, SC 29401
December 22, 1980

(32)

Dr. Martin Eastwood
Wolfson Gastrointestinal Laboratories
Western General Hospital
Edinburgh, Scotland

Dear Martin:

Had one hell of a year, but informative and finally encouraging. Came down with rheumatoid arthritis in January, following a severe throat infection while on a trip; and was in hospital and at home about six weeks. Spent the rest of the year on 12-16 coated aspirins (Ecotrin) and 6 (2.4g) Motrin with pain mainly in hands, wrists and varied in feet (earlier all over); and in all joints and muscles if tried to lower these. Read about as much in this area and prostaglandins as I did cancer in past two years, and some surprising similarities. Protected collagen and hyaluronic acid in joints, I hoped, with high C and B-complex vitamins; and joints progressively improved over the year. Terribly tired and was 1/2-2/3 time at work until about 3-4 months ago when went to full time. Took on my own, zinc and histidine throughout year, since these seem to be about one third down in blood of rheumatoid patients. Blood sedimentation rate went down progressively from 50 range to normal, but stamina very low an couldn't take down aspirin and Motrin. Tried during summer to convert to higher linoleic in my lecithin using polyunsaturated fats and did get the Motrin down. For the past 3 1/2 months I have been taking 1-6 capsules (0.4g each) a day (in addition to the vitamins, zinc, and histidine) of the seed oil of the evening blooming primrose (Efamol, which I bought in Canada); and which contains about 10% gamma linolenic acid. It comes from England and is called "Naudicell" there. J. N. McCormick and W. A. Neill at Northern General reported encouragment on rheumatology using 2g per day for 3 months, in the Lancet, Sept. 3, 1977, p. 508. I called him but he was on a months vacation and I succeeded in getting in touch with Dr. Robert Horrobin in Montreal, a brilliant doctor who has written extensively in this area as related to prostaglandins; and Dr. Robert Zurier, now head of Rheumatology at University of Pennsylvania Medical, who had worked with Prostaglandin E1 and subsequently with this oil in inhibiting induced arthritis in rats. Horrobin told me McCormick didn't get money for his planned additional tests. Tell him about 3 weeks ago, for the first time, I succeeded over a three-day period in bringing down the aspirin from 12 to 0 and have taken no more aspirin. Never before was I able to bring it down to 8 because of increased swelling and pain in the joints. Horrobin knew of encouragement in Copenhagen and Barcelona on arthritis, but felt not if taking aspirin, Indomethacin, etc. and thus not on rheumatoids. He seemed interested and pleased. Me too!!

The gamma linolenic acid is converted by the cells of the body as needed to Prostaglandin E1 which Horrobin indicates apparently controls the excessive formation of Prostaglandin E2 which is very excessive in rheumatoids and a factor in inflammation. We may run low or out of Prostaglandin E1 in the joints and thus get into this self-generating arthritic problem.

Best of luck in your work in Edinburgh and stop by Charleston again when you get a chance. Haven't written any further letters in cancer area this year except the recent enclosed one to Senator Hollings; and it looks like the hydrazine sulfate and Vitamin C are really demonstrating efficacy and being progressively accepted and understood for cancer control without toxicity.

Sorry so long, but thought you would be interested. With hope!

Merry Christmas.

Frank J. Ball

FJB/dr
Enclosure

May 12, 1992

4 Atlantic Street
Charleston, SC 29401

Dr. Burton J. Lee, III Physician to the President
The White House
Washington, DC

Dear Dr. Lee,

Many thanks for your thoughtful letter responding to my March 29th letter to the president that strongly reemphasized the serious cardiovascular dangers of stress-induced and diet-induced magnesium deficiency; and the major health benefits possible from substantial magnesium and anti-oxidant supplementation.

I most enjoyed reading the really superb long interview The President's Physician Speaks Out, in the April 1 - April 14 INTERNAL MEDICINE WORLD REPORT covering your White House Medical approach, very positive assessment as to the health of the president, and your quite active thoughts and participation relative to the U. S. Health-Care System. One certainly left it mighty impressed and much better informed.

The very next issue of INTERNAL MEDICINE WORLD REPORT contained the attached very convincing section on the extent and the major health effects of magnesium deficiency on chronic diseases; from Part 3 of a series on Chemical Sensitivities by Sherry A. Rogers, M.D. Reading the underlined part of the section, Magnesium Leads the Way, (less than five minutes) certainly strongly suggests both the need and the wisdom to daily replace the major fraction of dietary magnesium removed by industrial processing of our foodstuffs. In a phone call from Senator Hollings after the last letter to the president, he felt the president would now be taking magnesium, but many people do not like any extra pills particularly long term.

A couple of weeks ago I wrote the enclosed letter and attachment to six U.S. and foreign physicians familiar for most of the past decade with my completely successful control of severe rheumatoid arthritis without drugs by use of adequate gamma-linolenic acid present in authentic evening primrose oil. This polyunsaturated fatty acid is supposed to be adequately produced in all our cells as precursor of a critically important prostaglandin cellular hormone. When inadequately produced in our joint cells then inflammation, arthritis and other problems such as bone degeneration can occur; and adequate oral supplementation then appears most desireable. The end of that letter included the president's comment on his right hip joint at 2 AM following vigorous morning walking; and his recent question about his hip.

My letter P. S. and the attached US News and World Report covering recent major benefits from natural antioxidants, was topped this past week by the study showing that several hundred milligrams daily of Vitamin C may increase the lifetime of men by five to six years and women one year. Women now live seven years longer, but their plasma Vitamin C levels are as high as men taking 400-500 mg more Vitamin C than women. This is seen in the attached 1987 graph by P.G. Garry et al, and would thus seem wise for men to catch up.

Most Sincerely,

Frank J. Ball

FJB:kaj

March 29, 1992

4 Atlantic St.
Charleston, SC 29401

President George Bush
The White House
Washington, D.C.

Dear Mr. President

The TV presentation this week of you and Dr. Burton Lee leaving your annual physical with an overall perfect health report was truly great news; but I believe it was also great a year ago about a month before your atrial fibrillation. The brief newspaper report on your check-up referred three times to Dr. Burton Lee's concern that you need more "time off from his stress-filled job", he had recommended without success "him to go away for three weeks" and was trying to protect Bush from the pressures of the job because "stress hurts everybody". You owe it to Barbara, yourself and the country to take his advice; which I surely hope also included adequate daily (500mg) of oral magnesium to replace stress-induced magnesium lost most particularly from your heart, cardiovascular and cerebrovascular arteries that can decidedly induce heart arrythmias, vasospasms, heart attack and stroke.

Attached is a convincing page taken from the January 1992 medical journal Circulation supplement on Sudden Death, in a paper ELECTROLYTE ABNORMALITIES UNDERLYING LETHAL AND VENTRICULAR ARRYTHMIAS BY Leonard S. Gettes, M.D. at UNC Chapel Hill. Lethal arrythmias generated by magnesium deficiency and its correction by magnesium supplementation are briefly but well treated. Sixty percent of acute myocardial infarction patients die before reaching the hospital; but the last of seven large overseas double-blind tests showed that the half of the AMI patients who got 2225 mg of magnesium on arrival had in-hospital mortality one-sixth of the placebo patients. In all these hospital trials arrythmias and mortality showed very major reductions with intravenous magnesium. Therefore it certainly seems very likely that the double-blind half of the 40-50,000 acute myocardial infarction patients about the world who will fortunately get 2000 mg of intravenous magnesium when they arrive at the hundreds of hospitals participating in the Fourth International Study of Infarct Survival (ISIS-4) will definitively demonstrate the critical importance and efficacy of sufficient magnesium when this trial is completed at the end of 1992.

You have had a personal arrythmia warning which likely means your heart magnesium level was low at that time partially due to stress and partially to upset thyroid. It is terribly easy to remove the danger of magnesium deficiency; and all important to keep you healthy. Fritz Hollings' recent letter indicated he surely hopes you are following the advice; and on sitting next to Representative Arthur Ravenel at a recent South Carolina Society dinner; he mentioned he now regularly takes magnesium. He had told our newspaper at the time of your atrial fibrillation that he also had an atrial fibrillation problem; and we discussed magnesium and the heart at that time.

Last night at our supper club I met a delightful guest couple from Boston. When magnesium deficiency came up she told of the daughter of a doctor friend who was a very ardent runner and in the progessive festivities before her marriage had an arrythmia which was checked, ceased and she went on with the marriage plan. On the honeymoon flight to Hawaii over the Pacific she had a heart attack and died. This tragic event seems to me very likely due to magnesium deficiency from both running and sustained stress. From West Germany I have seen an estimate of 4000 heart attack deaths per year among their runners; which they estimate would be reduced very substantially by adequate

Congenital folic acid deficiency resulted in the spinal bifida of Ezra Adkins who you were hugging in my Feb. 11th letter; and probably caused the lack of the baby's brain in this past week's TV newsstory on planned baby death and organ supply. The New York Academy of Science is having a San Diego conference in May on Maternal Nutrition and Pregnancy Outcome which deals mainly with the terrible effects of folic acid deficiency; but discusses the decidedly detrimental effects of zinc, selenium, and Vitamins A, B_6 and B_{12} deficiency.

This month a retired M.D., Dr. Wilbur H. Caney and his wife visited with some most encouraging news relative to arthritis control using authentic oral evening primrose oil; discussed earlier in the middle of the Executive Summary of the Feb. 6th letter to Lee, Sununu, and Bush. The Caneys first visited a few years after my sustained success with oral evening primrose oil on severe rheumatoid arthritis; and she left taking the oil with Vitamins B_6, B_2, C and magnesium to try and control her severe arthritis. Two years later on passing through she was in great shape; and he reported 20-30 others with arthritis had found similar relief. Now several years later they reported over 200 with arthritis in the Southeast, New England and Bermuda had followed this same advice with 8 - 9 out of every 10 succeeding. Their only payment was theirs and their contacts satisfaction;and it went from a terribly pleased vascular surgeon to a Bermuda friend who went from her wheelchair back to tennis; and this convinced a number of arthritic contacts to try successfully.

With the hope and belief that by one means or another your health will continually improve with minimal stress degradation; and that the health of our country likewise continually improves over the next four years under your extremely able direction.

Most Sincerely,

Frank J. Ball

ps/ April 2, 1992

The attached April 6, 1992 TIME cover story The Real Power of Vitamins, just in is another surprisingly powerful presentation that speaks to the basic significance that has been increasingly evident ever since my 1983 letter was briefly discussed with you in Charleston. The TIME cover story should convince many Americans to improve their health by increased supplementation; and with hope that it may also beneficially influence Barbara and you.

FJB:kaj

cc: Barabara Bush
Vice-president Dan Quayle
Secretary Louis W. Sullivan
Dr. Burton Lee
Dr. John Sununu
Shirley M. Green
Senator Strom Thurmond
Senator Ernest F.Hollings
Representative Arthur Ravenel

February 6, 1992

Dr. Burton J. Lee

The Honorable John Sununu

President George Bush

EXECUTIVE SUMMARY

This letter was initiated to reinforce and transmit additional evidence about stress-induced magnesium loss and the resulting heart arrythmias sent to the Governor eight months ago (pages 1 and 2). I was concerned that despite the comments in Dr. Lee's letter to me, our high-stressed president might not be supplementing with magnesium.

Enclosed are December letters and literature trying to get the Medical University in Charleston, SC to quickly join the Fourth International Study of Infarct Survival definitively assessing the clinical efficacy of intravenous magnesium in heart attacks (page 2). The last of seven foreign double-blind studies just in covering patients treated on the day of their acute myocardial infarction showed a drop in the mortallity to one sixth among the magnesium treated as compared to the placebo patients.

Since the May and June 1991 letters to the Governor also covered the recently established marked benefits to the heart from high level oral beta-carotene, additional evidence of similar benefits from high levels of Vitamin E and Vitamin C; and the program of a New York Academy of Science Conference covering these opportunities next week in Arlington are discussed on pages 2 and 3.

As I happened to have collapsed and had to spend at doctor's orders a month in the hospital and at home blamed on sustained extreme exhaustion (page 3), a possiblity is suggested that stress and exhaustion might also have been a contributing factor in the president's collapse.

I happened to be the first in this country (1980) and perhaps the fifth in the world to correct very severe rheumatoid arthritis with no further use of high level drugs by oral use of evening primrose oil. My situation and recent successful demonstration in double-blind studies are covered on pages 3 to 5. The likely medical reason for success and subsequent use on cancer are covered on pages 5 and 6.

The present encouraging status of several effective, available and non-toxic cancer therapies that were briefly discussed and given to the vice-president during his Charleston visit in 1983 is covered on pages 6 and 7.

An existing provocative potential to inexpensively and relatively quickly reduce the major burgeoning health costs of the elderly by massively supporting further clinical demonstration of the considerable effectiveness of pharmacological levels of certain vitamins, antioxidants and other micronutrients on various major degenerative diseases of the elderly is discussed on page 9.

Dr. Virgil Brown's courageous comments are striking; and I have over most of the past decade been taking daily 800 units of Vitamin E, six grams of Vitamin C, 45 mg of beta-carotene, and 500mg of magnesium; in addition to a powerful multi-vitamin with minerals, because the evidence of benefit seemed sufficient to me.

Today Dr. George C. Rios' (Chairman Medicine, George Washington Medical) CARDIAC ALERT, (Feb. 1992) arrived and the eighth page under the title Breakthrough - Vitamin C Against Cholesterol Plaque dealt with Dr. Jialal's findings just above. Vitamin E, beta-carotene, and Vitamin C were reported respectively 45%, 90% and 95% effective in stopping the growth of LDL plaque in the laboratory; with Dr. Jialals' conclusion that "these dietary antioxidants prevent cholesterol accumulation and plaque build up."

Also today I was sent the enclosed two pages from a "recent" HARVARD HEALTH LETTER, which I have underlined, as reading this is very likely to further convince anyone our age to promptly start building up our antioxidant levels if you haven't already.

BEYOND DEFICIENCY: NEW VIEWS ON THE FUNCTION AND HEALTH EFFECTS OF VITAMINS

Enclosed is the program of a very pertinent New York Academy of Science Symposium being given in Arlington on February 9-12, 1992. Dr. Charles Hennekens is chairing a session, Effects of Vitamins on Cardiovascular Disease and Cardiovascular Risk Factors and is speaking on Beta Carotene Therapy for Cardiovascular Disease. Dr. I. Jialal's presentation Influence of Antioxidant Vitamins on LDL Oxidation (see clipping above) is in the same session, and I have made my reservations to attend.

Dr. Gladys Block (discussed middle of page 7), who examined 90 epidemiological studies on the role of Vitamin C and Vitamin C-rich foods on prevention of cancer and found the vast majority showed statistically signifigant protective effects; is speaking on Vitamin C and Cancer: Epidemicologic Evidence of Reduced Risk.

Incidentally, Dr. Charles Hennekens just above is also U.S. National Coordinator of the Fourth International Study of Infarct Survival assessing the efficacy of intravenous magnesium in acute myocardial infarctions, as discussed on the middle of page 2.

PERSONAL EXPERIENCE OF SUSTAINED EXCESSIVE STRESS, COLLAPSE AND HOSPITALIZATION

Of possible relevance to the president's collapse in Japan, at one time in my life in April 1979, I collapsed at work and spent a week in the hospital and three weeks at home at doctors orders; after a diagnosis of bradycardia of the heart blamed on sustained extreme exhaustion. This is mentioned on page 22 of my enclosed May 1980 "memory jogger" for presentation, Two years trying to aid in the understanding and presentation of natural generation and natural control of human cancer. I never had any heart problems before then or subsequently, other than a possible mid-systolic click. The increase in excessive stress and effort that apparently brought this on was that in addition to my job, (directing for thirty years a research laboratory of 100 plus, with 20-25 Ph. D.'s and 10-15 M. S.'s) I became involved in an overwhelming spare time effort trying to help understand and encourage certain non-toxic cancer therapies as evident in the enclosed memory jogger. These therapies were summarized in the 1983 letter that was very briefly discussed and given to the vice-president during his visit to Charleston at that time. That 1983 letter was attached to the Governor's letter with hopes it might improve the chance my letters would get through to the Governor.

PERSONAL EXPERIENCE WITH RHEUMATOID ARTHRITIS AND ITS CONTROL USING NATURAL GAMMA-LINOLENIC ACID WITHOUT DRUGS

In January 1980 in the month following a very severe throat infection on a business trip, I came down with very acute rheumatoid arthritis. Following hospitalization, partial

control of my arthritis required 12-14 aspirins (ECOTRIN) and 6 Motrins per day throughout 1980 to reduce the pain and swelling; but I still could not drive a car or tolerate more than two hours per day at work.

Very fortunately, I was apparently the first in this country and perhaps the fifth in the world to completely correct my rheumatoid arthritis in December 1980 without continued use of any aspirin and Motrin by continuous use of EFAMOL evening primrose oil containing gamma-linolenic acid along with an equal amount of Vitamin C. This same oil was subsequently shown by Doctors J. Booyens, C.F. Van der Merwe and I.E. Katzeff in South Africa to effectively control a large number of human cancer cell lines and to have an amazing effect against primary liver cancers. This was discussed in my 1983 letter to the vice-president and my enclosed 1983 letter to Dr. Jan Van Eys at M.D. Anderson. I later met Doctors Booyens and Katzeff at the 1984 George Washington Medical International Symposium on Prostaglandins and Leukotrienes in Washington.

Incidentally, the Mother Superior Emeritus with intestinal and liver cancer, on the last page of the 1983 letter to the vice-president and discussed in more detail in the enclosed 1983 letter to Dr. Jan Van Eys; continued further improvement using gamma-linolenic acid and high Vitamin C. She lived happily for an additional three more years, well into her eighties. She was sister-in-law of my wife's cousin, Rodney de Kay, who mentioned at the time he was a year ahead of George Bush at Andover and Yale, and is a cousin of Senator Pell.

Before coming down with rheumatoid arthritis, when looking for reasons why Vitamin C might be effective in cancer, I had come across a paper by Dr. David Horrobin relating Vitamin C and gamma-linolenic acid; and discussed it on page 25 of an August, 1979 letter to Doctors Ewan Cameron, Joseph Gold, and Harry Gregorie, shown in my enclosed May 1981 "memory jogger" on the presentation Pertinent Interrelationships Between Cancer, Rheumatoid Arthritis and the Evening Blooming Primrose. When searching the medical literature in August 1980 for possible approaches on rheumatoid arthritis, I happened to note a short 1977 paper in the The Lancet where a Dr. J.N. McCormick in Scotland had used evening primrose oil and claimed to have achieved apparent success after three months on four rheumatoid arthritis patients. I called there, but he was out for a month and had not gotten support for further work, so I called Dr. David Horrobin in Montreal and got him to send me this "vegetable oil for experimental purposes".

Dr. Horrobin however did not believe the gamma-linolenic acid in the evening primrose oil would help me unless I could very substantially reduce my quite high levels of aspirin and Motrin. I wouldn't agree to do this because I felt I couldn't do it and still spend my two hours per day at work. These particular drugs are now known to inhibit the excessive conversion of arachidonic acid (which we obtain from meat and fish) to our inflammatory cellular hormones (two-series prostaglandins) which keep us from bleeding to death on injury, etc. The same drugs however also inhibit the conversion of gamma-linolenic acid to the one-series prostaglandin, PGE-1 which resists inflammation.

Fortunately the EFAMOL evening primrose oil in conjunction with equal Vitamin C, and with the same level of drugs; to my surprise progressively increased my stamina so that full time at work was achieved after a month. One third reduction in aspirin for a day; however would markedly increase pain and swelling by the next day so was not reduced. After three and a half months; elimination of all aspirin and Motrin was achieved over a week with no swelling or pain at the end of 1980.

Two very severe relapses occured in 1984 and 1988. In both relapses I apparently inadvertently did not get the gamma-linolenic acid for a period of about a month. In the 1984 relapse I again required the same high level of drugs to partially reduce the

renewed severe arthritis symptoms, but was able to reduce the drugs to zero again after three months; but required somewhat higher levels of evening primrose oil. In the 1988 relapse the same high levels of drugs were required, but were so unpleasant on my stomach that I called South Africa and tried using the very high levels of gamma-linolenic acid that they used in control of primary liver cancer; as described in my 1983 letter. This controlled both pain and inflamation without drugs; and was successfully reduced back after about three months; but again somewhat higher levels were required.

I attended a presentation in London in November 1986, by J.J.T Belch, R.D. Sturrock et al at the annual British Society of Rheumatology meeting covering the first successful double-blind trial on 49 rheumatoid patients; where EFAMOL evening primrose oil (and that along with fish oil) were demonstrated to be fairly effective in controlling the arthritis compared to a placebo in an 18 month trial. Dr. Robert B. Zurier, Chief of Rheumatology at University of Massachusetts School of Medicine in Worchester, was also at that meeting; and has actively studied the effects of gamma-linolenic acid and PGE-1 on cells, animals and rheumatoid patients for more than a decade. He has just completed but not yet published, a very successful double-blind trial evaluating gamma-linolenic acid compared to placebo on 27 rheumatoid arthritic patients . Dr. David Horrobin, who initiated and pushed the potential use of gamma-linolenic acid in arthritis, cancer and other diseases has now just started a multi-location double-blind trial on 500 rheumatoid arthritis patients; but results may not be available for two years.

It may also be of interest to a highly stressed president and his physician that oral gamma-linolenic acid in evening primrose oil has been shown to attenuate stress response as does oral or intravenous magnesium. Several chapters in David Horrobin's 1990 book, discussed just below, deal with this opportunity. I found that the magnesium and evening primrose oil must be taken at different times of the day to achieve adequate absorption.

PROGRESS IN UNDERSTANDING AND USE OF GAMMA-LINOLENIC ACID IN THE MEDICAL FIELD

Dr. David Horrbin, a truly brillant and dynamic metabolic research scientist who postulated and pioneered this whole area, sent me the 600 page book, Omega-6 Essential Fatty Acids: Pathophysiology and Roles in Clinical Medicine, that he edited in 1990. There are 44 chapters that mainly cover the beneficial effects of oral intake of gamma-linolenic acid in evening primrose oil in an increasingly wide number of difficultly cured diseases.

This critically important gamma-linolenic acid is supposed to be produced in all our cells by 6-desaturation of the essential linoleic acid that is present in the polyunsaturated fats that we must eat. The cells convert the gamma-linolenic acid (γ-linolenic acid, GLA) to dihomo-gamma-linolenic acid (dihomo-γ-linolenic acid, DGLA) which is incorpated at low levels into the cellular membrane. This latter vital organic acid when needed is released in the cell and reacts with oxygen in the cell's cyclo-oxygenase enzyme to form the one-series cellular hormone, prostaglandin E1 (PGE-1). If PGE-1 or other cellular prostaglandin hormones (such as the two-series prostaglandins produced from arachidonic acid) leak from the cells into the blood they are immediately destroyed on passing through the lung, to minimize any effect on other cells.

Arachidonic acid in the platelets that swirl about in our blood are converted under certain stresses to the two-series prostaglandin, thromboxane (TXA2). This causes the platelets to clump together and the arteries and capillaries to contract thereby preventing our bleeding if injured. We take aspirin and Motrin to inhibit the detrimental excessive conversion of arachidonic acid to thromboxane or other two-series prostoglandins (cellular hormones). PGE-1 that cells can produce from gamma-linolenic acid has an effect directly opposite to thromboxane. As PGE-1 leaks into the blood, it causes the platelets to disaggregate and the arteries and capillaries to dilate.

PGE-1 thus influences aspects very important to us such as inflammation, vascular tone, cellular function, and cellular division. Certain cells of ours however can lose or partially lose the capability to make gamma-linolenic acid which can be directly influenced by our aging, our particular genetics, certain retroviral invasions, cancer, diabetes, etc. Adequate oral intake of gamma-linolenic acid then seems mighty smart when particular cells and tissue are deficient. This natural fatty acid has very little if any detrimental effect on cells that produce normal levels of gamma-linolenic acid; but has a tremendous effect on those cells whose activity has changed because of its deficiency.

In rheumatoid arthritis, certain cells in our joints start dividing (that shouldn't be dividing) before we encounter pain or swelling. Most of the cells in our body only divide several times in our lifetime; nerve and heart cells never divide; while skin, gut and blood cells divide constantly. I apparently was taking enough aspirin and Motrin to cut back stimulated arachidonic conversion to inflammation prosteglandins in my cells by perhaps 85%, which may have been required because of inadequate gamma-linolenic acid production in certain joint cells. I take orally about as much gamma-linolenic acid from evening primrose oil as the amount of arachidonic acid that I would be expected to injest as a carnivore. A research scientist, Dr. L.J. Zeitlin, from Scotland, who spent about six months in research studies at our medical university, controlled his previously severe psoriatic arthritis by completely giving up all meat or fish in his diet.

In retrospect, I now believe that gamma-linolenic acid deficiency may have been brought about by a retrovirus which could have caused my very sore throat infection just prior to my progressive development of acute rheumatoid arthritis over the following month. When I was put in the hospital, an in depth look was made by an infectious diseases M.D. for evidence of a viral infection; but none was found. Retroviruses can however, take over the genetics and transform certain cells so they begin continually dividing without leaving any evidence of the virus. PGE-1 produced from gamma-linolenic acid is a stand-out performer in kicking up cyclic-AMP, which at increased levels inhibits cell division. Whatever the reason there is certainly considerable satisfaction from the enjoyment of good health instead of being severly crippled for the past decade, and I have no doubt where to give credit.

After five successful double-blind placebo controlled trials, that tested oral evening primrose oil, the British Health Service now pay's for evening primrose oil (EPOGAM) to effectively control the very troublesome childhood and atopic eczemas which are very inadequately controlled with available drugs. EPOGAM has already become the most used prescription for that purpose in England and Germany; and its use is now underway in several other European countries and Australia. I know what a benefit that would be to both the child and family; since I had a brother (nine years younger) who had but grew out of severe childhood eczema.

PRESENT STATUS RELATIVE TO 1983 LETTERS TO BUSH AND VAN EYS

Although there has been extremely little government support over the past decade for any of the effective, available, and non-toxic cancer therapies discussed nine years ago in my 1983 letters to the vice-president and Dr. Van Eys; it has been satisfying to see that some substantial progress has nonetheless occured.

Inexpensive hydrazine-sulfate shown to be beneficial by Dr. Joseph Gold is now used all across Russia to prevent cachexia weight loss on cnacer patients after a Phase II study on 740 patients in Russia. There are now the first indications of NIH acceptance in this country; despite the very negative comments made by the NIH as indicated in my December 27, 1979 letter to Senator Hollings (pages 32 thru 34 in "memory jogger") and subsequently.

An earlier successful double-blind study on lung cancer by Dr. R.T. Chlebowski at Harbor UCLA Medical; and a recent Phase III double-blind trial headed by Dr. M.P. Kosty (at Scripps Clinic in San Diego) on 290 advanced lung cancer patients indicated survival of patients receiving hydrazine-sulfate was "far superior" to those not using it and side effects were "negligable".

David Horrobin now has various people conducting pertinent encouraging studies in England on the effects of gamma-linolenic acid on cancer; and there are forty pages discussing this area in his above book.

Lack of support stopped the very encouraging directed-hyperthermia treatment of cancer by Dr. Harry Le Veen in Charleston; although he is a featured lecturer at Cancer Hyperthermia Conferences overseas including Italy and Russia recently. His physician son, Dr. E.G. Le Veen is just now setting up in Charleston his father's highly effective hyperthermia equipment which Dr. Le Veen designed, built and used at MUSC. This will permit needed treatment of an eight year survivor following her hyperthermia treatment of inflammatory breast cancer which this same equipment treated way back then. I heard recently that Senator Cranston's prostate cancer is being treated at Stanford University in a research program studying the effects of directed-hyperthermia on cancer.

Following my retirement in 1984, for various personal reasons, I progressively disassociated myself from the extremely active spare time interst and too close involvement as to the beneficial effects of quite high Vitamin C, gamma-linolenic acid, hydrazine sulfate, and directed hyperthermia on cancer patients covered in my 1983 letters. While still attending meetings and reading that literature, my interest, activity and comnputer searching shifted to the apparent, very detrimental health effects on our hearts and arteries resulting from chronic deficiencies of magnesium or various antioxidants; and the apparent striking benefits of supplementation.

PERSONAL RECENT EXPOSURE TO VITAMIN C AND CANCER

Dr. Ewan Cameron, a cancer surgeon for thirty years and a brillant metabolic scientist (Hyaluronidase and Cancer, 1966) first demonstrated twenty years ago that high levels of intravenous or oral Vitamin C were markedly beneficial for terminal cancer patients. Dr. Linus Pauling aided in getting the work published in the Proceedings of National Academy of Science and both have worked dedicatedly over this period to get governmental support and acceptance from the medical establishment. Considerable progress has been made considering the level of resistance to medical publication and government support of Vitamin C and cancer. The last time I talked on the phone with Dr. Cameron he had completly rewritten the book, CANCER AND VITAMIN C (1979) but hadn't a suitable publisher. His death in 1991 is a real tragedy and setback; but his impact will live on as bowel-tolerance levels of Vitamin C takes it proper place in the control of human cancer.

In December a Supplemental Issue of The American Journal of Clinical Nutrition came in to the medical library with all 219 pages completely devoted to forty papers covering: "ASCORBIC ACID: BIOLOGIC FUNCTIONS AND RELATION TO CANCER" from a September 1990 conference at the National Institue of Health and sponsored by the National Cancer Institue. This conference and its complete publication permitted by the new NCI head, Dr. Samuel Broder, is by far the most encouraging step I've seen in the past decade since it might result in it now being respectable to conduct studies using Vitamin C on cancer; and also that the NCI might start providing truly adequate support to accelerate such studies.

The Forward to this compilation of papers relating Vitamin C and cancer is by Gladys Block, Donald E. Henson and Mark Levine of the National Cancer Institute and contains an amazingly encouraging statement to have come from the NCI.

"Evidence is presented on the role of ascorbic acid in cancer, including its effect on delaying tumor onset, delaying tumor growth, prolonging survival, reducing toxicity as a result of treatment, and increasing the efficacy of concomitant treatment"

Early last week I was in California and heard Gladys Block (who is now at the University of California at Berkley) make a presentation on her current work with Vitamin C to Dr. Linus Pauling and his staff as part of an interesting exchange of recent developments at both institutions, as indicated by the enclosed copy of that program. Discussions at the Institute about Vitamin C and AIDS with R.J. Juriwalla; and Vitamin C and human mammary tumor with C.S. Tsao followed up their presentation on these subjects at the above NCI conference.

A two hour lunch the next day with Gladys Block at Berkley left a most favorably impression and a belief that she may have been the major, but quiet sparkplug that brought to effective fruition this historic meeting that Doctors Pauling and Broder initiated.

A January 17, 1985 letter is enclosed that deals with a retired nuclear scientist who had severe bone and later spinal cancer; who had approached me five years earlier. He had visited Dr. Cameron in Scotland, took 10 grams per day of Vitamin C, and was quite pleased when this stopped his pain. Sometime later when the pain returned he called from Huntsville, Alabama and said Dr. Cameron had suggested that he visit me if he got into further trouble. I suggested that we just talk on the phone; and that he use his scientific skills to spread out his Vitamin C as much as possible so he could maximize it; and to use tasteless crystals of the half sodium salt of Vitamin C dissolve in orange juice. Fortunately as discussed in the letter, he got to 25 g of Vitamin C; and thus effectively controlled his pain and cancer for three years.

Unfortunately, he called me after he had just become bedridden with paralysis of the legs; and in our discussion of his situation it turned out he had reduced his Vitamin C to half. He shortly found that he could take his spread-out Vitamin C up to 35 g without bowel problems; and also took evening primrose oil. This stopped the pain and improved the quality of his life again; but unfortunately didn't correct the paralysis of his legs. He lived at home with his sister and over the next two years over the phone he still sounded great.

PRESIDENTIAL AND CONGRESSIONAL APATHY ABOUT ACUTE RUSSIAN THREAT

I happened to have seen the above H-Bomb scientist for the first time in October 1984 on a Dan Rather news program dealing with atomic-radiation induced cancer, which didn't mention that he had been taking Vitamin C. Three months later as discussed in my January 1985 letter, I again saw him on a Dan Rather program discussing his long term success with a gram per hour of Vitamin C every hour of the day. This was on the day the Mayo Clinic declared for the second time that Vitamin C was without question worthless on cancer. During the following year his sister wrote to me when he died in bed at home of an acute kidney infection brought on by catheter treatment.

I was very pleased to have possibly assisted this research scientist and also so inexpensively for more than five years. In our phone chats as two chemists, I came to the conclusion that his independent approach to the H-Bomb using Lithium 6 (he had gotten his Ph. D 20 years earlier on its isolation and properties) may have aided in a truly major and timely way in our very close race with the Russians for the H-Bomb in 1952-53. Very many called our participation in that race immoral; but we only beat the Russians to an H-Bomb by months, which is mighty scary in retrospect.

Twenty-five years after that explosion, almost inexcusable presidential and congressional apathy about the acute danger from Russia's greater and much faster growing thermonuclear

January 17, 1985

Doctors Linus Pauling and Ewan Cameron
Linus Pauling Institute of Science and Medicine
440 Page Mill Road, Palo Alto, CA 94306

Dear Doctors Pauling and Cameron,

Last night, as you know, NBC's Tom Brokaw reported that the Mayo Clinic had once again shown in this weeks New England Journal of Medicine that Vitamin C was worthless against cancer: while Dan Rather's CBS news program additionally reported that this debate was not yet over, as some doctors think it can help cure cancer. Their interview of a patient with cancer of the spine, who took 24 grams of Vitamin C per day; and of Dr. Pauling, who stated the Mayo Clinic study was not a test of the value of Vitamin C against cancer, were most encouraging

I was particularly intrigued to see that the patient interviewed was a retired atomic scientist in Alabama, who called me five years ago about the use of Vitamin C for control of bone cancer pain. By going to 24 grams spread evenly over the day, he was able to control the pain. This and subsequent events were described in the last paragraph on page 4 of the 1983 letter to Dr. Jan Van Eys, in the last paragraph on the opposing page(1982 letter), and on the second page of last months letter to Dr. Cathcart.

Although he and I chatted on the phone many times over these years, I first happened to see him a few months back in a Dan Rather news program concerned with cancers induced by exposure to atomic radiation. That CBS interaction presumably prompted their use of this provocative Vitamin C aspect and angle at this time. His expressed conviction of the cancer contol and better feeling, while dissolving his gram of "C" per hour; plus the Zoom blow-up of him reading the Cameron-Pauling CANCER AND VITAMIN C presents one side of the picture. It was surprising to also hear CBS estimate that over 100,000 cancer patients in America now take Vitamin C; but if some are doing it in place of traditional treatment, that could be a mistake.

This cancer patient and the mother with inflammatory breast cancer(also discussed in the same three letters) apparently both seriously reactivated cancer growth or worsened immunological control(after doing well on one or more years on high "C") when they lowered the dose from around 25 grams a day to about half. Subsequently reraising the "C" to previous levels or higher(along with some gamma-linolenic acid) apparently induced and maintained a second marked breast cancer regression in the mother. but did not adequately control her induced brain metastasis. This also seems a likely reason why the cancer induced spinal paralysis has not advanced for the last couple of years.

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Dr. Peter Greenwald, Director
Division of Cancer Prevention and Control
National Cancer Institute
Bethesda, Maryland 20892

December 15, 1992

4 Atlantic Street
Charleston, SC 29401

Dear Dr. Greenwald,

I appreciated very much your response to my Nov. 3rd letter and attachments to Dr. James O. Mason, Assistant Secretary of Health and Human Affairs, that had followed my contact with him after his concluding talk at the 8th International Symposium on Cancer Research in Charleston. Your discussion of dietary approach and studies on cancer prevention in your letter; and in your opening talk that I heard in Tucson in June at the 4th International Conference on Nutrition and Chemoprevention were certainly informative and encouraging. The 2nd International Conference in 1989 was in Charleston.

Almost all studies and particularly recent ones seem to indicate increased intake of antioxidants (Vitamin C, Vitamin E, beta-carotene and selenium) reduce cancer, cardiovascular and other degenerative diseases; with progressive improvements up to substantial multiples of our Recommended Dietary Allowance (RDA)values.

The supplemental 25mg per day of beta-carotene taken for six years by a random half of the 22,000 physicians (earlier also on aspirin in Dr. Charles Henneken's study) proved stunningly beneficial in lowerering to half the heart attacks, cardiac deaths, strokes and by-pass operations among the 1½% of these physicians whose double-blind was broken in 1990 instead of 1995. This higher level of beta-carotene added to check its decided beneficial effect against cancer, is fifteen times as much carotene as the rest of us average in our diet. I and many others have however, taken almost twice this amount of beta-carotene for years.

Extremely few of us, as you know, consume sufficient levels of the pertinent foods to even reach our RDA values. It is thus hard to understand why our public health officials do not now also encourage further beneficial use of available inexpensive vitamins and micronutrients; which particularly improve the health of the elderly.

Superoxide, Superoxide Dismutase and Cancer

This month's Scientific American has nine pages on Why Do We Age with decided emphasis on the critical importance of oxidative free radical attack. As seen in the enclosed two underlined pages, the main detected difference in fruit flies recently bred to survive twice as long was in the capability of their antioxidant enzyme, superoxide dismutase. Doctors Michael Rose and Thomas Johnson pictured and featured in this enclosure on the genetic interaction between survival increases and superoxide dismutase; and Dr. Bruce Ames, whose presentation Oxidants and Antioxidants in Aging and Cancer was discussed in the letter to Secretary Mason, were quite active participants in a 1988 conference The Biological Basis of Aging that I attended in San Francisco. Dr. Richard Cutler on the bottom of the second enclosed page, headed that conference and showed that among mammals; humans exhibit both the longest maximum life span potential and decidedly the highest superoxide dismutase levels.

Enclosed are some pages from a 1979 twenty-six page letter on Superoxide, Superoxide Dismutase, and Cancer written hopefully to assist in our understanding of why ten to fifty grams per day of oral Vitamin C administered by Dr. Ewan Cameron in Scotland to large numbers of terminal cancer patients had proven so surprisingly effective in control of pain, tumor growth, quality of life and time to mortality.

This literature search and letter evolved over a two week vacation (a very tolerant wife); largely prompted by L. Oberley's publication that had just showed very marked reduction of the superoxide dismutase levels in the energy producing mitochondria of cancer cells.

Copies of this letter were sent to well over a hundred scientists and physicians; and Dr. Linus Pauling kindly wrote back thanking for the letter copy and its references. Three months later he sent a brief publication covering his discovery of the superoxide radical in 1933. He had brillantly deduced based on quantum mechanics, that an oxygen molecule with an extra electron should have enough stability to exist. A student was told how to prepare and isolate it; and how to demonstrate its validity by paramagnetic measurements. Pauling named it superoxide and his student E. W. Neuman published the findings which were largely ignored for almost twenty-five years. The 1968 discovery of our antioxidant enzyme, superoxide dimutase; demonstrated the extreme importance of superoxide dismutase in protecting us from released superoxide radicals everywhere in our body; and in aerobic cells throughout all life processes. Vitamin C also protects us by reducing released active superoxide radicals back to oxygen.

Enclosed are some underlined pages from that 1979 letter with pertinent points that are still not common knowledge in the cancer field. Also the table showing precipitate drop of Vitamin C levels in our various tissues as we age; and the graph showing drop of our white blood cell ascorbate down to scurvy levels in conjunction with various cancers (with resulting severe collagen degradation to hydroxy proline) still merit serious consideration.

Fortunately for me, the botton half of page 25 was picked up just before sending out that letter; as it later turned out to be the key lead (beneficial interaction between increased levels of gamma-linolenic acid and Vitamin C to increase depleted anti-inflammatory cellular hormone, Prostaglandin E-1) that at the end of 1980 cured; and has continued to completely control my earlier extremely severe rheumatoid arthritis without drugs. Very severe relapes in 1984 and 1988 were apparently caused by month long inadvertent lack of the 9% gamma-linolenic acid in authentic evening primrose oil.

Dr. Robert Zurier's abstract (on page two of the letter to Secretary Mason) first demonstrated in the U. S. the double-blind efficacy of natural oral gamma-linolenic acid in control of rheumatoid arthritis. It was among only eleven of about 350 poster presentations that day picked at the American College of Rhematology meeting of 3000 rheumatologists for oral presentation and questions in the final 90 minute period in the auditorium.

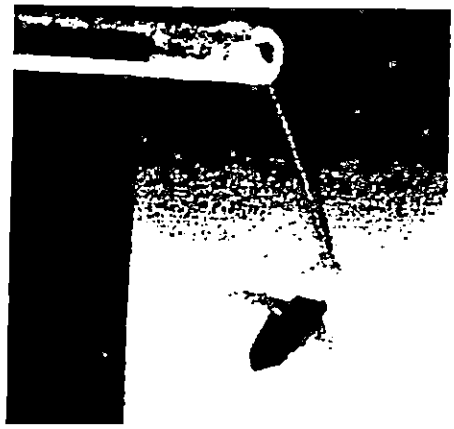
With hope that rheumatoid arthritis and cancer patients in the coming decade might progreessively get to effectively use high level, non-toxic ascorbic acid and gamma-linolenic acid to help control their devastating diseases. I surely appreciated simple, non-toxic complete control of my severe arthritis with no side effects over the past decade; and even more when I noted poster studies at the Atlanta meeting showing severe rheumatoid arthritis actually increases mortality comparable to severe heart problems.

Most sincerely,

Frank J. Ball

Frank J. Ball

cc: Those copied on October 29, 1992 letter to Doctors Burton Lee, James Edwards, Peter Gazes and James Spann



MICHAEL R. ROSE of the University of California at Irvine has significantly extended the life span of the fruit fly *Drosophila melanogaster* (*far left*) by selective breeding. The insect here, shown in flight, was tethered to fishing line by a drop of Duco Cement for an experiment in which Joseph L. Graves, now at Irvine, demonstrated that the long-lived flies are stronger than normal specimens: they can keep themselves airborne longer under a range of temperatures and humidity levels.

other evolutionary hypotheses will lie in identifying the genes, perhaps hundreds of them, that actually control the molecules that thwart or promote senescence. Many laboratories are now busy attempting to tease out some of the more influential genes.

Genetic Clues

Several investigators—among them Rose, Jazwinski and Thomas E. Johnson of the University of Colorado—are meeting that challenge by seeking genes that can prolong life in relatively simple organisms. "Aging is a puzzle you can understand only if you can compare normal with postponed aging," Rose says. "That tells you what the normal animals are missing. With humans, you don't have a control group."

After Rose created his hardy fruit flies, he and his colleagues compared the proteins made by the experimental and normal insects. One clear difference turns out to be that many of the long-lived flies produce an unusually active version of the antioxidant enzyme superoxide dismutase, which means they harbor a variant of the normal enzyme-specifying gene. Specifically, they produce a highly efficient version of the form of the enzyme typically found in the cytoplasm of cells. In fruit flies, as in humans and other organisms, superoxide dismutases defend against oxidative damage by helping to neutralize a dangerous free radical called superoxide. The genetic difference implies that one reason normal fruit flies age more quickly is that their free radical defenses are not as effective as those of the specially bred flies.

Of course, the variant of superoxide dismutase manufactured by fruit flies is sure to be just one of many factors that influence how quickly such flies age. Rose and Joseph L. Graves and their co-workers at Irvine have found, for instance, that the long-lived flies are more resistant to starvation because they store more fat. (Rose says the insects are so hefty that they spray fat in all directions if they are touched even lightly.) The flies are also less likely to dehydrate, in part because they stow more of the carbohydrate glycogen.

"The work on *Drosophila* is trial-run stuff for doing the same thing in mice," Rose says. "If we can create long-lived mice, specific genes, enzymes and cell processes involved in longevity should be revealed." As mammals, mice are genetically closer to humans than are fruit flies, and so they should have more to reveal about how people age. Mouse research should be more informative, that is, if someone will foot the bill for long-term studies, which Rose estimates would cost about $10 million.

Findings related to Rose's are coming out of Johnson's laboratory at Colorado. Johnson and his colleagues have wielded selective breeding to produce long-surviving versions of a tiny soil-dwelling worm known as *Caenorhabditis elegans*. They have also managed to prolong life in the species by generating random genetic mutations.

Like Rose's group, Johnson's team is attempting to identify the genes that are differentially expressed in long-lived and normal groups (differentially transcribed from DNA into messenger RNA, which is then translated into protein). In 1988 he reported that mutation of a single gene called *age-1* can increase the average life span of *C. elegans* by about 70 percent. Strikingly, the mutant worms produce elevated levels of antioxidants (both cytoplasmic superoxide dismutase and an enzyme called catalase) and are more resistant to the toxic effects of paraquat, a herbicide that leads to generation of the superoxide radical.

The mutation in the *age-1* gene seems to inactivate that gene, which means the encoded protein is no longer made. If the protein's elimination leads to increased production of antioxidants, then it is possible that the normal protein inhibits production of those substances.

THOMAS E. JOHNSON of the University of Colorado, who is examining petri dishes with a technician in his laboratory, has prolonged the life of another multicellular organism: the small, soil-dwelling worm *Caenorhabditis elegans* (*far right*). Johnson and his colleagues achieved the feat in two independent ways—by selectively breeding for longevity and by introducing a mutation in a single gene, called *age-1*. The group is now attempting to clone the *age-1* gene.

Why would an organism deliberately inhibit synthesis of such critical compounds? "I don't think its purpose is to kill the worm at a certain age," Johnson says. Rather he speculates that the inhibition may well be an undesirable effect of some other important function that has not yet been discovered. In other words, he thinks antagonistic pleiotropy is probably operating.

Once Johnson has cloned the *age-1* gene—which he hopes to accomplish soon—he plans to search for a counterpart in mice. If mice harbor a similar stretch of DNA, he might be on the track of a specific gene that could also be involved in human aging. Johnson is fond of a line from *Thus Spoke Zarathustra*, by Friedrich Nietzsche: "You have made your way from worm to man, and much in you is still worm." He is hoping Nietzsche's observation extends literally to the genetics of aging, although he realizes that the causes of senescence in *C. elegans* may be quite different from those in humans.

Jazwinski, aware that we have many genes in common with an even more primitive, single-celled organism, has focused his attention on baker's, or brewer's, yeast (*Saccharomyces cerevisiae*). He has identified several genes that prolong the yeast's life. The best studied of these, *LAG1* (*longevity assurance gene 1*), is more active in young cells than in old ones. Inducing extra *LAG1* activity in older cells, after expression has normally declined, extends their life by about a third. Most important, elderly yeast cells bearing the extra-active gene do not become immortal (as cancerous cells in multicellular organisms do); they simply operate youthfully longer.

Jazwinski does not know the function of the corresponding protein yet. Nevertheless, he has discovered that a similar gene is expressed in certain human cells. He is now isolating the human gene to determine whether it affects the life span of any human cells. He also intends to overexpress two other longevity assurance genes along with *LAG1* to see whether the combined effects are additive, synergistic or, possibly, destructive. And he expects to evaluate several other genes that his group has reason to believe might influence life span.

Radical Discoveries

Although the function of *LAG1* remains a mystery, the discovery that the antioxidant superoxide dismutase seems to affect longevity in both Rose's fruit flies and Johnson's worms dovetails intriguingly with growing enthusiasm for Harman's free-radical theory. Johnson notes that 25 years ago the theory was accepted as "an interesting hypothesis, perhaps true." Now increasing numbers of investigators are seriously entertaining the possibility that free radicals might indeed be a significant factor in aging.

Much of the evidence for free radicals is still based more on correlation than on clear demonstrations of cause and effect. For instance, if unrepaired damage caused by free radicals were a cause of aging, animals with a high metabolic rate—that is, who burned oxygen relatively quickly—would likely have shorter life spans than would species that consumed oxygen more slowly. The faster metabolizers, after all, would produce free radicals more rapidly. Indeed, the basal, or resting, metabolic rate of a species is inversely related to its life span; mice have a much higher rate than do humans, and they rarely live more than three years.

Cutler of the National Institute on Aging has uncovered other support. He finds that tissues of humans and other long-lived species produce more superoxide dismutase overall and are more resistant to oxidation. Cutler thinks humans age in part because their superior protection against oxidation is nonetheless insufficient to protect them forever. The reactive oxygenated molecules

4 Atlantic Street
Charleston, South Carolina
August 13, 1979

Dr. Ewan Cameron, Linus Pauling Institute of Sci. & Med., Calif.
Dr. Joseph Gold, Syracuse Cancer Research Institute, New York
Dr. Harry B. Gregorie, 37 King Street, Charleston, S. C.

Dear Doctors Cameron, Gold and Gregorie:

As you know, last summer and fall I wrote and distributed a series of letters discussing some biochemical literature evidence that seemed to help explain the decided efficacy of oral Vitamin C in cancer control that Dr. Cameron has been demonstrating in Scotland since 1972. Major attention was directed at the little realized extensive collagenase release characteristics of cancer tissue since ascorbic acid inhibits collagenase release and promotes new collagen formation. The two-page summary on Collagenase and Cancer, which was at the beginning of sixty typed pages and graphs in two of the letters to Dr. Gregorie, is attached for possible referral. All subsequent reading seems to support the thoughts expressed in this summary, but since it now appears that animal cancer tissue can consist of half or more unsuccessful defending macrophages, particularly in the growth zone, then the detrimental collagenase release may be largely coming from them, as will be discussed later. It would thus be even more important to provide adequate ascorbic acid to the defensive cells, since it has been quite definitely established that although macrophages already concentrate relatively high levels of ascorbic acid, they become progressively more successful with increasing blood levels of ascorbic acid. It is very satisfying to note during 1979 the increasing acceptance of the significance and medical value of oral Vitamin C in cancer and other applications; and the beginnings of highly merited grant support.

Literature evidence indicated cancer cells are progressively more damaged in their capability to produce energy by oxygenation; consequently from 60% to 99% of their nutrients end up in the blood as lactic acid, instead of the usual carbon dioxide. I had thus looked for any control approaches that recognized and took effective advantage of this situation. Dr. Gold's approach which used relatively nontoxic levels of oral hydrazine sulfate to decidedly prevent the continuous energy draining cyclic reconversion of lactic acid to glucose in the liver; and thus reversed the drastic weight loss (cachexia) of cancer patients seemed the most ingenious and most effective. Particularly now that Russian medical reports also show cachexia reversal using hydrazine sulfate on two-thirds of 225 evaluable patients with metastatic cancer (where all other therapy had failed); it seems totally inexcusable that Dr. Gold's grant requests for continued basic studies have not been approved or supported; and no supported clinical trials are underway in this country.

Dr. Manfred Von Ardenne's opposite approach which induced the cancer tissue to produce extremely high levels of lactic acid by raising the glucose level of the blood five fold for several hours had seemed equally brilliant. The resulting more than ten fold increase in the acidity of the cancer cells and their blood capillaries when combined with tolerable increases in body temperature resulted in cancer kill throughout the animal; and clinical follow-up was apparently getting underway in Dresden, East Germany. When what seemed our already critical and very seriously worsening military situation; prompted me this winter to twice send long concerned letters to all Senators and Representatives, it then seemed prudent, in consideration of Dr. Von Ardenne, to discontinue any further contact. This was most regretted as he sent English translations and his techniques, approach, and productivity in cancer metabolism were perhaps the most advanced I noted in the literature.

When looking up the Cameron-Pauling excellent 19-page review paper, "Ascorbic Acid and Cancer," in the February Cancer Research, I also came across L. W. Oberley and G. R. Buettner's seemingly very significant paper in the March issue of that journal. The latter paper clearly demonstrated that cancer cells no longer possess the protective superoxide dismutase enzyme in their mitochondira. This was intensely interesting; since as indicated in last year's letters, cancer cells have lessthan half as many mitochondria as the cell from which they were derived. Progressive damage to a cell's mitochondira would result in a progressive loss of the cell's ability to oxidize to carbon dioxide all of the pyruvic acid which is produced from glucose sugar or fatty acids in the cytoplasm of the cell. Since the cytoplasm can convert any excess pyruvic acid to lactic acid, this acid would then be excreted into the blood, as happens with all cancer cells. Progressive destruction of the protective superoxide dismutase in the mitochondria, by various feasible methods would result in a build up of superoxide radicals in the mitchondria. These radicals can reduce and thus inactivate the ferric iron in all the oxidative enzymes of the mitochondria, but they can be decomposed by reacting with ascorbic acid.

Earlier interest in superoxide and superoxide dismutase was briefly covered on page 16F of my July 24, 1978 letter to Dr. Gregorie; so I distributed some copies of this superoxide dismutase paper by Oberley with appended handwritten comments.

My somewhat excessive spare time reading was stopped when I collapsed at work; and spent a week in the hospital and three weeks at home during April at doctor's orders, with a diagnosis of bradycardia of the heart from sustained extreme exhaustion.

In the month or so before then, using recent books, I had attempted to simultaneously understand the relative metabolism and hormonal aspects of 1) cancer cells which continually divide, 2) brain cells which never divide, as compared to 3) certain body cells and most plant cells which can fluctuate wildly in division or energetics. I was then mainly interested in brain energy metabolism and the relative effects of the major hormones, such as the epinepherines (Adrenalin) and

6. The epithelium of the eye is exposed to higher oxygen levels and exhibits higher dismutase levels. Cataracts seem to form in this region and analyses of eyes with cataracts seem to be lower in dismutase. You may also remember last year an indication that eyes with cataracts appeared to have low ascorbic acid contents. Both superoxide dismutase and ascorbic acid convert superoxide radicals to hydrogen peroxide which is decomposed by our catalase enzyme.

Absence of Superoxide Dismutase in Cancer Cell Mitochondria

1. Early analysis methods assessed the superoxide dismutase level of cells by the efficacy exhibited for destruction of superoxide radicals. Conversion of normal cells to cancerous form did not change the indicated dismutase level very much; and it might either increase or decrease.

2. When it was realized that the superoxide dismutase in the cytoplasm contained copper-zinc catalyst, as opposed to manganese catalyst in the mitochondria dismutase; methods were devised to determine them separately.

3. Oberley's paper (Cancer Research 39, 1141; April 1979) now gives clear indication that the manganese superoxide dismutase is diminished in all tumors analyzed. The manganese dismutase has been indicated to be actually absent in the tumor cell lines of rat H 6 hepatoma, mouse L 1210 leukemia, mouse C 3H mammary carcinoma, mouse S 91 melanoma, and Morris hepatoma 3924 A. Human leukemia cells in Japan also exhibited low levels or absence of manganese superoxide dismutase.

4. Isolated mitochondria fragments from cancer cells gave indirect indication of substanial superoxide radical formation which was reduced to zero by superoxide dismutase addition. Superoxide dismutase will not penetrate through cell membranes, but when added does decompose any superoxide in the serum.

5. Since the superoxide radical appears to be an intermediate in many enzymatic oxygenation reactions, superoxide dismutase control of leakage or excessive concentrations that might damage other portions of the mitochondria should be most important. It would be expected that as mitochondria lost their superoxide dismutase capability, the superoxide and resulting hydrogen peroxide or hydroxyl radicals could attack the mitochondria membrane phospholipids, DNA, or RNA. If the cells which were being subjected to sustained slow mitochondrial damage had progressively built up sufficient capability to produce energy by glycolytic conversion of pyruvic acid to lactic acid in the cytoplasm, they might then survive and become cancer cells. This generally seems to take a long, long period involving at least 30 - 50 divisions over the years for most of our body cells, which derive their energy basically from the mitochondria.

Molecular and Cellular Biochemistry 84: 147–153 (1988)

Invited Paper

Role of antioxidant enzymes in cell immortalization and transformation

Larry W. Oberley[1] and Terry D. Oberley[2]

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Accepted 29 May 1988

Key words: superoxide dismutase, catalase, glutathione peroxidase, immortality, cancer, mitochondria

Summary

The role of antioxidant enzymes, particularly superoxide dismutase (SOD), in immortalization and malignant transformation is discussed. SOD (generally MnSOD) has been found to be lowered in a wide variety of tumor types when compared to an appropriate normal cell control. Levels of immunoreactive MnSOD protein and mRNA for MnSOD also appear to be lowered in tumor cells. Tumor cells have the capacity to produce superoxide radical, the substrate for SOD. This suggests that superoxide production coupled with diminished amounts of MnSOD may be a general characteristic of tumor cells. The levels of MnSOD in certain cells correlates with their degree of differentiation; non-differentiating cells, whether normal or malignant, appear to have lost the ability to undergo MnSOD induction. These observations are used to elucidate a two-step model of cancer. This model involves not only the antioxidant enzymes, but also organelle (particularly mitochondria and peroxisomes) function as a dominant theme in carcinogenesis.

Introduction

The hypothesis that free radicals are important in carcinogenesis is not a new one. Enthusiasm for this idea has waxed and waned over the years. Definitive evidence on this hypothesis has been difficult to obtain because of the elusive nature of free radicals. Recent advances in techniques and understanding have resulted in a clearer picture of the role of free radicals in cancer. It is the purpose of this paper to critically review the current state of our knowledge as well as suggest new avenues of study.

Antioxidant enzymes in tumor cells

Because of the difficulty in accurately measuring free radicals in living cells, investigators of the relationship between free radicals and cancer have focussed on measurements of antioxidant enzyme activities of normal and tumor cells. These enzyme activities will give an indication of how well a cell is protected against active oxygen species. Moreover, in normal cells, since the antioxidant enzymes are inducible, the levels of the antioxidant enzymes reflect the levels of their substrates – the active oxygen species. As we will see later, the latter assumption may not be true in tumor cells.

The data on the levels of antioxidant enzymes in tumor cells has been reviewed a number of times [1, 2, 3]. The general picture that has emerged is that tumor cells have abnormal activities of the antioxidant enzymes when compared to an appropriate normal cell control. In this paper, antioxidant enzymes will mean the superoxide dismutases (SOD), catalases (CAT), and peroxidases, of which

7. As mentioned in the previous letters, J.U. Schlegel (Tulane Medical et.al., J. Urol., Baltimore 103: 155-59 (1970) believed that the irradiation from chemilumiscent urine might be a factor in bladder cancer; and found that ingestion of 1-2 g. of ascorbic acid stopped chemiluminesence; and was beneficial in the prevention of bladder carcinoma. This irradiation was accelerated by bladder carcinogens, such as nitrosoamines or the natural 2-hydroxy anthranilic acid. It would now appear the observed chemiluminesence probably came from superoxide released as the body attempted to oxygenate carcinogens or from macrophages attempting to handle incipient cancer nodules. Sufficient ascorbic acid should remove escaped superoxide radicals in solution and stop chemiluminesence. Cancer prevention and control may also have come from improved macrophage vitality and kill capability which accompanies high blood ascorbic acid levels (Book 6, pages 81-82)

8. This chemiluminescence recalls a book by Albert St. Gyorji related to bioelectronics and cancer which was perused last year. This twenty year old book described and interpreted a series of simple but ingenious experiments where he dissolved into solvents various vitamins, biological co-factors, biologically active chemicals such as 2,4-dinitrophenol, etc. that he felt were involved in electron transfer reactions. By freezing the solvent solutions to the very low temperatures of liquid nitrogen; he was able to excite electrons to high energies by irradiation, and then follow the return of the sufficiently slowed electrons to their normal state by observing the immediate fluoresence or delayed phosphoresence in varying colors. His interpretation of these phenomena and their relationship to life processes and animal experiments was quite fascinating. Superoxide radicals would be right in line with his bioelectronic thinking, but I am not up on that area.

Potential Cause and Significance of Falling Ascorbic Content of White Cells and Increasing Ascorbic Content of Cancers

1. The level of ascorbic acid in the white cells of cancer patients progressively drops to quite low levels as is partially indicated in the graph on the following page from my July 7, 1978 letter to Dr. Gregorie.

2. This graph plots the increasing level of hydroxyproline excreted in the urine of mainly cancer patients compared to the decreasing ascorbic acid content of their white blood corpuscles. Hydroxyproline comes basically from decomposed collagen fibers; and apparently results in cancer patients, because the collagenase enzyme released from growing cancer tissue breaks down the collagen fibers that enmesh the cells of adjacent normal tissue. Hydroxyproline release would be expected to rise much faster when the collagenase releasing cancer cells grow on the bone, as the bone is mainly collagen fibers and mineral.

3. The dramatic effect of 1 g. ascorbic acid in reducing hydroxyproline excretion is shown in Table 2, alongside the graph. This is presumably due to the capability of ascorbic acid to turn off collagenase release; and promote collagen

Doctors Cameron, Gold, and Gregorie

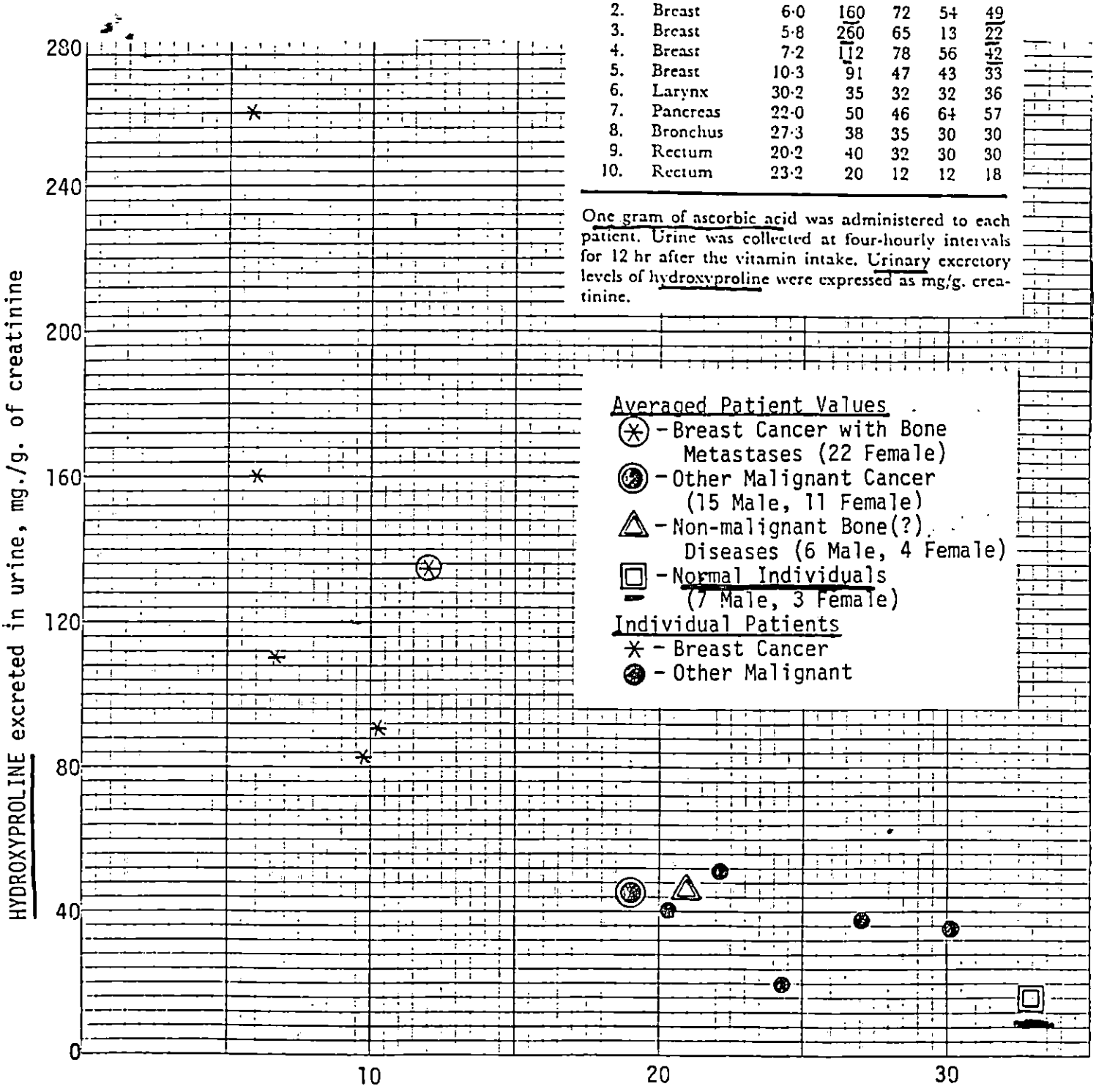
RELATIVE LEVELS OF LEUCOCYTE ASCORBIC ACID AND URINARY HYDROXYPROLINE
(with effects of 1g. ascorbic acid injestion on urinary hydroxyproline levels)

Basu, Raven, Dickerson, and William's Data
European Journal of Cancer 10, 507-09 (1974)

Table 2. Urinary excretory levels of hydroxyproline after a loading dose of ascorbic acid

Case no.	Site of tumour	LAA level ($\mu g/10^8$ W.B.C.)	UHP level (hours after a dose of ascorbate) 0	4	8	12
1.	Breast	9·8	84	50	46	52
2.	Breast	6·0	160	72	54	49
3.	Breast	5·8	260	65	13	22
4.	Breast	7·2	112	78	56	42
5.	Breast	10·3	91	47	43	33
6.	Larynx	30·2	35	32	32	36
7.	Pancreas	22·0	50	46	64	57
8.	Bronchus	27·3	38	35	30	30
9.	Rectum	20·2	40	32	30	30
10.	Rectum	23·2	20	12	12	18

One gram of ascorbic acid was administered to each patient. Urine was collected at four-hourly intervals for 12 hr after the vitamin intake. Urinary excretory levels of hydroxyproline were expressed as mg/g. creatinine.



FALLING VITAMIN C CONTENT OF VITAL ORGANS AND CELLS WITH INCREASING AGE

Book (4) Pages 78-79

Table 4.1. Ascorbate content (mg/kg wet weight) of human tissue (averaged values from the references)

Tissue	Fetuses	Newly born	Children	Adults	Old people	Reference
Adrenals			1190			Bessey and King (1933)
	1820	700	500	400	100	Giroud (1938)
		780	760			Ingalls (1939)
		581	540	393	230	Yavorsky *et al.* (1934)
		(4000 → 5000, unspecified age)				Roston (1962)
Leucocytes (white cells)		(250 → 350, unspecified age)				Masek and Hruba (1964)
		(250 → 350, unspecified age)				Lowry *et al.* (1946)
Brain		460	310		110	Yavorsky *et al.* (1934)
(For contents of cerebral cortex and cerebellar cortex see section 4.6)						
Pituitary		889 (0-9) (yrs); 950 (10-14) (yrs)		770 (20-29 yrs) 488 (30-39 yrs) 447 (40-49 yrs) 521 (50-59 yrs) 511 (60-69 yrs) 497 (70-79 yrs) 455 (80-89 yrs)		Schaus (1957)
(Hypophysis)		750 (24 yrs, female); 650 (48 yrs, male)				Melka (1936)
Eye lens		(5-55 with cataracts)		310		Euler and Malmberg (1936)
(For extensive analysis of eye tissues see Tables 4.2 and 4.3)						
Pancreas		365	265	152	95	Yavorsky *et al.* (1934)
			300 (20 mnths)			
Thymus		304	255		46	Yavorsky *et al.* (1934)
Kidney		153	110	98	47	Yavorsky *et al.* (1934)
	350	100	70	50	30	Giroud (1938)
Liver		149	155	135	64	Yavorsky *et al.* (1934)
			370 (20 mnths)			Bessey and King (1933)
			200	150	40	Giroud (1938)
		385				Ingalls (1939)
Spleen		155	135	127	81	Yavorsky *et al.* (1934)
Myocardium		73 (0-9 yrs) decreasing to 49 (80-89 yrs)				Schaus (1957)

The blood level stays around 10mg/kg in health even on aging. Increased ascorbic acid intake increases its level in vital organs.

Vitamin C and immunity: an assessment of the evidence

W. R. THOMAS & P. G. HOLT* *Division of Immunological Medicine, Clinical Research Centre, Watford Road, Harrow, Middlesex, and *Department of Microbiology, University of Western Australia, Perth Medical Centre, Shenton Park, Western Australia*

Clin. exp. Immunol. (1978), 32, 370-379

SUMMARY

The high concentration of ascorbate in leucocytes and its rapid expenditure during infection and phagocytosis suggests a role for the vitamin in the immune process. Evidence published to date shows an involvement in the migration and phagocytosis by macrophages and leucocytes, as well as the induction and expression of delayed hypersensitivity. Its effect on antibody production and complement levels is controversial but probably minimal. This study suggests there is room for further investigation into the effect of ascorbate on immunity, particularly with defined populations, but cautions the use of megadose therapy.

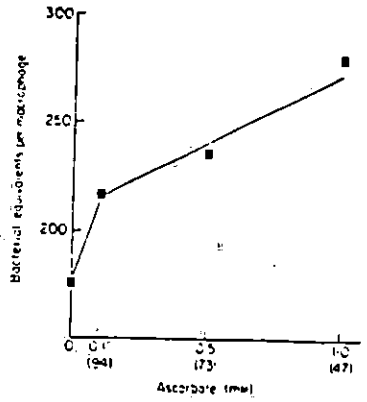


FIG. 1. Phagocytic activity of peritoneal macrophages after incubation with media supplemented with ascorbate. Monolayer cultures of mouse peritoneal macrophages were incubated for 20 hr with the concentration of ascorbate shown. Media containing fresh ascorbate was then added and after 1 hr their ability to phagocytose heat-killed radiolabelled *Pseudomonas aeruginosa* was measured. Results are the mean of three cultures and show the amount of radioactivity, in bacterial equivalents, accumulated after 2 hr incubation in media containing $18{\cdot}8 \times 10^7$ bacteria per ml. Details of the method used have been published (Thomas, Holt & Keast, 1974). Some cell death occurred during the incubation and the percentage viability of the cultures is shown in parentheses.

Vitamin C Regulation of Prostaglandin E1 Hormone Formation

While looking for the latest information on macrophages in human cancer, I looked into the August 1979 issue of Medical Hypotheses, and found (p. 849-58) an article by D. F. Horrobin, et. al., entitled THE REGULATION OF PROSTAGLANDIN E1 FORMATION: A CANDIATE FOR ONE OF THE FUNDAMENTAL MECHANISMS INVOLVED IN THE ACTIONS OF VITAMIN C. Dr. Horrobin is at the Clinical Research Institute of Montreal and wrote the book, Prostoglandins: Physiology, Pharmacology and Clinical Significance (1978). He reviewed in this paper as indicated in the abstract below the potential significance of his recent publication (Prostaglandins Med. 3: 129-37, 1979) which showed that ascorbic acid enhances the formation of prostaglandin hormones, such as PEG1.

ABSTRACT

Vitamin C stimulates the formation of PGE1 in human platelets. The effect occurs over the physiologically relevant range of concentrations. PGE1 is required for T lymphocyte function and plays a major part in the regulation of immune responses. PGE1 is also important in the regulation of collagen and ground substance metabolism, in cholesterol metabolism and in regulation of responsiveness to insulin. It is proposed that defective formation of PGE1 could account for many of the features of scurvy and for many of the reported therapeutic effects of vitamin C. If correct, vitamin C will be of value only in conjunction with an adequate supply of dihomogammalinolenic acid, the precursor of PGE1. Essential fatty acids, pyridoxine and zinc are all required to achieve this.

4 Atlantic Street
Charleston, S. C. 29401
May 12, 1983

The Honorable George Bush
The Vice President of the United States
Executive Office Building
Washington, D. C. 20501

Dear Mr. Vice President:

The level of dynamic movement, short-term clinical potential, and increasing public awareness of certain effective, available, and nontoxic cancer therapies (which are based on sound scientific and medical principles) have now reached such a degree of medical and possibly political significance that proper executive understanding and handling of this vitally important situation actually merits your attention.

Just reading the enclosed one and a half-page letter to Dr. George Keyworth II, will briefly aquaint you with earlier attractive nontoxic cancer therapies which are being tragically neglected. It will also permit some understanding of the enclosed astounding clinical results on liver cancer obtained this week from South Africa, which resulted (as postulated several years previously) from oral administration of an available nontoxic natural fat containing gamma-linolenic acid.

This week on May 11 the Public Broadcasting System TV presented for one hour a very different "War on Cancer" than is normally seen. I fortunately got to see the second half, which presented both the clinical potential of Dr. Joseph Gold's hydrazine sulfate for control of cancer cachexia (acute weight loss) and Dr. Ewan Cameron's approach using very high oral Vitamin C to restore immune capability and quality of life in terminal cancer patients. Nobel Laureates Linus Pauling and Albert Szent-Gyorgyi emphasized the National Cancer Institute's sustained acute deficiency in recognizing or supporting attractive nontoxic approaches to cancer therapy. Dr. Vincent DeVita pleasantly kept trying to justify NCI decisions. I heard the first half presented convincing biostatisics to demonstrate that the NCI's ten-year massive toxic approaches were largely losing not winning the cancer war, while causing extensive needless patient distress.

During this week exactly five years ago, the enclosed three letters were written to Dr. Ewan Cameron in Glasgow, Scotland, Dr. Joseph Gold in Syracuse, New York, and Dr. Manfred Von Ardenne in Dresden, East Germany. These letters were to encourage what had seemed the three most hopeful nontoxic cancer therapies noted in the medical literature; and to send each of them the medical literature of the other two. Dr. Cameron had pioneered the use of very high oral levels of Vitamin C to stimulate the immune system and thereby improve the quality of life and longevity of 500 terminal cancer patients per year in a Scotland District General hospital. Dr. Gold, Director of the Syracuse Cancer Research Institute, had brilliantly deduced the actual simple cause of the drastic and accelerating weight loss (cachexia) that kills more than half of cancer patients; and discovered that nontoxic levels of available hydrazine sulfate minimized weight loss and thereby benefited thousands of cancer victims. Dr. Von Ardenne was a very noted German atomic physicist with his own Institute, who had shifted his emphasis to become the most advanced European scientist in both local and whole animal body hyperthermia, which specifically killed just cancer tissue with properly induced heat. He also ingeniously combined both high body heat with five times normal blood glucose levels for some hours. This caused both the animal cancer and its metastases to produce such excessive cancer derived lactic acid, that they were more effectively destroyed.

These nontoxic cancer therapies (high oral Vitamin C, hydrazine sulfate, and hyperthermia) are being specifically brought to your attention at this time, because they constitute both available and effective nontoxic approaches to cancer therapy which separately and in combination seem to offer such striking present clinical potential to the 450,000 Americans who each year discover serious cancers, and the roughly similar number who die of it. If you get to look at the attached letters sent to Doctors Wyngaarden, Keyworth and DeVita and the thirty senators on the committees that control the funding and activity of the National Cancer Institute, I hope you will appreciate why they are being repeatedly approached.

Since these relatively effective and nontoxic cancer therapies (Vitamin C, hydrazine sulfate, and hyperthermia) have been tragically undersupported, often condemned, and thus underutilized over the past five years I, like others, have persistently attempted to arouse greater understanding and support at Senatorial, National Cancer Institute, and Executive levels. Senator Hollings has also written letters during this period relative to the NCI's total lack of support of Dr. Joseph Gold's grant requests to extend his brilliant studies on cachexia control. The NCI's consistent refusal of scientific or clinical support on hydrazine sulfate and their negative interpretation of successful Russian studies seriously retarded acceptance of this available and effective nontoxic product. The American Cancer Society, however, removed Dr. Gold and hydrazine sulfate from their "unproven methods" blacklist in 1980 and their recent financial support of studies underway at the UCLA School of Medicine has resulted in the positive paper, Association Between Improved Carbohydrate Metabolism and Weight Maintenance in Hydrazine Sulfate Treated Patients with Cancer Cachexia, (enclosed summary), by R. T. Chlebowski et al, to be presented at the May 22-24 meeting of the American Society of Clinical Oncology.

Senator Hollings also wrote Dr. Vincent DeVita and HHS Secretary Richard Schweiker about the NCI's continuing refusal of grant support to Dr. Harry H. LeVeen, who pioneered nontoxic clincal hyperthermia therapy in this country throughout the past decade; and who in conjunction with Dr. Ronald Pethig in England developed the most advanced and successful radiofrequency hyperthermia equipment, clinical techniques, and electronic prediction and evaluation methods. With the removal of hyperthermia from the American Cancer Society's "unproven methods" blacklist in 1980, NCI support was markedly increased over the next two years, as discussed in the letters to Dr. Wyngaarden and others. Dr. LeVeen's and the Medical University of South Carolina's brilliantly advanced proposals, equipment, and clinical techniques, were presented in their responses to the five-year NCI Phase I Request for Proposals - Evaluation of Equipment for Hyperthermic Treatment of Cancer awarded to five separate centers by the end of 1982; and the follow-up five-year RFP - Hyperthermia Quality Assurance Program being now awarded; but these were totally rejected. This occured despite the fact that his equipment and techniques were the most advanced and successful in this country for treating deep cancers, such as lung, and his sustained effort without any NCI support was a major factor in medical acceptance of the clinical potential of cancer hyperthermia therapy.

The enclosed letters to Doctors Wyngaarden, Keyworth, and DeVita, and a visit last October to Dr. Chabner at the NCI also implored support for the grant request of Dr. Nicholas DiLuzio, Chairman of Physiology at Tulane Medical, to accelerate broad acceptance in cancer control of his highly encouraging nontoxic natural immune stimulant, beta-1,3-glucan, but this grant request has just also been turned down by the NCI.

Finally, these letters and one to Dr. Jan Van Eys were to bring to their specific attention the likely major nontoxic cancer control potential inherent in natural and available gamma-linolenic acid which is the precursor of our "one" series prostaglandins (cellular hormones). Since October 1982, five medical reports and letters have been published on test tube studies in three South African medical universities that clearly demonstrated the striking capability of natural gamma-linolenic acid to induce "reversibility" or marked growth inhibition on both mouse and seven human cancer cell lines with no effect on comparable normal cells.

Now the enclosed published letter (mentioned at the beginning of this letter) shows major shrinkage of distended cancerous livers in liver cancer patients following use of oral gamma-linolenic acid for just one day or for two months, plus substantial pain reduction. In this first clinical test, both patients still died quickly like the 46 other liver cancer patients. On the other side of this "reversibility of cancer" letter is copied the INTRODUCTION and SUMMARY from the section on liver cancer in the definitive 1982 book on cancer, which realistically presents the almost complete lack of effective medical therapy for liver cancer. Of interest, a Mother Superior Emeritus with earlier intestinal cancer was told she apparently had developed metastatic liver cancer a year ago, but right away she took high oral levels of Vitamin C and evening primrose oil, which contains gamma-linolenic acid. This week, a year later, she is apparently in much better shape.

With one-fourth of us now expected to get cancer, we deserve much more executive consideration and encouragement of these viable nontoxic cancer therapies to more quickly minimize our extensive personal financial costs and grief and to reduce the likely tremendous federal health care expenses due to cancer. Four-fold reduction in our earlier worst cancer killer from increased use of Vitamin C is now widely acknowledged, as discussed in the letter to Dr. Van Eys; so why not promote much more extensive and quicker evaluation of such approaches in cancer therapy.

Since the odds are low that this letter will get through to you, it is also being sent to others with some potential and interest in beneficially influencing this situation.

Most sincerely,

Frank J. Ball

Frank J. Ball

FJB/dr
Enclosure

cc: Pres. J. B. Edwards
Dr. H. H. LeVeen
Dr. Ewan Cameron
Dr. N. R. DiLuzio
Dr. Jan Van Eys
Dr. Joseph Gold
Dr. D. R. Horrobin
Dr. W. P. Leary
Dr. Linus Pauling
Dr. Ronald Pethig
Dr. J. Booyens
Dr. J. H. Foster
Dr. C. F. van der Merwe
Dr. Mille H. Wiley

HHS M. Heckler
Mr. L. Mosedale
Dr. B. Chabner
Dr. V. T. DeVita
Dr. G. A. Keyworth, II

Sen. O. G. Hatch
Sen. E. F. Hollings
Sen. C. Pell
Sen. S. Thurmond
Sen. L. Weicker

Senators on Full and Appropriations Committees on Health & Human Services

Mr. Armand Hammer
Dr. William P. Longmire
Dr. John A. Montgomery

Gov. R. W. Riley

May 24, 1991

The Honorable John H. Sununu
Chief of Staff to the President
1600 Pennsylvania Avenue
Washington, D. C. 20500

Dear Governor,

Enclosed is a letter written today to Senator Hollings and a series of letters written in haste to Senator Thurmond, Senator Hollings, Representative Arthur Ravenel, and Dr. James E. Edwards, President of the Medical University of South Carolina. These letters all deal with the distinct possibility that President George Bush's atrial fibrillation and hyperthyroidism may have been brought on by chronic magnesium deficiency which was induced by sustained high-level stress and further aggravated in the short term by greater exercise than normal. Today's letter to Fritz also brings up recent evidence of the interaction of thyroxin and Vitamin C, and the recommendation that all patients with Grave's Disease be given ascorbic acid supplements.

Sustained stress thus not only can cause decidedly increased urinary excretion of your critically needed magnesium, but also consumes our limited body supply of ascorbic acid. How much you're affected by such losses is influenced by your own biochemical individuality, but it sure seems wise to have increased levels of such critical co-factors when there are no negative side effects.

In 1983 my wife and I met George and Barbara Bush at a reception for 50 couples at the home of Dr. John Hawk around the corner from us. Barbara and her sister attended Ashley Hall in Charleston, as did Mib. The Charleston visit may have been a screen since I believe I later heard he went directly to the Caribbean and helped arrange the Grenada success. The only reason I payed $500 to attend was to meet him and briefly bring up cancer control opportunities and to pass on the enclosed letter. He expressed interest and put the letter in his coat pocket, and I got the satisfaction of trying.

I hope these letters might possibly get through to you since you too may want to read about and give consideration to the likely potential cardiovascular benefits from high oral beta-carotene.

With the hope and belief that some good may come from all this,

Frank J. Ball

Frank J. Ball

cc: Senator Ernest Hollings
Senator Strom Thurmond
Representative Arthur Ravenel
Dr. James E. Edwards
Dr. Marcus Newberry
Dr. Peter Gazes

capability prompted acute fear and my first ever letters to Congressmen (top of page 1 and pages 39-46 of "memory jogger" Two Years Trying to Aid...) These long letters to Senator Hollings which discussed mainly the Russians threat, but partially on cancer, were sent to all Congressmen and hand delivered to very many Senator's offices; and got a much greater response than expected. This week a Senator Moynihan Letter To New York on Payback Time came in which got started coming down here way back then.

Courageous executive assessment and adroit marshalling of support to solve by far the most acute problems of the past decade, were magnificently handled by Presidents Regan and Bush. Almost the whole world now benefits from their determined and sustained steps with just adequate Congressional support that solved our acute Russian Communist and Mid-East problems. It was never truer: NEVER IN THE HISTORY OF MANKIND HAS SO MUCH BEEN OWED BY SO MANY TO SO FEW.

POTENTIAL FOR REDUCTION OF BURGEONING HEALTH COSTS FROM DEGENERATIVE DISEASES IN THE ELDERLY POPULATION

The President in his State of the Union message to congress has just focused on the mind-boggling 800 billion and expected 1600 billion annual health costs; and particularly the critical need to reduce present costs and restrain rapidly rising costs.

The biggest cost and the biggest opportunity to reduce cost will likely be among the various degenerative diseases which cause such havoc and cost to the elderly population. The cost to die of cancer in the US is now astronomical and you are subjected to much unpleasant chemotherapy and radiotherapy. We elderly are also smitten with a number of other degenerative diseases such as arthritis, osteoporosis, heart attacks, strokes, diabetes, arteriosclerosis, emphysema, etc. These are generally brought on by metabolic derangements induced by aging and by deficiencies that accompany aging. Such diseases have been minimized by proper supplementation with inexpensive micronutrients.

Recent studies indicate that in most degenerative diseases a peroxidative attack on the cell membranes of the tissue involved is occuring which makes them leaky. Other essential parts of the cell are also being attacked by the excessive oxidants. High levels of various anti-oxidants which are generally low in the elderly then usually seem to be decidely beneficial.

You won't find many medical professionals in this country who believe in or even know about the effective use of the micronutrients discussed in this long letter. However, if what is presented is valid (and it seems to be) and if the clinical demonstrations were supported to the extent they deserve (based on its evident potential) then very significant reductions in private and public health costs should be achievable with a much happier elderly population. Pharmacological levels of natural supplements are low cost; and when demonstrared effective do not have to wait a decade or more for approval as is the case with drugs.

It may even be worth while for a very busy president to look over parts of the information enclosed; to make up his own mind whether certain areas discussed (some of which are just now receiving some public attention) may merit consideration for personal use by himself and his wife. Executive support, if justified, would very materially shorten the time to widespread proper use, could substantially reduce health care costs, and improve public health.

If you just briefly look over the titles of the enclosed program (behind the stressed donkey) that is being given next week in Arlington covering the health effects of pharmacological levels of vitamins and antioxedants; you can quickly appraise the state of the art and its possible relevances.

4/11/93 This is discussed on last page of James Mason letter; and a copy of the program and abstracts for your Two was given at the White House gate to Dr. Burton Lee's secretary, along with handwritten letter to president relative to story that day on Nightline and boy with spinal bifida during conference. BJB

7 Atlantic St.
Charleston, S.C. 29

(Typed copy of handwritten letter)

August 8, 1992

Dear John and Molly,

Many thanks for your August 2 letter which enclosed a copy of the New York Times July 29 story on selenium deficiency; and the much higher levels of stroke deaths for men and women that is so evident across the South. The stroke death rate is also twice in the lower half of Georgia and South Carolina compared to the upper; likely because the vital minerals selenium and magnesium have been washed from the soil and waters.

This identical presentation (New York Times Service) ran the same day in our Post & Courier and featured Dr. Curtis Hames in Georgia who I happen to know; but did not include the last paragraphs discussing Dr. Herbert Langford. I had met him several times; but did not know he had died from stroke last year. Also the Charleston paper did not include the great maps showing state death rates in all states.

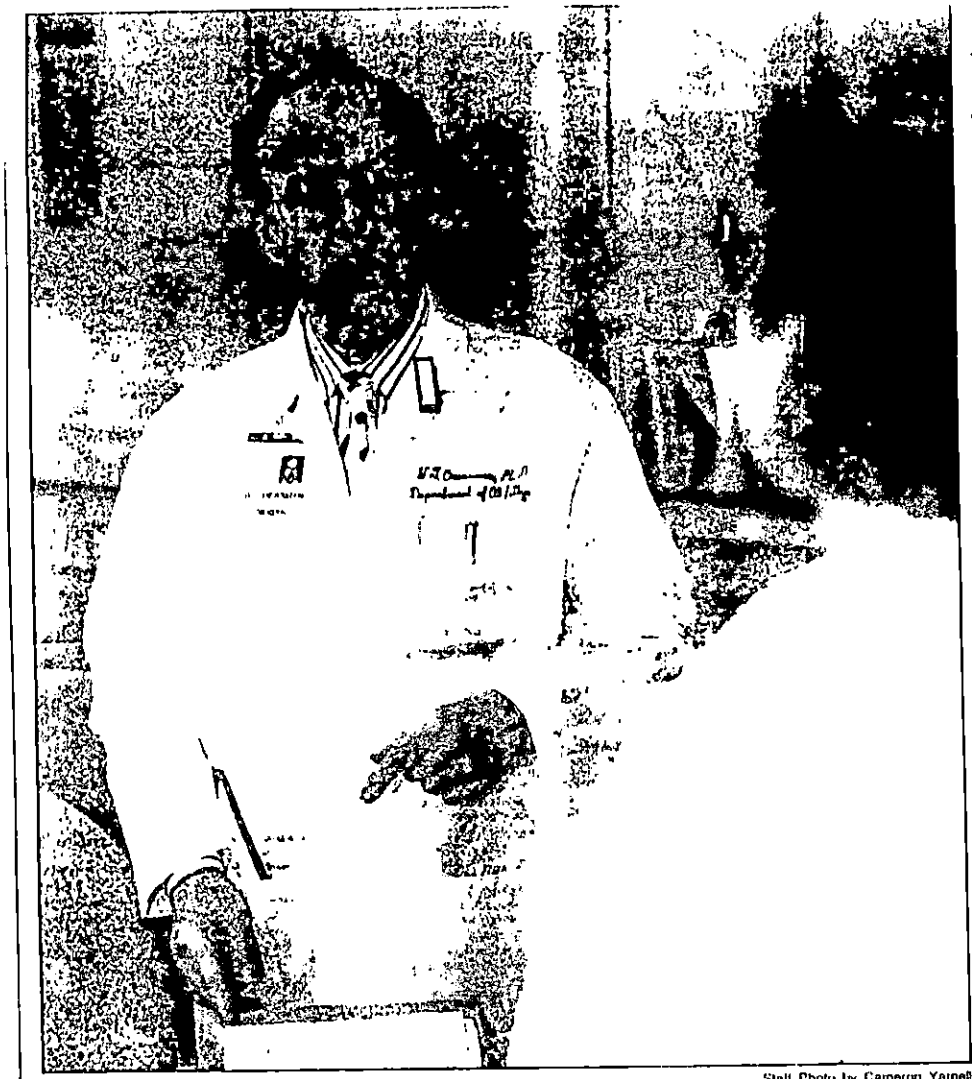
This story really brought back memories of the past decade since it was attendance after my retirement at a 1985 lecture by Dr. Herbert Langford at the Medical University on Calcium, Potassium, Sodium and Hypertension; that happened to progressively spark my later consuming interest in magnesium deficiency and the heart. After his talk I met and talked with Dr. Langford about some studies in Scotland and Japan; where low calcium markedly affected the properties of desmosome cells in the gut lining, resulting in increased colon cancer. This was his first talk at the Medical University; and we had never met. He amazingly remembered we had dated the same girl; and he wrote requesting my information as he was pushing the possible importance of low calcium on hypertension.

When digging into the medical literature on calcium and magnesium using computer searching the detriments of low magnesium seemed really important; so he was called and pertinent medical literature sent up to Dr. Langford, who was head of Endocrinology at Mississippi Medical.

The MUSC library 1963 book The Role of Magnesium in Biological Processes by J. Aikawa was copied and read. Then his 1972 The Relationship of Magnesium to Disease in Domestic Animals and in Humans and his 1982 Magnesium: Its Biological Significance were found in the library in Denver (where visited a son on fellowship) copied, read, and then Aikawa visited in Denver in early 1986. He gave me the 1980 Royal Society book, Environmental Geochemestry and Health from which I have copied page 195; which very clearly indicatres the importance of selenium which you two had stopped taking.

Dr. Curtis Hames, featured in The Times story, introduced himself to me at a 1987 Conference on Cardiovascular Epidemiology; because Dr. Peter Gazes, MUSC head of Cardiology, had sent him a copy of my thirty page 1986 letter on the serious dangers to our hearts from our chronic dietary magnesium deficiency and almost no magnesium in our water. We had a long discussion and some subsequent interchange of literature. He had won the MacArthur Award back then; and usefully pushed the real danger of selenium deficiency particularly in the South and on increased stroke death.

It was most upsetting to see about Dr. Langford's stroke death; since he and his charming wife seemed so vibrant and healthy when I last saw them at the 1990 Hypertension Conference in Jackson. He had invited Dr. Edward J. Rocella (quoted in this story) and I to supper at their home the night before the conference.



Staff Photo by Cameron Yarnell

Charleston oncologist Dr. William Creasman talks with a nurse recently at MUSC.

Local physician on front lines in cancer research

■ TAXOL ON WAY: Dr. William T. Creasman's research efforts have brought about the federal approval of the cancer-fighting drug taxol, which will be available this week.

By LYNNE LANGLEY
Of The Post and Courier staff

If not for Charleston oncologist Dr. William T. Creasman, the new cancer-fighting drug taxol might still be confined to laboratories and a few research centers. Instead, the drug will begin flowing to doctors and patients this week.

In record time, the federal government approved the use of taxol based in large part on research by Creasman and a medical group he founded.

Studies by Creasman and the Gynecologic Oncology Group have revolutionized the treatment of endometrial and vulvar cancer. Less-deforming operations helped as many women as radical surgery. Medicine gained a new understanding of the disease process.

His studies paved the way for endometrial cancer patients to take once-feared hormones, which can relieve menopausal symptoms and prevent osteoporosis and heart disease, he said.

The professor and chairman of the Medical University of South Carolina Department of Obstetrics and Gynecology credits the work of the entire group rather than his own. Some studies have made major contributions and others will have a major impact, he said.

"You are happy to see something you do come to fruition. You do not hit a home run every time. It is nice to think about (the successes), but you do not dwell on them. You go forward."

And he has.

He helped plan and develop the comprehensive cancer center at Duke University and is helping to found the Hollings Oncology Center at MUSC. He has written 240 published scientific papers, 13 book chapters, six abstracts and 10 audio-visual productions.

He has served as a chairman or officer in a long list of medical and scientific organizations and has addressed or moderated international gynecologic cancer meetings all over the globe.

His list of awards and honors fills two pages and includes recognition as one of this country's best physicians by magazines such as Town and Country and Good Housekeeping, as well as books such as the 1992 volume, "The Best Doctors in America."

Born in Miami, Ariz., Creasman graduated from Baylor University College of Medicine in 1960. He became interested in gynecologic oncology, all the cancers of the female pelvis, and specifically surgery during his residency at the University of Rochester Medical Center.

In those days, less than 1 percent of residents pursued a fellowship. He tackled a series of fellowships and advanced study at Rochester and later at the University of Texas M.D. Anderson Hospital and Tumor Institute in Houston.

His wife and two children took it in stride, he said with a smile. "There was a running joke around our house: 'What's one more year?'"

He returned to Rochester to teach in 1966, then to the tumor institute to teach surgery.

In 1970, he became director of gynecologic oncology at Duke University Medical Center, served as full professor and ran the gynecologic oncology division.

He could have spent his career there, he said. Then with a smile he added, "I need a new challenge now and then."

He looked at medical centers around the country and in 1986 chose MUSC, he said, because he liked Charleston and prospects at MUSC.

"I saw the potential for this place to take off. In the last four years, it has been exponential.

"Being on the ground floor of two cancer centers has been exciting. It's also been fun."

Please see DOCTOR, Page 4-B

Taxol offers promise in cancer battle

By LYNNE LANGLEY
Of The Post and Courier staff

Taxol expert Dr. William T. Creasman is looking for more answers.

"Everyone has jumped on taxol as the silver bullet," the Medical University of South Carolina professor said.

"In the last 20 years, platin was the most exciting cancer drug we had. At this point, taxol is equivalent to platin. Whether or not it will work out in the end awaits studies. It may very well be an extremely important drug, but the data is preliminary."

Studies he conducted at MUSC showed taxol markedly shrank tumors in one-third of ovarian cancer patients. That is very good, he said, considering none of those patients was improving on platin.

Most women are or become resistant to platin and no chemotherapy had been found to help them, he said.

Taxol is not a cure but does give a patient more time, he said. The drug is expensive and has side effects, including possible heart and bone marrow problems, he added.

"Ovarian cancer has been called

Please see TAXOL, Page 4-B

State agency workers earn

North Area police seek

DOCTOR

from Page 1-B

Creasman helped Duke plan for and gain the coveted National Cancer Institute designation as a comprehensive cancer center, one of 28 in the nation. Now he serves on the steering committee as MUSC seeks that designation for the Hollings Oncology Center.

MUSC's bid only can be helped by his taxol research and membership in the Gynecologic Oncology Group he helped found 20 years ago, he is convinced. The studies here prove MUSC is on the cutting edge of cancer work, he said. "It shows we have a track record. That is extremely important."

The group, sponsored by NCI, now has accepted about three dozen institutions, including Duke and recently MUSC.

A single center might need eight or 10 years to complete a study, but a cooperative group like GOG helps institutions work together and gain information much more quickly, he said. That means a new drug might be available years sooner or a new surgical treatment tested and accepted much faster, he said.

The GOG taxol studies on ovarian cancer, in which he takes part, played a key role in the U.S. Food and Drug Administration's approving and releasing the drug so quickly for treatment of resistant ovarian cancer, he said.

"The group has made a major, major impact on the way we treat gynecologic cancers. Therapies have been changed considerably.

"For me, the advantage of belonging to the group is I have access to drugs that are not otherwise available," he said, adding that only NCI has supplied taxol until now. "That puts us on the cutting edge. It allows us to do things we could not do otherwise."

Lowcountry patients benefit by receiving medicine and treatment offered only at a few places in the country, he pointed out.

"Some people might say, 'You are experimenting.' But it gets us further along the information curve. That is why we are as far along with taxol, because of the GOG studies. Hopefully, the patients of tomorrow will benefit from the patients of today."

TAXOL

from Page 1-B

the silent cancer." Creasman said of 20,000 to 21,000 cases diagnosed in this country each year.

Because symptoms such as indigestion and pelvic pressure are subtle, most cases are not diagnosed until they are very advanced, he said. That means the cure rate is very low and up to three-quarters of patients die, he said.

Taxol also may fight other types of cancer, Creasman noted. MUSC is studying taxol in endometrial cancer, breast cancer and solid tumors, he said.

So far, studies have shown taxol only effective against resistant ovarian cancer, cancer that has not responded to state-of-the-art drugs such as platin and its compounds, he said.

In four to six weeks, Creasman hopes to know whether taxol will help newly diagnosed ovarian cancer patients as a "first-line treatment."

First-line treatment now is not justified, he said, because of toxicity, thus side effects, expense and potentially limited supplies.

The average cost of a cycle of taxol is $695.25, according to Bernie Mogelever, spokesman for taxol manufacturer Bristol-Myers Squibb Co. He had no figures for a course of treatment, but doctors have estimated it might run $24,000 to $36,000.

Taxol will be available to physicians in Charleston and across the country by Tuesday, Mogelever said. There is and will continue to be enough taxol to meet the demand of patients and clinical studies such as Creasman is conducting, Mogelever added.

In the 1960s, the National Cancer Institute first tested a crude extract from the bark of the relatively rare Pacific yew tree and saw anti-cancer activity in the test tube. "It has a unique mechanism of action, completely different from any we had seen," Creasman said.

The extract was tremendously toxic and in short supply, he said. Phase 1 studies in humans, which usually demand 12 to 18 months, instead took 10 years.

NCI began Phase 2 research on specific cancers in the late 1980s. The studies, including Creasman's work at MUSC, tested only cancer patients who had failed on other treatments. The studies, completed in late 1991, showed the drug particularly promising in ovarian cancer, with a 30 percent to 35 percent success rate in resistant cancer.

Creasman then began a Phase 3 study of newly diagnosed patients. NCI, the sole source of taxol at the time, authorized the study by Creasman and other institutions belonging to Gynecologic Oncology Group, which he helped found.

Results from MUSC and the other centers went to GOG where a computer is analyzing the data and running quality control checks. Results will be announced when GOG meets early next month, he expects.

Last spring, he began a study to compare the success of taxol with other drugs in newly diagnosed ovarian cancer patients, he said. The first 150 of 600 expected patients are being treated with various combinations of drugs including platin, its compounds and taxol.

Answers from one study form questions for the next one, a process Creasman calls leap-frogging.

He also is looking at taxol dose. Higher doses affect bone marrow, he said, but molecular technology has provided a new drug that stimulates bone marrow and could help fight that side effect. A double dose of taxol appears more promising than anything yet seen, he said.

"We have not found the magic bullet (for gynecologic cancers). But taxol is one step along the way."

4 Atlantic Street
Charleston, S. C. 29401
February 4, 1983

Dr. Jan Van Eys, Chairman
Department of Pediatrics
M. D. Anderson Hospital and Tumor Institute at Houston
The University of Texas
Houston, Texas 77030

Dear Dr. Van Eys:

I very much appreciated the opportunity in December to talk with you in Houston about aspects of your 1982 publication Tumor-Host Competition for Nutrients and the timely 1982 book, Molecular Interrelations of Nutrition and Cancer that you co-edited. Your comment in the preface that thirty years had elapsed since one of these annual M. D. Anderson Symposiums on Fundamental Cancer Research had earlier focused on Nutritional Factors in Cancer Research seemed quite germane.

Our discussion, which was shortened by needs relating to the tragic shooting at M. D. Anderson, briefly covered a series of topics involved with nutrition and cancer. It seemed worthwhile to emphasize some of these in more detail, since better understanding may increase the potential for earlier broad acceptance. Since my spare time scientific interests over the past five years have been deeply involved in the metabolic interactions of ascorbic acid, hydrazine sulfate, or gamma-linolenic acid with human cancer, rheumatoid arthritis or diabetes our discussion with reference to your book and paper touched on these interrelationships as covered below.

The Effect of Dietary Vitamin C Levels on Carcinogenesis

The increasingly informed acceptance that Vitamin C, particularly from uncooked vegetables and by direct supplementation, may have been of major importance in the progressive four fold drop over the past fifity years in the death rate of the earlier worst cancer killer (stomach) seems most encouraging. There has been a steady drop in the death rate for men from stomach cancer, which in 1930 was about twice that of the next worst cancer killer (colon and rectum), and is now almost one-third of colon and rectum cancer, even though there has been no drop since 1930 in the high case fatality rate if stomach cancer occurs. Deaths from colon and rectal cancer in men and women rose steadily and substantially from 1930-45, then remained about the same for men, but have dropped steadily by about one fourth for women since 1945.

It was thus most encouraging to see the enclosed couple of pages of comments from the chapter, The Influence of Nutrition on the Development of Cancer Immunity and Resistance to Mesenchymal Diseases, by Dr. Robert A. Good (Research Director of Memorial Sloan-Kettering Cancer Center) making the case, that stomach cancer has likely been dramatically reduced by increasing levels of dietary Vitamin C and possibly Vitamin E. Cancer forming nitrosoamines, which result from microbial conversion of dietary nitrite constituents may be scavenged by Vitamin C in the diet, as postulated by J. H. Weisburger et al in 1977. Robert Good's recommendation that Vitamin C trials, alone or combined with Vitamin E, be conducted in China and elsewhere in the Far East where stomach cancer is still the number one killer (about ten times our present stomach cancer rate); and where oesophageal cancer may be their second cancer killer thus seems most appropriate. His favorable comments were also noted on the potential prophylatic importance of W. R. Bruce's findings that the mutagenic nitrosamines were present in the feces and colon contents of about 40% of the persons tested on the usual American or Canadian diet; and the indicated ability of Vitamin C to completely eliminate these nitrosamines from the gut contents and feces if larger amounts of Vitamin C (400-1000 mg/day) are taken. W. R. Bruce's chapter, On Early Measures of the Effects of Diet Change with Relation to Cancer Incidence indicated a number of provocative approaches he is employing to clarify in a short time the effect of fecal mutagens on colon cancer formation and the effects of intervention with Vitamin C and Vitamin E on this development. His studies following the appearance of colonic polyps reminds me of Dr. J. U. Schlegel's studies of the development of bladder polyps and their control with oral Vitamin C.

malignancies, and spontaneous malignancies. Dietary restriction, however, must be understood in fundamental molecular, cellular, endocrinological, or immunological perspective if these dramatic experimental observations are to be translated to practical application in man. Already, progress is being made in this direction.

Dietary manipulations that of themselves may be useful in addressing cancer are those in which a nutriment or dietary constituent may be added to the diet. One example is vitamin C. Vitamin C administration may provide a powerful approach to cancers of the gastrointestinal tract. Before the mid-1930s, stomach cancer was the most frequent cause of death from cancer in the U.S. Almost miraculously, in the mid-30s stomach cancer began to decline in frequency in the U.S., until, at present, it represents a cancer of relatively low frequency. When it occurs, however, it is still a highly lethal cancer, having essentially the same case fatality rate that it did in the early 1940s.

The dramatic decrease in deaths from this form of cancer and the increase in deaths from lung cancer represent the most dramatic change to occur in cancer incidence in modern medical history. There is little question that, if cigarette smoking could be stopped, most cases of lung cancer would gradually disappear. However, in spite of solid knowledge concerning the etiological role of cigarette smoking in pathogenesis of lung cancer, little progress has been made in decreasing the carcinogenic habit—the smoking of cigarettes. This would involve deprivation of something considered desirable by some, and it is not occurring, at least for the population in general.

In contradistinction to that pertaining for lung cancer is the situation with respect to stomach cancer. The case can be made that stomach cancer has been dramatically influenced by a dietary additive, vitamin C. The decline of stomach cancer in the U.S. began about 10–15 years following the advent of universal refrigeration and the introduction of widespread refrigerated shipping of food. These changes made possible the present American diet, which puts fresh fruits and vegetables on most American tables at almost every meal. This dietary change, coupled with promulgation of widespread use of vitamin C as a routine for children by pediatricians and general practitioners, may have led to the decline of stomach cancer.

By inhibiting the formation of nitrosamines high in the gastrointestinal tract, vitamin C may have led to the prevention of stomach cancer (Weisburger et al. 1977). This postulate can and should be tested in controlled studies in China and other areas of the Far East where stomach cancer is still rampant. In the Far East and in China in particular, stomach cancer continues to be the number one killing cancer. Further, over all of China the number 2 or number 3 killing cancer is esophageal cancer. Here too, formation of nitrosamines from dietary constituents by microbial catalysis of nitrosamine formation may be the crucial pathogenetic mechanism (Hsia et al. 1981). Administration of vitamin C alone or together with vitamin E to prevent this critical nitrosation and thus the formation of chemical carcinogens seems one reasonable approach to inhibition of both esophageal and stomach cancers. Surely this very safe and inexpensive nutriment, often in short supply in the regular diet in Eastern countries, could be tried as prophylaxis against one or two of the most common cancers in the world. Hopefully, if this approach is taken, the attempt at prophylaxis will be made in the form of a properly controlled clinical trial.

Recent studies by W. R. Bruce in Toronto have generated another set of observations (Bruce et al. 1977) that might be translated into an effective prophylactic approach to the most common cancer in America—colon cancer. Bruce discovered that feces and colon contents of persons on the usual American (or Canadian) diet frequently contain a somewhat labile N-nitroso compound—a nitrosamine—that he has shown to be mutagenic. This substance can be completely eliminated from the gut contents and feces if larger amounts of vitamin C (400–1000 mg/day) are taken as part of the diet. Vitamin E supplementation is also effective in inhibiting formation of this potential carcinogen. It is thought that, as oxidizing agents in sufficiently large amounts, these substances can inhibit the formation of the potential carcinogen that is usually produced by action of the microbial flora. If this is the case, prevention of polyp formation, abnormal differentiation of the gut epithelium, and cancer formation should follow appropriate nutritional therapy.

Perhaps trials to prevent cancer by these nutritional manipulations could be carried out in families with high frequencies of colon cancer. Alternatively, patients with primary immunodeficiencies who have high frequencies of cancer of the upper as well as lower GI tract and in whom action of microorganisms might be pathogenetically important, or even patients who have been subjected to partial or complete gastrectomy or vagal nerve operations for treatment of peptic ulcers, would be good subjects. GI cancers occur in very high frequency in these populations. Thus, it can be reasoned that sound dietary approaches to inhibition of cancers may be developed and that this line of inquiry can generate much important information in approaching several cancers of high frequency in different parts of the world.

NUTRITION AND IMMUNITY

The relation of immunity to nutritional state has received much attention in recent years. Indeed, considerable concern has focused on the immunodeficiencies associated with the protein-calorie (PC) malnutrition syndrome, which is widely distributed over the world (Kulapongs et al. 1977). In most settings, protein and PC malnutrition have regularly been associated with profound defects of cell-mediated immunities. By contrast, hyperglobulinemia and hypergammaglobulinemia, quite regularly found in these syndromes in most areas, have been taken as evidence of a relative sparing of humoral immunity during protein and PC malnutrition. The analysis of the influence of individual nutriments and of protein or PC malnutrition per se on immunological functions from studies of these syndromes under field conditions has been hampered by the

He had noted that urine can glow in the dark, and this glow ceases when a person takes Vitamin C. Since he thought such irradiation might be a factor in causing bladder cancer, he checked the effect of sustained oral Vitamin C on the bladder wall and found a significant reduction in bladder polyp formation and even a reduction in existing polyps which in time tend to become malignant. The paper covering that work significantly influenced Dr. Ewan Cameron's decision to try high (10 g/day) oral levels of Vitamin C on terminal cancer patients in Glasgow, Scotland, beginning in 1972. Indication of this unique restorative capability of Vitamin C was also well brought out in the chapter, Inhibition of Transformation and Oncogenic Progression by Ascorbic Acid: A Possible Role in Chemoprevention, by W. R. Benedict and P. A. Jones. Cell lines that would transform to cancerous form when treated with carginogens did not do so when exposed to Vitamin C up to three weeks later. Cell lines that had already been transformed by the action of carcinogens could be irreversibly transformed back to normal type cells by Vitamin C exposure unless the transformed cells had gone through additonal passages.

"Reversibility of Cancer:" Gamma-Linolenic Acid Deficiency-Dependence of Cancer Cells

We got to discuss only very briefly the three enclosed October publications that I had just received supporting the apparent validity of Dr. David R. Horrobin's detailed 1980 predictions on the use of gamma-linolenic acid in cancer control, which seem to be of true breakthrough importance with regard to the specificity of cancer cell growth control, the lack of effect on normal cells and the potential practical clinical significance. In vitro experiments from three different medical schools in South Africa clearly demonstrated that gamma-linolenic acid supplemention at 1 to 60 parts per million in the growth medium of a mouse melanoma cell line, a human oesophageal carcinoma cell line, and a human liver carcinoma cell line progressively and dramatically reduced cancer cell growth and changed morphological features of these malignant cells while having no effect on the similar normal cell lines.

The enclosed brilliant 1980 paper by Dr. Horrobin marshalled the literature data and its significance, which indicated that transformed cells and malignant cells appear to have largely lost their delta-6-desaturase enzymatic capability. This enzyme normally converts the usual abundant linoleic acid to low levels of gamma-linolenic acid which is taken up by cells and then converted as needed to the "1" series of prostaglandins (cellular hormones). He thus postulated in detail why this specific deficiency could be a fundamental factor in malignancy; and why replacement of gamma-linolenic acid might reverse the malignant trend.

The critically designed in vitro experiments of the South Africans now appear to have clearly demonstrated that low levels of gamma-linolenic acid (1-60 mg/liter in the growth medium, and we have about five liters of blood): 1) reduced the growth rate of a cultured human hepatoma (liver carcinoma) cell line by up to 87% compared to the untreated hepatoma control over a period of four days, 2) induced over a period of seven days pronounced morphological changes in a human oesophageal carcinoma cell line which culminated in cell death, and 3) achieved excellent replication and confirmation of gamma-linolenic efficacy (including up to 70% reduction in growth rate) in 156 separate cultures of a mouse melanoma cell line assessing cell viability, proliferation, and rates of DNA and protein synthesis using radioactive thymidine and methionine. No effect of gamma-linolenic acid was noted on the normal cell lines, and would not have been expected since it should already be produced in adequate quantities.

Duplicated below are the two perceptive and presicent paragraphs on cancer in Dr. Horrobin's 1979 MEDICAL HYPOTHESES publication, The Regulation of Prostaglandin E1 Formation: A Candidate for One of the Fundamental Mechanisms Involved in the Actions of Vitamin C. This was expanded a year later into his 18 page MEDICAL HYPOTHESES paper, The Reversibility of Cancer: The Relevance of Cyclic AMP, Calcium, Essential Fatty Acids, and Prostaglandin E1; which prompted the South African studies:

CANCER

The relationship between vitamin C and cancer is of major scientific and public interest and has recently been the subject of a major review (43). Early descriptions of scurvy suggest that, contrary to what might have been expected, there is enhanced cell proliferation with lack of the normal lines of demarcation between organs. Not mentioned in the review was the relationship between vitamin C deficiency and Sjögren's syndrome (44). This is a notorious example of a situation where the lymphocyte proliferation in the salivary or other glands is often extremely difficult to distinguish from malignant change. For example the latest edition of Harrison's Principles of Internal Medicine states of those with Sjögren's syndrome: "These patients are considered to have a disorder falling between neoplasia and hyperplasia which is diagnosed as pseudolymphoma" (54).

The roles of vitamin C deficiency in the development of cancer and of high vitamin C intake in the treatment of cancer (43,55,56) are subjects of major controversy. However the case for an adequate trial of such a non-toxic substance is very strong. The concept that vitamin C enhances PGE1 formation strengthens this case in two major ways. First there is strong evidence that the mechanisms whereby the immune system may naturally eliminate cancer are dependent on effective T lymphocyte function. PGE1 activates T lymphocytes. Second it has recently been demonstrated that a number of transformed cell lines lose the ability to convert linoleic acid to gammalinolenic acid (35,36). Loss of this enzyme may be a marker of malignant change. One consequence of it is that cancer cells are unable to make their own GLA, DGLA or PGE1 because they cannot utilise precursor linoleic acid. The significance of this observation is only beginning to be explored but the possibility that it is related to defective GAG formation and excess proliferation is a real one. High vitamin C levels would be expected to counteract the defect, partly by enabling cancer cells to make the best of any residual DGLA available to them and possibly also by enabling non-cancer tissues to increase their formation of PGE1 which might possibly regulate cancer growth. At present it must be stressed that these are no more than plausible possibilities.

Personal Exposure to Interaction of Gamma-Linolenic Acid, Vitamin C, Arthritis and Cancer

Since early 1978, except for most of 1980 when I was incapacitated with rheumatoid arthritis, much of my spare time has been spent in very directed medical library reading using computer searching as necessary in an attempt to better understand and present natural metabolic generation and control of human cancer, with particular emphasis on the beneficial interactions of Vitamins C and B_1, hydrazine sulfate, radiofrequency hyperthermia, and gamma-linolenic acid as present in evening primrose oil. Early efforts were aimed at hopefully helping Dr. Ewan Cameron broaden his understanding of the metabolic aspects involved in his relatively successful clinical studies employing a 10g/day dosage of oral Vitamin C on about 500 terminal cancer patients per year at the District General Hospital outside of Glasgow, Scotland. Quite extensive personal attention was also directed at trying to promote NCI support of the very innovative and practical contributions evidenced in Doctors Ewan Cameron's and Linus Pauling's use of Vitamin C for cancer control, Dr. Joseph Gold's successful use of hydrazine sulfate to control the devastating weight loss (cachexia) of cancer, and Dr. Harry H. LeVeen's successful development of both equipment and clinical techniques to kill deep tumors by using radiofrequency hyperthermia without damage to normal tissue. While these efforts substantially expanded the knowledge and interest of some important legislative and executive persons in these fields, almost complete lack of NCI support continues. Dr. Pauling did finally arrange to get some support of animal studies using Vitamin C on his seventh grant request, and arranged for some NCI support of limited clinical trials on Vitamin C at Mayo.

My rheumatoid arthritis seems to have been controlled with no deleterious side effects for two and a half years by two to three grams of evening primrose oil containing about 8% gamma-linolenic acid (150-250 mg) and two to four grams of Vitamin C per day as discussed in last weeks letter to Dr. Carlton Hazelwood at Baylor Medical. I also knew a number of people in Charleston and elsewhere who have been taking this oil, (now available in General Nutrition Corporation stores in most shopping malls) in combination with Vitamin C for various types of arthritic pain, emphysema, multiple sclerosis, etc., with evident palliation in most instances and with no observable detrimental effects over the last year and a half. The risk as I understood it to cancer victims who were taking very high levels of Vitamin C to improve their quality of life seemed right low compared to possible benefit, if they also wanted to try some of this vegetable oil.

Combined Oral Use of Vitamin C and Oral Primrose Oil (Gamma-Linolenic Acid) on Human Cancer

Over the past three years I have been approached by intimate friends who had relatives or friends with cancer; and who were familiar with my active reading on cancer and Vitamin C. Several cancer victims have also called me from out of state. When it seemed propitious, I would suggest that they buy the Ewan Cameron-Linus Pauling book, Cancer and Vitamin C; which is still available along with H. L. Newbold's supporting book, Vitamin C Against Cancer in paperback form on shopping mall bookshelves. If that interested them, I suggested progressively increasing their Vitamin C to as high a level as feasible, as determined by the apparent tendency to get diarrhea at just above the necessary levels to substantially increase blood ascorbic acid. In the past eighteen months because of my familiarity and experience with gamma-linolenic acid, I have also suggested to some who had observed a benefit from Vitamin C that they might find a possible additional benefit from progressively taking from 1 to 8 evening primrose oil capsules since I had taken these levels. There has thus developed a small amount of anecdotal experience when taking this combination which may interest you, even though I have not even seen most of the individuals involved. As far as I know all these cancer patients continued their treatments, if they were being given any treatment at that stage. This I very much favored even though I personally felt in some cases it might be detrimental.

In October I happened to have written a letter to an out of state cousin prompted by a long phone conversation from her. A typed copy of this handwritten letter is enclosed as it discusses some anecdotal experience with Vitamin C and evening primrose oil. While I presume this combination is probably being tried by cancer patients somewhere else in this country and abroad; I have not seen, read, or heard anything about it. As is perhaps normal in cancer, there have been some significant patient changes in the three and half months since the October letter and one of those five have died as discussed below.

The 65-70 year old mother whose inflammatory breast cancer had seemed to be in remission had seizures in November; and a CAT Scan indicated metastasis to the brain. She was thus given radiation treatments of the brain and did not have any "C" or evening primrose for probably six weeks. It turned out she had earlier taken her "C" down to half or less because she was doing fine and it was salty in the water. It seems dangerous to take the "C" level down and metastases should be harder to control. I understand her breast became inflamed and black and blue again during the six weeks period. Growth problems were also noted in the other breast; and a double mastectomy was recommended but not taken. Early in January she progressively took her "C" back up to the 20's and progessively quadrupled the actual 1-2 capsules per day of evening primrose oil she had been taking for the previous year to 7-8 now. I am told that both breasts now look normal; and she is now walking over a mile a day. A surgeon I know who happend to have examined her breast at the beginning when it was inoperable; and then perhaps six months later when it had returned to normal appearance told me at that time that he believed her cancer had earlier been misdiagnosed; since he had never known or heard of an inflammatory breast cancer remission.

The 80 year old man with pancreatic cancer on Long Island continued to take the powdered "C" in juice, continued living alone without pain, and was visited off and on by his grandson who lived near. He would not take the capsules of evening primrose oil or hydrazine sulfate (at my suggestion they got him to rub some of the oil on his hands and knees); and he died "peacefully" in mid December at home without pain; but extremely thin.

The Mother Superior Emeritus according to her brother-in-law last week continues to do very well on the same dosages of "C" and evening primrose oil.

Over this period the partially paralyzed scientist in Alabama increased his level of crystalline sodium ascorbate-ascorbic acid to 35 g per day which is the highest with which I have been involved. This was giving him some edema and he has ordered and will try calcium ascorbate. He sounds in good spirits at home; but his recent paralysis continues with no return of feeling; and he planned to increase the 4 capsules of evening primrose to 6 or possibly more.

4 Atlantic Street
Charleston, S. C. 29401
October 24, 1982

(Typed copy of handwritten letter)

Dear Charlotte,

In trying to handle cancer, I feel present evidence indicates it's a smart move to immediately take Vitamin C beginning at 2 grams and progressively increase at 2g per day to as high as you can. If one gets into loose bowel problems, drop back for a day or so and then keep trying to move up. Depending upon your need, you may have to stop at 15, 20, 25, 30 or more grams (1000 mg) per day. Hold at that; but check periodically to see if you need more, and don't go back down unless loosening of the bowels indicates a need to move lower.

Vitamin C is normally present at 10 mg/liter in the blood serum; but high oral levels of "C" can force this up several fold. The Vitamin C in your white cells is concentrated about 40-80 times the level in the blood serum. When we have cancer the level of "C" in the blood goes way down, finally to levels close to scurvy, which is close to zero in the blood serum. Vital organs and white cells hang on to Vitamin C, but at much lower than normal levels. It isn't realized, but cancer tissue can be composed of 5-85% of incompetent white cells (mainly the large macrophages), which are trying to control the cancer; but which are not effective at too low levels of ascorbic acid. Dr. Ewan Cameron, in his studies in Scotland, showed it is possible to overload the body with dying cancer tissue, if one starts at 10g "C" per day, but found no problem if he started at 2g and increased progressively at 1-2g per day.

Ascorbic acid ("C") at physiologically feasible levels has also been shown to cause cancer cells to revert back (transform) in test tube studies. This depended on the ascorbic level and probably also the extent to which the cancer cell had become glycolytic (producing latic acid vs. carbon dioxide) since more advanced cancer cells did not revert back.

Biostatistics seem to indicate little, if any, long-term benefit of the various chemotherapies on tumors. On about 15% of cancers (childhood leukemia, Hodgkin's disease) and similar white cell diseases, such as Burkitt's lymphoma (mostly in South Africa) and in testicular cancer one can get fair efficacy with chemotherapy. The chemotherapy kills back the cancer and other dividing cells, so doctors prescribe it, and patients want it; but it plays hobbs with the body's immune system.

I have seen various people take Vitamin C in combination with chemotherapy and apparently do much better than expected. Dr. Ewan Cameron, who is responsible for this Vitamin C development, has kept the level constant at 10g Vitamin C/day to get more reproducible and acceptable data. For the about 500 terminal cancer patients per year he treats in a District General Hospital outside of Glasgow, Scotland, he says all cancer patients benefit in the quality of life; and a fortunate few undergo dramatic recovery.

Recent studies on rats in Japan indicate ascorbic acid prevents the very detrimental killing of heart muscle cells by the most widely used cancer drug, Adriamyacin. The Japanese were beginning to conduct clinical studies on this potential.

A mother of a friend had inflammatory breast cancer with swollen nodes above and below the shoulder, black and blue arm, and couldn't close her hand, showed cancer cells in the breast on diagnosis (that wound wouldn't heal) and the cancer was diagnosed as inoperable. Her medical son up

North requested she be given only low levels of chemotherapy, since this form of breast cancer goes quickly to termination. On her own she went up progressively to 25g "C" per day, and took Evening Primrose Oil at, I believe, 2g (4 capsules) per day. This was sodium ascorbate-ascorbic acid fine crystals from Bronson's Pharmaceuticals, La Canada, California (about $20 per 1000g, 2.2 lb). When a teaspoon of this (4g, heaping 8g) is dissolved in orange juice you can hardly tell it. When she went up to 25g of "C" her wound progressively healed, the black and blue left her arm, she could then use hand and arm, the nodes went down, and the breast apparently went from hard, hot, inverted nipple, etc. to, I heard, fairly normal. It's a year later and she walks four miles a day with her husband, continues the ascorbic, and wasn't interested in the mastectomy, when she improved sufficiently for them to recommend it.

I hear from the son of an 80-year old fellow on Long Island, who has cancer of the pancreas (with a bypass operation last year to reduce jaundice). He has been taking 10-15g of calcium ascorbate from Bronson's ($15 per lb.) which his son got for him when he got worse about six months ago. He briefly tried sodium ascorbate-ascorbic acid; but had some swelling in his legs (probably from water retention) and I suggested the calcium form, which he has stayed with, has felt much better and has been free of pain during this time, while staying by himself at home. He hasn't yet taken Evening Primrose Oil or the hydrazine sulfate, that his son in Albany bought for him. A Mother Superior Emeritus (sister-in-law of the son) who had earlier been operated on for cancer of the intestines, and recently had CAT Scan indication of liver cancer, decided to take 15g of "C" and 2g (4 capsules) of Evening Primrose Oil. She continues to do very well, and is really delighted to have also gotten rid of severe arthritis, particularly in the hands and feet. The son told me when they operated on the liver, they found no cancer.

I talked today with a scientist at NASA, in Alabama, who has now controlled bone cancer pain for three years with about 25g of "C" a day. He took it at a gram an hour all day at the beginning to minimize the pain. He became paralyzed from the waist down recently and is bedridden at home and it turns out he had lowered his "C" to half some time back. He has been taking 4g of Evening Primrose for the past month and thinks he's having some feeling coming back now in his legs. The wife of another friend who was operated on the second time for brain cancer and had irradiation earlier this year is now taking 20g of "C"; and I hope she will begin Evening Primrose. Adequate Vitamin C seems to improve the quality of life, minimize expense, and you may be really lucky. It seems metabolically sound why it should work.

Best of luck to your friend,

Cappy

P.S.
This ended up long and rambling, but when someone considers supplemental or alternate therapy, and he must make the decision on his own, he needs information. The doctors can't support such unexpected therapy, and don't yet understand why they should. This letter is called "anecdotal" and doesn't involve any doctor's information. I'm seeing and hearing about more and more that seems very provocative; and it fits what I metabolically expect from my literature reading on ascorbic acid, hydrazine sulfate, cancer hyperthermia, and B-1,3 glucan. The middle two of those were on the American Cancer Society's quack list (unproven methods) until the past couple of years. I just heard last week that the American Cancer Society finally has come around and is finally going to support the work on hydrazine sulfate at UCLA Medical that came through successfully on a double blind trial.

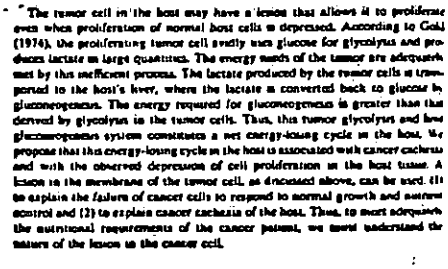
The friend's wife who had been operated on the second time for brain cancer, had been irradiated, and was then taking 20 g of "C" did start taking evening primrose oil at 2 capsules and raised it to 4 and now 6 capsules. She had lost thirty pounds and a week or so ago indicated she had gained five pounds, but told me on the phone today her doctor had just determined her weight had stabilized.

An additional friend who had prostate cancer with testicular removal and metastasized to the bone has worked up to 16 g of "C" over the past six weeks and has progressively increased the evening primrose oil from 2 to 4 to 6 capsules a day. He also takes a super B complex, 800 I.U. units of Vitamin E, and 10,000 units of Vitamin A. He is the first to have mentioned outside that he was also taking such unorthodox treatment at my suggestion, and a couple of his business acquaintances told me at a party this week that I better take out malpractice insurance, but that he looked better.

Hydrazine Sulfate and Human Cancer

An earlier anecdotal instance involved Vitamin C, evening primrose, and hydrazine sulfate and was that of an 82 year old man in Toledo who had had jaundice in the eyes, pain and debilitation, and had been opened and closed with the diagnosis of pancreatic cancer. He had phoned a distant surgeon, who had suggested he contact me; and I talked with him a dozen or more times over the five months until he died. He had immediately started the "C" and slowly took it up to 24 g, had gained some weight and felt better, then built up to 4 capsules of evening primrose and felt substantially better and more energtic so that he and his wife took trips and went to their vacation cabin in Canada. At some time (possibly halfway) he took the hydrazine sulfate at the levels recommended by Dr. Gold and felt this gave him still more stamina and the last I heard from him he had gained a total of fifteen pounds from his low point, and was still taking morning swims in Lake Erie. According to his wife he got progressively and very rapidly weaker over a period of one to two weeks and died I believe at home. She indicated over the phone that he had appreciated the improvement in stamina, etc., but what really mattered had been the ability to stop his pain. She also mentioned that in retrospect that his final rapid decline seemed to have coincided with his stopping the hydrazine sulfate. The data on page 577 in my 1982 copy of Cancer - Principles and Practice of Oncology indicates to me that when cancer of the pancreas is just opened and closed only about two percent get beyond six months. Since he seemed to be benefitting from 4 capsules of evening primrose oil per day and medical studies on scleroderma using 4, 8 and 12 capsules indicated progressive marked improvement; then higher levels might have helped him more also. I presume the hydrazine sulfate was a major factor in his weight retention.

The significance of Dr. Joseph Gold's widely accepted hypothesis that clarified the causes of the devastating weight loss of cancer are highlighted below in the last paragraph of George M. Padilla and Ivan L. Cameron's chapter, Nutrient Control of Proliferation in Normal and Tumor Cell Populations from your book.



"The tumor cell in the host may have a lesion that allows it to proliferate even when proliferation of normal host cells is depressed. According to Gold (1974), the proliferating tumor cell avidly uses glucose for glycolysis and produces lactate in large quantities. The energy needs of the tumor are adequately met by this inefficient process. The lactate produced by the tumor cells is transported to the host's liver, where the lactate is converted back to glucose by gluconeogenesis. The energy required for gluconeogenesis is greater than that derived by glycolysis in the tumor cells. Thus, this tumor glycolysis and host gluconeogenesis system constitutes a net energy-losing cycle in the host. We propose that this energy-losing cycle in the host is associated with cancer cachexia and with the observed depression of cell proliferation in the host tissue. A lesion in the membrane of the tumor cell, as discussed above, can be used (1) to explain the failure of cancer cells to respond to normal growth and nutrient control and (2) to explain cancer cachexia of the host. Thus, to meet adequately the nutritional requirements of the cancer patient, we must understand the nature of the lesion in the cancer cell.

As pointed out in our discussion, Dr. Gold came up with both this novel and very viable hypothesis as to the cause of cancer weight loss (cachexia), and also demonstrated that hydrazine sulfate (virtually non toxic at the levels required) effectively inhibits this energy draining recycling of cancer derived lactic acid to glucose by the liver. Hydrazine sulfate has thus been able to reduce weight loss, improve the quality of life, and often retard tumor growth. The National Cancer Institute has amazingly refused to support Dr. Gold's animal studies at the Syracuse Cancer Research Institute or any clinical studies on hydrazine sulfate for the past five years. Fortunately

independent clinical work here and extensive clinical testing in Russia supported his hypothesis and data. A successful comprehensive double blind clinical test of hydrazine sulfate was recently completed at Harbour UCLA and has been partially reported. The American Cancer Society, which had hydrazine sulfate on its black list until 1980, have just announced substantial support of the UCLA hydrazine sulfate clinical studies. Senator Ernest F. Hollings aided in a sustained attempt over several years to encourage NCI approval and support of Dr. Gold's various grant requests so that he could further extend this novel approach to cancer control, but without any success. My enclosed March 5, 1982 letter to Senator Hollings summarized the NCI's current tragic position on this very effective and inexpensive approach to cancer therapy. A long and really excellent article on Dr. Gold and hydrazine sulfate therapy just issued in the January 1983 copy of Penthouse; and a copy is enclosed.

The Ability of Streptozotocin to Induce Diabetes or Cancer

Our brief discussion of the capabilities of the naturally occurring drug, streptozotocin, to induce either diabetes or pancreatic cancer in mice as covered in your 1982 paper, Tumor-Host Completition for Nutrients, clarified your proposals on the mode of interaction of the B Vitamin, nicotinamide, in this situation. I had not really realized that this naturally occurring microbial drug was a nitrosourea, which decomposes to a nitrosoamine. Its regular use to induce cancer in mice certainly strengthens for me the likely high significance of the first page of this letter which covered the inducement of gastric and intestinal cancers by natural nitrosoamines; and the ability of adequate oral Vitamin C to completely eliminate such nitrosoamines from ones digestive system.

Incidentally, I checked out and looked through the 1981 book, Streptozotocin: Fundamentals and Therapy, M. K. Agarwal, Ed. and found it quite interesting if by chance you have not read it. The papers by M. Schneir and L. Golub, The Effect of Streptozotocin - Induced Diabetes on Collagen Catabolism, and by R. Crouch and M. Buse, The Effect of Streptozotocin on the Enzyme Superoxide Dismutase were particularly interesting to me because of my previous interests.

Diabetes, Cancer, Superoxide, Superoxide Dismutase and Vitamin C

You might be interested in looking over the enclosed August 31, 1979 letter which discussed a 1977 paper by B. Matovics in Hungary showing human diabetics exhibit drastically lower superoxide dismutase enzyme levels in their red blood cells than normal persons; and that streptozotocin very much lowers this same critical enzyme in rat blood and other vital organs. The superoxide radical as you know is an oxygen molecule with an extra electron, which is enzymatically produced and used in cellular reactions throughout the body. The superoxide dismutase enzyme destroys any escaping toxic superoxide radicals. Ascorbic acid can destroy excess superoxide by being oxidized to dehydroascorbic acid. Diabetics who are very low in superoxide dismutase enzyme have extremely high ratios of dehydroascorbic to ascorbic acid, which would be expected. These unusual interrelationships seemed to me to offer one explanation for the very serious vascular and arteriosclerosis problems that almost all diabetics eventually are smitten with; and why Vitamin C and now gamma-linolenic acid might be effective additions to therapy.

You probably know that the very widely used cancer drugs Adriamyacin, Cis-platinum and others appear to work via superoxide production. Enclosed is an August 13, 1979 letter that discussed the significance of L. W. Oberly and G. R. Buettner's revelations that the mitochondria (respiratory centers) of cells that become cancerous contain little or none of this critically important superoxide dismutase enzyme. Incidentally, I met these two scientists while on vacation at a 1981 conference on The Effects of Copper and Other Essential Metals on Inflammation put on by John Sorrenson at Little Rock. Sorrenson has developed copper containing superoxide dismutases such as copper aspirinate and copper penicillinate which (unlike the copper containing natural protein superoxide dismutase) can penetrate membranes and will likely be most important in controlling inflammation such as in arthritis, ulcers, diabetes, cancer and others. Oberly is working closely with him and has just written the two volume book SUPEROXIDE DISMUTASE which has not yet arrived at the medical library.

Macrophages (which when competent can kill cancer cells) and other white cells concentrate the ascorbic acid 40 to 80 times above the level in the blood; and use it to produce superoxide from oxygen which is then converted to hydrogen peroxide to kill bacteria or cancer cells. There thus seems good reason not to let ones ascorbic acid go down significantly in sickness, or particularly in sustained cancer. It is very little realized; but cancer tissue containing high levels of macrophages that look just like cancer cells, excrete lactic acid just like them, but are not doing their job which is to excrete hydrogen peroxide to kill the adjoining cancer cells, which do not contain the catalase enzyme that other cells have present to break toxic hydrogen peroxide back down to oxygen and water. In definitive analyses of the tissue from all the brain cancers and a number of colon cancers in Kansas for a year, the macrophage content varied from 5 to 85%. High levels of ascorbic acid and gamma-linolenic acid would thus seem mighty important in a cancer patient.

If you have gotten this far there's surely nothing wrong with your stamina and many thanks for your time in December and now. As you can see I'm sending copies of this letter to those mentioned in it.

Most sincerely,

Frank J. Ball

Frank J. Ball

Attachments

P.S. Last night I went by the medical library to see if there were any letters relative to gamma-linolenic acid in later issues of the South African Medical Journal. The attached letter and the reply by Prof. Boogens and Mrs. Dippenaar are interesting in that the number of human malignant cells lines that have responded to the low doses of gamma-linolenic acid has now increased from two to seven. Indicative of their thoroughness, the first paper covering the mouse melanoma cell line embraced a total of over 400 cultures.

I was also intrigued when riding out to work this morning to hear on the morning news that a California researcher had just claimed that a hormone like fatty acid product would stop the growth of cancer cells. Calling the radio station and then United Press, Int'l. in San Francisco brought out that Kenneth Feingold at the University of California in San Francisco and Mille H. Wiley at the Veteran Administration hospital had conducted the studies. They were said to have demonstrated for the first time that the fatty acid type hormone, Prostaglandin E1, when added to lymphoma cells over a period of five days had stopped 90% of malignant cell growth; and that the NCI and the Veteran Administration had funded the study. Prostaglandin E1 (PGE1) is, of course, produced by cells from gamma-linolenic acid. David Horrobin had postulated that the deficiency of PGE1 which would result when gamma-linolenic acid was deficient; could be the major factor in malignancy. This report is thus useful additional confirmation; but I presume they had to continuously add PGE1 over the five days since as I remember PGE1 has a half life of only about a minute in serum. It may last longer in vitro, since it is the lungs that pretty effectively remove any PGE1 on each passage of the blood.

CCS: Dr. M. K. Agarwal
Dr. W. R. Benedict
Prof. J. Boogens
Dr. W. R. Bruce
Dr. G. R. Buettner
Dr. M. Buse
Dr. Ewan Cameron
Dr. Ivan L. Cameron
Dr. R. Crouch
Mrs. N. Dippenaar
Dr. Kenneth Feingold
Dr. Joseph Gold
Dr. L. Golub
Dr. Robert A. Good
Dr. Carlton Hazelwood
Senator Ernest F. Hollings
Dr. David R. Horrobin
Dr. P. A. Jones
Dr. Harry H. LeVeen
Dr. B. Matovics
Dr. H. L. Newbold
Dr. L. W. Oberly
Dr. George M. Padilla
Dr. Linus Pauling
Dr. J. U. Schlegel
Dr. M. Schnier
Dr. John Sorrenson
Dr. J. W. Weisburger
Dr. Mille H. Wiley
Dr. Bruce D. Ball
Dr. James B. Edwards
Dr. H. B. Gregorie
Dr. I. E. Katzeff
Dr. W. P. Leary