The Synergistic Approach: The Future of Nutrition Therapy
by Robert Crayhon, MS

There is no cell in the body that requires one nutrient only, yet single
nutrient therapy has comprised the bulk of all nutrient intervention studies. This
is understandable, because the goal of research is to isolate the activity of
nutrients so their individual roles in the prevention of deficiency and the
treatment and prevention of disease can be discovered.

Clinically, however, single nutrient therapy is not as effective as multiple
nutrient intervention. Single nutrient deprivation and intervention studies are
useful for research purposes, but as the research cited below will show, when syner-
genic nutrient combinations are compared to single nutrient interventions, the combined
nutrient approach is both more effective and safer. Perhaps this is because multiple nutrient
intervention better approximates the nutrient distribution found in food.

No cell in the body uses only one nutrient. No nutrient in the body acts alone. Therefore, it should come as no
surprise that we need all of the nutrients in order to promote optimal cellular,
organ, and overall health. Because nutrients have powerful interactions with
other nutrients, the success of a nutrient therapy may depend more on the
synergistic interaction with a particular nutrient than merely the dose given. This
argues for both individualized therapy as well as synergistic ones. For example, The
First National Health and Nutrition Examination Survey (NHANES I) data shows that the Na:K ratio was more
strongly related to blood pressure than either nutrient alone.1

One of the reasons suggesting that
nutritional therapy should be done in
synergy is that deficiencies occur in
synergy.2 It is difficult to study riboflavin
deficiency in humans, for example, because it is so often accompanied by
deficiencies of other nutrients. Therefore, repleting all nutrients is often beneficial in
cases where a single deficiency is discovered.

Synergistic Interventions are Safer
The most important reason to use
nutrients in combination is not efficiency,
but safety. The ingestion of single, isolated
nutrients by the human genus is but 70
years old. This is at odds with the 2.6
million years of only ingesting nutrients
in synergistic combinations found in foods
of plant and animal origin. Throughout
our genetics' long history, they have never
encountered a single instance where a
food consumed supplied one or even a
small handful of nutrients. This is mirrored in our metabolism: all cellular
functions, including glycolysis, the Krebs
cycle, the energy transfer cycle, cellular
housekeeping, eicosanoid metabolism,
neurotransmitter metabolism, anti-
oxidant defense, immune strength, and
detoxification all depend on an optimal
supply of virtually all nutrients.

The homeocytome raising effects of
niacin have been noted in human studies.
In a multicenter randomized, placebo-
controlled trial, the effects of niacin
compared with placebo on homocysteine
levels in a subset of 62 participants with
peripheral arterial disease were
examined. During the screening phase,
titration of niacin dose from 100 mg to
1000 mg daily resulted in a 17% increase
in mean plasma homocysteine level from
13.1 to 16.3 micromol/L. At 18 weeks after
randomization, there was an absolute
55% increase from baseline in mean
plasma homocysteine levels in the niacin
group and a 7% decrease in the placebo
group.2 Animal studies have shown that
taking pyridoxine with niacin eliminates
its hyperhomocysteinemia-raising effects. Human
trials using niacin along with all of the
homocysteine lowering nutrients—folate,
cobalamin, and pyridoxine—are
warranted.4

Beta carotene is another nutrient
which does not complete safety when
taken alone. Beta carotene alone does
lead to regression of oral leukoplakia, a
precancerous lesion.4 However, beta
carotene supplements appear to increase
the incidence of lung cancer in smokers.8
This may be due, however, to the fact that
taking beta carotene alone does not supply the other nutrients—vitamin E and
vitamin C—which are needed to help
prevent beta carotene from oxidizing and
itself becoming a cell damaging free
radical. The Linxian study showed that
vitamin E, selenium and beta carotene
supplementation led to lower cancer
rate.7 This shows that the synergistic
combination of beta carotene can lead to
positive results. However, not all
synergistic research in cancer prevention
has yielded positive results. Beta carotene
and vitamin E taken together did not lead
to protection against pancreatic cancer8
or colorectal adenomas9 in the ATBC
(alpha tocopherol beta carotene) trial.

Beta carotene in its unoxidized form
appears to be an anticarcinogen, but its
oxidized products appear to facilitate
carcinogenesis. The carcinogenic response
in lung tissue to high-dose beta-carotene
supplementation reported in the human
intervention trials is caused by the instability of beta-carotene in the free
radical-rich environment in the lung,
particularly in cigarette smokers.10 This
is especially possible because smoke
decreases tissue levels of other
antioxidants, such as ascorbate and
alpha-tocopherol, which normally have a
stabilizing effect on the unoxidized form
of beta-carotene. Nutritional intervention
using a combination of antioxidants such
as beta-carotene, alpha-tocopherol,
lycopene, and ascorbate as anticarcinogenic agents would be a more
appropriate way to reduce cancer
incidence in smokers. Then we can
perhaps duplicate with supplementation
the epidemiological results suggesting
that a high beta carotene intake through
diet is chemoprotective against lung
cancer. Foods rich in beta carotene are
rich in other antioxidants, including
ascorbate, polyphenols, and other
carotenoids.11,12

Iodine and selenium are two nutrients which are essential for thyroid function.
Yet supplementing with iodine in the absence of selenium can do more harm
than good. High iodine intake during selenium deficiency can permit thyroid
tissue damage as a result of low thyroidal
GSH-Px activity during thyroid stimulation.13

The Synergistic Effect Benefits Nutrient Absorption
Vitamin C and other antioxidants are
known to enhance iron absorption.11 Zinc
is a nutrient which can be thought of as
synergistic with almost every other
nutrient, for a lack of adequate zinc can
lead to a lack of absorption of other
nutrients, particularly fat soluble
vitamins such as vitamin A and vitamin
E.14 EFAs have now been shown to
increase calcium absorption from the gut.
Synergistic Antioxidant Studies in Cancer Prevention: Successes and Failures

Antioxidants are a great example of how nutrients work together, particularly for inhibition of cancer cell growth. The effect of the carotenoid lycopene alone or in association with other antioxidants was studied on the growth of two different human prostate carcinoma cell lines (the androgen insensitive DU-145 and PC-3). Lycopene alone was not a potent inhibitor of prostate carcinoma cell proliferation. However, lycopene together with alphatocopherol, at physiological concentrations (less than 1 microM and 50 microM, respectively), resulted in a strong inhibitory effect of prostate carcinoma cell proliferation, which reached values close to 90%. Perhaps this synergistic effect of nutrients on cancer prevention in human epidemiological studies explains why fruits and vegetables appear to have more protective ability than interventions with single nutrients such as beta carotene.

Nicacin and Chromium

Both chromium and nicacin have been found to lower cholesterol. Often, high doses of nicacin are needed to achieve this effect. A study of two subjects given 100 mg of nicacin with 200 mcg of chromium chloride found that that combination lowered cholesterol.

The two subjects given nicacin and chromium experienced significant blood lipid lowering effects. The first subject had a cholesterol level of 10.13 mmol/L (389 mg/dL). Daily supplementation for four weeks with 100 mcg of nicotinic acid (nicacin) and 200 micrograms of chromium chloride led to a decrease in serum cholesterol to 8.86 mmol/L (342 mg/dL).

Further supplementation for four months led to a further decrease in serum cholesterol to 7.35 mmol/L (280 mg/dL).

The second subject had a cholesterol level of 8.73 mmol/L (337 mg/dL). Four weeks of supplementation lowered the level to 7.33 mmol/L (260 mg/dL). When supplementation was discontinued, the cholesterol level rose slightly. When supplementation was reinstituted, the cholesterol level decreased to 6.88 mmol/L (258 mg/dL). While this is a small study, it demonstrates that the cholesterol lowering effects that are typically achieved with large doses of niacin can be obtained with smaller doses of nicacin taken along with chromium.

Chromium does not work effectively in the absence of nicacin, according to animal research. This could explain why humans do not uniformly achieve lipid and/or blood sugar lowering effects on chromium supplementation. Sixteen healthy elderly volunteers were divided into three groups and given either 200 micrograms Cr, 100 mg nicotinic acid, or 200 micrograms Cr + 100 mg nicotinic acid daily for 28 days and evaluated on days 0 and 28. Fasting glucose and glucose tolerance were unaffected by either chromium or nicotinic acid alone. In contrast, the combined chromiumnicotinic acid supplement caused a 15% decrease in a glucose area integrated total (p less than .025) and a 7% decrease in fasting glucose. These data suggest that the inability to respond to chromium supplementation may result from suboptimal levels of dietary nicotinic acid, and once again demonstrate the power of the synergistic effect.

Fatty Acid Synergy

One of the questions raised by research in fatty acids is, which fatty acid has the most anti-inflammatory effects? EPA or DHA? A mouse model of lupus-induced renal disease suggests that EPA and DHA combined have a greater anti-inflammatory and renal-protective effect than either fatty acid alone.

GLA and Lipoic Acid

The power of the synergistic effect is demonstrated in a couple of studies where gamma linolenic acid (GLA) and lipoic acid were given alone and in combination. Two multicenter, randomized, placebo-controlled trials in humans with diabetic neuropathy have shown significant benefits of GLA as compared with placebo in neurophysiological parameters, thermal thresholds, and clinical sensory evaluations in diabetic neuropathy.

Fifteen clinical trials have been performed examining lipoic acid as a treatment for diabetic neuropathy, showing that intravenous and oral administration have both equal benefit. Doses ranged from 600-1800 mg per day, with trials lasting anywhere from 4-24 months. These two nutrients were given together in a provocative animal study. After 6 weeks of diabetes, 2 weeks of lipoic acid treatment corrected 20% sciatic motor and 14% saphenous sensory deficits. Lipoic acid also corrected a 49% diabetic deficit in sciatic endoneural blood flow. Treatment of diabetic rats with low doses (20 mg kg(-1) day(-1)) of lipoic acid and GLA, while having modest effects on their own, showed evidence of marked synergistic action in joint treatment, completely correcting motor nerve conductivity velocity (NCV) and blood flow deficits. Another animal study also showed that the GLA-lipoic acid combination is effective in improving both electrophysiological and neurochemical correlates of experimental diabetic neuropathy.

More Synergistic Effects

A 16-week, randomized, double-blind, placebo-controlled crossover trial of a combination of glucosamine HCL (1,600 mg/day), chondroitin sulfate (1,200 mg/day), and manganese ascorbate (228 mg/day) in degenerative joint disease (DJD) of the knee or lower back was conducted in 34 men. This combination therapy led to a marked reduction in symptoms of knee osteoarthritis with no side effects.

Male erectile dysfunction has been studied by an interventive study using arginine, ginkgo extract, vitamin E, and an RDA multivitamin supplement. The results were positive, with over 70% of those studied noting improvement.

Focus for future research for examining the synergistic effects of nutrient therapy should include:

- Folic acid, inositol, selenium, and St. John's Wort have all been found effective for alleviating depression.
- Low zinc and omega 3 fatty acids have also been observed in depressed patients. Combining all of these therapies may yield greater success than either alone.
- Acetyl-L-carnitine, phosphatidyl choline, phosphatidyl serine, inositol, ginkgo standardized extract, and vitamin E have all

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- demonstrated the ability to help relieve some of the symptoms of Alzheimer’s disease and slow its progression. A trial using all of these therapies may yield even more substantial results.

- Nutrients that have been found to help treat PMS include calcium and magnesium.

- Vitamin C, taurine, potassium, and magnesium help lower blood pressure. A trial using all of these nutrients may show that together they have a synergistic effect greater than the sum of the parts.

- Carnitine and CoQ10 work together to improve cellular energetics and promote heart health.

- A trial combining them with heart-healthy nutrients such as vitamin E, taurine, and magnesium and potassium should be conducted in patients with arthralgias and congestive heart failure.

- Because riboflavin, calcium, and feverfew all appear to help prevent migraine headaches, they should be studied together in a human trial.

- Research suggests that vitamins A, C, E, selenium, zinc, copper, and dietary fatty acids have powerful effects on immune function. Studies using all of these nutrients should be employed.

- HIV patients demonstrate a decrease in zinc, selenium, and glutathione. There is a progressive decrease for carotenoids, zinc, selenium, and vitamin E with the severity of disease.

- Few serious and large trials of antioxidants have been conducted in HIV-infected patients. The more promising candidates for presenting synergistic effects seem to be N-acetyl cysteine, beta-carotene, selenium, and zinc.

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