Essential Trace Elements and Cancer

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Abstract

The immune system (immunoglobulins, cell mediated immunity, phagocytosis complement, lysosomes, interferon, metabolic function, hormones, metabolic and respiratory alkalosis) is the natural mechanism which defends against cancer. Trace elements zinc, selenium, molybdenum, and manganese augment this natural mechanism. Zinc is essential for normal development and maintenance of the thymus. Reduced antibody synthesis during zinc deficiency relates in part to interference with T-Iymphocyte helper function. Zinc promotes B-cell function by acting as a mitogen for animal and human lymphocytes. Zinc is essential for the normal bactericidal and phagocytic function of granulocytes. Zinc's essential role in protein synthesis makes it essential for normal complement production. Acrodermatitis enteropathica, failure to absorb zinc because of an inborn error of metabolism, is marked by all the above defects. Blood and serum from cancer patients generally show subnormal zinc levels. Zinc prevents the growth of experimentally induced cancers. Zinc deficiency depresses killer cell activity. Zinc deficiency promotes cancer by inhibiting normal vitamin A and lipid metabolism and DNA repair. The parents of pyroluric patients presumably deficient in zinc have an increased incidence of cancer. The average American diet is deficient in zinc and this may be a factor in our national cancer epidemic. A deficiency in molybdenum has been cited as a possible factor in the causation of esophageal cancer. Molybdenum has anti-neoplastic properties. Molybdenum and also manganese prevent the formation of some experimentally induced cancers. Manganese may augment bactericidal actions of antibiotics. Elevated serum copper levels have been described in patients with a variety of carcinomas. Copper is a biological antagonist of vitamin C and zinc.

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Introduction

Most doctors are amazed when a patient spontaneously (without medical interference) recovers from cancer. Simple mechanical cures are possible for some outgrowing cancers. Pedunculated tumors of the skin may fall off and cancerous polyps in the digestive tract may outgrow their blood supply, drop off and be excreted. Ingrowing cancers, even basal cell cancer of the skin which occurs around the upper lip and nose, need to be removed surgically or by cautery. Since most cancers will never fall off, how does the body cure itself?

The body cures itself by the action of the immune system (immunoglobulins, cell mediated immunity, phagocytosis, complement lysosomes and interferon) and metabolic

function (hormones, metabolic and respiratory alkalosis) (Chandra, 1981).

Cancerous changes probably occur daily in the human body but the abnormal cancer cells, if in the blood, will normally be phago-cytized by stationary macrophages which line the vessels of the lungs, liver and spleen. If the cancerous cell is attached to a normal cell, a wandering macrophage or a thymus T-cell called a "killer cell" will recognize the cancerous cell as foreign and engulf it.

The hormones of the body may enhance or cause cancer. Unnatural female sex hormones such as diethylstilbesterol (DES) may lead to vaginal adenomatosis, while prostate cancer in males may be controlled by DES, the identical artificial sex hormone.

Cancer grows rapidly in young people, i.e. ovarian, breast, seminoma, but these cancers in older people may progress slowly over a ten year period. This observation is probably related to the endocrine status of these patients. Thyroid supplements are known to increase the growth of some cancers. Some cancers may produce their own polypeptide growth factors so a specific antibody will eventually be made to control the cancer.

The Body Cures Cancer Daily

Each cell has natural defenses against cancer which can be likened to other body functions: liver-like detoxification is performed by the cell in the smooth endoplasmic reticulum; immune-like functions occur in the peroxisomes; lysozymes are like stomach acids and enzymes; and cell membranes are analogous to our normal skin with its acid skin barrier. One exception is DNA repair which is strictly a function of cellular prevention of cancer. A normal cell's own proof reading system can identify and cover small mistakes (Science News, 1980a). Massive rearrangements of genetic material rather than local subunit changes are necessary for most people to overload the mutation correction rate (Science News, 1980b). It is likely that each individual's cancer susceptibility can be determined in the test tube by measuring the repair ability of the donor's cells.

For example, cells of xeroderma pigmentosa patients are defective in the ability to repair small changes in DNA such as those caused by ultraviolet radiation from the sun. Such persons are unusually susceptible to skin cancer. One hundred and fourteen patients with the genetic defect revealed no excess of other types of cancer (Science News, 1980b). The xeroderma pigmentosa patient apparently has enough repair capability to correct mutations in other tissues. Cancer occurs in the skin because the mutation rate exceeds the capacity for correction. Mutations can be viewed as mini cancers; since mutations are always occurring, mini-cancers are always being formed but are mostly repaired.

In preventing cancer one needs to choose nutrients which augment any of the cellular and organismic defense mechanisms reviewed. This is the foundation for the claim that vitamin C, E and A prevent cancer. In this paper we review the data which suggest that zinc, selenium, molybdenum and manganese are essential to the prevention of cancer and the excess copper is associated with increased cancer.

Selenium is Needed but Overrated

In the research field of trace metals and carcinogenesis selenium has gained a disproportionate amount of attention. Reviews of the literature emphasize selenium's antioxidant properties, inhibition of tumor growth and inverse epidemiological correlations with cancer (Schrauzer, 1979). The inhibitory effect of selenium on growth of tumors has again been documented (Greed-er, 1980), although there is some disagreement (LaFond et al., 1979; Robinson, 1980). For example, in Hodgkins disease and non-Hodgkin malignant lymphoma the mean serum levels of selenium were not different from those of the control group (Cal-autti et al., 1980).

Some researchers incriminate zinc in cancer because it reduces the symptoms of selenium toxicity, perhaps implying that zinc may be a selenium antagonist (Schrauzer, 1979). In addition, some scientists have reported the accumulation of zinc in various tumors (Pories, 1973). Rats receiving zinc

deficient diets exhibit significant reduction of tumor growth. And the final bit of evidence against zinc is that serum zinc is inversely correlated with blood selenium while blood selenium is inversely correlated with cancer (Schrauzer, 1977; Schrauzer, 1979). The evidence that zinc is a carcinogenic selenium antagonist is incidental and superficial. Selenium and zinc may be inversely correlated in blood; yet it is not logical to conclude that selenium is a poison like the zinc-antagonists: lead, cadmium and mercury. Nor do we consider these toxic elements selenium protagonists! The fact that we know selenium and zinc are essential suggests a similar function or a reciprocity instead of a zinc and copper-like antagonism. More clinical studies are needed, yet no one has reported that zinc administration lowers selenium in blood. The hypothesized inverse relationship of zinc and selenium in blood is probably unrelated to any physiological competition and is not found in the present data available from hair analysis.

Zinc reduces selenium toxicity yet this is hardly evidence to assume that zinc is an anti-selenium factor (Schrauzer, 1977). Zinc has many roles in the detoxification of heavy metals, i.e. lead and cadmium, and the detoxification of alcohol and selenium as well (Pfeiffer, 1979). Excess zinc supplementation does not lead to any increase in tumor induction (Walters, 1975) as would be predicted by the anti-selenium hypothesis.

Zinc and Cancer

Many researchers have reported that zinc inhibits the development of cancer and that low serum zinc is associated with several forms of cancer. In 1959, Addink and Frank reported that blood and serum from cancer patients generally show subnormal zinc levels when the tumor is associated with tumors rich in zinc. Return to normal levels was associated with a favorable prognosis. High levels of zinc, 300 ppm, decrease tumor incidence and increase the latent period of PYB6 induced neoplasms in mice (Mulhern, 1980). Aqueous zinc acetate injected intraperitoneally prevented tumor growth in 50 to 70 percent of male mice previously inoculated with L1210 leukemia cells. Subcutaneous injections in a different strain did not prevent tumor growth but significantly increased mean survival (Phillips and Sheridan, 1976). Delves et al. (1973) have described subnormal plasma zinc levels in leukemic children. Response to chemotherapy was associated with increases in plasma zinc to normal levels. Zinc salts actually retard the induction of tumors when the carcinogen DMBA is applied to the cheek pouch of the hamster (Poswillo et al., 1971). Zinc deficient diets depress killer cell activity against EL-4 tumor cells in mice (Fernandes et al., 1979). Killer cells probably hold the key to immunosurveillance against cancer (Gershon and Metzler, 1978; Herberman and Holden, 1978).

Experimental zinc deficiency in animals, has produced parakeratosis, a precancerous epithelial change (Lin et al., 1977). Zinc levels were reduced in all specimens (serum, hair, esophageal tissues) of subjects with esophageal cancer (Lin et al., 1977). Zinc deficiency has been shown to increase the susceptibility in animals to chemical carcinogens that produce esophageal cancer (Fong et al., 1978). Low zinc levels due to phytate consumption have a promoting effect on precarcinomatous esophageal tumors (Rensburg et al., 1980). Populations having an unusually high risk for esophageal cancer tend to subsist on zinc-deficient diets, predominantly cereal, and have a low intake of animal products (Warwick and Harington, 1973). Rensburg et al. (1980) found that minimal levels of zinc intake which ensure optimal body growth rate are inadequate to provide maximal resistance to esophageal carcinogenesis.

Garofalo et al. (1979) of Sloan Kettering have found zinc deficiency in 20 to 30 percent of patients with epidermoid cancer of the head and neck, and in some patients with other cancer. Fisher et al. (1976) reported that patients with metastatic osteosarcoma had depressed serum zinc. Dehyd-rotestosterone/testosterone (DHT:T) ratios of less than one were characteristic of prostate cancer and were usually preceded by a reduction in prostatic zinc concentration (Habib et al., 1979). McBean et al. (1974) reported subnormal serum zinc levels in patients

with prostatic cancer.

Zinc may prevent cancer via the metabolism of high density lipoprotein (HDL), vitamin A and DNA synthesis. In a 24 year study of business and professional men, 32 men who died from cancer had the highest mean HDL, a significant difference from survivors (Keys, 1980). High levels of zinc supplementation in normal subjects, 440 mg of zinc sulfate per day for five weeks, result in a 25 percent decrease below baseline levels of HDL (Hooper, 1980). Zinc may exert a prophylactic anti-cancer effect by preventing elevation of HDL.

Zinc is essential for the production of retinal binding protein—the transporter of vitamin A (Smith, 1977). Zinc deficiency masquerading as vitamin A deficiency, i.e. night blindness, is well known. The knowledge of vitamin A in inhibiting hyperplasia and cancer has been reproduced in many fields of medicine, i.e. dermatology and cell culture laboratories. A deficiency of zinc may contribute to hypoplasia and cancer by inhibiting vitamin A metabolism.

Zinc is an essential component of the enzymes involved in DNA synthesis and repair. Zinc is an essential nutrient for axonal transport. Both functions contribute to the prevention of cancer. Both Bloom's syndrome and xeroderma pigmentosa patients have an increased cancer incidence because of a failure in DNA repair and ultimately DNA synthesis. DNA polymerase I and III are zinc metalloenzymes essential in DNA synthesis and repair. Zinc metalloenzyme thymidine kinase is also essential for DNA synthesis and ligases involved in the repair process may also be zinc dependent enzymes (Riordan, 1976). The activity of these enzymes is decreased during zinc deficiency. Werner's syndrome is a disease marked by increased cancer, probably caused by DNA repair and slowed axonal transport defects. Zinc is essential to normal and rapid axonal transport (Edstrom and Mattsson, 1975; Baker and Amos, 1978), which is probably a factor in the increased cancers of Werner's syndrome. Collage-nases are zinc metalloenzymes (Prasad, 1976) which prevent the action of tumor angiogenic factor. This factor is responsible for the essential vascularization of tumor which depends on increased collagen synthesis (Messer, 1979).

Relatives of Pyrolurics Have Cancer

The schizophrenic is reported to be less susceptible to cancer than non-schizophrenic groups. In the ten years since we first recognized pyroluria as a type of schizophrenia we have had an inordinate number of relatives of our pyroluric patients fall ill with cancer. We postulate that this may be caused by a life-long borderline deficiency in zinc and B6 (Pfeiffer, 1978). Zinc and pyri-doxine deficiencies are associated with marked immunodepression particularly cell mediated immunity (Horrobin et al., 1979; Chandra, 1980). Pyroluria is a form of schizophrenic porphyria similar to acute intermittent porphyria where both pyrrole and porphyrins are excreted in the urine in excess. Hematoporphyrins accumulate in various tumors: i.e., human bladder carcinoma and bronchogenic carcenoma (Kinsey et al., 1978). Untreated porphyries and pyrolurics probably both have increased cancer incidence.

Yet there exist some conflicting data which suggest that zinc or zinc excess is a factor in some cancers. Cancer tissue zinc is increased in cancer of the breast (Santo-liquido, 1976) and malignant tumors of the cervix and corpus uteri (Roguljic et al., 1980). However, cancers normally sequester all important nutrients. Edwards (1976) found zinc had no inhibitory effect on chemical carcinogenesis in the cheek pouch of syrian hamsters receiving supple-mentary zinc. The absence of zinc from the diet significantly enhanced the anti-tumor activity of cyclophosphamide, 5-fluorouracil and methotrexate (Capel et al., 1980). A diet deficient in zinc resulted in a significant decrease in the number of inbred Balb/c female mice developing transplantable plasmacytoma compared to pair fed and ad-lib-itum fed control mice (Fenton et al., 1980), although the size of the tumor relative to body weight was decreased in the zinc deficient group. Minkel et al. (1979) found zinc deficiency slowed the growth of ascites tumor but the effects were not reversed by

zinc supplementation and, therefore, could not be attributed to zinc deficiency.

Tumor inhibition is a general effect of deficiency of any nutrient which is involved in protein synthesis, irrespective of cell type, cell growth rate, species or site of growth (Frost et al., 1981). In view of the fact that zinc is required for cell division and protein synthesis, it is not surprising to observe a decrease in tumor growth as a result of a short term zinc deficiency. Long term effects of a deficiency result in immune defects which cancel this benefit and promote tumor growth.

The remainder of the conflicting data is probably resolvable by the realization that either a deficiency or toxic level of zinc impairs the immune response to non-H2 allogenic tumor cells in mice. Animals maintained on a zinc-deficient diet for as little as two weeks develop a severe impairment in their ability to generate a cytotoxic response in the face of tumor challenge. If mice are treated with toxic doses of dietary zinc, a similar impairment of cell mediated cytotoxic response (T-cells) occurs. Both abnormalities are corrected by a return to normal zinc homeostatis. Studies which show zinc promoted cancer are probably zinc excess experimental diets.

These observations are supported for virus growth as well as tumors. Cunning-ham-Rundles et al. (1979) found that zinc is an essential nutrient for growth of tumors as well as viruses. Yet virus growth is inhibited by excess zinc (Polatnicketal., 1978).

Zinc and Immune Function

The immune system probably accounts for most of the body's defense against cancer. Zinc deficiency causes atrophy of the thymus and other lymphoid tissue and produces abnormalities in both cellular and humoral immunity (Beisel et al., 1981). Rats fed a zinc deficient diet have reduced antibody forming cell response (Chandra and Au, 1980). Cytotoxic response of spleen cells of zinc deficient mice immunized in vivo was also decreased.

The primary organ site of zinc deficiency in immunity is the thymus gland (Good et al., 1979). Zinc deficiency produces progressive thymic involution and progressive loss of T-cell immunity in mice and rats (Pekarek, 1980). The gland can be restored by the addition of zinc to the diet. The thymus glands of rats fed with zinc deficient diets weigh less than the controls (Chandra and Au, 1980). These effects on the thymus are related to a reduced level of thymic hormone Factor Thymique Serum (FTS) (Pah-wa, 1979). Zinc deficiency drastically reduces the concentration of this thymic hormone which drops progressively after the second week of zinc restriction. Zinc repletion restores to normal FTS and thymphocyte function (Cunningham-Rundles et al., 1979) Laboratory animals who receive zinc supplementation maintain their FTS at even higher levels, and for a longer time, than do control animals receiving laboratory chow ad lib (Good et al., 1979). In mice and humans, levels of FTS usually decline rapidly after onset of sexual maturation as the thymus involutes. This may not be a normal process but rather the beginning of that disease called aging. Zinc supplementation may delay the involution of the thymus in adolescents and possibly restore some function to the adult thymus. In severely zinc deficient animals and patients, FTS is suppressed and delayed cutaneous hypersensitivity and skin graft rejections do not occur. A local application of zinc sulphate to the skin restores responsiveness apparently by direct absorption (Beisel et al., 1981).

Reduced antibody synthesis during zinc deficiency relates in part to interference with T-lymphocyte helper function (Koller, 1980). Nutritional repletion of zinc in zinc restricted animals restores thymus and T-cell dependent antibody mediated responses (Fraker et al., 1978; Luecke et al., 1978; Fernandes et al., 1979). The thymus has important regulatory roles in antibody synthesis, particularly IgG (Pearson, 1976). Humoral antibody synthesis is decreased during zinc deficiency (Good et al., 1979). A deficiency of zinc has been shown to result in the inhibition of the IgG response of A/J mice (DePasquale-Jardieu and Fraker, 1979). Zinc deficient mice had significant reductions in IgG and IgM production. After four days on the zinc adequate diet,

previously zinc/caloric deficient male mice were able to completely repair both the IgM and IgG responses (Zwickl and Fraker, 1980). Lead and cadmium are antibody suppressive (Roller, 1980). Zinc is an antidote to these poisons (Pfeiffer, 1978; Papaioannou et al., 1978).

Zinc promotes B cell function by acting as a mitogen for animal and human lymphocytes (Ruhl et al., 1971; Chesters, 1972; Hart, 1978; Gross, 1979; Cunningham-Rundles et al., 1979). Zinc treatment significantly increases the lymphocyte response to phytohemaglutinin, lipopolysaccharide and concavalin A (Mulhern, 1980; Duchateau et al., 1981). The beneficial effect of zinc supplementation on the lymphocyte probably relates to DNA synthesis necessary for the production of B cell clones. Zinc is a key nutrient for rapidly dividing cells (Williams and Loeb, 1973; Berger and Skinner, 1974).

Zinc is clearly essential to both B and T cell function. In addition a number of patients with common variable immunodeficiency are zinc deficient (Good et al., 1979). These patients have a deficiency in thymus cell immunity and antibody production. Zinc supplements correct the associated GI malfunctions, skin rashes, B and T cell abnormalities. Zinc is essential to immune defense against bacterial infection probably via B cell, T cell macrophage and granulocytic function.

Excess zinc (and probably low zinc) when tested in vitro inhibits the bactericidal and phagocytic function of macrophages and neutrophils (Beisel et al., 1981) See page 32 to explain paradox). Zinc augments the bactericidal action of streptonigrin, an antibiotic (White et al., 1981). Both low and high dosages of zinc inhibit the phagocytic capacity of mouse peritoneal macrophages (Karl et al., 1980). A parabolic correlation between leukocyte zinc content and neutrophil phagocytic capacity has been observed. Zinc deficient animals have impaired neutrophil phagocytic activity (Lennard, 1980). Some functions of granulocytes in prostatic fluid and prostate tissue are regulated by zinc (Stankova et al., 1976). In addition the bacteriocidal actions of zinc have been documented by several workers (Avigad and Bernheimer, 1976; Schlievert et al., 1977). Human amniotic fluid, rich in zinc (Brandes et al., 1980), is bacteriostatic and useful as an adjunct in wound healing (Faulk et al., 1980). Zinc is essential for the activity of bacitracin (Mosberg et al., 1980).

It has been suggested that diminished levels of serum corticosterone are responsible for the loss of immune responsiveness in zinc deficient animals (DePasquale-Jar-dieu and Fraker, 1979). Whatever the exact mechanism it is clear that zinc is essential to most functions of the immune system. Acrodermatitis enteropathica (AE) an inborn error of zinc metabolism (Moynahan and Barnes, 1973; Lombeck et al., 1975) is marked by depressed T cell activity (Oleske, 1978; Good et al., 1979), thymic hypoplasia and severe combined immunodeficiency (Good et al., 1979). Serum levels of zinc are low but three to four times the normal zinc requirement by mouth corrects the condition (Gartside and Allen, 1975; Good et al., 1979; Cunningham-Rundles et al., 1979).

The Population is Zinc Deficient

Unfortunately very few people have adequate zinc nutrition. In fact, the average American appears to ingest only 8.5 mg of the needed 15 mg RDA (which is probably low) (Wolf et al., 1977; Holden, 1979). Zinc deficiency may be a factor in our national cancer epidemic.

Molybdenum and Cancer

A deficiency of molybdenum has been sited as a possible factor in the causation of esophageal cancer (Yang, 1980; Luo et al., 1981). In China where esophageal cancer is the second most common cancer in men, multiple negative correlations between the mortality rates of this cancer and the concentration of trace metals molybdenum and zinc in cereals and drinking water have been found. Lower levels of molybdenum were found in the serum, hair, and urine of the inhabitants of high risk areas as compared with those from low risk areas. The molybdenum content in surgically removed esophageal cancer specimens was significantly

lower than those in normal esophageal tissues.

Molybdenum administration reduces the incidence of N-nitrososarcosine ethyl ester (NSEE) induced stomach cancer in mice. Molybdenum supplementation also decreased the incidence of NSEE induced cancer of the esophagus and fore stomach in rats (Luo et al., 1981). Nitrosamines are naturally occurring carcinogens.

Molybdenum probably exerts its anti-cancer effect by reducing nitrosamines and their precursors i.e. nitrate, nitrite and secondary amines in the diet. Molybdenum is essential to a number of oxidation reduction enzymes of bacteria and algae, which convert these dangerous nitrogen compounds to ammonia in the soil (Schrauzer, 1976). Plants contain less nitrite and nitrate in molybdenum rich regions. This theory is supported by the fact that contents of nitrosamines and their precursors in staple food collected from high risk areas was higher than those of low risk areas (Luo et al., 1981). Molybdenum fertilizer is used in China to reduce nitrates in foods, because grain and vegetables are the largest dietary source of nitrosamine precursor (Yang, 1980). Molybdenum dichloride has antineoplastic properties which inhibit the growth of Ehrlich ascites tumors in mice (Kopf-Maier et al., 1979). Molybdenum is the biological antagonist of cancer promoting copper (Ward, 1978; Nederbragt, 1980) even in the fetus (Meinel et al., 1979). Molybdenum fertilizers increase ascorbic acid content of grains and vegetables (Luo et al., 1981).

Manganese and Cancer

Underwood (1977) has found manganese comparable to molybdenum in concentration in animal tissues and fluids of all species so far examined. An anticarcino-genic effect of manganese dust upon tumor induction by nickel subsulfide was reported by Sunderman et al., (1974). Sarcoma incidences of 96 to 100 percent of rats receiving Ni3S2 were reduced to 63 percent by manganese dust. Manganese alters the subcellular distribution of carcinogenic nickel (Sunderman et al., 1976). This particular anticarcinogenic effect was local, specifically related to the site of injection rather than systemic.

Rensburg et al. (1980) found that sarcoma incidence in rats receiving I.M. injections of 3, 4, benzopyrene (BP) and manganese dust were significantly less than in rats that received BP alone. Manganese may exert its anticarcinogenic effect by activating superoxide dismutase (Marklund, 1978). Without manganese the mitochondrial superoxide dismutase would be inactive and accumulation of superoxide anion could be mutagenic (Aston, 1980). Manganese also augments the bactericidal action of strepton-igrin, an antibiotic (White et al., 1981).

Elevated Serum Copper Promotes Cancer

Zinc, manganese and molybdenum lower serum copper and increase urinary copper excretion (Underwood, 1977; Pfeiffer, 1978) The biological antagonism of copper with anticarcinogenic molybdenum and zinc suggests excess copper may be cancer promoting. Much of the research literature supports this hypothesis.

Elevated serum copper levels have been described by patients with a variety of carcinomas. Zinc to copper ratios are decreased in all neoplastic kidney tissues (Karcioglu et al., 1978). O'Leary and Feldman in 1970 demonstrated that the degree of elevation of serum copper in women with cervical carcinoma increased as the disease advanced and those patients who responded to treatment had nearly normal serum copper. Albert et al. (1972) reported that patients with bladder carcinoma displayed elevated serum copper which was also correlated with the stage of the disease. Elevated serum copper has been reported in patients with mammary carcinomas (deJorge et al., 1975b), bronchial carcinoma (Kolaric et al., 1975), and gastric carcinomas (Kelderling and Scharpf, 1954). Fisher et al. (1976) and Breiter et al. (1978), have described elevations of serum copper in patients with osteosarcoma. The degree of elevation of serum copper correlated with the extent and activity of the disease. The highest copper levels were associated with metastatic spread of

the disease.

Serum copper and ceruloplasmin are increased in primary lung cancer (Buffe et al., 1967; Rimbaut and Buffe, 1972; Rimbaut et al., 1976; Mateo et al., 1979). Workers in copper refineries showed an increase in pulmonary cancers (Sunderman, 1978). Copper was significantly concentrated in malignant cervical and endometrial tumors. Copper is concentrated in malignant melanomas (Kolaric et al., 1975; Bram et al., 1980). Fisher et al. (1981) found serum copper levels elevated in malignant melanoma. Copper levels reflected the degree and extent of tumor activity.

Copper refinery workers also have an increased incidence of lymphomas and leuk-emias (Sunderman, 1978). In a study of 236 patients with malignant lymphomas elevation in serum copper occurred and was correlated with the degree of spread of the cancer (Hrgovcic et al., 1973b). Patients responding to treatment generally displayed a less elevated serum copper. Patients who subsequently relapsed were generally observed to display increased serum copper levels before the clinical signs of the cancer were detected.

Elevated serum copper in children (Tess-mer et al., 1973) and adults (Hrgovcic et al., 1973a) have been demonstrated in Hodg-kin's disease. The higher the serum copper the more active the disease. Copper decreased in patients responding to therapy and increased on relapse. Warren et al. (1969) also reported a close correlation between serum copper and the prognosis of Hodgkin's disease. Hrgovcic et al. (1973) reported similar findings in acute leukemic patients. The degree in elevation of serum copper correlated with the percentage of blast cells in the bone marrow. Illicin (1971) and Delves et al. (1973) have reported elevated serum copper in acute leukemia and a decline in serum copper associated with the therapeutic response.

Oxidized ascorbic acid and copper protein ascorbate oxidase are probably elevated in leukemia (Lohmann et al., 1979). Elevated serum copper probably decreased serum levels of the anticarcinogenic vitamin C (Cameron et al., 1979). Growth stimulating tripeptide GHL in hepatoma cells functions as a copper transport factor (Pickart et al., 1980).

Loeb (1977) and Roguljic et al. (1980) suggest copper is carcinogenic because it decreased the fidelity of DNA synthesis in vitro. Copper antagonizes zinc which is essential for normal DNA synthesis. Fisher and Shifrine (1978) have postulated a mechanism of decreased ceruloplasmin catabolism explaining the elevated serum copper in cancer patients.

In contrast to the above data, Kamamoto (1973) found copper inhibited carcinogenesis in rats caused by DL-ethione. There exists a copper-zinc superoxide dismutase (Underwood, 1977). Copper, an essential nutrient, is not a complete biological demon, although copper decreases the catalytic activity of lysozyme (Chung et al., 1981).

Conclusion

In summary, selenium, zinc, molybdenum and manganese are needed by the cancer patient in order to prevent and to increase the chances for natural immunological remission of cancer. We emphasize that a failure of the immune surveillance system is central in the development of cancer. Zinc is needed by every aspect of the immune protective system. In contrast, elevated serum copper is associated with and probably increases in various cancers.

The Practical Nutritional Approach to Cancer Control

Many of the chemotherapeutic agents for cancer are antifolates; therefore, the dietary supplements should contain no added folate. This rules out the use of most commercial multi vitamin preparations which have 400 mcg of folic acid. The patient should take vitamin C to tolerance and doses of 10 to 20 grams per day are well tolerated. The usual side effect is diarrhea with the maximal tolerated dose.

Vitamin A should be given in a dose of 50,000 u/day. This is usually well tolerated in older patients but younger patients may have dull headaches and loss of appetite. If this occurs the dose is reduced to 10,000

or 25,000/day. These numbers look large but remember that a dinner of calves liver with carrots and beets will provide 25,000 u of vitamin A at a single sitting.

Vitamin E should be given in doses of at least 400 u AM and PM. The optimal dose to suppress cancerous growth has not been determined. Some of our patients have taken 2,000 u AM and PM for years without any evidence of toxicity.

Selenium should be given in a dose of 100 mcg AM and PM. This is available in tablets of 50 mcg and the proposed dose is usually well tolerated. Again the usual side effect is diarrhea. Larger doses can produce vomiting and fever with influenza-like symptoms.

Molybdenum should be given to the cancer patient in a dose of 500 mcg per day. This can be two tablets of 150 mcg AM and PM or one drop of five percent ammonium molybdate per day.

Manganese is poorly absorbed from the gastrointestinal tract so much larger doses than the usual five mg per day should be given. We usually give 50 mg of manganese as the gluconate AM and PM. Most of the blood manganese is contained in the erythrocyte so changes in blood manganese can be monitored at four monthly intervals—the life of the red blood cell. In older patients manganese may elevate the blood pressure and produce dull headaches. When this occurs the patient should reduce the oral dose or use nuts and tropical fruits as a source of manganese.

Zinc is ordinarily needed at a dose of 15 mg per day and any salt of zinc is well absorbed. The cheapest salt at present is the gluconate. Cancer patients should be given a double dose, namely 15 mg of zinc as the gluconate AM and PM.

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Letters to the Editor

To the Editor

In the last issue of the Journal of Orthomolecular Psychiatry, an editorial by Drs. Hoffer and Osmond draws attention to the paper by Drs. Tkacz and Hawkins dealing with tardive dyskinesia.

I am in private practice since 1954 and I have been prescribing routinely to my schizophrenic patients a combination of at least 500 mg of Niacin or Niacinamide and 500 mg of vitamin C, q.i.d. or t.i.d., concurrently with the antischizophrenic drugs. As I look back now, I had only a very few slight cases, four or five, of tardive dyskinesia, observed since that time, which promptly responded to Deaner. In some cases I did not have to discontinue the antischizophrenic drugs. I have attributed this success to Deaner, but it is quite possible that Niacin and vitamin C were the real reason for the lack of tardive dyskinesia. The majority of my patients also receive routinely vitamin B Complex. As mentioned in the editorial I find it very exciting to think that orthomolecular psychiatry will prevent tardive dyskinesia.

I would also like to share my observations on a few cases of epilepsy treated with Dilantin. The addition of vitamin B6 in doses of around 600 mg per day, in all cases of gingivitis completely removed this side effect. In temporal lobe epilepsy there was a definite improvement of the mental symptoms.

This is not a double blind study! I would be very interested in other observations.

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To the Editor

A. .Hoffer's article reviewing the adrenochrome hypothesis in the Journal of Orthomolecular Psychiatry, Volume 10, Number 2, 1981, is most rewarding. However, I feel there are some considerations about my observations that may be worthy of expressing, so others can examine their practices for parallel experiences. He appears to have considered cerebral allergy in only a percentage of schizophrenic patients. My experience differs radically from this, and it is in that cerebral allergies are observed in all schizophrenic patients. Our clinical experience differs, because I have examined all of my patients in this light, and he has examined

only his nutritionally refractive patients in this light.

I have found a few patients who did not recover on their five day avoidance period; however, when these are given stimulation such as electric shock treatment, they do usually recover and then are testable. Something between five and ten percent of my patients receive electric shock treatment simply because they do not recover adequately on their five days' avoidance. This can likely be explained as an extinction of disuse. If a response is inhibited long enough, its reflex capacity is trained out; however, it can be stimulated back to function again. As far as I know, there really is no other way known at this time that these patients can recover other than electric shock. This in no way diminishes the need for examining their reactions to environmental substances and their nutritional needs.

Another difference would be that somehow the impression is given that vitamin dependency and cerebral allergy are two different camps. In my experience, these really are the same thing. Any persons sufficiently deficient in certain nutrients and thus diminished enzyme functions will be symptom reactive to their environment, simply because they do not have the proper chemistry to handle these environmental contacts.

What is a model or hypothesis that will explain this universality of reactions to environmental substances in schizophrenics and nonschizophrenics, as well as account for the development of this selective syndrome called schizophrenia? The hypothesis runs like this. There is a central disease process. It is based on adaptive addiction to environmental substances. The state of adaptation is a state of disordered function but not the most extreme state of disordered function, since it is an adaptation. The stress of this addictive state disorders the nutritional state of the patient in that it disorders every system, including such as acid base balance, carbohydrate metabolism, amino acid metabolism and lipid metabolism. Monitoring any one of these systems during this state of adaptive addiction reveals disordered function in respects of varying degrees. Genetics makes a difference as to where the weak links are as the system fails. Other factors are such as prior injury or infection or the presence of toxicity. One aspect of disordered amino acid metabolism is such as to be appropriately included in the adreno-chrome hypothesis. Certainly there is evidence that excessive methylation and improperly handled methylation, as well as these facts being associated with oxidative mechanisms, produce an assortment of substances capable of evoking hallucinations and many less intense central nervous system maladaptive responses. This is simply a part of the breakdown that occurs in this state of adaptive addiction.

We do find tryptophan frequently deficient, but equally we find tyrosine deficient, and the common syndrome of low blood pressure, weakness and low systemic temperature appears to be a reflection of that deficiency. I am not sure how this deficiency comes about, whether by demand from the illness itself or otherwise. In any event, I have not found that giving tyrosine, which corrects this syndrome", increases schizophrenia. However, at the same time all of these patients have been receiving at least 500 mg of nicinamide three times a day, 4 grams of vitamin C three times a day, and B6 ranging from 50 mg of phosphory-lated B6 to 500 mg of pyridoxine three times a day. These supportive nutrients may well have protected them from having a reaction to the tyrosine. It is interesting that phenylalanine does not provide the same values as tyrosine, and it is not uncommon to find a patient complaining of symptoms when given phenylalanine but symptom relief when given tyrosine. However, one subject given tyrosine as 1000 mg at bedtime for restless legs who was not systematically taking the larger doses of niacinamide or vitamin C did develop a sore tongue which was relieved by the administration of niacinamide. Within one hour of giving 100 mg of niacinamide intramuscularly, the sore tongue was relieved. Subsequent oral supplementation of niacinamide prevented the sore tongue from being present, even though the tyrosine supplementation was continued. It is quite important to under-

stand the competing mechanisms that do occur in nutrients, and in this case, we would assume that if a person is receiving tyrosine for Parkinsonism, low blood pressure, restless legs, low temperature or weakness that they should at the same time be receiving vitamin C and niacinamide.

Systematically through the years, I have demonstrated as aspects of the central degenerative disease process that first of all acid base balance followed by disordered carbohydrate metabolism, then fat metabolism and more recently amino acid metabolism. Surprises have been emerging in this study. Excessive methylation is obvious as occurring through disordered methionine metabolism as simply a basic disordered metabolism of the adaptive addictive process. Specific amino acid needs are in evidence, as well as specific amino acid intolerances. There has emerged internal evidence of the protein intolerance producing bouts of hyperammonemia. Therefore, I added a provocative test for ammonia. During this provocative test, I have found everything in the book to emerge, including all the schizophrenic and manic depressive symptoms as well as the minor central nervous system and somatic symptoms. Therefore, I am becoming convinced that hyperammonemia is one of the central kingpins in symptom production in this central disease process, and that the way the patient may respond to that hyperammonemia depends on other chemical factors, some of which are likely genetic in origin.

I have recently also been able to show that a neutralization for ammonia can be arranged through finding the minute amounts that relieve symptoms. This can be provided either sublingually or subcutaneously. The basic treatment, of course, is not providing neutralization which would not at all treat the central disease process but would be avoidance and spacing below the symptom production, as well as providing all the nutrients that are necessary which include vitamins, minerals and amino acids. Manganese is emerging as a very important mineral that is deficient in a lot of people and helps predispose them to their hyperammonemia.

I have been consistently doing an immunology vs. a non-immunology differential diagnosis. My conclusions are that very seldom do immunologic reactions have anything to do with food reactions. Therefore, food allergy is really a misnomer. These are simply maladaptive reactions to foods, chemicals, and inhalants based on the disordered chemistry that the person has.

It appears that even though genetics, prior infection and prior injury enter into the cause of the reactions, the most common cause that runs through all of these cases is the frequency with which they contact a substance. This has the effect of wearing out the body's chemistry and making it incapable of handling the stress of the contact. Therefore, maneuvering these contacts becomes the central kingpin around which a program is built. Then, the building blocks of nutrition are appropriately arranged according to the laboratory evidence. The system is the same, whether we are talking about schizophrenia, ulcerated colitis, migraine headache or diabetes mellitus, maturity-onset type.

Sincerely,

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