South Med J. 1988 Aug;81(8):1042-6.

# Virgil Sydenstricker: special reference to niacin deficiency encephalopathy.

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## Abstract

Virgil Sydenstricker was a member of a notable American family which included authoress Pearl S. Buck and the eminent epidemiologist Edgar Sydenstricker. Dr. Sydenstricker's contributions in the fields of hematology and nutritional disease are legion. His landmark work in sickle cell anemia characterized a definite symptom complex with specific hematologic findings and inheritance pattern. He wrote on the complications of malnutrition and attempted to delineate the specific effects of individual nutritional factors. Dr. Sydenstricker and his associate H. M. Cleckley first described the syndrome of niacin deficiency encephalopathy. Today, the syndrome is still occasionally reported. Niacin deficiency should be considered when unexplained acute confusional states or neurologic deficits occur in the setting of malnutrition, antituberculous drug use, or chronic partial nutritional deficiency with acute increase in metabolic demand.

PMID: 3043684 [PubMed - indexed for MEDLINE]

Nutr Cancer. 2003;46(2):110-8.

# Niacin and carcinogenesis.

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## Abstract

The dietary status of niacin (vitamin B3) has the potential to influence DNA repair, genomic stability, and the immune system, eventually having an impact on cancer risk, as well as the side effects of chemotherapy in the cancer patient. In addition to its well-known redox functions in energy metabolism, niacin, in the form of NAD, participates in a wide variety of ADP-ribosylation reactions. Poly(ADP-ribose) is a negatively charged polymer synthesized, predominantly on nuclear proteins, by at least seven different enzymes. Poly(ADP-ribose) polymerase-1 (PARP-1) is responsible for the majority of polymer synthesis and plays important roles in DNA damage responses, including repair, maintenance of genomic stability, and signaling events for stress responses such as apoptosis. NAD is also used in the synthesis of mono(ADP-ribose), often on G proteins, with poorly understood roles in signal transduction. Last, NAD and NADP are required for the synthesis of cyclic ADP-ribose and nicotinic acid adenine dinucleotide (NAADP), two mediators of intracellular calcium signaling pathways. Disruption of any of these processes has the potential to impair genomic stability and deregulate cell division, leading to enhanced cancer risk. There are various sources of evidence that niacin status does have an impact on cancer risk, including animal models of leukemogenesis and skin cancer, as well as epidemiological data from human populations.

PMID: 14690785 [PubMed - indexed for MEDLINE]

Nutr Cancer. 2003;45(1):124-31.

# Chronic DNA damage and niacin deficiency enhance cell injury and cause unusual interactions in NAD and poly(ADP-ribose) metabolism in rat bone marrow.

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## Abstract

Previous work has shown that niacin deficiency in rats increases the severity of ethylnitrosourea (ENU)-induced anemia and leukopenia and the long-term development of cancer. The current study was initially designed to characterize changes in bone marrow cell populations during ENU treatment in this model. Weanling Long-Evans rats were fed diets containing 0 or 30 mg/kg of added niacin for a period of 2-3 wk. ENU treatment started after 1 wk of feeding and consisted of either 4 or 8 doses of ENU delivered by gavage, every other day. Niacin deficiency (ND) alone caused a significant depression in nucleated red blood cells (30%), and a sporadic effect on granulocytes (+23% after 4 doses of vehicle, -29% after 8 doses of vehicle). ENU treatment, after only 4 doses, caused a large decline in the numbers of bone marrow cells, and this effect was enhanced by ND (ENU decreased lymphocytes by 66% in pair-fed (PF) and 86% in ND, granulocytes by 41% in PF and 64% in ND, and nucleated red blood cells by 63% in PF and 71% in ND). Cell cycle distribution suggested that bone marrow cells in niacin-adequate rats, but not ND rats, mounted a compensatory proliferative response during chronic ENU exposure. ND alone caused an 80% decrease in bone marrow NAD+ levels at all time points. Surprisingly, chronic exposure to ENU (which should cause DNA damage and NAD+ utilization) led to a 2.8-fold increase in NAD+ content in ND marrow cells. This finding led to a second study in which ND and niacin-adequate PF control rats received 7 doses of ENU or vehicle (CON), after which all rats received 1 dose of ENU. In this study, modestly enhanced bone marrow NAD+ in chronically treated PF rats was used to synthesize 2-fold greater amounts of poly(ADP-ribose) than seen after one acute dose of ENU, while this did not occur in chronically treated ND rats, in spite of a 2.8-fold increase in bone marrow NAD+. This study has shown that bone marrow cell populations are sensitized to ENU treatment by ND, that NAD+ pools are regulated in response to

DNA damage, and that NAD+ localization and/or utilization in the nucleus is altered during ND and chronic DNA damage.

PMID: 12791512 [PubMed - indexed for MEDLINE]

J Nutr. 2002 Jan;132(1):115-20.

# Pharmacological intakes of niacin increase bone marrow poly(ADP-ribose) and the latency of ethylnitrosourea-induced carcinogenesis in rats.

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## Abstract

Cancer chemotherapy agents cause short-term leukopenia during treatment and the development of secondary leukemias after recovery from the original disease. We reported that niacin deficiency in rats increases the severity of nitrosourea-induced leukopenia and the subsequent development of cancers. This study was designed to test the effects of supplementing an already high quality diet with pharmacologic levels of niacin. For a period of 4 wk, nontumor-bearing weanling Long-Evans rats were pair-fed AIN-93M diets that were niacin adequate (30 mg/kg diet) or pharmacologically supplemented (4 g/kg diet) with nicotinic acid (NA) or nicotinamide (Nam). One week after the initiation of niacin feeding protocols, ethylnitrosourea (ENU) treatment began (12 doses, 30 mg/kg by gavage, every other day). ENU treatment caused leukopenia, which was not prevented by niacin supplementation. At the end of ENU treatment, all rats were switched to a niacin-adequate diet and monitored. Within 36 wk after the start of treatment, all of the ENU-treated rats either lost 5% of peak body weight or had palpable tumors > 1 cm in diameter, and were necropsied. Supplementation with NA or Nam at 4.0 g/kg diet (combined analysis) increased the latency of the ENU-induced morbidity curve, relative to niacin-adequate controls. Morbidity could be attributed in almost all cases to some form of neoplasm, with leukemias the predominant form. In short-term studies, supplementation with either NA or Nam caused dramatic increases in bone marrow NAD(+) (1- to 1.5-fold), basal poly(ADP-ribose) (3- to 5-fold) and ENU-induced poly(ADP-ribose) levels (1.5-fold). These data show that supplementation of a niacin-adequate, high quality diet with pharmacologic levels of nicotinic acid or nicotinamide increases NAD(+) and poly(ADP-ribose) levels in bone marrow and may be protective against DNA damage.

PMID: 11773517 [PubMed - indexed for MEDLINE]

FEBS Lett. 2001 Sep 14;505(2):255-8.

# Hyperlipemia: a role in regulating UCP3 gene expression in skeletal muscle during cancer cachexia?

Busquets S, Carbó N, Almendro V, Figueras M, López-Soriano FJ, Argilés JM.

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## Abstract

Rats bearing the Yoshida AH-130 ascites hepatoma showed an increased expression of both uncoupling protein-2 (UCP2) (two-fold) and UCP3 (three- to four-fold) in skeletal muscle (both soleus and gastrocnemius). The increase in mRNA content was associated with increased circulating concentrations of fatty acids (two-fold), triglyceride (two-fold) and cholesterol (1.9-fold). Administration of nicotinic acid to tumor-bearing rats abolishes the hyperlipidemic increase associated with tumor burden. The vitamin treatment also resulted in a decreased UCP3 gene expression in soleus muscle but not in gastrocnemius. It is concluded that circulating fatty acids may be involved in the regulation of UCP3 gene expression in aerobic muscles during experimental cancer cachexia. Since the UCP3 protein could have a role in energy expenditure, it may be suggested that hypolipidemic agents may have a beneficial role in the treatment of the cachectic syndrome.

PMID: 11566186 [PubMed - indexed for MEDLINE]

Mutat Res. 2001 Apr 18;475(1-2):7-20.

# DNA damage from micronutrient deficiencies is likely to be a major cause of cancer.

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## Abstract

A deficiency of any of the micronutrients: folic acid, Vitamin B12, Vitamin B6, niacin, Vitamin C, Vitamin E, iron, or zinc, mimics radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions, or both. For example, the percentage of the US population that has a low intake (<50% of the RDA) for each of these eight micronutrients ranges from 2 to >20%. A level of folate deficiency causing chromosome breaks was present in approximately 10% of the US population, and in a much higher percentage of the poor. Folate deficiency causes extensive incorporation of uracil into human DNA (4 million/cell), leading to chromosomal breaks. This mechanism is the likely cause of the increased colon cancer risk associated with low folate intake. Some evidence, and mechanistic considerations, suggest that Vitamin B12 (14% US elderly) and B6 (10% of US) deficiencies also cause high uracil and chromosome breaks. Micronutrient deficiency may explain, in good part, why the quarter of the population that eats the fewest fruits and vegetables (five portions a day is advised) has about double the cancer rate for most types of cancer when compared to the quarter with the highest intake. For example, 80% of American children and adolescents and 68% of adults do not eat five portions a day. Common micronutrient deficiencies are likely to damage DNA by the same mechanism as radiation and many chemicals, appear to be orders of magnitude more important, and should be compared for perspective. Remedying micronutrient deficiencies should lead to a major improvement in health and an increase in longevity at low cost.

PMID: 11295149 [PubMed - indexed for MEDLINE]

Cancer Detect Prev. 2000;24(3):295-303.

# Nutrient intake and esophageal cancer in the Caspian littoral of Iran: a case-control study.

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## Abstract

The purpose of this study was to investigate the possible contribution of different dietary nutrients in the development of esophageal cancer (EC) in the Caspian littoral of Iran. Forty-one cases and 145 members of their households were matched for age and gender with 40 non-blood-relative controls and 130 members of their households for their nutrient intake. A standard 24-hour dietary recall questionnaire was used to estimate the daily intake of energy, protein, P, Fe, Na, K, vitamins C and A, thiamin, riboflavin, and niacin. Dietary nutrient deficiency was defined as less than 75% of the World Health Organization human nutritional requirements, except for P, Na, and K, for which the United States Recommended Dietary Allowances were followed. The results indicate the following: (1) The mean daily intake of all nutrients, except for riboflavin, was significantly lower in cases than in control subjects ($P < .05$); (2) with the exception of protein, riboflavin, and phosphorus, significant correlation was observed between the pattern of nutrient intake and health status of the study subjects ($P < .05$); and (3) dietary deficiency of niacin and phosphorus was associated significantly with the risk of EC development among case and control households ($P < .01$-$.001$), indicating that persons living in case households with dietary deficiencies of these nutrients have more than twice the risk of developing EC tumors than those living in control households. In conclusion, apparently some nutrients, such as P and niacin, may play a role in the etiology of esophageal cancer, and the status of these nutrients may be used eventually as an epidemiologic predictive marker for EC in the Caspian littoral of Iran and perhaps other regions.

PMID: 10975293 [PubMed - indexed for MEDLINE]

J Nutr. 2000 May;130(5):1102-7.

# Niacin deficiency in rats increases the severity of ethylnitrosourea-induced anemia and leukopenia.

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## Abstract

Many chemotherapeutic agents function by damaging the DNA of rapidly dividing cells, leading to side effects in the bone marrow, including anemia and leukopenia during chemotherapy and the development of secondary leukemias in the years following recovery from the original disease. We have created an animal model of alkylation-based chemotherapy, in nontumor-bearing rats, to investigate the effect of niacin deficiency on the side effects of chemotherapy [2 x 2 design, niacin-deficient (ND) vs. pair-fed (PF) control, and ethylnitrosourea (ENU) vs. vehicle control (C)]. Weanling Long-Evans rats were fed ND diet or PF niacin replete diet for 4 wk. ENU or C treatment started after 1 wk of feeding and consisted of 12 doses delivered by gavage, every other day. At 4 wk postweaning, niacin deficiency and ENU treatment ended, the rats were fed a high-quality control diet (AIN-93M) and the recovery of blood variables was monitored. ND alone decreased growth rate and caused anemia and neutrophilia. ENU treatment alone caused anemia, lymphopenia, neutropenia and an increase in circulating reticulocytes. In combination, ND and ENU treatment synergistically decreased hematocrit. ND prevented the ENU-induced increase in reticulocyte numbers observed in control rats. ND also increased the severity of ENU-induced lymphopenia. A combination of ND and ENU abolished the neutrophilia caused by ND alone. In summary, ND significantly increased the susceptibility of young Long-Evans rats to ENU-induced bone marrow suppression, suggesting that niacin-deficient cancer patients may benefit from supplementation.

PMID: 10801905 [PubMed - indexed for MEDLINE]

Ann N Y Acad Sci. 1999;889:87-106.

# Micronutrient deficiencies. A major cause of DNA damage.

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## Abstract

Deficiencies of the vitamins B12, B6, C, E, folate, or niacin, or of iron or zinc mimic radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions, or both. The percentage of the population of the United States that has a low intake (< 50% of the RDA) for each of these eight micronutrients ranges from 2% to 20+ percent. A level of folate deficiency causing chromosome breaks occurred in approximately 10% of the population of the United States, and in a much higher percentage of the poor. Folate deficiency causes extensive incorporation of uracil into human DNA (4 million/cell), leading to chromosomal breaks. This mechanism is the likely cause of the increased colon cancer risk associated with low folate intake. Some evidence, and mechanistic considerations, suggest that vitamin B12 and B6 deficiencies also cause high uracil and chromosome breaks. Micronutrient deficiency may explain, in good part, why the quarter of the population that eats the fewest fruits and vegetables (five portions a day is advised) has about double the cancer rate for most types of cancer when compared to the quarter with the highest intake. Eighty percent of American children and adolescents and 68% of adults do not eat five portions a day. Common micronutrient deficiencies are likely to damage DNA by the same mechanism as radiation and many chemicals, appear to be orders of magnitude more important, and should be compared for perspective. Remedying micronutrient deficiencies is likely to lead to a major improvement in health and an increase in longevity at low cost.

PMID: 10668486 [PubMed - indexed for MEDLINE]

Ann N Y Acad Sci. 2002 May;957:250-9.

# Protective effects of a novel niacin-bound chromium complex and a grape seed proanthocyanidin extract on advancing age and various aspects of syndrome X.

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## Abstract

Aging is the progressive accumulation of changes with time that are responsible for the ever-increasing likelihood of disease and death. The precise cascade of pathological events mainly responsible for aging are still not clearly understood, but enhanced production of free radicals and its deleterious effects on proteins, nucleic acids, and fats, as well as enhanced glycosylation of proteins and DNA are prevalent during aging. Insulin resistance may be a common etiology, at least in part, behind the pathobiological alterations of advancing age. Prevalent age-related disorders such as cardiovascular diseases, obesity, and cancer have been associated with impaired glucose/insulin metabolism and its consequences. This leads to future strategies to combat the aging process and chronic disorders such as the components of syndrome X associated with aging. Increasing the intake of antioxidants and/or substances recognized to enhance insulin sensitivity is a natural means of combatting the glucose/insulin perturbations and free radical damage. Accordingly, ingestion of niacin-bound chromium and natural antioxidants such as grape seed proanthocyanidin extract has been demonstrated to improve insulin sensitivity and/or ameliorate free radical formation and reduce the signs/symptoms of chronic age-related disorders including syndrome X. These natural strategies possess a highly favorable risk/benefit ratio.

PMID: 12074977 [PubMed - indexed for MEDLINE]