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Journal
ABSTRACTS**Nuclear factor-kappa Beta (nNfkbB)****IKKBETA LINKS INFLAMMATION****AND TUMORIGENESIS IN A MOUSE MODEL OF COLITIS-ASSOCIATED CANCER.**

A link between inflammation and cancer has long been suspected, but its molecular nature remained ill defined. A key player in inflammation is transcription factor NF-kappaB whose activity is triggered in response to infectious agents and proinflammatory cytokines via the IkappaB kinase (IKK) complex. Using a colitis-associated cancer model, we show that although deletion of IKKbeta in intestinal epithelial cells does not decrease inflammation, it leads to a dramatic decrease in tumor incidence without affecting tumor size. This is linked to increased epithelial apoptosis during tumor promotion. Deleting IKKbeta in myeloid cells, however, results in a significant decrease in tumor size. This deletion diminishes expression of proinflammatory cytokines that may serve as tumor growth factors, without affecting apoptosis. Thus, specific inactivation of the IKK/NF-kappaB pathway in two different cell types can attenuate formation of inflammation-associated tumors. In addition to suppressing apoptosis in advanced tumors, IKKbeta may link inflammation to cancer.

Cell. 2004 Aug 6;118(3):285-96

REACTIVE OXYGEN SPECIES PROMOTE TNFALPHA-INDUCED DEATH AND SUSTAINED JNK ACTIVATION BY INHIBITING MAP KINASE PHOSPHATASES.

TNFalpha is a pleiotropic cytokine that induces either cell proliferation or cell death. Inhibition of NF-kappaB activation increases susceptibility to TNFalpha-induced death, concurrent with sustained JNK activation, an important contributor to the death response. Sustained JNK activation in NF-kappaB-deficient cells was suggested to depend on reactive oxygen species (ROS), but how ROS affect JNK activation was unclear. We now show that TNFalpha-induced ROS, whose accumulation is suppressed by mitochondrial superoxide dismutase, cause oxidation and inhibition of JNK-inactivating phosphatases by converting their catalytic cysteine to sulfenic acid. This results in sustained JNK activation, which is required for cytochrome c release and caspase 3 cleavage, as well as necrotic cell death. Treatment of cells or experimental animals with an antioxidant prevents H₂O₂ accumulation, JNK phosphatase oxidation, sustained JNK activity, and both forms of cell death. Antioxidant treatment also prevents TNFalpha-mediated fulminant liver failure without affecting liver regeneration.

Cell. 2005 Mar 11;120(5):649-61

NF-KAPPAB: LINKING INFLAMMATION AND IMMUNITY TO CANCER DEVELOPMENT AND PROGRESSION.

There has been much effort recently to probe the long-recognized relationship between the pathological processes of infection, inflammation and cancer. For example, epidemiological studies have shown that approximately 15% of human deaths from cancer are associated with chronic viral or bacterial infections. This Review focuses on the molecular mechanisms that connect infection, inflammation and cancer, and it puts forward the hypothesis that activation of nuclear factor-kappaB (NF-kappaB) by the classical, IKK-beta (inhibitor-of-NF-kappaB kinase-beta)-dependent pathway is a crucial mediator of inflammation-induced tumour growth and progression, as well as an important modulator of tumour surveillance and rejection.

Nat Rev Immunol. 2005 Oct;5(10):749-59

CARDIOVASCULAR EVENTS ASSOCIATED WITH ROFECOXIB IN A COLORECTAL ADENOMA CHEMOPREVENTION TRIAL.

BACKGROUND: Selective inhibition of cyclooxygenase-2 (COX-2) may be associated with an increased risk of thrombotic events, but only limited long-term data have been available for analysis. We report on the cardiovascular outcomes associated with the use of the selective COX-2 inhibitor rofecoxib in a long-term, multicenter, randomized, placebo-controlled, double-blind

trial designed to determine the effect of three years of treatment with rofecoxib on the risk of recurrent neoplastic polyps of the large bowel in patients with a history of colorectal adenomas. METHODS: A total of 2,586 patients with a history of colorectal adenomas underwent randomization: 1,287 were assigned to receive 25 mg of rofecoxib daily, and 1,299 to receive placebo. All investigator-reported serious adverse events that represented potential thrombotic cardiovascular events were adjudicated in a blinded fashion by an external committee. RESULTS: A total of 46 patients in the rofecoxib group had a confirmed thrombotic event during 3,059 patient-years of follow-up (1.50 events per 100 patient-years), as compared with 26 patients in the placebo group during 3,327 patient-years of follow-up (0.78 event per 100 patient-years); the corresponding relative risk was 1.92 (95% confidence interval, 1.19 to 3.11; P=0.008). The increased relative risk became apparent after 18 months of treatment; during the first 18 months, the event rates were similar in the two groups. The results primarily reflect a greater number of myocardial infarctions and ischemic cerebrovascular events in the rofecoxib group. There was earlier separation (at approximately five months) between groups in the incidence of nonadjudicated investigator-reported congestive heart failure, pulmonary edema, or cardiac failure (hazard ratio for the comparison of the rofecoxib group with the placebo group, 4.61; 95% confidence interval, 1.50 to 18.83). Overall and cardiovascular mortality was similar in the two groups. CONCLUSIONS: Among patients with a history of colorectal adenomas, the use of rofecoxib was associated with an increased cardiovascular risk.

N Engl J Med. 2005 Mar 17;352(11):1092-102

NF-KAPPAB REGULATION IN THE IMMUNE SYSTEM.

The nuclear factor-kappaB (NF-kappaB)/REL family of transcription factors has a central role in coordinating the expression of a wide variety of genes that control immune responses. There has been intense scientific activity in the NF-kappaB field owing to the involvement of these factors in the activation and regulation of key molecules that are associated with diseases ranging from inflammation to cancer. In this review, we focus on our current understanding of NF-kappaB regulation and its role in the immune system and inflammatory diseases. We also discuss the role of NF-kappaB proteins as potential therapeutic targets in clinical applications.

Nat Rev Immunol. 2002 Oct;2(10):725-34

GASTRIC CANCER ORIGINATING FROM BONE MARROW-DERIVED CELLS.

Epithelial cancers are believed to originate from transformation of tissue stem cells. However, bone marrow-derived cells (BMDCs), which are frequently recruited to sites of tissue injury and inflammation, might also represent a potential source of malignancy. We show that although acute injury, acute inflammation, or transient parietal cell loss within the stomach do not lead to BMDC recruitment, chronic infection of C57BL/6 mice with *Helicobacter*, a known carcinogen, induces repopulation of the stomach with BMDCs. Subsequently, these cells progress through metaplasia and dysplasia to intraepithelial cancer. These findings suggest that epithelial cancers can originate from marrow-derived sources and thus have broad implications for the multistep model of cancer progression.

Science. 2004 Nov 26;306(5701):1568-71

N-3 FATTY ACIDS AND PREGNANCY OUTCOMES.

PURPOSE OF REVIEW: To discuss new data from the literature on the relationship between the supply of n-3 polyunsaturated fatty acids during pregnancy and pregnancy outcomes, evaluated as the fatty acid composition of blood and breast milk, fetal and infantile development and maternal health. **RECENT FINDINGS:** Supplementation of alpha-linolenic acid in high doses or docosahexaenoic acid in low doses did not result in a significant enhancement of the blood docosahexaenoic acid status of the offspring. In contrast, supplementation of docosahexaenoic acid in relatively high doses led to significant increases in infantile docosahexaenoic acid values and to a significant enhancement of breast milk docosahexaenoic acid content. Electroretinogram data obtained during the first week of life and pattern-reversal visual evoked potentials investigated at 50 and 66 weeks postconception were significantly associated with the docosahexaenoic acid status of the infant at birth. Children whose mothers received docosahexaenoic acid supplementation during pregnancy and lactation scored better in mental processing tests carried out at 4 years than children whose mothers received placebo. **SUMMARY:** Beneficial health outcomes are more likely to result from supplementation with docosahexaenoic acid itself, rather than its precursor alpha-linolenic acid. Trials have shown that a higher maternal docosahexaenoic acid intake during pregnancy may be favourable for the visual and cognitive development of the offspring. The significant positive association between maternal docosahexaenoic acid intake during pregnancy and the children's mental processing scores at 4 years suggest that optimization of the docosahexaenoic acid status of expectant women may offer long-term developmental benefits to their children.

Curr Opin Clin Nutr Metab Care. 2005 Mar;8(2):161-6

THE OXFORD-DURHAM STUDY: A RANDOMIZED, CONTROLLED TRIAL OF DIETARY SUPPLEMENTATION WITH FATTY ACIDS IN CHILDREN WITH DEVELOPMENTAL COORDINATION DISORDER.

BACKGROUND: Developmental coordination disorder (DCD) affects approximately 5% of school-aged children. In addition to the core deficits in motor function, this condition is associated commonly with difficulties in learning, behavior, and psychosocial adjustment that persist into adulthood. Mounting evidence suggests that a relative lack of certain polyunsaturated fatty acids may contribute to related neurodevelopmental and psychiatric disorders such as dyslexia and attention-deficit/hyperactivity disorder. Given the current lack of effective, evidence-based treatment options for DCD, the use of fatty acid supplements merits investigation. **METHODS:** A randomized, controlled trial of dietary supplementation with omega-3 and omega-6 fatty acids, compared with placebo, was conducted with 117 children with DCD (5-12 years of age). Treatment for 3 months in parallel groups was followed by a 1-way crossover from placebo to active treatment for an additional 3 months. **RESULTS:** No effect of treatment on motor skills was apparent, but significant improvements for active treatment versus placebo were found in reading, spelling, and behavior over 3 months of treatment in parallel groups. After the crossover, similar changes were seen in the placebo-active group, whereas children continuing with active treatment maintained or improved their progress. **CONCLUSIONS:** Fatty acid supplementation may offer a safe efficacious treatment option for educational and behavioral problems among children with DCD. Additional work is needed to investigate whether our inability to detect any improvement in motor skills reflects the measures used and to assess the durability of treatment effects on behavior and academic progress.

Pediatrics. 2005 May;115(5):1360-6

DIRECTLY QUANTITATED DIETARY (N-3) FATTY ACID INTAKES OF PREGNANT CANADIAN WOMEN ARE LOWER THAN CURRENT DIETARY RECOMMENDATIONS.

During pregnancy, (n-3) PUFA are incorporated into fetal brain and retinal lipids. Docosahexaenoic acid [DHA, 22:6(n-3)], in particular, is required physiologically for optimal development and function of the central nervous system. Maternal intake of (n-3) PUFA must be sufficient to maintain maternal tissues stores and meet fetal accrument. Recommendations for pregnant women include an Acceptable Macronutrient Distribution Range (AMDR) of 0.6-1.2% of energy for (n-3) PUFA intake in the current Dietary Reference Intakes, and > or =300 mg/d of DHA suggested by the International Society for the Study of Fatty Acids and Lipids working group. The present study directly quantitated the (n-3) PUFA intake, including DHA, of pregnant, Canadian women (n = 20) in their 2nd and 3rd trimester. Fatty acid intakes were quantitated in triplicate by lipid extraction and GLC of 3-d duplicate food collections calibrated with an internal standard before homogenization. Total fat intakes were also estimated using dietary analysis software from simultaneous 3-d food records to corroborate biochemical analyses. The mean (n-3) PUFA intake was 0.57 +/- 0.06% of energy, with 65% of the women below the AMDR. The mean DHA intake was 82 +/- 33 mg/d, with 90% of

the women consuming <300 mg/d. Nutritional education of pregnant women to ensure adequate intakes of (n-3) PUFA for optimal health of mother and child and the inclusion of DHA in prenatal vitamins may be pertinent.

J Nutr. 2005 Feb;135(2):206-11

ESSENTIAL FATTY ACID TRANSFER AND FETAL DEVELOPMENT.

Docosahexaenoic acid (22:6n-3) and arachidonic acid (20:4n-6) are important structural components of the central nervous system. These fatty acids are transferred across the placenta, and are accumulated in the brain and other organs during fetal development. Depletion of 22:6n-3 from the retina and brain results in reduced visual function and learning deficits: these may involve critical roles of 22:6n-3 in membrane-dependent signaling pathways and neurotransmitter metabolism. Transfer of 22:6n-3 across the placenta involves specific binding and transfer proteins that facilitate higher concentrations of 22:6n-3 and 20:4n-6, but lower linoleic acid (18:2n-6) in fetal compared with maternal plasma, or in the breast-fed or formula-fed infant. However, human and animal studies both demonstrate that maternal diet impacts fetal 22:6n-3 and 20:4n-6 accretion. After birth, parenteral lipid, human milk and infant formula feeding all result in a marked decrease in plasma 22:6n-3 and 20:4n-6 and an increase in 18:2n-6. Estimation of fetal tissue fatty acid accretion suggests that current preterm infant feeds are unlikely to meet in utero rates of 22:6n-3 accretion. Consideration needs to be given to whether fetal plasma 22:6n-3 and 20:4n-6 enrichment and the low 18:2n-6 facilitates accretion of 22:6n-3 and 20:4n-6 in developing tissues.

Placenta. 2005 Apr;26 Suppl A:S70-5

CAN PRENATAL N-3 FATTY ACID DEFICIENCY BE COMPLETELY REVERSED AFTER BIRTH? EFFECTS ON RETINAL AND BRAIN BIOCHEMISTRY AND VISUAL FUNCTION IN RHESUS MONKEYS.

Our previous studies of rhesus monkeys showed that combined prenatal and postnatal n-3 fatty acid deficiency resulted in reduced visual acuity, abnormal retinal function, and low retina and brain docosahexaenoic acid content. We now report effects of n-3 fatty acid deficiency during intrauterine development only. Rhesus infants, born to mothers fed an n-3 fatty acid deficient diet throughout pregnancy, were repleted with a diet high in alpha-linolenic acid from birth to 3y. Fatty acid composition was determined for plasma and erythrocytes at several time points, for prefrontal cerebral cortex biopsies at 15, 30, 45, and 60 wk, and for cerebral cortex and retina at 3 y. Visual acuity was determined behaviorally at 4, 8, and 12 postnatal weeks, and the electroretinogram was recorded at 3-4 mo. Total n-3 fatty acids were reduced by 70-90% in plasma, erythrocytes, and tissues at birth but recovered to control values within 4 wk in plasma, 8 wk in erythrocytes, and 15 wk in cerebral cortex. At 3 y, fatty acid composition was normal in brain phospholipids, but in the retina DHA recovery was incomplete (84% of controls). Visual acuity thresholds did not differ from those of control infants from mothers fed a high linolenic acid diet. However, the repleted group had lower amplitudes of cone and rod ERG a-waves. These data suggest that restriction of n-3 fatty acid intake during the prenatal period may have long-term effects on retinal fatty acid composition and function.

Pediatr Res. 2005 Nov;58(5):865-72

A QUANTITATIVE ANALYSIS OF PRENATAL INTAKE OF N-3 POLYUNSATURATED FATTY ACIDS AND COGNITIVE DEVELOPMENT.

Although a rich source of n-3 polyunsaturated fatty acids (PUFAs) that may confer multiple health benefits, some fish also contain methyl mercury (MeHg), which may harm the developing fetus. US government recommendations for women of childbearing age are to modify consumption of high-MeHg fish to reduce MeHg exposure, while recommendations encourage fish consumption among the general population because of the nutritional benefits. The Harvard Center for Risk Analysis convened an expert panel (see acknowledgements) to quantify the net impact of resulting hypothetical changes in fish consumption across the population. This paper estimates the impact of prenatal n-3 intake on cognitive development. Other papers quantify the negative impact of prenatal exposure to MeHg on cognitive development, and the extent to which fish consumption protects against coronary heart disease mortality and stroke in adults. This paper aggregates eight randomized controlled trials (RCTs) comparing cognitive development in controls and in children who had received n-3 PUFA supplementation (seven studies of formula supplementation and one study of maternal dietary supplementation). Our analysis assigns study weights accounting for statistical precision, relevance of three endpoint domains (general intelligence, verbal ability, and motor skills) to prediction of IQ, and age at evaluation. The study estimates that increasing maternal docosahexaenoic acid (DHA) intake by 100 mg/day increases child IQ by 0.13 points. The paper notes that findings were inconsistent across the RCTs evaluated (although our findings were relatively robust to changes in the weighting scheme used). Also, for seven of the eight studies reviewed, effects are extrapolated from formula supplementation to maternal dietary intake.

Am J Prev Med. 2005 Nov;29(4):366-74

MATERNAL FISH OIL SUPPLEMENTATION IN LACTATION AND GROWTH DURING THE FIRST 2.5 YEARS OF LIFE.

Fish oil addition to infant formulas has raised concern on whether increased intake of n-3 long-chain polyunsaturated fatty acid (n-3LCPUFA) affects infant growth. The objective of this study was to determine whether maternal fish oil supplementation during 0-4 mo of lactation influences growth in infancy and early childhood. In a randomized, blinded intervention trial, lactating Danish mothers with a fish intake below the population median were randomized to 4.5 g/d fish oil or olive oil. A reference group of 53 mothers with a fish intake in the highest quartile of the population and their infants were included in the study. Head circumference, weight, length, skinfold thickness, and waist circumference of children were measured at 2, 4, and 9 mo and at 2.5 y. One hundred children completed the intervention trial, and 72 were followed up at 2.5 y together with 29 from the reference group. Growth in weight, length, and head circumference did not differ between the randomized groups up to 9 mo, but at 2.5 y, body composition differed significantly. Children in the fish oil group had larger waist circumference body mass index (BMI; 0.6 kg/m²; $p = 0.022$), and head circumference compared with those in the olive oil group. Adjusted for sex, ponderal index at birth and current energy intake, BMI at 2.5 y was associated with docosahexaenoic acid in maternal erythrocytes after the intervention. In conclusion, the n-3LCPUFA intake of lactating mothers may be important for growth of young children. The long-term effect on weight and BMI remains to be investigated.

Pediatr Res. 2005 Aug;58(2):235-42

MATERNAL FISH OIL SUPPLEMENTATION IN LACTATION: EFFECT ON DEVELOPMENTAL OUTCOME IN BREAST-FED INFANTS.

Docosahexaenoic acid (DHA) accumulates in the brain during the 1st and 2nd years of life. The objective of this study was to see if an increased content of DHA in breast-milk via maternal fish oil (FO)-supplementation affects mental development in term infants. One hundred twenty-two Danish mothers with a habitual fish intake below the population median were randomized to 4.5 g.d(-1) of FO or olive oil (OO) for the first four months of lactation. Fifty-three mothers with habitual fish intake in the highest quartile were included as reference group. The effect of the resulting increase in infant DHA-intake and RBC-DHA level was assessed on problem solving ability at nine months and language at one and two years of age. Infants in the three groups performed equally well on the problem test and no association was observed between problem solving and erythrocyte-DHA at four months. Passive vocabulary at one year was lower in the children of the FO- compared with the OO-group ($P < 0.05$), but no differences were found at two years of age. Word comprehension at one year was inversely associated with erythrocyte-DHA at four months. The trial indicates a small effect of DHA levels in breast-milk on early language development of breast-fed infants.

Reprod Nutr Dev. 2005 Sep-Oct;45(5):535-47

BREASTFEEDING, VERY LONG POLYUNSATURATED FATTY ACIDS (PUFA) AND IQ AT 6 1/2 YEARS OF AGE.

AIM: Breastfeeding seems to be favorable for cognitive development. Could levels of polyunsaturated fatty acids (PUFA) explain this? METHODS: Pregnant mothers were recruited consecutively at maternity care centres. PUFA were analysed in colostrum and breast milk at 1 and 3 mo. The product-precursor ratios of n-6+n-3 PUFA were examined as measures of activity in respective steps in the fatty acid metabolic chain. Also, the quotient between DHA and AA was analysed. The children were tested with the full WISC-III at 6.5 y. RESULTS: First, the influence of length of breastfeeding was analysed by multiple regression together with relevant cofactors (except for PUFA). In the best models, 46% of the variation in total IQ was explained. Length of breastfeeding contributed significantly to total IQ (beta = 0.228, $p = 0.021$), verbal IQ (beta = 0.204, $p = 0.040$) and performance IQ (beta = 0.210, $p = 0.056$). There were no significant single correlations between PUFA and measures of cognitive development. However, in multiple regression analysis of colostrum, significant beta-coefficients were found for steps 4+5 in the fatty acid metabolic chain (beta = 0.559, $p = 0.002$). If length of breastfeeding and gestation week were added to steps 4+5, this three-factor model could explain 67% of the variation of total IQ. Introducing length of breastfeeding and gestation week together with the quotient DHA/AA (beta = 0.510, $p < 0.001$) yielded a three-factor model, which explained 76% of the variation in total IQ. CONCLUSION: Our findings could be interpreted as supporting the importance of high levels of PUFA for cognitive development. However, the sample is small and the results must be interpreted with caution.

Acta Paediatr. 2004 Oct;93(10):1280-7

THE METABOLIC SYNDROME.

The metabolic syndrome is a common metabolic disorder that results from the increasing prevalence of obesity. The disorder is defined in various ways, but in the near future a new definition(s) will be applicable worldwide. The pathophysiology seems to be largely attributable to insulin resistance with excessive flux of fatty acids implicated. A proinflammatory state probably contributes to the syndrome. The increased risk for type 2 diabetes and cardiovascular disease demands therapeutic attention for those at high risk. The fundamental approach is weight reduction and increased physical activity; however, drug treatment could be appropriate for diabetes and cardiovascular disease risk reduction.

Lancet. 2005 Apr 16-22;365(9468):1415-28

ENDOGENOUS SEX HORMONES AND METABOLIC SYNDROME IN AGING MEN.

BACKGROUND: Sex hormone levels in men change during aging. These changes may be associated with insulin sensitivity and the metabolic syndrome. **METHODS:** We studied the association between endogenous sex hormones and characteristics of the metabolic syndrome in 400 independently living men between 40 and 80 yr of age in a cross-sectional study. Serum concentrations of lipids, glucose, insulin, total testosterone (TT), SHBG, estradiol (E2), and dehydroepiandrosterone sulfate (DHEA-S) were measured. Bioavailable testosterone (BT) was calculated using TT and SHBG. Body height, weight, waist-hip circumference, blood pressure, and physical activity were assessed. Smoking and alcohol consumption was estimated from self-report. The metabolic syndrome was defined according to the National Cholesterol Education Program definition, and insulin sensitivity was calculated by use of the quantitative insulin sensitivity check index. **RESULTS:** Multiple logistic regression analyses showed an inverse relationship according to 1 sd increase for circulating TT [odds ratio (OR) = 0.43; 95% confidence interval (CI), 0.32-0.59], BT (OR = 0.62; 95% CI, 0.46-0.83), SHBG (OR = 0.46; 95% CI, 0.33-0.64), and DHEA-S (OR = 0.76; 95% CI, 0.56-1.02) with the metabolic syndrome. Each sd increase in E2 levels was not significantly associated with the metabolic syndrome (OR = 1.16; 95% CI, 0.92-1.45). Linear regression analyses showed that higher TT, BT, and SHBG levels were related to higher insulin sensitivity; beta-coefficients (95% CI) were 0.011 (0.008-0.015), 0.005 (0.001-0.009), and 0.013 (0.010-0.017), respectively, whereas no effects were found for DHEA-S and E2. Estimates were adjusted for age, smoking, alcohol consumption, and physical activity score. Further adjustment for insulin levels and body composition measurements attenuated the estimates, and the associations were similar in the group free of cardiovascular disease and diabetes. **CONCLUSIONS:** Higher testosterone and SHBG levels in aging males are independently associated with a higher insulin sensitivity and a reduced risk of the metabolic syndrome, independent of insulin levels and body composition measurements, suggesting that these hormones may protect against the development of metabolic syndrome.

J Clin Endocrinol Metab. 2005 May;90(5):2618-23

MERCURY IN COMMERCIAL FISH: OPTIMIZING INDIVIDUAL CHOICES TO REDUCE RISK.

Most attention to the risks from fish consumption has focused on recreational anglers and on fish caught by individuals, but the majority of fish that people eat are purchased from commercial sources. We examined mercury levels in three types of fish (tuna, flounder, bluefish) commonly available in New Jersey stores, sampling different regions of the state, in communities with high and low per capita incomes, and in both supermarkets and specialty fish markets. We were interested in species-specific levels of mercury in New Jersey fish and whether these levels were similar to data generated nationally by the Food and Drug Administration (FDA; mainly from 1990 to 1992) on the same types of fish. Such information is critical for providing public health advice. We were also interested in whether mercury levels in three common species of fish differed by region of the state, economic neighborhood, or type of store. We found significant species differences, with tuna having the highest levels and flounder the lowest levels. There were no significant differences in mercury levels as a function of type of store or economic neighborhood. There was only one regional difference: flounder from fish markets along the Jersey shore had higher mercury levels than flounder bought in other markets. We also examined mercury levels in six other commonly available fish and two shellfish from central New Jersey markets. There were significant differences in availability and in mercury levels among fish and shellfish. Both shrimp and scallops had total mercury levels < 0.02 ppm (wet weight). Large shrimp had significantly lower levels of mercury than small shrimp. For tuna, sea bass, croaker, whiting, scallops, and shrimp, the levels of mercury were higher in New Jersey samples than those reported by the FDA. Consumers selecting fish for ease of availability (present in > 50% of markets) would select flounder, snapper, bluefish, and tuna (tuna had the highest mercury value), and those selecting only for

price would select whiting, porgy, croaker, and bluefish (all with average mercury levels < 0.3 ppm wet weight). Flounder was the fish with the best relationship among availability, cost, and low mercury levels. We suggest that state agencies responsible for protecting the health of their citizens should obtain information on fish availability in markets and fish preferences of diverse groups of citizens and use this information to select fish for analysis of contaminant levels, providing data on the most commonly eaten fish that will help people make informed decisions about risks from fish consumption.

Environ Health Perspect. 2005 Mar;113(3):266-71

MECHANISMS OF INSULIN RESISTANCE IN HUMANS AND POSSIBLE LINKS WITH INFLAMMATION.

Insulin resistance is a major player in the pathogenesis of the metabolic syndrome and type 2 diabetes, and yet, the mechanisms responsible for it remain poorly understood. Magnetic resonance spectroscopy studies in humans suggest that a defect in insulin-stimulated glucose transport in skeletal muscle is the primary metabolic abnormality in insulin-resistant type 2 diabetics. Fatty acids appear to cause this defect in glucose transport by inhibiting insulin-stimulated tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) and IRS-1 associated phosphatidylinositol 3-kinase activity. A number of different metabolic abnormalities may increase intramyocellular/intrahepatic fatty acid metabolites; these include increased fat delivery to muscle/liver as a consequence of either excess energy intake or defects in adipocyte fat metabolism and acquired or inherited defects in mitochondrial fatty acid oxidation. Understanding the molecular/ biochemical defects responsible for insulin resistance is beginning to unveil novel therapeutic targets for treatment of the metabolic syndrome and type 2 diabetes.

Hypertension. 2005 May;45(5):828-33

ANTI-INFLAMMATORY EFFECTS OF RESVERATROL IN LUNG EPITHELIAL CELLS: MOLECULAR MECHANISMS.

Resveratrol (3,4',5-trihydroxystilbene) is a polyphenolic stilbene found in the skins of red fruits, including grapes, that may be responsible for some of the health benefits ascribed to consumption of red wine. Resveratrol has been shown to have antioxidant properties and can act as an estrogen agonist. This study examined the anti-inflammatory effects of resveratrol on human airway epithelial cells. Resveratrol and the related molecule quercetin, but not deoxyrhapontin, inhibited IL-8 and granulocyte-macrophage colony-stimulating factor release from A549 cells. Neither the estrogen receptor antagonist tamoxifen nor the glucocorticoid antagonist mifepristone altered the inhibitory effect of resveratrol. The mechanism of resveratrol action was investigated further using luciferase reporter genes stably transfected into A549 cells. Resveratrol and quercetin inhibited NF-kappaB, activator protein-1-, and cAMP response element binding protein-dependent transcription to a greater extent than the glucocorticosteroid dexamethasone. These compounds also had no significant effect on acetylation or deacetylation of core histones. Resveratrol, but not estradiol or N-acetyl cysteine, inhibited cytokine-stimulated inducible nitric oxide synthase expression and nitrite production (IC50 = 3.6 +/- 2.9 microM) in human primary airway epithelial cells. Resveratrol also inhibited granulocyte-macrophage colony-stimulating factor release (IC50 = 0.44 +/- 0.17 microM), IL-8 release (IC50 = 4.7 +/- 3.3 microM), and cyclooxygenase-2 expression in these cells. This study demonstrates that resveratrol and quercetin have novel nonsteroidal anti-inflammatory activity that may have applications for the treatment of inflammatory diseases.

Am J Physiol Lung Cell Mol Physiol. 2004Oct;287(4):L774-83

IN VIVO QUERCITRIN ANTI-INFLAMMATORY EFFECT INVOLVES RELEASE OF QUERCETIN, WHICH INHIBITS INFLAMMATION THROUGH DOWN-REGULATION OF THE NF-KAPPAB PATHWAY.

Quercetin is a common antioxidant flavonoid found in vegetables, which is usually present in glycosylated forms, such as quercitrin (3-rhamnosylquercetin). Previous in vitro experiments have shown that quercetin exerts a bigger effect than quercitrin in the down-regulation of the inflammatory response. However, such results have not been reproduced in in vivo experimental models of intestinal inflammation, in which quercetin did not show beneficial effects while its glycosides, quercitrin or rutin, have demonstrated their effectiveness. In this study, we have reported that the in vivo effects of quercitrin in the experimental model of rat colitis induced by dextran sulfate sodium can be mediated by the release of quercetin generated after glycoside's cleavage by the intestinal microbiota. This is supported by the fact that quercetin, but not quercitrin, is able to down-regulate the inflammatory response of bone marrow-derived macrophages in vitro. Moreover, we have demonstrated that quercetin inhibits cytokine and inducible nitric oxide synthase expression through inhibition of the NF-kappaB pathway without modification of c-Jun N-terminal kinase activity (both in vitro and in vivo). As a conclusion, our report suggests that quercitrin releases quercetin in order to perform its anti-inflammatory effect which is mediated through the inhibition of the NF-kappaB pathway.

Eur J Immunol. 2005 Feb;35(2):584-92

ISOLATION AND CHARACTERIZATION OF POLYPHENOL TYPE-A POLYMERS FROM CINNAMON WITH INSULIN-LIKE BIOLOGICAL ACTIVITY.

The causes and control of type 2 diabetes mellitus are not clear, but there is strong evidence that dietary factors are involved in

its regulation and prevention. We have shown that extracts from cinnamon enhance the activity of insulin. The objective of this study was to isolate and characterize insulin-enhancing complexes from cinnamon that may be involved in the alleviation or possible prevention and control of glucose intolerance and diabetes. Water-soluble polyphenol polymers from cinnamon that increase insulin-dependent in vitro glucose metabolism roughly 20-fold and display antioxidant activity were isolated and characterized by nuclear magnetic resonance and mass spectroscopy. The polymers were composed of monomeric units with a molecular mass of 288. Two trimers with a molecular mass of 864 and a tetramer with a mass of 1,152 were isolated. Their protonated molecular masses indicated that they are A type doubly linked procyanidin oligomers of the catechins and/or epicatechins. These polyphenolic polymers found in cinnamon may function as antioxidants, potentiate insulin action, and may be beneficial in the control of glucose intolerance and diabetes.

J Agric Food Chem. 2004 Jan 14;52(1):65-70

ANTIOXIDANT PROPERTIES OF ROASTED COFFEE RESIDUES.

The antioxidant activity of roasted coffee residues was evaluated. Extraction with four solvents (water, methanol, ethanol, and n-hexane) showed that water extracts of roasted coffee residues (WERCR) produced higher yields and gave better protection for lipid peroxidation. WERCR showed a remarkable protective effect on oxidative damage of protein. In addition, WERCR showed scavenging of free radicals as well as the reducing ability and to bind ferrous ions, indicating that WERCR acts as both primary and secondary antioxidants. The HPLC analyses showed that phenolic acids (chlorogenic acid and caffeic acid) and nonphenolic compounds [caffeine, trigonelline, nicotinic acid, and 5-(hydroxymethyl)furfuraldehyde] remained in roasted coffee residues. These compounds showed a protective effect on a liposome model system. The concentrations of flavonoids and polyphenolic compounds in roasted coffee residues were 8,400 and 20,400 ppm, respectively. In addition, the Maillard reaction products (MRPs) remaining in roasted coffee residues were believed to show antioxidant activity. These data indicate that roasted coffee residues have excellent potential for use as a natural antioxidant source because the antioxidant compounds remained in roasted coffee residues.

J Agric Food Chem. 2005 Apr 6;53(7):2658-63

A CHLOROGENIC ACID-INDUCED INCREASE IN GLP-1 PRODUCTION MAY MEDIATE THE IMPACT OF HEAVY COFFEE CONSUMPTION ON DIABETES RISK.

Recent prospective epidemiology links heavy coffee consumption to a substantial reduction in risk for type 2 diabetes. Yet there is no evidence that coffee improves insulin sensitivity and, at least in acute studies, caffeine has a negative impact in this regard. Thus, it is reasonable to suspect that coffee influences the risk for beta cell "failure" that precipitates diabetes in subjects who are already insulin resistant. Indeed, there is recent evidence that coffee increases production of the incretin hormone glucagon-like peptide-1 (GLP-1), possibly owing to an inhibitory effect of chlorogenic acid (CGA — the chief polyphenol in coffee) on glucose absorption. GLP-1 acts on beta cells, via cAMP-dependent mechanisms, to promote the synthesis and activity of the transcription factor IDX-1, crucial for maintaining the responsiveness of beta cells to an increase in plasma glucose. Conversely, the "glucolipotoxicity" thought to initiate and sustain beta cell dysfunction in diabetics can suppress expression of this transcription factor. The increased production of GLP-1 associated with frequent coffee consumption could thus be expected to counteract the adverse impact of chronic free fatty acid overexposure on beta cell function in overweight insulin resistant subjects. CGA's putative impact on glucose absorption may reflect the ability of this compound to inhibit glucose-6-phosphate translocase 1, now known to play a role in intestinal glucose transport. Delayed glucose absorption may itself protect beta cells by limiting postprandial hyperglycemia — though, owing to countervailing effects of caffeine on plasma glucose, and a paucity of relevant research studies, it is still unclear whether coffee ingestion blunts the postprandial rise in plasma glucose. More generally, diets high in "lente carbohydrate", or administration of nutraceuticals/pharmaceuticals which slow the absorption of dietary carbohydrate, should help preserve efficient beta cell function by boosting GLP-1 production, as well as by blunting the glucotoxic impact of postprandial hyperglycemia on beta cell function.

Med Hypotheses. 2005;64(4):848-53

A RANDOMIZED TRIAL OF LOW-DOSE ASPIRIN IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN.

BACKGROUND: Randomized trials have shown that low-dose aspirin decreases the risk of a first myocardial infarction in men, with little effect on the risk of ischemic stroke. There are few similar data in women. **METHODS:** We randomly assigned 39,876 initially healthy women 45 years of age or older to receive 100 mg of aspirin on alternate days or placebo and then monitored them for 10 years for a first major cardiovascular event (i.e., nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes). **RESULTS:** During follow-up, 477 major cardiovascular events were confirmed in the aspirin group, as compared with 522 in the placebo group, for a nonsignificant reduction in risk with aspirin of 9% (relative risk, 0.91; 95% confidence interval, 0.80 to 1.03; $P=0.13$). With regard to individual end points, there was a 17% reduction in the risk of stroke in the aspirin group, as compared with the placebo group (relative risk, 0.83; 95% confidence interval, 0.69 to 0.99; $P=0.04$), owing to a 24% reduction in the risk of ischemic stroke (relative risk, 0.76; 95% confidence interval, 0.63 to 0.93; $P=0.009$) and a nonsignificant increase in the risk of hemorrhagic stroke (relative risk, 1.24; 95% confidence interval, 0.82 to 1.87; $P=0.31$). As compared with placebo, aspirin had no significant effect on the risk of fatal or nonfatal myocardial infarction (relative risk, 1.02; 95% confidence interval, 0.84 to 1.25; $P=0.83$) or death from cardiovascular causes (relative risk, 0.95; 95% confidence interval, 0.74 to 1.22; $P=0.68$). Gastrointestinal bleeding requiring transfusion was more frequent in the aspirin group than in the placebo group (relative risk, 1.40; 95% confidence interval, 1.07 to 1.83; $P=0.02$). Subgroup analyses showed that aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and myocardial infarction among women 65 years of age or older. **CONCLUSIONS:** In this large, primary-prevention trial among women, aspirin lowered the risk of stroke without affecting the risk of myocardial infarction or death from cardiovascular causes, leading to a nonsignificant finding with respect to the primary end point.

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VASCULAR DEMENTIA: DISTINGUISHING CHARACTERISTICS, TREATMENT, AND PREVENTION.

Vascular dementia (VaD) is the second-most-common cause of dementia in the elderly, after Alzheimer's disease (AD). VaD is defined as loss of cognitive function resulting from ischemic, hypoperfusive, or hemorrhagic brain lesions due to cerebrovascular disease or cardiovascular pathology. Diagnosis requires the following criteria: cognitive loss, often predominantly subcortical; vascular brain lesions demonstrated by imaging; a temporal link between stroke and dementia; and exclusion of other causes of dementia. Poststroke VaD may be caused by large-vessel disease with multiple strokes (multiinfarct dementia) or by a single stroke (strategic stroke VaD). A common form is subcortical ischemic VaD caused by small-vessel occlusions with multiple lacunas and by hypoperfusive lesions resulting from stenosis of medullary arterioles, as in Binswanger's disease. Unlike with AD, in VaD, executive dysfunction is commonly seen, but memory impairment is mild or may not even be present. The cholinesterase inhibitors used for AD are also useful in VaD. Prevention strategies should focus on reduction of stroke and cardiovascular disease, with attention to control of risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, and hyperhomocysteinemia.

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REDUCED INCIDENCE OF AD WITH NSAID BUT NOT H₂ RECEPTOR ANTAGONISTS: THE CACHE COUNTY STUDY.

BACKGROUND: Previous analyses from the Cache County (UT) Study showed inverse associations between the prevalence of AD and the use of nonsteroidal anti-inflammatory drugs (NSAID), aspirin compounds, or histamine H₂ receptor antagonists (H₂RA). The authors re-examined these associations using data on incident AD. **METHODS:** In 1995 to 1996, elderly (aged 65+) county residents were assessed for dementia, with current and former use of NSAID, aspirin, and H₂RA as well as three other "control" medication classes also noted. Three years later, interval medication histories were obtained and 104 participants with incident AD were identified among 3,227 living participants. Discrete time survival analyses estimated the risk of incident AD in relation to medication use. **RESULTS:** AD incidence was marginally reduced in those reporting NSAID use at any time. Increased duration of use was associated with greater risk reduction, and the estimated hazard ratio was 0.45 with ≥ 2 years of exposure. Users of NSAID at baseline showed little reduction in AD incidence, regardless of use thereafter. By contrast, former NSAID users showed substantially reduced incidence (estimated hazard ratio = 0.42), with a trend toward greatest risk reduction

among those with extended exposure. Similar patterns appeared with aspirin but not with any other medicines examined. CONCLUSIONS: Long-term NSAID use may reduce the risk of AD, provided such use occurs well before the onset of dementia. More recent exposure seems to offer little protection. Recently initiated randomized trials of NSAID for primary prevention of AD are therefore unlikely to show effects with treatment until participants have been followed for several years.

Neurology. 2002 Sep 24;59(6):880-6

ASPIRIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS: A SUMMARY OF THE EVIDENCE FOR THE U.S. PREVENTIVE SERVICES TASK FORCE.

BACKGROUND: The use of aspirin to prevent cardiovascular disease events in patients without a history of cardiovascular disease is controversial. **PURPOSE:** To examine the benefits and harms of aspirin chemoprevention. **DATA SOURCES:** MEDLINE (1966 to May 2001). **STUDY SELECTION:** 1) Randomized trials at least 1 year in duration that examined aspirin chemoprevention in patients without previously known cardiovascular disease and 2) systematic reviews, recent trials, and observational studies that examined rates of hemorrhagic strokes and gastrointestinal bleeding secondary to aspirin use. **DATA EXTRACTION:** One reviewer read and extracted data from each included article and constructed evidence tables. A second reviewer checked the accuracy of the data extraction. Discrepancies were resolved by consensus. **DATA SYNTHESIS:** Meta-analysis was performed, and the quantitative results of the review were then used to model the consequences of treating patients with different levels of baseline risk for coronary heart disease. Five trials examined the effect of aspirin on cardiovascular events in patients with no previous cardiovascular disease. For patients similar to those enrolled in the trials, aspirin reduces the risk for the combined end point of nonfatal myocardial infarction and fatal coronary heart disease (summary odds ratio, 0.72 [95% CI, 0.60 to 0.87]). Aspirin increased the risk for hemorrhagic strokes (summary odds ratio, 1.4 [CI, 0.9 to 2.0]) and major gastrointestinal bleeding (summary odds ratio, 1.7 [CI, 1.4 to 2.1]). All-cause mortality (summary odds ratio, 0.93 [CI, 0.84 to 1.02]) was not significantly affected. For 1,000 patients with a 5% risk for coronary heart disease events over 5 years, aspirin would prevent 6 to 20 myocardial infarctions but would cause 0 to 2 hemorrhagic strokes and 2 to 4 major gastrointestinal bleeding events. For patients with a risk of 1% over 5 years, aspirin would prevent 1 to 4 myocardial infarctions but would cause 0 to 2 hemorrhagic strokes and 2 to 4 major gastrointestinal bleeding events. **CONCLUSIONS:** The net benefit of aspirin increases with increasing cardiovascular risk. In the decision to use aspirin chemoprevention, the patient's cardiovascular risk and relative utility for the different clinical outcomes prevented or caused by aspirin use must be considered.

Ann Intern Med. 2002 Jan 15;136(2):161-72

A RANDOMIZED TRIAL OF ASPIRIN TO PREVENT COLORECTAL ADENOMAS

BACKGROUND: Laboratory and epidemiologic data suggest that aspirin has an antineoplastic effect in the large bowel. **METHODS:** We performed a randomized, double-blind trial of aspirin as a chemopreventive agent against colorectal adenomas. We randomly assigned 1,121 patients with a recent history of histologically documented adenomas to receive placebo (372 patients), 81 mg of aspirin (377 patients), or 325 mg of aspirin (372 patients) daily. According to the protocol, follow-up colonoscopy was to be performed approximately three years after the qualifying endoscopy. We compared the groups with respect to the risk of one or more neoplasms (adenomas or colorectal cancer) at least one year after randomization using generalized linear models to compute risk ratios and 95% confidence intervals. **RESULTS:** Reported adherence to study medications and avoidance of nonsteroidal antiinflammatory drugs were excellent. Follow-up colonoscopy was performed at least one year after randomization in 1,084 patients (97%). The incidence of one or more adenomas was 47% in the placebo group, 38% in the group given 81 mg of aspirin per day, and 45% in the group given 325 mg of aspirin per day (global $P=0.04$). Unadjusted relative risks of any adenoma (as compared with the placebo group) were 0.81 in the 81-mg group (95% confidence interval, 0.69 to 0.96) and 0.96 in the 325-mg group (95% confidence interval, 0.81 to 1.13). For advanced neoplasms (adenomas measuring at least 1 cm in diameter or with tubulovillous or villous features, severe dysplasia, or invasive cancer), the respective relative risks were 0.59 (95% confidence interval, 0.38 to 0.92) and 0.83 (95% confidence interval, 0.55 to 1.23). **CONCLUSIONS:** Low-dose aspirin has a moderate chemopreventive effect on adenomas in the large bowel. *N Engl J Med. 2003 Mar 6;348(10):891-9* A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. **BACKGROUND:** Experimental studies in animals and observational studies in humans suggest that regular aspirin use may decrease the risk of colorectal adenomas, the precursors to most colorectal cancers. **METHODS:** We conducted a randomized, double-blind trial to determine the effect of aspirin on the incidence of colorectal adenomas. We randomly assigned 635 patients with previous colorectal cancer to receive either 325 mg of aspirin per day or placebo. We determined the proportion of patients with adenomas, the number of recurrent adenomas, and the time to the development of adenoma between randomization and subsequent colonoscopic examinations. Relative risks were adjusted for age, sex, cancer stage, the number of colonoscopic examinations, and the time to a first colonoscopy. The study was terminated early by an independent data and safety monitoring board when statistically significant results were reported during a planned interim analysis. **RESULTS:** A total of 517 randomized patients had at least one colonoscopic examination a median of 12.8 months after randomization. One or more adenomas were found in 17% of patients in the aspirin group and 27% of patients in the placebo group ($P=0.004$). The mean (\pm SD) number of adenomas was lower in the aspirin group than the placebo group (0.30 \pm 0.87 vs. 0.49 \pm 0.99, $P=0.003$ by the Wilcoxon test). The adjusted relative risk of any recurrent adenoma in the aspirin group, as compared with the placebo group, was 0.65 (95% confidence interval, 0.46 to 0.91). The time to the detection of a first adenoma was longer in the aspirin

group than in the placebo group (hazard ratio for the detection of a new polyp, 0.64; 95% confidence interval, 0.43 to 0.94; P=0.022). CONCLUSIONS: Daily use of aspirin is associated with a significant reduction in the incidence of colorectal adenomas in patients with previous colorectal cancer.

N Engl J Med. 2003 Mar 6;348(10):883-90

REGIONAL DISTRIBUTION OF CYCLOOXYGENASE-2 IN THE HIPPOCAMPAL FORMATION IN ALZHEIMER'S DISEASE.

Cyclooxygenase-2 (COX-2), a key enzyme in prostanoid biosynthesis, may represent an important therapeutic target in Alzheimer's disease (AD). In the present study, we explored the regulation of COX-2 in the hippocampal formation in sporadic AD. Using semiquantitative immunocytochemical techniques, we found that in AD cases (vs. age-matched controls) neurons of the CA1-CA4 subdivisions of the hippocampal pyramidal layer showed elevation of COX-2 signal; COX-2 levels correlated with amyloid plaque density. In contrast, the level of COX-2 immunostaining in the dentate gyrus granule neurons was not elevated in AD. No expression of COX-2 in cells with glial morphology was found in any case examined. In parallel, in vitro studies found that neurons derived from transgenic mice with neuronal overexpression of COX-2 are more susceptible to beta-amyloid (A β) toxicity, with potentiation of redox impairment. The results indicate elevated expression of neuronal COX-2 in subregions of the hippocampal formation in AD and that such elevation may potentiate A β -mediated oxidative stress.

J Neurosci Res. 1999 Aug 1;57(3):295-303

AN UPDATE ON ASPIRIN IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE.

BACKGROUND: In 1988, the aspirin component of the Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of 22,071 apparently healthy men was terminated early, due principally to a statistically extreme (P<.00001) 44% reduction in the risk of a first myocardial infarction (MI). The Cardio-Renal Drugs Advisory Committee recommended that the US Food and Drug Administration approve professional labeling of aspirin to prevent first MI. The agency did not act on this recommendation because the only other trial, the British Doctors' Trial of 5,139 men, showed no significant benefits. Since that time, 3 additional randomized trials (which included men and women) of aspirin in the primary prevention of MI have been published. **METHODS:** A computerized search of the English literature from 1988 to the present revealed 5 published trials: the Physicians' Health Study (22,071 participants), the British Doctors' Trial (5,139), the Thrombosis Prevention Trial (5,085), the Hypertension Optimal Treatment Study (18,790), and the Primary Prevention Project (4495). **RESULTS:** Among the 55,580 randomized participants (11,466 women), aspirin was associated with a statistically significant 32% reduction in the risk of a first MI and a significant 15% reduction in the risk of all important vascular events, but had no significant effects on nonfatal stroke or vascular death. **CONCLUSIONS:** The current totality of evidence provides strong support for the initial finding from the Physicians' Health Study that aspirin reduces the risk of a first MI. For apparently healthy individuals whose 10-year risk of a first coronary event is 10% or greater, according to the US Preventive Services Task Force and the American Heart Association, the benefits of long-term aspirin therapy are likely to outweigh any risks.

Arch Intern Med. 2003 Sep 22;163(17):2006-10

INFLAMMATION AND ATHEROSCLEROSIS.

Atherosclerosis, formerly considered a bland lipid storage disease, actually involves an ongoing inflammatory response. Recent advances in basic science have established a fundamental role for inflammation in mediating all stages of this disease from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis. These new findings provide important links between risk factors and the mechanisms of atherogenesis. Clinical studies have shown that this emerging biology of inflammation in atherosclerosis applies directly to human patients. Elevation in markers of inflammation predicts outcomes of patients with acute coronary syndromes, independently of myocardial damage. In addition, low-grade chronic inflammation, as indicated by levels of the inflammatory marker C-reactive protein, prospectively defines risk of atherosclerotic complications, thus adding to prognostic information provided by traditional risk factors. Moreover, certain treatments that reduce coronary risk also limit inflammation. In the case of lipid lowering with statins, this anti-inflammatory effect does not appear to correlate with reduction in low-density lipoprotein levels. These new insights into inflammation in atherosclerosis not only increase our understanding of this disease, but also have practical clinical applications in risk stratification and targeting of therapy for this scourge of growing worldwide importance.

Circulation. 2002 Mar 5;105(9):1135-43

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