chain polyunsaturated fatty acids. In the latter case, plasminogen-activator inhibitor levels tend to rise, implying an inhibition of endogenous fibrinolysis and a prothrombotic modification of the hemostatic system that would tend to oppose the antithrombotic platelet effect of ω-3 very-long–chain polyunsaturated fatty acids.[13] Very recently, another exception was identified. It was demonstrated that the fatty-acid composition of the background diet had an impact on the extent of postprandial factor VII activation, occurring after consumption of fatty meals. Volunteers living on a diet based on olive oil during preceding weeks were found to exhibit an attenuated postprandial response to a standard fat load as compared with what was seen after diets based on saturated fat or ω-6 polyunsaturated fat.[14,15] The mechanism explaining this newly discovered phenomenon is not known, and the clinical impact of the finding was also unknown until now.

Most experimental and epidemiologic data indicate that low-fat diets rich in complex carbohydrates, dietary fiber, and with a low glycemic index have a number of cardioprotective effects as compared with high-fat diets rich in saturated fats and poor in fruits, vegetables, and grain products. Two clinical trials have provided the hard evidence and showed that mortality from coronary heart disease may decline approximately 50% with the right diet.[16–18] What type of fat to choose for the low-fat diet is a matter of debate. The Lyon Diet Heart Trial[17,18] indicated that rapeseed oil is a good choice, possibly because of its content of ω-3 linolenic acid. And the recent GISSI-P trial indicates that a moderate intake of ω-3 very-long–chain polyunsaturated fatty acids may be recommendable.[19] From a blood-lipid perspective, saturated fats should be avoided and unsaturated vegetable oils be preferred. Among the vegetable oils, olive oil has a disadvantage because it is associated with poorer lipid profiles than several other oils (e.g., sunflower oil, rapeseed oil). However, olive-oil consumption seems to result in better oxidation resistance of lipoproteins, a desirable effect. Until we are more certain about their overall health effects, I believe that we should leave it up to each individual's sensoric preferences to decide what kind of unsaturated vegetable oil to use in moderation in the daily diet.

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A Cocktail Approach to Antioxidant Therapy

The production of free radicals (reactive oxygen and nitrogen species) is a steady-state event in respiring cells, and it is now recognized that uncontrolled production of these reactive species is the primary cause of numerous disease conditions.[1] To combat the damaging effects of free-radical injury, several approaches are commonly used, including antioxidant therapy, metal chelation, and the encapsulation of antioxidant enzymes such as superoxide dismutase and catalase or gultathione peroxidae in a liposome delivery system. Although the genetic approach targeted at overexpressing these antioxidant enzymes appears to be promising in animal models, its efficacy and relevance in human disease condition is presently unclear. Therefore, antioxidant supplementation remains a useful and practical strategy as adjunct therapy in many clinical conditions.

Sickle-cell anemia is a molecular disease caused by a point mutation of the hemoglobin molecule. The mutation produces sickle hemoglobin that polymerizes during deoxygenated conditions believed to cause blood-vessel occlusion, leading to the painful sickle crisis. In normal hemoglobin, it is estimated that about 3% of oxyhemoglobin is oxidized to methemoglobin daily, with the concomitant production of superoxide anion.[2–4] Sickle hemoglobin has been reported to exhibit accelerated autooxidation under various conditions.[5–7] Hence, enhanced oxidative stress indicated by increased susceptibility to lipid peroxidation[8] and increased generation of free radicals has been found in sickle red cells.[9] In common with other forms of genetic anemia such as the thalassemias and glucose-6-phosphate dehydrogenase deficiency, sickle-cell patients have an enhanced oxidative stress due to an overall low-antioxidant status, and improvements have been shown by antioxidant therapy (for review, see Chan et al.[10]).

In search of drug therapy for sickle-cell patients, Ohnishi and

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Ohnishi developed an ex vivo red-cell model in which the reversible formation of the "dense red cell" could be used to test the efficacy of certain drugs that may reduce or reverse the formation of dense cells.[11] In the accompanying paper by Ohnishi et al.,[12] this red-cell model was tested against an array of natural and pure antioxidants, which resulted in significant reduction of dense-cell formation and lipid peroxidation. A combination of antioxidants afforded further reduction in these endpoint measurements of oxidative stress, indicating significant synergistic effects when these compounds are used in concert. With this information, the investigators extended this cocktail approach in a small clinical trial of sickle-cell patients. Treatments with an antioxidant cocktail for 6 mo was shown to improve hematocrit values and reduce the number of sickle crises and afforded an overall sense of wellness. The improvement of hematocrit was found to be superior to the improvement with hydroxyurea treatment.[13] Therefore, a cocktail approach to antioxidant therapy has been shown to be effective and without unwanted side effects. In their study, the cocktail consisted of a combination of lipophilic vitamin E (1200 IU), hydrophilic vitamin C (6 g), and 6 g of a natural product, aged garlic extract. Aged garlic extract contains thioallyl and other compounds that have been demonstrated to have considerable antioxidant activity.[14] In rodents, aged garlic extract was proven effective in reducing doxoribicin-induced cardiotoxicity[15] and attenuating ischemic brain damage.[16]

The antioxidant nutrients are a collection of endogenous and exogenous compounds that generally serves as free-radical scavengers.[17] Apart from their differences in solubility and, hence, differential distribution in distinct cellular compartments, a complex interaction exists in which one antioxidant can recycle another oxidized species, thus allowing regeneration of certain antioxidants.[10] The ability of one antioxidant to regenerate another oxidized species is highly dependent on the redox potential of the antioxidant.[18] For example, biologically relevant electron donors such as vitamin C, gultathione, and ubiquinol have been shown to effectively regenerate the membrane-bound vitamin E from the vitamin E radical.[19–21] Irrespective of whether it is chemical or enzymatic, the regeneration reactions are fueled by the electron-derived form from the oxidation of foods (NADH, Nicotinamide adenine dinucleotide, reduced or NADPH, Nicotinamide adenine dinucleotide phosphate, reduced); therefore, cellular redox cycling in an organism is tightly coupled with its energy status.[10] Thus, it can be expected that, during prolonged energy deficit or inadequate production of NADH, NADPH, or a lack of glutathione reductase activity due to inadequate intake of riboflavin, the ability of the organism to produce sufficient reducing equivalents for recycling oxidized products would be compromised. Conversely, intakes of plant phenolic compounds and flavonoids may add to the total antioxidant pool.[22–23] The extent to which these new classes of compounds fits with the antioxidant network in humans requires more detailed and systematic studies. However, we should be aware that the ability of an organism to maintain its overall antioxidant potential is dependent on factors other than amount of antioxidant intake. The total energy intake, intake of other trace nutrients such as riboflavin and selenium, and the intake of newer classes of phenolic, flavonoids, and thioallyl (a component of the aged garlic extract) antioxidants would collectively contribute to the total antioxidant pool. In clinical settings, those other factors can become limiting due to disease state that consumes antioxidants, as in the example of chronic inflammation, where there is an overproduction of free radicals.

The dosages of antioxidant vitamins used in that study were high and beyond levels required for plasma and tissue saturation; for vitamin C in particular, the level exceeded the upper limit of safety recommendations.[24] In view of the potential prooxidant effects of certain antioxidant vitamins in high dosages, systematic studies targeted at defining the minimum dose required in a cocktail combination that can achieve a maximum response are merited. In summary, the study by Ohnishi et al. is a fine example of a journey in science that develops from benchside to bedside. Although bone-marrow transplantation is an effective treatment of sickle-cell anemia, its high cost and limitation with strict type-match requirements between the donor and the recipient preclude its use as a widespread treatment. The findings of Ohnishi's paper further shed light on the clinical efficacy of a cocktail approach of antioxidant therapy over that of a single antioxidant supplementation for the treatment of a molecular disease.

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Retinoids and Cancer Prevention: Crossing the Line Between Food and Drug

The foods we eat, or at least our long-term dietary patterns, increase or decrease our risk for getting cancer. We can use food to prevent or treat cancer in two different ways. The first is diet modification.[1] We can eat less fat, stop smoking, drink less alcohol, or eat more fruits and vegetables. The second is to use foods, nutrients, or drugs derived from nutrients as cancer chemopreventative agents.[2,3] We nutritionists often think of these approaches as being different. We all know many people who stop and start smoking, drinking, and dieting regularly. Yet, we tend to think of diet modification as a long-term, holistic, "natural," non-specific method of health maintenance. We all know people who eat herbs (such as St. John's Wort and gingko biloba), nutrients (such as vitamin C and antioxidant complexes), and nutrition-based drugs for years in the hope that they will prevent disease. Yet, we think of chemoprevention as being harsh, effective, and narrowly focused on short-term treatments or prevention of cancer.

This narrow focus may have been especially true for retinoid (vitamin A) research. Researchers made exciting and rapid progress in retinoid genetics, metabolism, and cell differentiation in the 1980s and 1990s.[4] This progress occurred at the same time, but generally in different laboratories, as exciting and rapid developments in ascertaining the causes, consequences, and prevention of vitamin A deficiency.[5] The explosion in information was difficult to assimilate and use effectively. Retinoid research essentially split into two camps. "Retinoid" researchers, mostly working in the United States and Europe, investigated cellular mechanisms of differentiation, and cancer chemoprevention. "Vitamin A" researchers, mostly working in the developing countries, investigated the effects of dietary intervention and modification on vitamin A deficiency. There were Retinoid conferences and Vitamin A conferences (few scientists attended both). However, the lines between "diet" modification and "drug"-based chemoprevention are not so difficult to cross. The retinoid family of nutrients provides some of the most successful nutrient-based cancer chemopreventatives we have, and is used in some of the most successful diet modification programs. Research on diet modification programs using vitamin A have been summarized elsewhere.[5] Retinoids as cancer chemopreventive agents are reviewed in this issue.[6]

Retinoids are powerful chemicals that regulate cell differentiation and proliferation. Cancer involves the disruption of normal cell differentiation, so it was obvious that retinoid status might influence a cell's potential for malignant transformation. Early studies showed that vitamin A deficiency could lead to cancer in animals, and that retinoids could interfere with cancer initiation and progression in cell culture.[6,7] These exciting results were followed by many more studies, which are summarized in this interesting review.[6]

As often happens in science, results from these studies give a more complex and somewhat less promising picture of the relationship between retinoids and cancers than we had originally hoped for. First, retinoids seem to block cancer progression by more than one mechanism. Retinoids appear to stimulate apoptosis or cell differentiation, and to inhibit cancer cell proliferation. Second, retinoids have successfully blocked secondary tumors in a few cancers (especially head and neck cancer), but have not been successful for many others. Of course, the effectiveness of many of these retinoid treatments can be improved when we learn which retinoid works best on what tumor, and the most appropriate dosage and duration of treatment. Even so, in a rare cancer (promyelocytic leukemia) in which retinoid metabolism is clearly defective and retinoic acid treatment results in clear remissions, resistance limits the effectiveness of the retinoid treatment. Therefore, recent advances in retinoid science have focused on modifying retinoids to decrease their toxicity or increase their longevity of action. New retinoids are being synthesized specifically for cancer prevention,[8] and new methods are being developed to stabilize concentrations by blocking retinoid metabolism.[9] Basic research on the metabolism of retinoids in the eye led to tests for vitamin A deficiency, and contributed to developing dietary guidelines for vitamin A.[10,11] Similarly, this new explosion of information on retinoids, cellular differentiation, and cancer prevention could be used to complement and inform research and public health efforts on the dietary requirement for vitamin A. Someday, we will know how retinoid receptor genetics and retinoic acid metabolism influence vitamin A status and requirements in individuals.

We have made a beginning. We have identified many proteins that are up-regulated by retinoids, though we still have not used them to measure vitamin A status.[12] We have identified a handful of individuals with major genetic defects in retinoid metabolism and have shown how these defects relate to retinoid status.[13] However, we do not even know whether other obvious genetic mutations in retinoid metabolism (such as those seen in promyelocytic leukemia) influence the amount or kind of vitamin A-rich foods we should eat. Should people with promyelocytic leukemia eat more carotenoids and less retinol? Or is retinoid metabolism so highly regulated that normal dietary variations simply do not matter? We do not know. It is always difficult to extend basic research to health applications.[14] But, part of the difficulty is probably traced to the lack of communication between most "retinoid" and "vitamin A" researchers.

Therefore, the presence of this "retinoid" review in a nutrition journal is a positive development. This is not the first time we have crossed the line between diet and drug, nor is it the first time that there has been a lack of communication between scientists researching foods as "diet" and foods as "drugs." Other examples are alcoholic beverages and tobacco. In fact, western scientists and doctors are now in the curious position of using one set of diet-derived drugs (retinoid formulations) to combat cancers caused to a large extent by other diet-derived drugs (nicotine, cigarette tars, and alcohol[15]). People in poorer nations will seldom be able to use these expensive retinoid drugs to combat cancer, but instead must rely on less expensive diet modifications. Let us hope that knowledge derived from retinoid genetic and cancer-prevention studies will soon be used to improve vitamin A dietary interventions, to the benefit of all.

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