Antioxidant vitamins and $\beta$-carotene: effects on immunocompetence$^{1,2}$

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ABSTRACT Adequacy or deficiency in the micronutrient status of an individual deeply affects its immunocompetence. Among the different micronutrients, antioxidative vitamins and $\beta$-carotene are particularly effective in modulating immune functions and host defense against microorganisms or other invasive processes. This involves antigen-specific humoral or cell-mediated reactions of the immune system as well as nonspecific inflammatory processes. Owing to the interactions between micronutrient status and immunocompetence, the assessment of the micronutrient status of an individual can help to predict the risk of specific diseases associated with a deficient or suppressed immunocompetence, eg, infection or cancer. By the appropriate intervention it should be possible to modify this risk as has been shown in a number of carefully controlled studies. Assessment of the immunocompetence of an individual by measuring a limited number of key parameters of the immune system can help in the very early detection of specific micronutrient deficiencies. Am J Clin Nutr 1991;53:383S-5S.

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In the past decades, nutritional science and immunology have developed into an interdisciplinary field of work that becomes increasingly interesting for both areas. Two starting points should be emphasized: 1) comprehension of the mechanisms of interaction between nutrition and immunity and 2) determination of the clinical relevance of different symptoms, such as inflammation, cancer, and autoimmune disease. Regarding the field of "vitamins and immunity," the name Axelrod must be mentioned, whose scientific work between 1940 and 1970 has shaped this area decisively.

Although the interest in this topic has temporarily died down because of the successful introduction of antibiotics, and science has endeavored to fight noxes rather than to strengthen the patient, it has been recognized in recent times that a definite mounting of these ailments is only possible when the immunocompetence of the host is restituted. The most recent review of the American Medical Association has precisely characterized the present situation in speaking of "great gaps in knowledge" and of the fact that immunologists have too little knowledge of nutritional science and nutritional scientists have too little knowledge of the field of immunology. Also a great hindrance for scientific progress in this area is the lack of adequate methods for parallel investigation of nutritive and immunological questions. Here, an important part are animal models, which are often ill suited for both areas. Especially, immunological methods are missing for the different species relevant in nutritional sciences. Both nutritional science and immunology are old disciplines. But often old disciplines have difficulties in establishing new interdisciplinary areas.

The correlation between protein malnutrition and immune deficiencies is relatively well documented and comprehensible in its mechanisms. Here it is immediately clear that an energy and substrate deficiency is responsible for the consequences. Studies in third-world countries serve to demonstrate this correlation, since severe protein deficiency diets are hardly found in western industrial nations and therefore cannot be investigated here.

In western industrial nations, science concentrates more on risk groups, where marginal deficits can be counted on, that also have effects on immunocompetence and therefore on morbidity. Such risk groups would be newborn children, older people, pregnant women, athletes, smokers, vegetarians, persons under medication, persons being fed parenterally, immobilized persons, etc. When all known risk groups are combined, it amounts to approximately three times the total population: we are not talking about marginal groups of the population, but about everyone. In addition, a sociodemographic development intensifies the problem by further overaging the population and coupling higher risks leading to multimorbidity.

A problem concerning micronutrients, vitamins, minerals, and trace elements, can be seen in the fact that, although methods for detecting these substances in blood exist, the matching functional tests are missing that serve to demonstrate the relevance of the value measured for health. On grounds of practicality, the functional test should not be invasive or should at least be performed on easily accessible biological material. Vitamin A represents a favorable case as it is detectable in blood by high-pressure liquid chromatography (HPLC), but for which a suitable functional test is also available with impression cytology.

Especially in the preventive sense, it is important to recognize the first signs of a decline into deficiency. For this, the concept of storage represents a good starting point. To ensure optimal supply, it is not only important that the compartment of distribution, for example blood, contains micronutrients at a normal

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level, but also that the reservoirs are filled up. The first sign of deficiency will be the emptying of the body's reservoirs. This is usually difficult to measure and in many cases the question of which are the relevant body reservoirs remains unanswered. Often, no change will be detectable in the blood. One should think here, for example, of osteoporosis, which leads to a continuous emptying of the bone reservoir of calcium, while the blood calcium level often may even be raised. This is similar for vitamin A where blood levels only show differences when the liver reservoirs are emptied. Here, turnover measurements may present new possibilities for the future.

Concerning the functional results, immunology may surely be suited to make early reactions accessible for measurement, since one can assume that subclinical infection susceptibility or manifest infections will be preceded by disturbances of the immunocompetence. Advances in immunological detection methods allow the early registration of deficits or active suppression on the cellular or humoral level. This may concern antigen-specific reactions in the sense of antibody production or T-cell mediated immunity, but also may concern the effecter systems that can react antigen-independently, such as chemotaxis, phagocytosis, complement, opsonization, oxidative and hydrolytic reactions of decomposition, mediator systems of the cytokin-type, mucous tissue defense mechanisms, cilia, etc.

A vituous cycle valid for most micronutrients is also of significance since immunocompetence is reduced by malnutrition, because of which infectious gastrointestinal diseases often develop that lead to malabsorption, so that the taking in of micronutrients is reduced further. When putting up a scale of the different states of nutritional supply, at least four steps must be taken into account: 1) deficiency, 2) sufficient supply, 3) optimal supply, and 4) overoptimal supply. At all stages, immunology can be an important help for decisions. Here, one will have to introduce the relatively new term of immunotoxicology, a special area that is developing rapidly and will permit a sensitive judgement of every intervention.

To illustrate on another example, deficiency in the essential element zinc will lead to characteristic immunological consequences upon malnutrition, such as atrophy of lymphatic tissues, leukopenia, reduced antibody responses, reduced production and release of cytokines, impaired cytotoxicity of immune cells, declined levels of thymic hormones etc. When increasing the supply of zinc up to the level of overoptimal supply, negative effects can be detected, such as blocking of membrane receptors, inhibition of cytoskeletal function, inhibition of calcium transport, changes in membrane fluidity etc. By measuring a wide range of functional parameters of the immune system, it should therefore be possible to clearly delimit the areas of sufficient and optimal supply from deficiency and overoptimal supply. In this approach clinical, epidemiological, animal, and in vitro studies should complement each other to acquire the evidences needed.

How difficult this can be in the case of a single micronutrient is shown by the example of the element iron, which is usually reduced in blood upon infection. This deficiency of iron, however, does not lead to an increased susceptibility to infections, and supplementation of iron does not improve the liability to infections under these conditions. Iron overload, on the other hand, does not lead to infections but to hemochromatosis with failure of heart and liver function. It has been shown in extensive cohort studies that were carried out in third-world countries that single micronutrients are excellent predictive parameters with regard to the mortality in such a population. In this connection, interactions with immunocompetence are of major importance. For example, it has been observed in populations of Indonesia with a marginal vitamin A deficit that mortality is raised by a factor of 2.7 in comparison to a normally supplied collective of the same population. When Bitot spots were detectable as a sign of a considerable vitamin A deficit the mortality of this group was even increased by a factor of 6.6.

Intervention studies with vitamin A have shown that this mortality rate can be lowered by 30–50% when the supply of vitamin A is normalized. Looked at from this point of view, vitamin A can be considered an essential antinfecious factor that increases and stabilizes immunocompetence and reduces the beginning of infections. Similar studies have been performed for other infectious diseases, eg, measles in Tanzania, where mortality could be reduced from 13% to 6%, which means more than half.

As far as the mechanism of the effect of vitamin A is concerned, it could be shown that blastogenesis of lymphocytes as well as the activity of the natural killer cells can be raised by addition of vitamin A in vitro. Another important question is that of the connection between decreased immunocompetence and malnutrition at old age. Concerning this, it should be noted that malnutrition at old age is as unnatural and unnecessary as a reduction of immunocompetence at old age. It can be considered proven that by dietetic measures an improvement of the immunity situation of old persons can usually be achieved.

In discussing vitamin A, the fact is surely of importance that with the provitamin β-carotene a micronutrient stands to disposition that is completely unquestionable toxicologically, but that can ensure the supply of vitamin A. That, on top of this function as provitamin A, β-carotene has further protective functions per se is knowledge of the past few years. Especially the long-term deleterious effects of radiation can be compensated by β-carotene, whereas the immunosuppressant effects of radiation have already been known for some time. Here, one should think of Herpes labialis at excessive ultraviolet radiation. But, the preventive effects of β-carotene go further and evidence is increasing that preventive effects against tumors also exist. Here, studies are being performed that will clarify the connection beyond doubt in the next few years.

New data also show immunostimulant effects for vitamin E. For example, it could be shown that clearance of E coli from blood after infection can be improved at a highly significant level when the supply of vitamin E is optimal. A similar result is presented by the fact that mortality of rate on application of pathogenic germs was clearly reduced under supplementation of vitamin E. Similar results were also shown for other species, eg, chickens. That humoral immunity is also effected can be deduced from investigations that show increased production of antibodies under vitamin E supplementation. A shift from IgM to IgG is also described.

It is justified to combine the antioxidant micronutrients into a group showing relatively uniform effect spectra. To this, the antiinflammatory effect as a result of interactions with activated oxygen compounds would belong, but also the interference with the metabolism of arachidonic acid. Especially the metabolites of arachidonic acid are major mediators in the inflammatory process and represent a number of single functions, eg, chemotaxis, phagocytosis, and intracellular killing. Also, processes
such as the degranulation of granulocytes can be influenced, which opens the way to allergies.

Paradox reactions are not uncommon for these regulations, with a low concentration leading to stimulation, for instance, whereas high concentrations change into inhibition. Despite synergistic effects between the antioxidant micronutrients, the different vitamins and trace elements cannot replace each other, rather coupled redox-reactions must be counted on, in which several redox-systems, e.g., α-tocopherol, ascorbate, glutathion, etc., are involved. It is therefore important in this area to optimize the state of supply for all essential components. Besides the vitamins already mentioned, most likely some trace elements—copper, zinc, or selenium—belong to this. The clinical relevance of these considerations becomes particularly evident, for instance, on regarding the risk group of persons being fed parenterally, whose state of supply of micronutrients is only monitored and improved in the fewest cases. One is not rarely surprised in the intensive care units when a pneumonia occurs, in spite of antibiotic cover, because the immunocompetence of the patient is badly compromised. Usually, the immunocompetence of the patient is not surveyed either, since, especially for the cellular immune functions, no flow-through-cytometer is available that would enable quick assessment.

Especially under these marginal conditions, it seems important in these cases to rather do a little too much than to do too little in the supplementation of micronutrients, particularly as an overdose is tolerable in most cases. Progress in this important field, however, primarily requires specific experimental and clinical research, which surely will not get by without interdisciplinary initial stages.