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VITAMIN E : TOXICOLOGICAL EVALUATION AND  
ITS ROLE ON CELL-MEDIATED IMMUNITY

BY

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## Introduction

Vitamins are defined as carbon compounds needed in small amounts for various functions of animal cells. However, megavitamin therapy is also advocated for treating numerous clinical disorders unrelated to vitamin deficiency without rational basis. Vitamin C, E and B<sub>12</sub> have been widely used in medical society. Many physicians routinely use vitamins for placebo like effects (Melmon and Morrelli, 1972). Vitamin consumptions have been dramatically increased during the last decade both through self prescription and from fortified vitamin supplemented foods.

Vitamin E, alpha-tocopherol, is one of fat soluble vitamins, which is widely used as vitamin supplement and an ingredient in cosmetic preparations. It is also being employed as a drug in the treatment of some clinical problems such as muscular dystrophies, habitual abortion, cardiovascular disease, acne, aging etc (Horwitt 1980, Moriguchi 1984). There are many controversies concerning the effects of vitamin E in man or even in animals. Ayres (1974) reported that in patient taking vitamin E in doses of 400 to 800 IU or more daily had severe nocturnal leg cramps and the symptoms ceased when vitamin E was discontinued. Toone (1973) reported that vitamin E can reduce the nitroglycerin consumption in the patients with ischaemic heart disease.

Many vitamin preparations available in the market are composed of vitamin A and vitamin E in combination. Since both of them are fat soluble vitamins, long term toxicity of vitamin A has been generally recognized. Drug interaction between vitamin A and vitamin E may also exist. Moore (1940)

and Davies & Moore (1941) reported that rats given vitamin E in their diet store up to ten times as much vitamin A in the liver as compared to control. In contrast, the vitamin A store disappeared much more rapidly in animals maintained on a diet deficient in both vitamin A and E than in animals receiving dl-alpha-tocopherol. Moreover, vitamin E supplement as low as 1 mg per rat weekly slowed down the depletion rate of vitamin A when the initial reserve of vitamin A in rat liver was more than 30,000 IU (Cawthorne 1968). It is, therefore, likely that vitamin E may potentiate the toxicity of vitamin A.

Controversy also exists regarding the effect of vitamin E on the immune system. Prasad (1980) reported that the effect of megadoses of vitamin E, 300 IU given daily for 3 weeks, produced a significant depression in bactericidal activity of leukocytes and mitogen induced lymphocyte transformation. In addition, the person taking megadose of vitamin E was shown to have a decrease in lymphocytes counts (Goodwin 1983). On the contrary, Yasunaka (1982) found that a daily low dosage of vitamin E consumed enhanced mitogen responsive significantly. Therefore, the long term effect of vitamin E on the immune system needs to be further investigated.

One of the other interesting properties of vitamin E is the ability of the antioxidant activity (Freeman 1982, Nishikimi 1980). There was a theory that tissue of unsaturated lipids are continually under attack by free radicals, which may be either of random origin or produced in metabolic reactions, and that in the presence of oxygen they become peroxidized (Freeman 1982, Green 1972). According to one theory, alpha-tocopherol functions in vivo reacts with free radicals and thereby inhibits the tissue

peroxidation process of unsaturated lipids (Green 1972). There are many drugs and chemicals that can produce free radicals or superoxide anions such as paraquat, one of the herbicidal chemicals. Two primary hypotheses for explaining the mechanisms of paraquat toxicity are :- 1) paraquat toxicity may be due to the peroxidation of cell membranes by activating forms of oxygen generated during reduction of the parent compound or 2) cell damage occurs as a result of depletion of reducing equivalents during reduction of the parent compound (Bus 1974). Thus, it is conceivable that vitamin E may play some role in prevention of paraquat toxicity.

In this thesis, we attempt to clarify several points related to the toxicological evaluation of vitamin E, and its role on modifying the toxicities of other potentially toxic substances. The objectives of thesis can be summarized as follows:-

1. To evaluate vitamin E (dl-alpha-tocopherol acetate) toxicity in animals

1.1 to determine the subacute toxicity in rats

1.2 to study the effects of vitamin E on blood clotting in rats treated with vitamin E

1.3 to study allergenic and irritant effects of vitamin E on rabbit skins

1.4 to study the effects of vitamin E on the function of cell-mediated immune system

2. The role of vitamin E in modifying the toxic effects of the other potentially toxic substances

2.1 to study the effect of vitamin E on vitamin A (retinyl acetate) toxicity in rats

2.2 to study the effect of vitamin E on paraquat (1,1-dimethyl-4,4-bipyridylium dichloride) toxicity in rats.