

## SUMMARY

The study presented in this thesis was carried out in order to investigate the specific step in which vitamin E plays in controlling DNA-thymine synthesis. Subjects were children between 8 months to 2 years of age and were obtained from the orphanage of Chulalongkorn Hospital. The metabolism of deoxyribonucleic acid of the bone marrow was studied before and after vitamin E administration.

No consistent improvement was observed in anaemic children after treatment with folic acid, vitamin B<sub>12</sub>, ascorbic acid and iron by Whitaker et al. (12). But hematologic response appeared after vitamin E and high protein diets were given. They suggested that vitamin E deficiency could be a primary cause of abnormal maturation of erythrocyte precursors. Dinning (29) suggested that the regulation of nucleic acid turnover was a primary metabolic function of vitamin E. It is possible to postulate that the aberration in erythrocyte maturation in vitamin E-deficient animal is related to the altered nucleic acid metabolism. A marked decrease in the synthesis of DNA-thymine from <sup>14</sup>C-formate and in DNA-thymine concentration were observed while no change in the incorporation of <sup>3</sup>H-thymidine into DNA-thymine after vitamin E administration was noted in malnourished children studied by Khuankong (11). It seems possible to conclude that vitamin E affects some steps in the synthetic pathway from formate to thymidine

but not the incorporation of preformed thymidine into DNA.

The present study was carried out in vitro. Human bone marrow cells were incubated with thymidine-methyl-<sup>3</sup>H (0.005  $\mu$ mole), orotic-6-<sup>14</sup>C (2.4  $\mu$ moles), uridine-2-<sup>14</sup>C (0.2  $\mu$ mole) and deoxyuridine-2-<sup>14</sup>C (0.4  $\mu$ mole). <sup>3</sup>H-thymidine incorporated into DNA was used to determine the rate of overall DNA synthesis in the bone marrow cells. Orotic-6-<sup>14</sup>C acid, uridine-2-<sup>14</sup>C and deoxyuridine-2-<sup>14</sup>C were used to measure the specific step of DNA synthesis by determining <sup>14</sup>C-thymine isolated from DNA of the incubated bone marrow.

An inverse correlation between plasma vitamin E level and <sup>14</sup>C-DNA thymine synthesized from these <sup>14</sup>C-precursors was obtained throughout the experiment ( $r = 0.97$ ,  $p < 0.05$ ). Vitamin E did not significantly affect the incorporation of <sup>3</sup>H-thymidine into DNA. Thymine concentration was found to be decreased in the same manner as the decrease in de novo thymine synthesis. The reduction of thymine concentration was interpreted to be due to a total decrease in DNA synthesis.

There was no change in mono carbon pool size during the period of study. Hemoglobin concentration and hematocrit values did not significantly change during the experimental period.

The erythropoietic process in megaloblastic anaemia due to vitamin E deficiency was found to be accelerated by the abnormality in

one or several steps in the pathway of nucleotide biosynthesis, especially in thymidine synthesis. Vitamin E could erase this abnormality by correcting these steps.

From the present study, it seems logical to conclude that vitamin E exerts some effect at methylation step in the pathway of thymidine synthesis. It may function by 1) controlling the enzymatic activity of the enzyme dihydrofolate reductase or thymidylate synthetase directly or 2) by controlling the synthesis of either one or both enzymes, resulting in a decreased thymine synthesis when vitamin E is increased.