Chapter 5

CONCLUSION AND RECOMMENDATION

Hemoglobinopathies, the thalassemias and abnormal hemoglobins are very prevalent in Thailand. These common genes, α-thalassemia, β-thalassemia, and Hb E ($\alpha_2\beta_2^{26Glu\rightarrow Lys}$), in different combinations result in a spectrum of clinical syndromes ranging from asymptomatic to a severe chronic hemolytic anemia. β-thalassemia/Hb E disease, as a result of β-thalassemia interacted with Hb E, is a common clinical disorder causes not only medical care problems but also in socio-economic problems in our country. It was evident that two types of β-thalassemia designated as classical β-thalassemia or β-thalassemia$_1$ (β-thal$_1$) and mild-β-thalassemia or β-thalassemia$_2$ (β-thal$_2$) on the basis of the interaction of these genes with Hb E. From the clinical evidence, the β-thal$_1$/Hb E disease with hemoglobin types of E+F is found to have clinical manifestations more severe than that of the β-thal$_2$/Hb E disease which has hemoglobin types of E+F+A. The precise diagnosis of β-thal$_1$ and β-thal$_2$ traits is very difficult or impossible because the hematologic data were similar. This studies attempt to characterize the heterozygotes by studying the hemoglobin synthesis. Reticulocytes from venous blood were incorporated with ^{3}H-leucine according to methods described by Lingrel et al. 1963). The labelled globin chains were fractionated on CMC chromatography and the radioactivity of each chain was measured

by Liquid scintillation counter. The radioactivity and specific activity of each globin chain relative to α chain were determined.

Seven cases of obligatory β-thalassemia$_1$ trait were studied for comparison with nine obligatory β-thalassemia$_2$ traits and with seven normal controls as well. The means of hematologic data values of the β-thal$_1$ trait revealed similar, except for the significantly less MCH, to that of the β-thal$_2$ trait. However the hematologic data of both heterozygotes showed significant hypochromic microcytic red cells when compared to the normal controls. The means of radioactivity β/α ratio of the β-thal$_1$ and β-thal$_2$ traits were 0.44 $\pm$ 0.014 and 0.50 $\pm$ 0.02 respectively, which were significantly different. ($P < 0.001$).

Five heterozygotes for Hb E were also studied for the radioactive incorporation. Although the constitution of Hb E around 27 % in a heterozygote, the mean non α to α chain ratio; $\beta+\beta^E/\alpha$ was 0.97 $\pm$ 0.04, which was close to the β/α ratio of normal control, 0.92 $\pm$ 0.05 . This indicated the balance globin chain synthesis between non α chains (β and β^E chains) and α chain.

Six patients with β-thal$_1$/Hb E disease were studied for the globin chain synthesis in comparison with five patients with β-thal$_2$/Hb E disease. The means of MCH and quantitative Hb E of the former revealed significantly less than that of the latter. The mean radioactivity globin chain ratios of total β chain to α chain; β^E/α (no β chain) in β-thal$_1$/Hb E disease, and $\beta+\beta^E/\alpha$ in β-thal$_2$/Hb E disease were 0.40 $\pm$ 0.07 and 0.51 $\pm$ 0.07 respectively, which were

statistically different. ($P < 0.05$).

From the clinical observations and hemoglobin chain synthesis in this study, it is evident that the β-thal$_1$/Hb E disease apparently has severe clinical manifestations than that β-thal$_2$/Hb E disease. The peptide mapping studies of the slow β-chains corresponding to Hb E in both diseases were carried out in order to exclude the possibility of the different amino acid alteration. But the peptide mapping indicated that the variants in both diseases were identical to the peptide mapping of Hb E ($\alpha_2\beta_2^{26Glu \rightarrow Lys}$). Therefore it is most likely that the different clinical and hematologic findings of the two diseases are, at least in part, due to the different expressivity of the β-thal$_1$ and β-thal$_2$ genes upon the interaction of Hb E. Although the hematological findings of the two heterozygotes are similar, the measurements of globin chain synthesis could be used to designate of the β-thal$_1$ and β-thal$_2$ trait.

Since the β-thal$_1$ and β-thal$_2$ genes are evident, it is no doubt that three possible interactions; homozygosity for β-thal$_1$ (β-thal$_1$/β-thal$_1$), double heterozygote for β-thal$_1$ and β-thal$_2$ (β-thal$_1$/β-thal$_2$) and homozygosity for β-thal$_2$ (β-thal$_2$/β-thal$_2$) exist. Based on the different suppression effect on the normal β chain synthesis by the β-thal$_1$ and β-thal$_2$ genes, a hypothesis on different clinical manifestations of the three genotypes can be predicted. The homozygosity for β-thal$_1$ should be the most severe disorders, and the patients probably expire during childhood. Expectation of hemoglobin types is entirely Hb F (no Hb A) since the β-thal$_1$

expresses complete suppression of β chain in the interaction of Hb E. The β-thal$_1$/β-thal$_2$ probably presents modrate clinical manifestation. The homozygote for β-thal$_2$ is believed to be mild hemolytic anemia and probably found in adult. Both β-thal$_1$/β-thal$_2$ and β-thal$_2$/β-thal$_2$ diseases would have Hb types of A+F. It is of interest to carefully study the hemoglobin chain synthesis in Cooley's anemia (believed to be homozygous β-thalassemia) especially in patients with Hb types of A+F in adolescent or in adult in order to understanding the effect of gene interactions.