CORRESPONDENCE

The Sphere of Influence of the Beta-Thalassemia Mutation

To the Editor:

The recent article by Conley et al.1 on the hereditary persistence of fetal hemoglobin presents some interesting data which relate to the etiology of thalassemia. Ingram and Stretton2 postulate that beta-thalassemia is due to a mutation within or close to the beta gene resulting in decreased beta chain production and a compensatory increase in delta chain (hemoglobin A\textsubscript{2}) and gamma chain (hemoglobin F) production. This assumes that the beta-thalassemia mutation has an active role in the regulation of beta chain production but a passive role in delta chain and hemoglobin A\textsubscript{2} production. An alternative is that the beta-thalassemia mutation actively resets both beta and delta chain production.

Conley’s data have some bearing in this regard. Assuming that the hereditary persistence of fetal hemoglobin is due to an inactivation of both the beta and delta genes,3,4 the values for hemoglobin A\textsubscript{2} can be rearranged in the following manner:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Hb A\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>2.50</td>
</tr>
<tr>
<td>AF</td>
<td>1.63</td>
</tr>
<tr>
<td>AT\textsubscript{h}</td>
<td>4.90</td>
</tr>
<tr>
<td>F\textsubscript{Th}</td>
<td>2.60</td>
</tr>
<tr>
<td>FF</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Hb A\textsubscript{2} Produced by Each Set of Allelic Delta Genes

<table>
<thead>
<tr>
<th>Hb A\textsubscript{2}</th>
<th>Produced by Each Set of Allelic Delta Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25</td>
<td>1.25</td>
</tr>
<tr>
<td>1.63</td>
<td>inactive</td>
</tr>
<tr>
<td>2.45</td>
<td>2.45</td>
</tr>
<tr>
<td>2.60</td>
<td>inactive</td>
</tr>
<tr>
<td>inactive</td>
<td>inactive</td>
</tr>
</tbody>
</table>

The following points are of interest. If partial suppression of beta chain synthesis by the beta thalassemia mutation is capable of producing a relative and absolute increase in delta chain synthesis, then complete suppression of beta chain synthesis by the mutation of hereditary persistence of fetal hemoglobin should also stimulate increased delta chain production by the remaining delta gene. However, hemoglobin A\textsubscript{2} in AF is only 1.63, a minor increase compared to 2.45 for a single set of delta alleles for thalassemia trait. In addition, in F-thalassemia, with almost complete suppression of all beta chain synthesis the production by the remaining allelic set of delta genes (2.60) is not much greater than with thalassemia trait alone (2.45).

These data would seem to indicate that in beta-thalassemia, delta chain production is actively reset by the beta-thalassemia mutation and capable of little variation despite the presence of significant stimuli for greater production; and that the ‘setting’ that keeps normal delta chain production at a fraction of that of the beta chain is unaffected in the hereditary production of fetal hemoglobin, and again capable of little variation despite the presence of significant stimuli for greater production. Such a broader affect of the beta-thalassemia mutation to active regulation of beta and delta (and perhaps gamma) chain production also helps to explain such entities as thalassemia trait with isolated elevation of hemoglobin A\textsubscript{2}, and the paradoxically normal hemoglobin A\textsubscript{2} level in thalassemia major.5

Such an assumption naturally has its objections. For example, in heterozygous thalassemia-A\textsubscript{2}, the level of both hemoglobin A\textsubscript{2} and A\textsubscript{2}\textsuperscript{2} are approximately doubled.7,8 If the thalassemia mutation were to actively affect delta chain synthesis, it would have to affect both allelic genes and thus require the existence of a diffusible regulator.9 Such a regulator would have to demonstrate remarkable specificity for the normal beta chain since the interaction between hemoglobin S and C with beta thalassemia demonstrates a lack of effect of betathalassemia on beta chain mutations.

Despite these objections the possibility of a diffusible regulator is sufficiently plausible that the effect of thalassemia major marrow homogenate upon hemoglobin production by normal marrow culture deserves investigation.

David E. Comings, M.D.
Cook County Hospital
Chicago, Ill.

From www.bloodjournal.org by guest on September 13, 2017. For personal use only.
Hereditary persistence of fetal hemoglobin is an anomaly in which there is complete suppression of function of the gene that determines the structure of the \( \beta \) chain of globin. Our initial studies of this abnormality led us to suggest that the primary defect might be a deletion of this gene.\(^1\) Discovery that function at the \( \delta \) chain locus also is wholly suppressed\(^2\) made this hypothesis unattractive because it seemed necessary to postulate a double deletion, an event unlikely to recur.\(^3\) An alternative proposal is that the structural genes for these hemoglobin polypeptides are under the control of an operator gene, mutation of which leads to inhibition of function of both.\(^2\)\(^4\)

However, a single chromosomal abnormality may account for both deficiencies. The genes determining the structure of the \( \beta \) and \( \delta \) chains are linked;\(^5\)\(^6\) and recent observations indicate that hemoglobin Lepore consists of part of a \( \beta \) chain and part of a \( \delta \) chain, the abnormality presumably resulting from unequal crossing over of the involved chromosome.\(^7\) A similar mechanism may be involving contiguous loci provides a simple hemoglobin. An overlapping deletion involving contiguous loci provides a simple and adequate explanation for the occurrence of this anomaly. Synthesis of the fetal hemoglobin is considered to be the result of compensatory production of \( \gamma \) chains.\(^1\)\(^8\)

The nature of the regulator that determines the proportions of hemoglobins A and F in normal persons is unknown. A plausible assumption is that production of \( \beta \) chains in some way inhibits synthesis of \( \gamma \) chains. In fetal life, production of hemoglobin A is low, increasing rapidly near term; fetal hemoglobin decreases as hemoglobin A appears. In hereditary persistence of fetal hemoglobin, production of \( \beta \) chains does not occur, and synthesis of \( \gamma \) chains is not suppressed even in adult life. Fetal hemoglobin is produced in an amount precisely sufficient to compensate for the deficit of hemoglobin A.

Hereditary persistence of fetal hemoglobin provides a unique opportunity to examine autosomal gene dose relationships, since the proportion of hemoglobin synthesized under the direction of the single unopposed gene readily can be measured.\(^9\) Our data show that A-F heterozygotes had, on the average, 72.4 per cent hemoglobin A, indicating that one \( \beta^A \) gene can direct the synthesis of this percentage of the total hemoglobin produced. These heterozygotes had a mean
haps the production of β chain genes is inhibited and globin synthesis occur in thalassemia, as suggested by Comings, does not seem necessary to explain the observations that have been made. Furthermore, variations in the proportions of hemoglobins A₂ and F are not solely the result of genetic effects but are known to occur during normal development as well as in certain acquired disorders. The possibility must be taken into account that thalassemia may lead to alterations in the proportions of the minor hemoglobin components by nongenetic as well as by genetic mechanisms.

C. Lockard Conley, M.D.,
The Johns Hopkins University School of Medicine Baltimore, Md.

REFERENCES
CORRESPONDENCE


To the Editor:

In connection with your recent editorial on the thymus,* I should like to give you some more details about the cases of familial lymphopenia (i.e., "lymphocytophthisis" or "alymphocytosis") which we had the opportunity to study in Bern.

I was a young pathologist when Glanzmann (Professor in Pediatrics) and Riniker, a friend of mine, described their cases. Since Riniker worked in the same Institute as I did, we often discussed this disease. Both Glanzmann and Riniker were convinced that the extreme lack of lymphocytes in these children was due to a loss of lymphocytes secondary to some unknown vulnerability of the cells (therefore, "phthisis"). The disease was first recognized as being a special form of agammaglobulinemia in 1957. I did the autopsy of that child myself, and remember very well that I did not find the thymus at first. All other lymphatic organs were very small and practically free of lymphocytes. The thymus was found, on serial sectioning, to be attached to the thyroid. Since you wrote in your editorial that "the Swiss authors did not mention the status of thymus gland in their cases," I assume that our original papers have not come to your attention. In these publications the rudimentary thymus is described in detail, also the fact that there was incomplete descent of this organ, and a lack of Hassal bodies. These latter findings led us to postulate in these reports that a developmental defect of the thymus was probably of primary importance in this condition. Therefore, we could no longer accept Glanzmann's and Riniker's view of a "phthisis" (they had not examined the thymus) and preferred the non-committal term of "familial lymphopenia." About one year later, the group of my friend Hitzig in Zürich saw similar cases which he chose to call "alymphocytosis" or "hereditary lymphoplasmoctytic dysgenesis." I am sorry for all these different names coming from Switzerland, but at first we were not certain that we were dealing with the same condition. Now, the term "familial lymphopenia" is also accepted by Hitzig (see: Hitzig, W., and Cottier, H.: The antibody deficiency syndromes. In The Plasmaproteins, W. Hitzig, ed. [Springer, to be published this spring]). I know only that the condition is familial; the final proof of a hereditary disorder is still lacking.

I was pleased to read that Rosen, Gitlin and Janeway found exactly the same maldevelopment of the thymus in their cases; so apparently did Dr. Good. I thought I should bring the above to your attention since they are the original descriptions of this type of agammaglobulinemia.

HANS COTTIER, M.D.
Visiting Scientist
Medical Research Center
Brookhaven National Laboratory
Upton, N. Y.

REFERENCES
