The Distribution of the Thalassemia Gene:  
A Historical Review

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IN 1925, Cooley and Lee,34 working in Detroit, described a severe, hypochromic, microcytic, hemolytic anemia in children of Italian, Greek and Syrian ancestry. Somewhat earlier, a similar but milder syndrome had been delineated in Italy by a number of investigators working in that area. (For detailed and thorough reviews of the pertinent literature see references 30, 93, 115, and 126.) With the discovery of the asymptomatic carrier state51,61,63,65,67 about 1940, the essential unity of these various disorders as well as the hereditary nature of the anemia was soon appreciated, although a thorough understanding of the genetic background has not yet been achieved.109 The prevalence of this disease among peoples of the northern and eastern shores of the Mediterranean Sea was obvious almost from the start and is reflected in such designations as Mediterranean anemia and Mediterranean syndromes as well as in the more popular name, thalassemia.185

The purpose of this report is to review the geographic distribution of the thalassemia gene and to summarize briefly, from a historical standpoint, the evolution of our current concepts of the thalassemia syndromes. A discussion of the clinical, hematologic and pathologic aspects of the disease is beyond the scope of this paper. An attempt has been made to record some of the significant literature relative to the occurrence of thalassemia in areas outside of Italy and Greece. A critical evaluation of all these reports, however, has not been carried out since many appear in journals not readily available. It is likely, therefore, that some of the publications quoted, particularly those appearing before 1940, deal with diseases other than thalassemia as it is currently defined. Nevertheless, it is believed that the majority of the cases fulfill the major criteria of thalassemia and merit inclusion in this review.

The diagnosis of thalassemia has, in the past, been based almost entirely on morphologic grounds. Such diagnostic criteria as aniso- and poikilocytosis, hypochromia, microcytosis, stippling, target cells, the associated changes in osmotic fragility of the red cells, and evidence of a hemolytic anemia need...
not be dealt with at length. To these morphologic features have been added an appreciation of the refractoriness of thalassemia to iron therapy and more recently, the presence of normal or high serum iron levels. As time has gone by, the marked variability of the thalassemia states, both from a clinical and hematologic point of view, has become apparent. This realization has helped identify a number of mild, bizarre, hypochromic anemias, particularly in families of patients with Cooley’s Anemia, as members of the thalassemia complex. Finally, the demonstration of increased amounts of fetal hemoglobin in most cases of thalassemia major as well as in some of the less severe examples of this syndrome has provided us with an additional diagnostic criterium.

During this period of development, which we may refer to as Phase I, the genetic transmission of thalassemia was under investigation particularly by Angelini, Caminopetros, Valentine and Neel, and Silvestroni and Bianco. The concept developed that Cooley’s Anemia represented the homozygous state for the defect of thalassemia, while the less severe forms of the disease were manifestations of heterozygosity for the same genetic abnormality.

During Phase I, which encompassed roughly the period from 1925 to about 1950, thalassemia was detected in three main areas of the world. In this country the studies of Cooley in Detroit, Dameshek in Boston, Smith in New York, and Valentine and Neel in Rochester indicated a significant incidence of the defect in individuals of Italian, Greek, Syrian and Armenian origin. Significantly, the disease appeared to be present in the United States in several other national groups in small numbers, but in particular in Chinese almost all of whom originated from the area around Canton and Hong Kong. In Europe, Silvestroni and Bianco, to mention only two of the more active hematologists engaged in studies of this disease, made careful surveys of the Italian mainland and islands and noted a remarkable prevalence in the Po Delta area with an incidence of as high as 20 per cent in some small communities near Ferrara. Sicily proved to be almost as important a source of the disease. Studies by Caminopetros in Greece and others in the eastern Mediterranean proved the frequent occurrence of thalassemia in Greece, Crete, Cyprus (which has one of the highest rates of involvement yet found), Syria and Turkey. Isolated reports of significance also appeared from Egypt, Spain, Portugal and from Palestine where Schieber described the disease in two Jews originating in the Bucharian area near the southeast banks of the Caspian Sea. The latter article is of interest, incidentally, in Schieber’s accurate observations and predictions on the remarkable sensitivity of the red cells of dark skinned races to hemolysis by sulfonamides and the fava bean in what is probably the first description of the hemolytic defect now known to be related to a genetic abnormality of glutathione metabolism. The third focus of involvement has been to some extent overlooked, in part because of the journals in which the relevant articles appeared. A number of reports from India, China, and the Philippines described occasional cases of hypochromic microcytic anemias oc-
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curring in these regions which satisfied most if not all criteria for the diagnosis of thalassemia.

In addition to these three major areas, isolated case reports dealing with thalassemia involved patients of Argentinian, Brazilian, Mexican, English, German, French, Bulgarian, American Indian, and American Negro origin.

The second stage of development of our understanding of thalassemia actually had its origin in the work of Silvestroni and Bianco in the mid 40's with the description of microcytosis. Nevertheless, it was not until approximately 1950 that, from a practical standpoint, Phase II can be said to have gotten underway. The discovery of the abnormal hemoglobins, their modes of transmission, and their distribution, provided not only an answer to some of the perplexing problems related to thalassemia, but also served as a powerful stimulus to renewed interest in the entire subject of the thalassemia states. An explanation was now apparent for some of the variability encountered in this group of anemias, as well as for some of the atypical family histories which had been a source of great worry to geneticists interested in this disease. Double heterozygosity for thalassemia and Hgb S was recognized as the genetic basis of thalassemia-Hgb S disease or microcytosis. In rapid succession, largely through the use of paper electrophoresis, the discovery of thalassemia-Hgb C disease, thalassemia-Hgb E disease, and thalassemia-Hgb II disease followed. One instance each of thalassemia-Hgb G disease and thalassemia-Hgb D disease may also have been encountered. The most recent advance in our knowledge of thalassemia stems from the work of Kunkel and others who identified, in carriers of the thalassemia trait, an increase in the amount of the hemoglobin A$\alpha$ fraction of normal adult hemoglobin, using starch block electrophoresis. Although a similar increase may be found in several other conditions it is of interest that the presence of thalassemia in the heterozygous state can now be substantiated by quantitative changes in at least one parameter in the blood of almost all carriers of this condition.

From the genetic standpoint, several concepts have evolved during the course of Phase II. We have already alluded to the double heterozygosity for thalassemia and the abnormal hemoglobins. The presumption has been that the responsible genes are transmitted as non-allelic characteristics, although the possibility of linkage was not ruled out. More recent studies by Ranney and Ceppellini suggest, however, a close relationship between the sites of genetic control of the hemoglobins and the usual form of thalassemia. Furthermore, it is becoming increasingly apparent that several genetic factors, not necessarily closely linked, rather than a single pair of alleles may be operating in the genesis of thalassemia. At least one of these is directly or indirectly related to the gene controlling the synthesis of fetal hemoglobin. Our own studies on a group of five families with thalassemia, in each of which one or more members had virtually no abnormality except a striking rise in fetal hemoglobin, while other siblings had more or less classic signs of thalassemia, provides strong suggestive evidence for the independent segregation of at
least two of these factors. Similar instances of high Hgb F sibships have been recorded by Edington and Lehmann,48 Jacob and Raper,81 Motulsky,102 Went and MacIver,184 and Spear.168 Since evidence for thalassemia is lacking in some of these families it must be concluded that the genetic control of Hgb F is not allelic to that of thalassemia, but that the latter is capable of exerting a profound effect on fetal hemoglobin formation by some form of genetic interaction. Finally, recent studies have brought up the probability that several genetic varieties of hypochromic microcytic anemia may be masquerading under the name of thalassemia.66,67 In support of this concept are such findings as the normal values for A2 among some thalassemia-like carriers, and the presence of hereditary conditions, such as the Lepore trait, which tend to mimic the morphologic aspects of classical thalassemia.

Concomitant with this renewed interest in thalassemia have come numerous reports of the disease from many areas of the globe. Ample confirmation of the presence of thalassemia along the northern and eastern shores of the Mediterranean has been provided by many studies2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19 including those of Carracassi, Ceppellini and Pitzus2 in Sardinia utilizing the increase in Hgb A2 level. In areas where Hgb S is found, such as in Sicily, southern Italy and portions of Greece, thalassemia-Hgb S disease has been repeatedly demonstrated. One of the most significant studies in Phase II was carried out in Thailand98 and may be said to have led to the discovery of Hgb E.26 Following the report of an extremely high incidence of Cooley’s Anemia in that area, the characteristics of thalassemia-Hgb E disease were elucidated28 and numerous reports of Cooley’s Anemia and its variant with Hgb E appeared from Indonesia,50,70,107,124,151,180,181 Ceylon,45,71 Burma,118 Malaya,69 and Indochina.15 Reports of thalassemia in a Sikh colony from the Punjab living in Vancouver150 are now amply confirmed by a significant prevalence of thalassemia in various parts of India.13,24,41,67,105,178 The presence of Hgb S, D, and E in this area makes it likely that numerous examples of these variants will soon be described. More recently from China,37,51,114,147,149,188 the Philippines,87 Thailand,99 and Indonesia51 have come reports of both Cooley’s Anemia and the combination of thalassemia with Hgb H. And from Persia,133 Iran13,121 and the Kurdistan region of Iran, Iraq and Turkey96 we find other significant foci of the thalassemia gene. Perhaps the last frontier, as it were, seems to be opening up now with reports of thalassemia in Tunisia,115,129,130 Algeria,88,115,120,125,135,136 the Belgian Congo,36,170 and South Africa.16,22

We are now in a position to summarize what has been a truly remarkable development. Almost every reported case of thalassemia has originated in peoples inhabiting or originating in the broad band indicated on the map in figure 1. That the prevalence of the gene for thalassemia is notably high throughout this area cannot be doubted. It exists in combination with the genetic abnormalities of hemoglobin in regions where the two are both present. The lack of reports of thalassemia from certain areas within this band is undoubtedly more a reflection on the lack of medical facilities for studying the disease than on its absence from the region. Figures are unfortunately lacking on the true incidence of the gene for thalassemia, but extensive
studies, such as those utilizing the increase in A₂ levels, may help provide these data.

It is interesting to speculate on how thalassemia achieved so widespread a geographic distribution and in what way its incidence has been maintained at such high levels. Unfortunately, a definitive answer to each of these questions is lacking. Perhaps the most attractive hypothesis relative to the distribution of thalassemia is that mass migrations and commerce served to carry the genetic defect eastward to China from a single focus in the northern Mediterranean basin. At least one individual, Brumpt, contends, however, that thalassemia may have arisen in Indochina and moved westward while another, Sheba, suggests an Armenian origin with spread both to the east and west. It is possible to find prehistoric migrations as well as later movements of peoples to support each of these hypotheses. Although spontaneous mutations arising in a number of areas must always remain a possibility, this suggestion provides a less plausible explanation for the observed distribution of thalassemia.

An answer to the question as to why a potentially lethal gene like thalassemia continues to be so prevalent is also unavailable at present. The rates of spon-
taneous mutation needed to offset the normal loss of the thalassemia gene through the mortality of the homozygote are far greater than have been observed in man. There is no evidence for the proposal that thalassemia heterozygotes have a higher index of fertility than other individuals. There is, on the other hand, some evidence suggesting that a state of balanced polymorphism may be operating to maintain the thalassemia gene at its present level in a manner analogous to that which is presumed to operate in the case of sickle cell disease. Although the data are far from conclusive, it has been suggested that partial resistance to malarial infection is the reward for harboring this abnormal genetic constitution. Intensive studies are under way to test this proposal and their results will be awaited with great eagerness.

There remains finally the problem of explaining some of the sporadic reports of thalassemia in such groups as Argentinians, American Negroes, Germans, and so forth who presumably have no obvious common origin with the peoples represented in the broad band depicted in figure 1. Many of these reports appeared before 1950 and may represent diseases other than thalassemia, as was commented on by Schwartz and Hartz in reference to some of the cases they reported as thalassemia in the American Negro. In others, the possibility of admixture with the peoples of the thalassemia belt is extremely likely, although it may have occurred in the remote past. The reports of thalassemia from Australia, England, Germany, Eastern Europe (Roumania, Bulgaria, Yugoslavia, and Russia) and Central and South America (Argentina, Brazil, Mexico, and Cuba) are probably in this category. Spontaneous mutations in areas of the globe other than those indicated in figure 1 cannot be ruled out, but seem unlikely. Another possibility, that of different genetic varieties of thalassemia whose world wide distributions have not yet been delineated, is assuming increasing importance. Finally, it is possible that the thalassemia belt may have to be extended to take in at least parts of Central and South America, more of Europe, as well as most of central and northern Africa. In this regard, anthropologists and archeologists have speculated that the disappearance of the Peruvian Incas as well as the pre-Columbian Mayan Indians may have been contributed to by the presence of a fatal hemolytic process similar to thalassemia. These speculations are based upon the finding of paleontological specimens showing bone changes consistent with those seen in severe hemolytic processes. Similar bone findings have been reported in skulls of ancient Egyptians as well as Frenchmen of the Gallo-Roman period. Also, the significant incidence of thalassemia in the American Negro may reflect an as yet undetected focus of the disease in the gold coast area of Africa, although Edington's studies in this region failed to disclose such a focus.

**Summario in Interlingua**

Es presentate—super le base de un bibliographia de 190 titulos ab le litteratura de lingua anglese, francese, german, hollandese, italian, e espaniol—un revista del distribution geographic del gen pro thalassemia insimul con un breve summario del evolution historic del conception currente del syn-
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Dromes de thalassemia. Un discussion del aspectos clinic, hematologic, e pathologic del morbo es foras del objectivos del articulo. Esseva facite le effortio de includer un parte del litteratura concernite con le occurrentia de thalassemia in areas altere que Italia e Grecia.

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