THALASSEMA (MICROKARTEROCYTOSIS) AND DREPANOCYTOSIS
THEIR FORMS AND GENETICS

by

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Both the analysis of the casuistry of the disease described by Cooley in 1925 and which is particularly characterized by anemia with erythroblastosis, hyperhemolisis, splenomegaly and particular changes both of the skeleton and of the cardiovascular system and the analysis of the casuistry classified in Italy under different names and which was later acknowledged to belong to the morbid form described by Cooley show clearly the existence of several courses, that, in a certain way, bear some difference in the blood picture.

It is acknowledged that most cases described in the Italian pediatric literature under different names, more frequently known under the name of Jaksch Hayem Luzet anemia must be considered as belonging to Cooley's anemia having a subchronic form, whose onset and end is in infancy (Gerbasi). Two forms could already be detected in childhood: the already mentioned subchronic form and the chronic one with a longer course which reaches its complete morbid form generally during the pre-school age and can continue also during the school age.

Such two forms bear the same peripheral blood and marrow picture with the exception of a more marked peripheral erythroblastosis and hemolysis in the subchronic form.

Skeletal X-ray can be detected with greater difficulty in the subchronic form but pathological observation of the skull bears changes that bring back the ones described in the chronic form (Gerbasi) and in those cases in which it was possible to prolong the life of the little patients with apt therapeutic proceedings the facial skull changes of the skeleton appear clearly (Gerbasi) as I myself could see in cases that came under the range of my personal observation.

The cases described in adults and with a more chronic course must be added to the forms already described and occurring in children.

In 1940 Pachioli assumed that such form occurring in adults with a longer and milder course confines «through dull nuances » with the haematological abnormality detected in the members of the family of individuals suffering from Cooley’s anemia, essentially characterized by a true microcytosis, hypochromia and increased resistance of erythrocytes.
Yet in 1941 and 1942 agreeing with Gansslen to put under a sole group together with elliptocytosis, spherocytosis and drepanocytosis also Cooley’s anemia I have taken into evidence the possibility of detecting also in this disease, as it had been done for the three other diseases by Gansslen and Lambrecht, a latent form detected in apparently healthy individuals and characterized by changes of the shape and volume of the Hb contents and of the maximal resistance of the red cells and a compensated form in which a slight anemia can be detected with increased spleen volume and a full-blown form characteristic in Cooley’s anemia patients.

Dameshek also classed under hereditary hemolytic syndrome the spherocytosis, drepanocytosis and Cooley’s anemia. The same year when Cooley’s work about anemia was issued in the States and which was called after him, Rietti in Italy described the first cases of hemolytic jaundice with increased erythrocytes resistance. Such disease which was more precisely defined in the works by Greppi and Micheli and in other observations of the Italian literature is especially characterized by an icterus anemia with an increased spleen volume of a very different entity. The haematologic picture is characterized by a generally slight anemia (sometimes with a normal number of red cells) in which the red cells show colour changes, morphological and osmotic as in Cooley’s anemia. Generally no erythroblast are detected in the peripheral blood and, if any, they are scanty. The bone marrow picture should, compared with the one of Cooley’s anemia, show some differences only of a functional order bearing in certain cases some aspects almost equal (Marmont). Changes of the osteoporotic type in the skeleton are detectable, though of an entity inferior to those observed in Cooley’s anemia.

A macro or normocytic form of the disease has been described (Fanconi, Patrassi) while from the hematologic point of view Momigliano Levi had already described two forms, one with normochromic elliptocytosis slightly hypochromic and a form with poikilocytosis and hypochromic elliptocytosis.

Also in the apparently healthy members of the family of these patients slight hematologic changes have been detected which we can consider equal to those observed in the members of the family of Cooley’s anemia patients.

In Italy the relation that such disease has with Cooley’s anemia is still under discussion. Indeed the first statements of identity between the two diseases have been done by Italian pediatricians (Frontali and Rasi 1937, Fornara 1940).

Morbid forms similar to the hemolytic icterus with increased resistance of erythrocytes have been described in the States at any rate as Cooley’s anemia attenuated forms (Wintrobe), of an anerythroblastic type, moderate form (Dameshek), thalassemia minor (Valentine and Neel). Lately in Switzerland a case was described by Rhor under the same name of familial hypochromic anemia, Cooley’s anemia of the adult.

It was also shown that from the cases of hemolytic icterus with increased resistance of erythrocytes, which is the slight anerythroblastic type of Cooley’s anemia of the American authors we go through a dull degree of slighter and slighter cases to the apparently healthy individuals that are carriers of the slightest hematologic changes: microcytosis with increased resistance of erythrocytes (Wintrobe and associates, Dameshek, Smith.). Valentine and Neel have called attention to the fact that in some of the carriers of
thalassemia the hematological abnormalities can be so scanty as to be discriminated only by careful laboratory studies though sometimes hardly detectable.

Consequently it is evident that Cooley's anemia, the hemolytic icterus with increased resistance of erythrocytes, the slight hematological stigmata detected in the apparently healthy members of the families of both groups of patients can be put under a sole morbid form.

All cases classed under such morbid form that, as we have already said, can declare themselves through cases ranging from a slight hematologic abnormality in apparently healthy individuals to the severest forms of Cooley’s anemia such as the subchronic ones with the onset and end in infancy, can surely be grouped in rather omogenous groups: latent form (hematological stigmata), compensated form (slight cases of hemolytic icterus with increased resistance of erythrocytes and Cooley’s anemia.

This idea essentially agrees with what Dameshek says to distinguish three forms: the severest (a marked anemia, increased hyperhemolisis, splenomegaly, significant changes in the skeleton and the presence of numerous erythroblasts in the circulating blood), the moderately severe form in which nothing is detectable by a physical examination and only a slight hypochromic anemia is detectable.

The researches I made in 1941 and 1942 showed that patients affected with Cooley’s anemia are always born of parents bearing both stigmata (what V. Angelini observed) and such morbid condition is hereditary and transmitted as dominant trait since carriers of stigmata are heterozygous, while patients affected with Cooley’s anemia are homozygous, I have therefore admitted a dominant hereditary trait with homozygous lethal effect.

Chini has pointed out the possibility of a bilateral heredity of Cooley’s disease.

The further researches of American authors have confirmed the obrigatoriness of homozygosity in patients suffering from Cooley’s anemia born of both parents heterozygous owing to the pathologic trait (Dameshek, Smith, Valentine and Neel.).

Strauss, Daland Fox admittend a type of dominant inheritance for the cases they described as familial microcytic anemia.

Dameshek too, has admittend a Mendelian dominant mechanism.

Neel and Valentine submitted to statistical enquiries their own data and those gathered from literature and they agreed upon statistical and theoretical, data expected to be found in an hereditary type thalassemia major-homozygote, thalassemia minor-heterozygote (1944-1947).

Also the statistical values which Caracci came to discriminating the Italian casuistry relative to Cooley’s anemia by Lenz’s method agree upon the theoretical ones to be found in an hereditary type in which the disease would only appear under homozygous conditions. Vecchio came to the same conclusion.

Silvestroni and Bianco, who have confirmed the dominant hereditary trait of hematological stigmata which they called microcytemia in 1946, denied the compulsory homozgyous condition for the onset of Cooley’s anemia that they admitted in 1947.

These authors have also admitted that carriers of stigmata and patients affected with hemolytic icterus with increased resistance of erythrocytes called by them constitutional
microcytic anemia are heterozygous for the same dominant trait. Muratore (1947) came to the same conclusions.

The morbid conditions which we are dealing with are united not only for their hematologic behaviour but also from the genetic point of view.

It is not yet clear enough for certain authors why carriers of stigmata give birth to individuals with stigmata always at times; at others they give birth to individuals with hemolytic icterus with increased resistance of erythrocytes.

Silvestroni and Bianco say that owing to still unknown causes the hematological abnormality sometimes originates a constitutional microcytic anemia. Muratore to explain such condition calls forth the possible existence of other conditions that may be of an hereditary character such as a factor of pathological hypermolysis coming from the other ascending familial branch.

Such hypothesis of Muratore bears substantially an identity with the one suggested by McIntosh and Wood for Cooley’s anemia, that is, the existence at the same time of two nonallellomorphic dominant factors.

I am of the opinion that what we have observed can be explained with the knowledge we have about biological genetics.

The hematologic change, which is at the bottom of the morbid conditions we are dealing with, as I have assumed, is the dominant hereditary trait that at the heterozygous determines the slightest hematologic changes in apparently healthy individuals and the compensated form on which we have already dealt with and according to Silvestroni and Bianco and Muratore also determines the severest cases of hemolytic icterus with increased resistance of erythrocytes. The different expression of the gene in a single subject determines the different seriousness of the morbid condition.

It is known that the expressions (intensity of trait in individuals genotypically equal for the same factor) depends on other genetic or environmental factors. Owing to the different expressions of the gene we have a changeable dominancy for which the character can range from the slightest hematologic abnormality detectable only by very careful hematologic researches to a complete picture of the hemolytic icterus with increased resistance of erythrocytes.

When both parents have the same trait children can be born bearing the trait at the homozygous state, in double dose. These are the subjects in which Cooley’s anemia appears.

What we have dealt with thus far has a complete explanation in what I, for the first admitted, that is, the existence of a dominant gene with homozygous lethal effect.

Having admitted the genetic and hematologic relations that put under the same class the individuals bearing the three conditions: stigmata, hemolytic icterus with increased resistance of erythrocytes, Cooley’s anemia, it is logical to try to establish a unique denomination specifying the single states.

The denominations which come within the range of the anemia cannot be used because in the latent form there is no anemia. The ones reflecting the form of red cells are not specific because the red cells in the conditions we are dealing with have not a specific form. If we want to stick to the last idea, in order to use also a word that may find a
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checking in the one of the other hereditary icterus-anemias (spherocytosis, elliptocytosis, drepanocytosis), the term of microkarterocytosis can be suggested which calls the two essential characteristics, microcytosis and globular hyperresistance (μαρτερός = resistant).

The idea of hyperresistance is not limited to the behaviour towards hypotonic solutions but reflects also the one towards the mechanical traumata (Tolentino).

We can otherwise accept the term thalassemia suggested by Whipple and Bradford recently so widely spread in the American literature.

In any case it is necessary to add to the generic term for every form a specific term determining it.

Valentine and Neel have called Cooley's anemia Thalassemia major and the forms described in the American literature as slight or anerythroblastic Cooley's anemia and consequently the hemolytic icterus with increased resistance of erythrocytes and also the hematologic stigmata detectable in apparently healthy individuals as Thalassemia minor.

I am of the opinion that two conditions that from the clinical point of view and owing to the intensity of hematologic changes are perfectly distinguishable cannot be classed under only one term. I think, therefore, that the minor form must be distinguished maintaining the term of minor for the hemolytic icterus with increased resistance of erythrocytes, classing the stigmata as thalassemia minima.

The genetic relations and the terminology pertaining to the different forms can, however, be defined as follows: Thalassemia (Microkarterocytosis)-heterozygote-minima-stigmata, heterozygote-minor-hemolytic icterus with increased resistance of erythrocytes, homozygote-major-Cooley's anemia.

Having admitted the inheritance of Cooley's anemia and of stigmata (latent, compensated and full-blown form of Cooley's anemia) in my researches published in 1941 and 1942 owing to the constant presence of a particular facial aspect of stigmata carriers characterized by the width of high cheekbone arches I at that time suggested the hypothesis that hematologic stigmata were a pathologic character arisen through mutation in a paleo-Mediterranean race, showing as a normal character the particular aspect of cheekbones.

The researches carried out lately by Graziosi on skeletons belonging to the paleolithic period that were found in the cave of S. Teodoro at Acquedolci in the province of Messina (Sicily) have not only shown that such individuals bore a particularly large face with high cheekbone arches but moreover in one of these skeletons was to be seen a generalized osteoporosis that according to the author was due, besides the causes relative to the situation of the fossil, also to a different ante mortem constitution of the tissue itself attached to the pathological state of the individual.

If we mean it in this way, such changes can help us to admit the existence in certain superior paleolitical Mediterranean adults of a disease capable of producing a generalized osteoporosis as we observe in the hemolytic icterus with increased resistance of erythrocytes.

The results of Graziosi's researches have determined me to identify in such human type of S. Teodoro the Mediterranean race where possibly sprang the mutation responsible for thalassemia.
The necessary starting point for the studies of the genetics of drepanocytosis was due to Emmel's (1917) interesting discovery that elongating the observation in sealed wet preparation most red cells in the blood of individuals with sickle cell anemia are able to sickling.

Following this method Sydenstricker and Huck (1923-24) could show that there exist among the negroes, individuals otherwise healthy having red cell capable under this procedure, to sickling. Both authors showed that the disease can appear under two forms: a latent one detecting sickling by Emmel's method and a full-blown form accompanied by anemia, icterus and the other symptoms of the disease.

The possibility of revealing by the sealed wet preparation method the latent form in a certain number of negro individuals allowed the observation of the genetic link existing between the simple haematologic trait and the fullblown disease assuming that it is transmitted with a dominant hereditary characteristic.

Among the negroes drepanocytosis as a latent form is fairly spread and it can be assumed that seven per cent of them develop it.

In the States rare cases of sickle cell anemia even among white individuals have been noticed. Wintrobe refers that at least for nine of these observations, one of which was personal seem unchallengeable. Such observations deal with individuals of Greek and Italian extraction, most of the latter born of Sicilian ancestors. That the said disease exists among Italian people is shown by the research carried out in Italy (Maggiore, Pontoni, Cassano and Benedetti, Carnevale, Paradiso and Lanza, Silvestroni and Bianco).

In 1949 together with Dr. Purrazzella I observed two pedigrees belonging to two Sicilian children suffering from sickle cell anemia. In both families only one of the parents was a carrier of sickle cell trait, whilst the other one was hematologically normal.

To find out sickling both in this and further researches I used Singer and Robin tests, mixing one drop of the blood being tested and one drop of Escheria coli culture, observing the mixture up to twenty-four, forty-eight hours after preparation.

The study of the genetic behaviour in thirteen individuals bearing the sickling phenomenon (two with splenomegalic hemolitic anemia) made us assume that the sickle cell character is monomorphic hereditary with a variable expression, because in our observations drepanocytosis, in the hetherozygous state was observed both as a simple haematologic trait detectable with sickling tests in individuals otherwise healthy, and as a real icterus anemic morbid state.

Just then we wondered what should be the clinic and hematologic aspect of homozygous individuals for the character under discussion as such condition was neither apparent in the matter we were studying nor any description was known in literature.

The presence of this hereditary character among individuals of European races was understood by us as due even to very ancient crosses with people of the negro races among whom this anomaly is widespread.

Such idea is supported by the fact that the admixture of blood of white people living along the coasts of the Mediterranean sea with negro people is historically shown.

The later study (1950) of another family has shown the presence of sickle cell cha-
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cacter transmitted to three following generations and the appearance of an individual with sickle cell anemia born of parents both carriers of the sickle cell trait. Such behaviour can make one doubt whether the patient was an homozygous subject.

Recent observations of genetic situations similar to those of the family described in this paper have made workers doubt whether the sickle cell anemia can be present only in homozygous subjects. Beet (1949) came to such conclusion as he examined a Bantu family in North Rhodesia. Neel (1949) is of the opinion that the sickle cell anemia is due to the homozygous state of the morbid character; he observed that the forty-two parents examined of twenty-nine patients all showed a positive sickling phenomenon (only in 13 instances both patents were studied). Then Silvestroni and Bianco observed the sickling phenomenon present in both parents of the patients studied.

Besides the cases previously described there exist in literature other observations (Stewart, Wollstein and Kredel, Cooley and Lee, Russel and Taylor, etc.) in which one only of the parents showed the morbid character.

A positive objection can be moved to such casuistry that either the traits were unknown for not having used a very sensible test capable of showing sickling or that there existed another hereditary morbid character which summing up the sickle cell character had given rise to the onset of the anemic splenomegalic disease.

In particular that in the other parent might have existed Cooley's trait (thalassemia minima) since the onset of splenomegalic anemic disease has been observed in individuals whom one parent showed the sickle cell trait and the other thalassemia minima (Silvestroni and Bianco, Powell, Rodarte, and Neel).

This objection cannot be made for the study matter of our first paper where we assumed the existence of sickle cell anemia in heterozygotes. To research sickling we used Singer and Robin test keeping under control the slide up to 24 hours after preparation. We have always considered such a test equally sensible for further proofs of control with other tests proposed later on. The negative results we got can be considered exact.

Moreover, the haematologic study of the two parents who did not show sickling was complete and it gave absolutely normal results and they were such as to reject the existence in them of thalassemia minima or any other hereditary haematologic character.

The results of our researches shown above cause us to draw the conclusion than in drepanocytosis the disease can appear either in the heterozygous state due to the greater expression of morbid gene (even Powell Rodarte and Neel say that it is possible that in a few persons a single Sk gene may rarely produce sickle cell disease) or in the homozygous state due to the double dose of the morbid gene.

Such genetic situation is analogous to thalassemia where the disease can occur in the heterozygous patient (thalassemia minor — Rietti and Greppi disease) and in the homozygous state (thalassemia major — Cooley's disease) as I have already assumed (Gatto 1941-1947).

A support to this hypothesis can be given by comparing the severity of the disease in the cases of heterozygous drepanocytosis and in the homozygous ones.

Out of the three cases I considered the homozygous one showed a severer anemia and much more tumultuous haemolytic crises.
During the genetic researches on thalassemia and drepanocytosis three clinic cases have come under the range of my observation. I have studied them together with Dr. Purrazzella. They showed the clinic picture of a slight Cooley. The haematologic study of the parents of these three patients showed that one parent was the carrier of the thalassemia minima and the other one of the sickle cell trait. Clinic cases of chronic splenomegalic icterus anemias with a genetic situation similar to ours have been described by Silvestroni and Bianco and by Powell, Rodarte and Neel.

The aspect of the morphological and colouring characters of the red cells of the patients studied by us were in favour of the existence of alterations pertinent of the two morbid characters: thalassemia and drepanocytosis. This datum only together with the one of having observed the two traits in the parents make us think of the co-existence of the two morbid traits in patients and in consequence of this we propose to call the disease thalassodrepanocytosis.

Powell, Rodarte and Neel have pointed out the different genetic aetiological situations that can be laid at the basis of this disease.

They can be summited up as follows under three different situations:

It might be the interaction of the two genes located on two different chromosomes and that there is in it a type of non allelic factor interaction.

It might arise in consequence of the greater expression of one of the two characters and it might be the case of either thalassemia minor or of drepanocytis anemia where the other character should have no importance in determining the onset of the disease but for its presence as a trait.

It might be the case of two genes located in the same chromosome either in the same locus (multiple allelomorphy) or in two different loci.

Thus far the scarce casuistry published does not allow a statistical investigation capable of resolving the above said problem.

At the end of this paper we wish to draw attention to the practical importance of the researches of genetics on the diseases under discussion.

The therapeutical aids, at present at our disposal, cannot give recovery from the diseases we have dealt with, therefore it could be useful to profit by prophylactic expedients.

The results of the genetic researches have shown the ways by which these diseases can occur out of two haematologic traits in individuals otherwise healthy.

The acknowledgment of the carriers of these traits before marriage is to be suggested, since it is from the cross of two carriers that the severest forms of the disease springing from these traits occur.

The eugenic experiences that Gerbasi already pointed out, a corollary of the studies on genetics we have dealt with in this paper, are at the present moment the only concrete means we have to oppose these diseases.
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SUMMARY

Thalassemia, that I propose to call Microkarterocytosis, can be divided into three forms to be distinguished under the names of minima (healthy carriers), minor (Rietti and Greppi's disease), major (Cooley disease).

It can be inferred that Thalassemia is a mutation developed in a Mediterranean superior paleolitic race that showed also the character high cheek bones.

In my researches of 1941-42 I for first showed that thalassemia is a dominant hereditary character with homozigotic lethal effect (heterozigotes the healthy carriers, homozigotes Cooley' patients).

Heterozigotes through an increased expression of the morbid gene develop Rietti and Greppi disease, as I inferred in 1949.

The researches on genetics that I carried later on Drepanocytosis have shown a behaviour equal to that observed in Thalassemia.

In Drepanocytosis the heterozigote condition determines the healthy carriers and the less serious cases of sickle cell anemia, the condition of homozigote the most serious form of this anemia.

A morbid form clinically similar to the slight cases of Cooley disease is detectable in subjects whose parents show separately one the Thalassemia-stigmata and the other the Drepanocytosis-stigmata. For this latter form the name of Thalassodrepanocytosis is suggested.

The presence of drepanocytosis in individuals of European races can be explained with very ancient crosses with individuals of negro races.
La Thalassemia, che io propone di denominare Microkarterocytosis, può essere distinta in tre forme per le quali ho proposto le denominazioni di minima (portatori sani), minor (malattia di Rietti e Greppi), e maggiore (malattia di Cooley).

Si può supporre che la Thalassemia sia una mutazione inizialmente presente in una razza paleolitica superiore mediterranea che presentava anche il carattere zigomi sporgenti.

Nelle mie ricerche del 1941-1942 ho per primo dimostrato che la Thalassemia è un carattere ereditario dominante con effetto letale omozigotico (eterozigoti e portatori sani, omozigoti gli ammalati di Cooley).

La malattia di Rietti e Greppi si manifesta pure negli eterozigoti per aumentata espressività del gene morbo, come ho ammesso nel 1949.

Ricerche di genetica da me ulteriormente condotte sulla Drepanocytosis hanno dimostrato un comportamento analogo a quello osservato nella Thalassemia.

Nella Drepanocytosis lo stato di eterozigoti determina i portatori sani ed i casi meno gravi di anemia a cellule falciformi, lo stato di omozigoti le forme più gravi di questa anemia.

Una forma morbosa clinicamente simile ai casi lievi di malattia di Cooley si riscontra in soggetti, i cui genitori presentano uno la stigmata Thalassemia e l’altro la stigmata Drepanocytosis. Per questa forma morbosa si propone la denominazione di Thalassodrepanocytosis.

La presenza della Drepanocytosis in individui di razze europee può essere spiegata con incrocio anche molto antichi con individui di razza negra.

La Thalassémie, que je propose de dénommer Microkarterocytosis, peut se subdiviser en trois formes pour lesquelles j'ai proposé les dénominations suivantes: moindre (porteurs sains), mineur (maladie de Rietti et de Greppi), et majeur (maladie de Cooley).

On peut supposer que la Thalassémie soit un changement qui se serait opéré dans une race paéolithique supérieure méditerranéenne, qui présentait encore les caractères zygotiques saillants.

Au cours des recherches que j'ai effectuées en 1941-1942 j'ai, le premier, démontré que la Thalassémie est un caractère héréditaire dominant à effet mortel homozygote (génotèrèzygothès les porteurs sains, homozygotes les malades de Cooley).

La maladie de Rietti et Greppi se manifeste également dans les hétérozygotes par l'augmentation de l'expressivité du gène morbide, ainsi que je l'ai admis en 1949.

Les recherches de génétique que j'ai ultérieurement effectuées sur la Drépanocytosis ont mis en évidence un comportement analogue à celui observé dans la Thalassémie.

Dans le Drépanocytosis l’état d’héthrozygote détermine les porteurs sains et les cas moins graves d’anémie et les formes falciformes. Les maladies de Cooley se manifestent également dans les hétérozygotes par l'augmentation de l'expressivité du gène morbide, ainsi que je l’ai admis en 1949.

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La Drépanocytosis, qui est une maladie d’hérédité dominante avec effet fatale, a été récemment décrite à l'âge adulte.

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La Thalassemie, qui io vorschlage Mikrokarterocytosis zu nennen, kann in drei Formen unterschieden werden, für die ich vorgeschlagen habe, die Bezeichnung minima (gesunde Träger), minor (Rietti-Greppi’s Krankheit), major (Cooley’s Krankheit), zugeben.

In meinen Versuchen von 1940-1941 habe ich als Erster gezeigt, dass es sich um einen hereditären dominanten Charakter mit letalem Effekt handelt (heterozygoten die gesunden Träger, homozygoten die Cooley’s Kranken).

Ich nehme an, dass die Thalassemie eine Mutation ist, die in einer Oberen paläolithisch-mediterranischen Rasse, die auch den Charakter vorstehende Jochbeine hatte, vorgekommen ist.

Genetische Versuche, die ich zuletzt in Drepanocytosis durchgeführt habe, haben in dieser Krankheit ein Verhalten gezeigt, dass jenem der Thalassemie gleichartig ist.