MEDITERRANEAN HEMOPATHIC SYNDROMES

By V. CHINI, M.D., AND C. MALAGUZZI VALERI, M.D.

FROM investigations made during the past ten years in our laboratory and on the basis of several recently published reports, we are now in a position to attempt a classification of Cooley's anemia and allied conditions. We have used the term "Mediterranean hemopathic syndromes" for a group of blood conditions which have a high incidence among the populations of some Mediterranean countries, and which have in common certain hematologic abnormalities, which represent different varieties of one great group of constitutional and hereditary blood diseases.

To this group belong, among others, two clinically well-defined and easily diagnosed forms, that is, Cooley’s anemia, or Mediterranean anemia, and a hemolytic syndrome which about twenty years ago was popularized by Italian authors as "hemolytic jaundice with decreased red cell fragility."

Cooley's anemia being universally known, it is superfluous to mention here its clinical features and blood picture. It was first described as a clinical entity by Cooley and collaborators, and several American and European authors have widely contributed to its study. On the continent it has been the object of investigations particularly by Caminopetros and various Italian workers (Cassano; Ravenna and Cannella; Ortolani; Ortolani and Castagnari; as well as by many others).

The so-called "hemolytic jaundice with decreased red cell fragility" was first described in Italy by Rietti and Greppi (1928). Numerous cases have been published subsequently by Italian authors and more recently by others. It is a familial hemolytic jaundice with a constitutional and hereditary element. Its fundamental feature, and the one which differentiates it from Minkowski-Chauffard's hemolytic anemia (acholuric jaundice), is the presence of an increased instance of the red cells to hypotonic solutions. Other less constant features are hypochromic microcytosis and in nearly all cases ovalocytosis and poikilocytosis.

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Clinically, its differential characteristics are a less intense degree of anemia, less intense and less frequent hemolytic crises, and less favorable results from splenectomy.54, 125, 135, 142, 166, 219

The clinical and hematologic features of the condition just described have led us to put it in the same general category with Cooley’s anemia. Several investigators,106, 107, 118 especially American authors (Wintrobe et al.271; Atkinson14; Dameshek,91 and others), have interpreted such cases as “mild” or “asymptomatic” forms of Cooley’s anemia272, 277 and the prevalent opinion now is that there exists one disease entity—that is, Cooley’s anemia—which may appear under at least two fundamental forms, that is, (a) “severe” form, the classic Cooley’s disease, which develops nearly exclusively in children, has a rapidly fatal course, and is characterized by an intense degree of anemia, splenomegaly with erythropoietic metaplasia of the spleen, and by typical bone changes; and (b) a “mild” form (“hemolytic jaundice with decreased red cell fragility” of Italian authors), whose course is less rapid, allowing patients to reach adult age. With this latter form should be grouped a good number of cases which have been described as “Cooley’s syndrome” or “Mediterranean anemia of adults.”5, 9, 17, 25, 49, 53, 78, 80, 91, 95, 100, 104, 105, 117, 128, 132, 150, 152, 157, 167, 173, 187, 226, 237, 263, 266

Observations in a large series of cases, investigations of the familial element and on the modes of transmission of the fundamental characters of the two conditions, analysis of well-defined clinical and hematologic pictures have allowed us to develop a broader aspect of this group of conditions and a more satisfactory classification of the various forms.

These investigations, which began with the work of Caminopetros32, 31, 33 and others,225 have been further developed by several Italian (Angelini8; Micheli and collaborators155, 168; Pontoni207; Gatto123, 124, 126; Chini51, 54, 57, 179; Silvestroni and Bianco227-243) and American workers (Dameshek81, 82; Valentine and Neel176, 177, 262; Smith247, 248; McIntosh and Wood162; Cooley79).

By proposing the term “Mediterranean hemopathic syndromes” we do not intend to suggest that such conditions affect exclusively Mediterranean ethnic groups: cases have been published recently from other parts of the globe whose clinical and hematologic pictures may be included in this group of diseases.31, 48, 82, 86, 96, 97, 110, 120, 122, 126, 140, 219, 223, 234, 260 However, they represent isolated cases, the diagnosis of some of which might be worth reconsidering.

On the other hand, there seems to be little doubt that the conditions under discussion have a particularly high incidence among some populations in the Mediterranean region (Greece, Mediterranean islands, southern Italy, Italian district of Ferrara) and among some ethnically related populations.†

(†) Among the members of families with cases of Cooley’s anemia the presence

* Therapeutic attempts have been made with splenectomy. 67a, 92, 125, 130, 138, 166, 240, 246, 252

† Further statistical study may reveal the existence of blood diseases belonging to this group in other countries. In any case it is justified to state that their incidence is by far higher among the inhabitants of some Mediterranean regions. Therefore, the suggested term, “Mediterranean hemopathic syndromes,” seems to us appropriate and has been adopted for the sake of simplicity.
can invariably be found of subjects (parents, brothers and other siblings) who exhibit some hematologic changes, the most frequent and characteristic being an increased red cell resistance to hypotonic solutions. This feature, which was first pointed out by Caminopetros\cite{33} and by Angelini,\cite{8} has been confirmed by numerous other observations and is now a generally accepted characteristic.

Together with the decreased red cell fragility, other blood changes are found, the most common being hypochromia, microcytosis and leptocytosis. Hypochromic microcytosis with decreased red cell fragility is the fundamental hematologic picture found in siblings of cases of Cooley's anemia (Caminopetros; Angelini; Micheli and collaborators; Gatto, Chini; Silvestroni and Bianco; Smith; Valentine and Neel; Dameshek; and others).

This blood picture, which is also found in siblings of cases of "hemolytic jaundice with decreased red cell fragility" (Rietti; Greppi; and others), has been termed by Chini as "Mediterranean hematologic disorder.\textsuperscript{33} Valentine and Neel called it "mild" form of Cooley's anemia or "thalassemia minor" (thalassemia minima, according to Gatto\textsuperscript{127, 128}). Silvestroni and Bianco, who found these changes in a number of cases from numerous observations among Italians from the South,\textsuperscript{22, 227, 229, 230, 231} called it "microcytemia.\textsuperscript{233 -236, 237, 241, 247} However, as it is pointed out by Dameshek and by Smith, a microcytic anemia is in these cases often accompanied by the presence of large, pale, thin macrocytes, whose hemoglobin content is unevenly distributed within the cell (target cells or leptocytes) and which are to be considered as characteristic elements.\textsuperscript{248}

Therefore, the "Mediterranean hematologic disorder" with the same fundamental blood change (decreased red cell fragility) is present in siblings of cases of Cooley's anemia and "hemolytic jaundice with decreased red cell fragility."

From the point of view of the nosologic affinity of the two main forms\textsuperscript{51, 54, 228 -235, 238, 239} one can hardly overlook the importance of this common element, and we think it justified to assume that both forms affect subjects who are "carriers" of the mentioned hematologic taint. This point has been stressed by Gatto,\textsuperscript{123, 124, 129} Chini\textsuperscript{51, 54} and, as the result of a great number of observations, by Silvestroni and Bianco.\textsuperscript{226, 230, 236, 239, 241, 242}

Carriers of the "Mediterranean hematologic disorder" are found in those regions and among the populations where Cooley's anemia is incident (it is probable that many cases go undiagnosed). The disorder represents a necessary early stage for the appearance of Cooley's anemia.

Subjects who are carriers of the disorder may appear to be quite healthy, and have no complaints. The disorder is usually detected if it is looked for among families with cases of Cooley's anemia and of "hemolytic jaundice with decreased red cell fragility" or accidentally as the result of routine investigations. It is apparently transmitted as a dominant characteristic (Gatto\textsuperscript{123, 124; Dameshek\textsuperscript{82; Smith\textsuperscript{247, 248; Silvestroni and Bianco\textsuperscript{210})}, and its presence has been followed up in three to four generations of the same family tree.

In many cases the disorder is accompanied by an anemic state. The anemia of these cases cannot be ascribed to any appreciable cause; it is benefited but slightly
by the usual antianemic remedies (liver extracts, iron, blood transfusions); it may last for years or decades; slight splenomegaly may be present. These cases may exhibit very different pictures.

The prevalence in some cases of one or the other morphologic changes may in time permit the nosologic isolation of well-defined syndromes and the use of an appropriate terminology (for instance, the "target cell" syndrome of Dameshek; the "target-oval cell" syndrome of the same author; "ovalo-poikilocytic hypo-

![Diagram of a family tree](image)

**Fam. Br. Angelo**

**Fig. 1.—Example of Transmission of the "Mediterranean Hematologic Disorder" through Three Generations**

<table>
<thead>
<tr>
<th></th>
<th>Hb</th>
<th>Eryth.</th>
<th>Color</th>
<th>Anis.</th>
<th>Poik.</th>
<th>Ellipt.</th>
<th>Target</th>
<th>Simmcl test red blood cells</th>
<th>Mx%</th>
<th>Mn%</th>
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<td>+</td>
<td>+</td>
<td>66.7</td>
<td>22.3</td>
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<td>72</td>
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<td>+</td>
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<td>13</td>
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<td>14.4</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>56</td>
<td>10.9</td>
</tr>
</tbody>
</table>

* Cousins.

chromic anemia" of Micheli and collaborators;"familial microcytic anemia" of Strauss and collaborators;"constitutional microcytic anemia" of Silvestroni and Bianco; etc.). It may well be that some forms, similar to those just mentioned, belong to this group (cases of Fanconi; Cooley; Rundles and Fall; Stransky and Regala; etc.), but it is quite possible that some forms which have been included in it will some day be differentiated and separated. For the time being these forms may be put together as "varieties" which need to be better known and more satisfactorily classified. Anemia is usually
Table 2.—Mediterranean Hematropic Syndromes: Forms with no Anemia and with Red Cell Changes of Different Type (Carriers of the "Mediterranean Hematologic Disorder")

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Jaundice</th>
<th>Splenomegaly</th>
<th>Hepatomegaly</th>
<th>Van der Breech test</th>
<th>Serum Bilirubin mg %</th>
<th>thalassemia</th>
<th>Hemolytic Index</th>
<th>Erythrocytes in millions</th>
<th>Hemoglobin (%)</th>
<th>Color index</th>
<th>Mean corpuscular diameter, microns</th>
<th>Mean corpuscular volume cubic micron</th>
<th>Anisocytosis</th>
<th>Poikilocytosis</th>
<th>Erythrocyte</th>
<th>Target cells</th>
<th>Fragility test</th>
<th>Simmel test red blood cells resistant to hypotonic saline</th>
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<td>Masc. M. 46</td>
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<td>D.R. 0.50</td>
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<tr>
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### Table 3—Mediterranean Hemopathic Syndromes: Forms with Anemia of Different Type

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<th>Fragility test</th>
<th>Simmel test red blood cells resistant to hypotonic saline</th>
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<tr>
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<td>Hemoglobin</td>
<td>Hb %</td>
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<td>------</td>
</tr>
<tr>
<td></td>
<td>Target cells</td>
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<th>Splenomegaly</th>
<th>Hepatomegaly</th>
<th>van der Berg test</th>
<th>Serum Bilirubin mg.%</th>
<th>Thrombin Time</th>
<th>Retinoblasts %</th>
<th>Hemolytic index (norm = 1)</th>
<th>Serum Fe %</th>
<th>% Hemoglobin</th>
<th>Erythrocytes in millions</th>
<th>MCV</th>
<th>MCH</th>
<th>Anisocytosis</th>
<th>Poikilocytosis</th>
<th>Elliptocytes</th>
<th>Fragility test</th>
</tr>
</thead>
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<td>+</td>
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<td>+</td>
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markedly hypochromic, less frequently hyperchromic (Patrassi and Taglioni197; Chini15; Muratore17). In the hypochromic cases there is nearly always microcytosis; with hyperchromia, macrocytosis may also be found. In nearly all cases marked ovalocytosis is observed; in many cases aniso-poikilocytosis is prevalent, and in some we find schistocytosis similar to that found in Cooley’s anemia74, 155, 156, 157; that is to say, morphologically one finds a blood picture very much resembling Cooley’s anemia, with the exception of circulating erythroblastosis.

We can, therefore, refer to these various pictures as varieties of the anemic form of the "Mediterranean hematologic disorder." Some of these varieties are poorly defined; others resemble very nearly Cooley’s anemia.

The clinically well-defined varieties of this anemic form are usually hypochromic, microcytic, ovalocytic, aniso-poikilocytic and schistocytic. Besides, in many cases stippled cells and "target" cells (Dameshek) are present but the latter do not appear to be characteristic of these forms. There is marked hyperplasia and erythroblastic anaemia of the bone marrow. In spite of discordant views, a distinction has to be made here between this type of anemia—even its hypochromic microcytic variety—and achylic hypochromic anemia (idiopathic hypochromic anemia), differentiating points being its ethnographic distribution, the high iron content of the blood (Chini, and Perosa60; Perosa20), the nearly absent response to iron therapy, the usual presence of normal gastric secretion, the absence of some clinical signs which are usually found in idiopathic hypochromic anemia, such as glossitis, dystrophic changes of the fingernails, Plummer-Vinson syndrome.

In numerous cases of "Mediterranean hematologic syndrome" we find a marked hemolytic element. These cases are more readily recognizable clinically and have been termed "hemolytic jaundice with decreased red cell fragility" (Rietti212, 213, 215, 216; Greppi134). The picture is that of the "Mediterranean hematologic disorder" with anemia of one or the other variety (increased resistance to hypotonic solutions, occasional ovalocytosis, presence of target cells: "oval-target cell syndrome" of Dameshek 82). There is marked hyperplasia and erythroblastic anaplasia of the bone marrow, but no erythroblasts are found in the circulating blood and hemolysis is increased. In some cases the hemolytic index reaches values as high as in acholuric jaundice. Operation is followed by a reduced hemolysis, but there is no effect on the morphologic changes, which in some cases are even more accentuated after splenectomy. In fact, some cases after splenectomy show a marked and persistent erythroblastemia. The postoperative picture resembles more closely that of Cooley’s
Table 4—Mediterranean Hemopathic Syndromes: Forms with Hemolytic Jaundice (Hemolytic Jaundice with Decreased Red Cell Fragility, of Italian Authors)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Fractin</th>
<th>Jaundice</th>
<th>Spleenomegaly</th>
<th>Hemolytic</th>
<th>Van den Bergh test</th>
<th>Serum Bilirubin mg./%</th>
<th>Tachypnea</th>
<th>Reticuloocytes %</th>
<th>Hemoglobin Index (norm. = 1)</th>
<th>Serum Fe %</th>
<th>Erythrocytes in millions</th>
<th>Hemoglobin (%)</th>
<th>Color index</th>
<th>Mean corpuscular volume</th>
<th>Autocytosis</th>
<th>Reticuloynthesis</th>
<th>Elliptocytosis</th>
<th>Fragility test</th>
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<td>41</td>
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<td>+++</td>
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<td>55</td>
<td>0.87</td>
<td>73</td>
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* Spleenectomy.
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<th>Hemolytic Index (norm = 1)</th>
<th>Serum Fe %</th>
<th>Erythrocytes in millions</th>
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<th>Color index</th>
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* Metrorrhagia.
anemia chiefly on account of the erythroblastemia and in some cases because of bone lesions as seen in the x-ray films.2

(7) Besides these varieties of the "Mediterranean hematologic disorder" with jaundice and hyperhemolysis, cases are seen in which jaundice is evident but no increased hemolysis is found. The hemolytic index of these patients is normal or even lower than in normal cases, in spite of the obvious presence of jaundice and of the high values of bilirubin in the blood by the indirect test. In the absence of increased hemolysis we cannot term them as cases of hemolytic jaundice. These cases have some points in common with the so-called "juvenile intermittent jaundice of Meulengracht or nonhemolytic prehepatic jaundice" and they represent a fairly large number of cases of "Mediterranean hemopathic syndromes" (Patrassi and Taglioni; Cassano and Benedetti; Chini; Malaguzzi-Valeri; Castaldi and Leonardi).

It has been suggested by various authors and recently confirmed by the work of Perosa on hemoglobin tolerance curves, that in subjects affected with this type of jaundice, there is a derangement of the liver function in the sense that the transformation of bilirubin from the "indirect" to the "direct" form and its subsequent elimination from the blood do not take place.

A "hepatic" factor of this type may be present even in the full fledged case of "hemolytic jaundice with decreased red cell fragility," in which a more or less marked hyperhemolysis is found. In fact, in these cases one often finds a discrepancy between the hemolytic index and the values of the "indirect" bilirubin of the blood, and also a delayed direct Van den Bergh reaction. These findings have been interpreted in various ways; for instance, they have been ascribed to liver dysfunction, to the presence of an abnormal pigment not detected by Nencki's reagent, etc. (investigations on this subject are being carried out in our Institute).

(8) All these different forms have some common fundamental elements which permit us to consider them as belonging to one great group. These elements are:
(a) Their nearly exclusive limitation to Mediterranean people; (b) The presence of a constitutional, familial and hereditary element; (c) The increased resistance of the red cells to hypotonic solutions.

Therefore, we find it justified to collect them in one group under the term of "Mediterranean hemopathic syndromes," and to consider the "Mediterranean hematologic disorder" as their fundamental pathogenetic factor.

The pathogenesis of the single clinical pictures is still very obscure.

On the basis of our present knowledge, mainly from the analysis of the familial tendency of these syndromes, it seems to us that something can be said on the pathogenetic connections between the so-called "Mediterranean hematologic disorder" and Cooley's anemia and on the etiopathogenesis of the so-called "hemolytic jaundice with decreased red cell fragility."

With regard to Cooley's anemia, one important point has been brought to evidence from the study of the parents of the patients, and that is that where the investigation has been adequate, both parents of an individual affected with Cooley's
Table 6. —*Mediterranean Hepatocytic Syndromes: Fames with Jaundice but with no increased Hemolysis*

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<th>Jaundice</th>
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<th>Hepatosplenomegaly</th>
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<th>Tolonna Test</th>
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* Spleenectomy.
anemia have been found to be carriers of the "Mediterranean hematologic disorder."

It was Caminopetros\(^34, 35\) who first called attention to this point, even if he did not stress it as a fundamental feature in the familial tendency of the disease, and it was confirmed by Angelini\(^8\) and later by Micheli, Penati, Momigliano-Levi\(^166\) and others (Panoff\(^189\)).

In 1939, Chini,\(^51, 92\) on the basis of the reports from Caminopetros, Angelini and Micheli, stressed the unusual fact of the presence of a hematologic taint in both parents of patients suffering from Cooley's anemia and stated that the findings could not be ascribed to mere coincidence.\(^51, 97\)

Subsequently (1941), further reports from other authors (Ortolani and Vallisneri\(^187, 263\); Wintrobe and collaborators\(^274\); Atkinson\(^44\); Pehu and Leriche\(^89\)) led Chini\(^64\) to state that "this bilateral hereditary tendency was to be considered as a fundamental factor in the pathogenesis of Cooley's anemia."

Independently, in 1941–1942, Gatto\(^123, 124\) made his first report on the results of his investigations on the members of the families of 8 cases of Cooley's anemia. His conclusions were that increased resistance of the red cells to hypotonic solutions and microcytosis, as a rule hypochromic and accompanied by ovalocytosis and poikilocytosis, were constantly present in both parents of patients with Cooley's anemia. According to Gatto, this trait ("hyperresistant microcytosis") "is a dominant hereditary characteristic which is carried as a heterozygous gene and Cooley's anemia develops only in subjects whose parents are both affected with the disorder and who carry the hematologic characteristic as a homozygous gene." The bilateral hereditary element in these cases has been subsequently confirmed by various authors (Pierce\(^204\); Valentine and Neel\(^176, 177, 262\); Dam-eshek\(^82\); Smith\(^247, 248\); McIntosh and Wood\(^162\); Trincao\(^260\), etc.,\(^16\) and recently in Italy by Burgio\(^27\); Careddu and Magrassi\(^41\); Silvestroni and Bianco\(^\)) in a large number of cases.\(^238, 241\)

In Gatto's opinion, Cooley's anemia is an example of dominant hereditary characteristic with lethal homozygous effect.

In the present state of our knowledge this seems to be the fundamental fact which has been agreed upon from the study of the familial tendency of Cooley's anemia and allied syndromes.

It would therefore appear that Cooley’s anemia represents the most severe of the "Mediterranean hemopathic syndromes." Its severity seems to be caused by the lethal homozygous effect of the presence of the trait in both parents.*

* As Chini pointed out in 1941, if it is true that typical Cooley's anemia only affects those subjects whose parents are both carriers of the "Mediterranean hematologic disorder," then we should not use the term of mild forms of Cooley's anemia to indicate the various forms of "Mediterranean hemopathic syndromes" or the cases of apparently healthy carriers of the "Mediterranean hematologic disorder." In cases of "Mediterranean hemopathic syndromes," only one of the parents is a carrier. In a typical case of Cooley’s anemia we never see a gradual attenuation of the symptomatology, so as to make it possible to identify the case with one or the other variety of the "Mediterranean hemopathic syndromes," and we never see a case of "Mediterranean hemopathic syndrome" becoming so severe as to resemble a typical case of Cooley’s anemia. One could use the term of "mild" forms in these cases, as suggested by some American authors, if there existed a transition in some of them from the mild to the severe form. This
Of this trait we know only some features which are more readily detectable; the decreased red cell fragility and often the hypochromic microcytosis; also, according to Dameshek, the "target" cells or leptocytes and, according to Smith, the thin and pale macrocytes and the stippled cells. These physical and morphologic changes reveal the presence of a more profound structural disorder of the red cell whose essence is still obscure (Pontoni; Chini; Rietti). Other characteristics of the trait (first described by Caminopetros and in Italy by Gatto, followed by Chini, Silvestroni and Gentili) are in the somatic line: The presence of the "Mediterranean hematologic disorder" is frequently found in subjects with high and thick zygoma cheek bones (facies microcytica, according to Silvestroni and Gentili). What we have often found is an increased distance between the zygomas. However, it should be noted that this characteristic is frequently found among the population of Southern Italy and that on the other hand subjects who exhibit a mongoloid face may not be carriers of the "Mediterranean hematologic disorder," though they may be affected with some other blood disturbance.

With regard to "hemolytic jaundice with decreased red cell fragility," here also some family members of the patients are carriers of the "Mediterranean hematologic disorder," though only one parent is affected and not both as in Cooley's anemia.

In some family members of cases affected with this condition, a constitutional hyperhemolytic state is also found, either in the same family side of the carrier or in the opposite.

This characteristic is in some cases quite evident, in others only slightly pronounced (slight increase of the red cell fragility, and at the same time an in...

view finds confirmation in the clinical analysis of Cooley's anemia and of those "Mediterranean hemopathic syndromes" whose characteristics are well-defined. In a sense, the terminology suggested by Valentine and Neel of "thalassemia major" (Cooley's anemia) and "thalassemia minor" seems to us more appropriate; though "thalassemia minor" would seem to include well-defined syndromes, some of which are of marked severity and for which the term "minor" could hardly seem acceptable. It should be noted that for the carrier state, Gatto used the term "thalassemia minima." While the view expressed in this paper has, on one hand, more consideration of the genetic factors, whose etiopatho-

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crease of the maximal resistance; spherocytosis). Some authors have suggested the term of "mixed" forms of hemolytic jaundice, and in a wide sense, of "hemolytic diathesis," common to both forms. However, the observations with regard to this group of cases are still isolated and it is not possible at present to come to any conclusions.

It is quite possible that the presence of a constitutional hemolytic factor may be of importance in the pathogenesis of some "Mediterranean hemopathic syndromes" which show a marked hemolytic element. This should be more common in those regions where the "Mediterranean hematologic disorder" and hyperhemolysis are comparatively frequent events. And such is the case in some districts of Southern Italy, the origin of the majority of the presently published cases of "hemolytic jaundice with decreased red cell fragility."

This, however, is not the only factor which may be responsible for the hemolytic element of the condition; the structural changes in the red cells may play their role (microschistocytosis or the cause may lie in a combination of various morbid factors, as well as in splenopathic conditions, in a wide sense. In this respect, we can hardly overlook the importance of malaria, whose role has also been discussed with regard to Cooley's anemia.

A hemolyzing action of blood plasma has been found by Frontali and Rasi; however, this has not been confirmed by Chini and collaborators, who could detect it only in cases in which the blood cholesterol values were very low.

The question is still very obscure. We still do not know why and how carriers of the hematologic characteristics of acholic jaundice at a certain time become affected with hyperhemolysis. In some cases we find an intercurrent illness; in others the real cause cannot be found, the hemolytic character of the condition being then termed "idiopathic."

Very little has been known regarding factors which determine or help in the transition from the simple stage of "hematologic disorder" to that of anemia in its different varieties (ovalo-poikilocytosis, etc.). Occasional factors, such as infectious diseases, hemorrhages, abundant menstruations, food deficiencies, endocrine disturbances, etc., may contribute, but constitutional and hereditary elements of various type may intervene, and this side of the question is now being widely investigated (significance of ovalocytosis; presence in some family groups of some other hemopathic condition; possible influence of malaria on carriers of the trait).

With regard to the fundamental structural derangement of the red cells which is the cause of their abnormal physical sedimentation rate, etc., and morphologic state, the question is still obscure.

As has been said before, there probably exists a profound biochemical alteration of the red cells which is most intense in Cooley's anemia, but may be present in a lesser degree in the other "Mediterranean hemopathic syndromes."

As suggested by Whipple and Bradford for Cooley's anemia, in the other syndromes of the group there is also possible the presence of an abnormal capacity
for utilizing iron and elaborating hemoglobin. This hypothesis is supported by the presence of erythroblasts with a red fluorescence in the bone marrow (Freudenberg and Esser\textsuperscript{113, 114}) and by other abnormalities in the metabolism of porphyrin (Lichtwitz\textsuperscript{114}, Vannotti\textsuperscript{264}, Tropp and Peneff\textsuperscript{265}), by the high values of blood iron in spite of the constant and in some cases quite marked hypochromia (Perosa\textsuperscript{201}; Chini and Perosa\textsuperscript{60}; Amato\textsuperscript{8}; Cartwright\textsuperscript{12}), and by the variations in the resistance of hemoglobin to alkaline denaturation in Cooley's anemia (Vecchio\textsuperscript{266}; Bianco\textsuperscript{22}; Putignano and Fiore-Donati\textsuperscript{209}). It appears, however, that there is no change in the crystallographic and spectrophotometric characteristics of hemoglobin (Marmont and Bianchi\textsuperscript{159, 160}).

In spite of the methodical work of Bussi\textsuperscript{29} and of Astaldi and collaborators, on erythroblastometric curves and on bone marrow maturation, there is no conclusive evidence of the significance of microcytosis and on the question of its interpretation as a congenital abnormality.

Lehndorff, Caminopetros\textsuperscript{35} and others (Chini\textsuperscript{11}, Gatto\textsuperscript{124, 128}; Fanconi\textsuperscript{99}; Heilmeyer\textsuperscript{135}; etc.) favor the hypothesis that the hematologic abnormality which is fundamental in Cooley's anemia, that is the 'Mediterranean hematologic disorder,' is due to a process of 'mutation' in some groups of Mediterranean populations.

That a process of 'mutation' may have particularly affected some Mediterranean groups which are still recognizable from their facial configuration (width and thickness of the zygoma cheek bones) was pointed out by Gatto in 1942 and recently confirmed by the results of investigations carried out by Graziosi, on fossilized skulls from the superior paleolithic ages found in Sicily.

The high incidence of the 'Mediterranean hematologic disorder' in some regions (investigations carried out among Americans of Italian descent by Valentine and Nee\textsuperscript{176, 177}; in Italy by Silvestroni and Bianco\textsuperscript{229, 230, 241}; Careddu\textsuperscript{49}; Careddu and Magrassi\textsuperscript{41}; Leonardi and collaborators\textsuperscript{116}; Bianco\textsuperscript{23}; our own investigations still under way; by Banton\textsuperscript{18} in Cyprus), and the etiopathogenetic connections of the disturbance with the various 'Mediterranean hemopathic syndromes,' including Cooley's anemia, represent a subject of great social importance. The widespread diffusion and the intensity of the morbid characteristics which are transmitted to their descendants by the carriers of the trait had been stressed by Chini\textsuperscript{11} in 1939 and particularly emphasized by Caminopetros (1937, 1938). Such diffusion is now being more widely revealed through large scale investigations on the incidence of the 'Mediterranean hematologic disorder' among the population of some districts of Italy.

Caminopetros\textsuperscript{35} had suggested the necessity of advising the carriers of the trait against marriage. The recently established evidence that Cooley's anemia only appears in individuals whose parents are both carriers of the 'Mediterranean hematologic disorder' is of great importance in this respect, and especially if it receives further confirmation, will allow for a less extreme view with regard to marriage limitations. In fact, as suggested by Silvestroni and Bianco, and as we
have been advising for some time to the family members of our own cases, it would be sufficient to discourage marriage between persons who are both carriers of the disorder.

Paleontologic investigations have revealed the presence of particular skeletal lesions, especially of the skull, in the skeletons of individuals belonging to races now nearly completely extinct.

The analysis of skulls found in ancient cemeteries or belonging to mummies still in a state of very good preservation, of skeletons from ancient native populations of America, Incas from Peru (Williams\textsuperscript{273}), Indians from Colombia (Feingold and Case\textsuperscript{101}), Aztecs from Mexico, Maya Indians from Yucatan (Moore\textsuperscript{179}) (it should be noted that the Indians from the northern parts of South America and those from Mexico appear to have a common origin) in some necropolises from Arkansas (Wakefield and collaborators,\textsuperscript{269} etc.), has shown the existence of the same typical and unmistakable skeletal lesions which we now find in individuals suffering from sickle cell anemia, Cooley’s anemia, or, to a lesser extent, in cases of ‘Mediterranean hemopathic syndromes’ (Perox and Viterbo, etc.). Not without foundation do students of paleontology believe that the extinction of those ancient populations was contributed to by the high incidence among them of some blood diseases which probably developed through processes of human mutation on a widely hereditary and familial basis (Williams and Moore). The recent report of cases of sickle cell anemia among some native populations of Mexico, whose anthropologic characteristics are very similar to those of ancient Aztecs (Wallace and Killingsworth\textsuperscript{269}) has led some authors to believe that those remnants of a disappearing race have inherited from their ancestors some genetic characteristic.

We still do not know whether such bone lesions are to be ascribed to blood diseases similar to sickle cell anemia or to Cooley’s anemia or to some other hemopathic condition with a more or less accentuated hemolytic character (bone lesions, which radiologically resemble those found in Cooley’s anemia are also seen, and in some cases quite marked, in acholuric jaundice and in other forms of hemolytic anemia [Gänslen\textsuperscript{119}; Caffey\textsuperscript{32}; Perosa and Viterbo, etc.\textsuperscript{64, 76, 85, 218, 244}], or even to nonhemopathic conditions. The study of the paleolithic skulls found in the caves of St. Teodoro, Sicily, has revealed the presence in them of diffuse osteoporosis (Gatto; Graziosi). Osteoporosis of this type has been observed by Adachi\textsuperscript{17} in prehistoric skulls in Egypt. Owing to war restrictions and to lack of proper equipment, we have been unable to carry out a group of investigations which we had planned here in Puglia (necropolis of Canne). We are not aware that other investigations of this kind have been carried out elsewhere, except those of Caponnetto\textsuperscript{38} on 25 skulls belonging to the Anatomical Museum of Catania, Sicily. In 13 of them the author found osteoporosis, in some cases a moderate degree of radial striation of the skull.

It can be assumed with some foundation that the diseases—probably blood conditions—which had been the cause of the characteristic lesion of the skeleton, contributed to the gradual extinction of those ancient races.

Paleontology thus throws light on the history of disappeared populations offer-
ing new possibilities of interpretation. It can lend justification to the warning of Caminopetros, because there is no doubt that the spreading of the "Mediterranean hematologic disorder" with its dominant character will inevitably lead, through an increase in the number of marriages between carriers of the disturbance, to the appearance of an always increasing number of cases of "Mediterranean hemopathic syndromes" and of fatal cases of Cooley's anemia.

The study of the "Mediterranean hemopathic syndromes" represents a great chapter open to research which involves difficult problems of clinical, historical and social importance.

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