IN 1911 DÖHLE reported the presence of round blue-staining bodies in the cytoplasm of leukocytes of patients with scarlet fever. They were transient in nature, appearing at the time of the exanthem and persisting only for as long as 6 days. These bodies, which now bear his name, have subsequently been observed transiently in patients with other infectious diseases such as erysipelas, diphtheria, typhus, tuberculosis, measles, and with severe thermal burns.

May in 1909 had noted similar leukocytic inclusions in a patient who was otherwise well, but in this case the cytoplasmic bodies were persistent and were associated with giant platelets. In 1945 Hegglin described the presence of Döhle bodies, also in association with giant platelets, in three members of the same family, thus showing that this syndrome may be familial and is likely hereditary. In Hegglin’s report a father and his two sons had the anomaly in association with chronic thrombocytopenia. Recently Wassmuth et al. and Petz et al. have reported briefly on the second and third families with this anomaly.

Because of the unusual nature of this condition and the scarcity of reports in the English literature, we will describe a fourth family with the May-Hegglin anomaly.

CASE REPORT

A six-year-old white female was first seen at the Children’s Hospital Medical Center in September 1961, for evaluation of purpura of 2 months’ duration. History revealed that the patient had been in good health until July 1961, when purpura and ecchymoses were first noted. A platelet count at that time was 142,000/mm³. Ten days later, spontaneous bleeding from the nose and mouth and hematuria were noted. On admission to the local hospital the patient’s platelet count was 30,000/mm³. Treatment with oral triamcinolone,* 48 mg. per day, was begun. No further bleeding occurred at
that time but new purpuric areas continued to appear and the platelet count remained low.

In mid-August 1961, gradual tapering of the dose of triamcinolone was begun, but when it had been reduced to 40 mg. per day, spontaneous bleeding from the nose and mouth recurred and the triamcinolone was increased to 48 mg. per day. Despite this high level of steroid medication the platelet count remained low and the patient continued to have intermittent bleeding from the nose and mouth.

No history of recent infection or exposure to unusual drugs or toxins could be elicited. The family history was normal in all respects.

Physical examination revealed an alert, chubby girl with a marked Cushingoid appearance who was in no acute distress. Temperature 100 F., pulse 88 per minute, respirations 20 per minute, blood pressure 95/65, weight 55 pounds (90th percentile), height 44 inches (25th percentile).

Examination of the skin revealed extensive purpuric lesions 1–15 mm. in diameter over the entire body as well as the mucous membranes of the mouth. Petechiae were especially numerous over both cheeks, sharply coinciding in distribution with the increased adipose tissue in this region. Severe dental caries were present. The liver was palpable 3 cm. below the right costal margin. The spleen and lymph nodes were not palpable.

The remainder of the physical examination was within normal limits.

Laboratory examinations: Hemoglobin 11.8 Gm. per cent, hematocrit 36 per cent, red blood count 3,900,000/mm.³, MCV 92.4 cu. µ, MCH 28.0 µg., MCHC 30.8 per cent, reticulocytes 8.0 per cent, platelets 6,000/mm.³, white blood count 19,600/mm.³ with a differential of 60 per cent polymorphonuclear leukocytes, 19 per cent band forms, 4 per cent metamyelocytes, 12 per cent lymphocytes, 5 per cent monocytes, and 1 nucleated red cell per 100 white blood cells. Bleeding time (Ivy) 30 minutes (normal 2–7 minutes).

Examination of the peripheral smear revealed that the few platelets present were enlarged and bizarre in shape with some platelets up to 8 µ in diameter. The leukocytes contained Döhle bodies. This latter finding persisted in blood smears repeated throughout the 2-month hospital stay. Examination of a bone marrow aspirate from the iliac crest revealed increased numbers of megakaryocytes with no platelet formation. Döhle bodies were found in the myelocytes, metamyelocytes, band forms, and polymorphonuclear neutrophils and eosinophils of the bone marrow, but none were seen in the cells of the lymphocytic or monocytic series. The erythroid elements appeared normal.

Urinalysis: pH 7.0, specific gravity 1.023, albumin 0, sugar 0, acetone 0, many red blood cells, many white blood cells. Urine culture contained more than one million colonies of Escherichia coli per ml. Stool guaiac 3 plus.

Non-protein nitrogen 33 mg. per cent, (18 mg. per cent 2 days later), fasting blood sugar 87 mg. per cent, electrolytes normal. All liver function tests were normal. Five L.E. preparations during the hospital stay were negative. Blood Hinton test negative. Urine negative for 5-hydroxy-indole acetic acid.

Hospital course (see fig. 1). The patient was placed on sulfisoxazole* for her urinary tract infection and started on prednisone, 40 mg. per day. Because of the possibility that prolonged high doses of steroid may have been suppressing platelet production, the dose of prednisone was tapered over a 10-day period to 5 mg. per day. The platelet count did not increase and the patient developed spiking temperatures to 104 F., new petechiae and purpura, and bleeding from the nose and mouth. Multiple cultures of the throat, urine, and blood were negative.

Intravenous infusion of a suspension of fresh platelets was followed by fever and chills and no elevation of platelet count 12 hours after administration. Oral prednisone was resumed at 40 mg. per day but fever and purpura continued. The patient developed intense frontal headaches, slight papilledema, and mild right hemiparesis, suggesting intracranial bleeding. In view of these symptoms, a splenectomy was performed on October 9, 1961. At no time prior to the splenectomy was the patient's platelet count above 7,000/mm.³.

The splenectomy was well tolerated and the patient did not require blood or platelet

*Gantrisin (Roche).
transfusions. There were no postoperative complications. The spleen weighed 88 Gm. (normal). Pathologic examination showed evidence of congestion, hyperplasia, and some minimal vascular intimal thickening. There was nothing to suggest lupus erythematosus. Following splenectomy the patient was maintained on prednisone. In the early postoperative period the platelet count did not rise above 9,000. Her steroid medication was changed from prednisone to oral hydrocortisone, 40 mg. per day, with no change in the platelet count. The hydrocortisone was gradually tapered and then discontinued. The tapering and withdrawal of the steroids was associated with a return of the fever to 104 F. No cause could be found for this and prednisone was reinstituted, but the fever and thrombocytopenia continued. Prednisone was again discontinued and once more an intensive but unrevealing search was made for infection or evidence of systemic lupus erythematosus or other connective tissue disease.

Intravenous hydrocortisone in a dose of 200 mg. per day was begun. Within 12 hours the patient became afebrile and remained so throughout the rest of her hospital stay. Forty-eight hours after the intravenous hydrocortisone was begun the platelet count was 55,000 and therapy was changed to oral hydrocortisone, 200 mg. per day. During the next week her platelet count rose to 196,000/mm$^3$ and the hydrocortisone was decreased to 100 mg. per day.

The patient was discharged in good clinical condition on hydrocortisone, 100 mg. per day. She has since been followed at frequent intervals as an outpatient and the hydrocortisone has been slowly tapered to its present level (4/5/62) of 15 mg. per day. As the dosage was lowered, there was a gradual fall in platelets to 44,000/mm$^3$. Since then it has remained in the range of 80,000–100,000/mm$^3$. There has been no evidence of petechiae or purpura, she has remained afebrile, and there is no evidence of neurologic sequelae.

Special studies: Additional studies were performed on the patient and the remainder of her family in an effort to characterize further this anomaly.

In table 1 are listed the hematologic findings in the available members of the family. It will be noted that both the patient's mother and one of her two brothers also had Döhle bodies in their leukocytes. Their platelet counts were repeatedly normal although giant platelets were consistently present on Wright-stained smears. There was no evidence in their past medical history to suggest purpura or a bleeding tendency. Complete blood typing failed to reveal any evidence of linkage of the May-Hegglin anomaly to the blood
<table>
<thead>
<tr>
<th>Family Member</th>
<th>Age (years)</th>
<th>Hb. Gm.%</th>
<th>WBC mm.³</th>
<th>Platelets mm.³</th>
<th>Purpura</th>
<th>Döhle Bodies % of Neutrophils</th>
<th>Giant Platelets</th>
<th>Blood Type</th>
<th>Haptoglobin Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>6</td>
<td>11.8</td>
<td>19,660</td>
<td>1,000</td>
<td>yes</td>
<td>present—85%</td>
<td>present</td>
<td>A₁A₂CcDe,M,S,</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Jk⁺,Jkᵇ,Leᵇ,Kpᵇ</td>
<td>2-2</td>
</tr>
<tr>
<td>Brother</td>
<td>17</td>
<td>15.5</td>
<td>6,400</td>
<td>266,000</td>
<td>no</td>
<td>present—76%</td>
<td>present</td>
<td>H,A,CcDe,N,S,</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Jkᵇ,F,Leᵇ,Kpᵇ</td>
<td>2-2</td>
</tr>
<tr>
<td>Brother</td>
<td>14</td>
<td>14.2</td>
<td>6,900</td>
<td>244,000</td>
<td>no</td>
<td>absent</td>
<td>absent</td>
<td>A₁A₂Cde,MN,S,</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Jkᵇ,P,Leᵇ,Kpᵇ</td>
<td>2-2</td>
</tr>
<tr>
<td>Father</td>
<td>47</td>
<td>14.0</td>
<td>11,600</td>
<td>297,000</td>
<td>no</td>
<td>absent</td>
<td>absent</td>
<td>H,A,CcDe,MN,S,</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Jkᵇ,P,Leᵃ,Kpᵇ</td>
<td>2-2</td>
</tr>
<tr>
<td>Mother</td>
<td>43</td>
<td>13.0</td>
<td>7,000</td>
<td>246,000</td>
<td>no</td>
<td>present—83%</td>
<td>present</td>
<td>A₁A₂Cde,MN,S,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Jk⁺,Jkᵇ,Leᵇ,Kpᵇ</td>
<td>2-2</td>
</tr>
</tbody>
</table>
DOHLE BODIES AND PLATELET ABNORMALITY 661

groups. Unfortunately the patient’s mother had no living relatives; therefore, search for other affected members was not possible.

**Histochemical studies:** To characterize further the Döhle bodies, peripheral blood smears were submitted to a number of special stains.* Aside from a positive reaction for ribonucleic acid with methyl-green pyronine, stains for lipid (Sudan Black), mucopolysaccharide (Periodic Acid-Schiff), and desoxyribonucleic acid (Feulgen) were negative.

To test the dual hypothesis that the Döhle bodies might represent phagocytosed platelet material and that the patient’s plasma contained a factor responsible for it, the patient’s leukocyte-free plasma was incubated with a suspension of fresh normal white cells and platelets at 37°C. Wright-stained smears examined at periodic intervals for 12 hours failed to reveal the presence of Döhle bodies or other phagocytosed particles in the normal white blood cells.

The mother’s prothrombin consumption time and bleeding time were normal.

Peripheral smears of 161 patients with thrombocytopenia that had been seen at the Children’s Hospital Medical Center in the past 5 years were carefully reviewed and in none were Döhle bodies seen.

**DISCUSSION**

This is the fourth report showing the familial nature of the May-Hegglin anomaly. Our patient fulfills the criteria for classification as an example of the May-Hegglin anomaly with Döhle bodies in her leukocytes in association with giant platelets continuously for a period of 6 months in the absence of severe infection or other known underlying cause. In addition, two members of her family have also been found to have this anomaly on repeated examinations.

Döhle bodies are usually 1–2 μ in diameter (fig. 2). There is generally only one in a cell but occasionally there may be more. There is no consistent localization within any particular area of the cytoplasm. With Wright’s stain they appear sky blue in color and are easily visible against the pinkish-gray cytoplasmic background. They are amorphous in shape but tend to be circular or elliptical in outline.

The Döhle bodies are negative with fat and glycogen stains but appear red after staining with methyl-green pyronine, suggesting that they have a large ribonucleic acid content. It has been demonstrated* that after the cells are incubated with ribonuclease the Döhle bodies no longer stain with the pyronine, confirming that they are composed of ribonucleic acid. This has suggested that they represent areas of the cytoplasm that have failed to mature. Döhle bodies may be observed in the myelocytes, metamyelocytes, band forms, neutrophilic leukocytes, eosinophils and basophils. They are most easily and most consistently seen in the neutrophilic leukocytes.

The platelets in the May-Hegglin anomaly show marked variations in size and shape. Cigar-shaped and elliptical-shaped forms are common although the large round forms predominate (fig. 3). Normal platelets may be as large as 4 μ in diameter* while platelets as large as 15 μ have been observed* in this condition. Although it is common to see large and bizarre platelet forms in

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*We are grateful to Dr. John Craig, Pathologist, Boston Lying-in Hospital, for his kind assistance in the performance of these tests.
idiopathic thrombocytopenic states, the platelets in this condition are even more striking. However, the size of the platelets in our family was not as striking as that reported by others. In addition, the platelets show uneven and scant granulation, with eccentrically placed hyalomeres.

Including the present report, four families with the May-Hegglin anomaly have been described. In addition, three isolated cases have also been reported. Table 2 summarizes the data in all cases reported to date.

From our data and that of Hegglin, Wassmuth, and Petz, it appears that this anomaly follows an autosomal dominant mode of inheritance.

We agree with Davidscn that the patient reported by Leitner probably does not represent a true case of the syndrome inasmuch as the patient was acutely ill with an apparent septicemia that was accompanied by thrombocytopenia, a hemolytic anemia and an apparent leukemoid reaction. No autopsy was performed and no family members were found to have this anomaly when studied. Since Döhle bodies may appear in toxic states, their presence in the patient described by Leitner is not surprising and does not in itself constitute sufficient evidence for including this patient with the others who have been demonstrated to have the anomaly permanently.

Excluding the report of Leitner from the tabulation, it is noted that nine of the 24 cases reported have had thrombocytopenia in association with their morphologic abnormality. Although no member of the kindred reported by Wassmuth was found to have thrombocytopenia at the time of study, the possibility, as shown in our patient, that this is transitory in nature and was not evident at the time of their examinations cannot be excluded. In Hegglin's family all members had thrombocytopenia; in Wassmuth's there was none. It is of interest that in our family one member, the patient, has had thrombocytopenia and two do not. The exact reason for this variable but increased incidence of thrombocytopenia in this condition is not apparent but there are several theoretical possibilities. The first is that the syndrome consists of Döhle bodies, giant platelets, and thrombocytopenia, and that there is variable expressivity of the latter in different families. An alternative explanation is that the abnormal platelet morphology reflects a disturbance of megakaryocyte or platelet metabolism which under the stress of ill-defined "trigger" factors, such as infections, drugs, or toxins, results in thrombocytopenia.

*We wish to thank Dr. R. Sheets for supplying us with slides from his family with the May-Hegglin anomaly.

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Fig. 2.—Pale blue Döhle body in cytoplasm of neutrophil of patient with the May-Hegglin anomaly (peripheral smear, Wright stain).

Fig. 3.—Giant platelet in peripheral blood smear of patient with the May-Hegglin anomaly. (Similar abnormal platelets were present in the affected relatives who had normal platelet counts.)

Fig. 4.—For contrast, a neutrophil from a patient with the Chediak-Higashi syndrome, showing several large irregular cytoplasmic inclusions. (The typical slate-green color is appreciated better in the original blood smears.) (Peripheral smear, Wright stain.)
Figs. 2-4.—See legends, facing page.
Table 2—Summary of All Cases of the May-Hegglin Anomaly Reported to Date

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Propositus Age</th>
<th>Sex</th>
<th>Döhle Bodies</th>
<th>Giant Platelets</th>
<th>Platelet Count</th>
<th>Clinical Findings</th>
<th>Outcome</th>
<th>Family Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>May, R.⁹</td>
<td>24</td>
<td>f</td>
<td>present</td>
<td>present</td>
<td>not known, appeared normal on smear</td>
<td>transient edema and erythema of legs</td>
<td>not known</td>
<td>not performed</td>
</tr>
<tr>
<td>1909</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hegglin, R.⁷</td>
<td>50</td>
<td>m</td>
<td>present</td>
<td>present</td>
<td>10,000–30,000</td>
<td>purpura</td>
<td>died 14 yrs. after diagnosis, cause unknown</td>
<td>two sons with the anomaly, both thrombocytopenic; 30 other members of kinship found to be normal patient’s mother, sister, and three children found to be normal</td>
</tr>
<tr>
<td>1945</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Leitner, S., et al.¹⁰</td>
<td>45</td>
<td>m</td>
<td>present</td>
<td>present</td>
<td>50,000</td>
<td>pneumonia, purpura, anemia</td>
<td>died shortly after admission, no autopsy unknown</td>
<td>not performed</td>
</tr>
<tr>
<td>1954</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Scholer, V., et al.¹¹</td>
<td>30</td>
<td>m</td>
<td>present</td>
<td>present</td>
<td>25,000–110,000</td>
<td>No evidence of illness</td>
<td>not stated</td>
<td>thirteen members of 3 generations found to have the anomaly: 9 males, 4 females, ages 4–73; all well father and 2 sons found to have the anomaly; all well patient’s mother and brother affected; both well</td>
</tr>
<tr>
<td>1960</td>
<td></td>
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</tr>
<tr>
<td>Wassmuth, D., et al.⁸</td>
<td>(not stated)</td>
<td></td>
<td>present</td>
<td>present</td>
<td>normal</td>
<td>No evidence of illness</td>
<td>not stated</td>
<td></td>
</tr>
<tr>
<td>1961 (abstract)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petz, A., et al.¹³</td>
<td>(not stated)</td>
<td></td>
<td>present</td>
<td>not stated</td>
<td>mild thrombocytopenia</td>
<td>No evidence of illness</td>
<td>not stated</td>
<td></td>
</tr>
<tr>
<td>1960 (abstract)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Oski, F., et al. ¹⁰</td>
<td>6</td>
<td>f</td>
<td>present</td>
<td>present</td>
<td>1,000–220,000</td>
<td>severe purpura</td>
<td>presently thrombocytopenic</td>
<td></td>
</tr>
<tr>
<td>1962</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Of the many leukocytic anomalies that have been described, the only one that might be confused with the May-Hegglin anomaly is that seen in the Chediák-Higashi syndrome. However, when blood smears from the two conditions are compared, the morphologic and staining differences between the two types of granulocytic inclusions are readily apparent (figs. 2 and 4). In the Chediák-Higashi anomaly (fig. 4) the cytoplasm of the neutrophilic leukocytes contains numerous giant, coarse granules that appear refractile and stain greenish-gray with Wright's stain. Some of the lymphocytes contain inclusions as well, generally single and staining red or the color of the nuclear chromatin. The granules of the eosinophils have been described as giant in size. Platelet morphology is generally normal but thrombocytopenia may develop terminally.

The clinical picture in the two conditions is also quite dissimilar. In the May-Hegglin anomaly the patient is generally well, while patients with the Chediák-Higashi anomaly may have repeated pyogenic infections, photophobia, pale optic fundi, excessive sweating, disturbances of pigmentation, hepatosplenomegaly, lymphadenopathy, and generally die from this poorly understood condition.

At present, one can only speculate on the relationship between the abnormal platelet morphology and the development of thrombocytopenia in the May-Hegglin anomaly. Although this anomaly may easily be overlooked in the clinically well patient, it appears more than coincidence that 9 of 24 cases described to date had thrombocytopenia in association with their anomaly. The relationship between the Döhle bodies and the platelet defect is equally obscure.

All patients with thrombocytopenic purpura should be examined for this anomaly. Although this defect is apparently rare, with further observations it is hoped that this anomaly will be better defined as to incidence, course, and prognosis. In addition, family studies are worthwhile in all such patients.

**Summary**

A six-year-old girl with thrombocytopenia was found to have the May-Hegglin anomaly, consisting of Döhle bodies in the leukocytes in association
with giant platelets. This was also observed in the patient’s mother and brother who had normal platelet counts. The familial nature of this anomaly is again confirmed, and the world literature reviewed. Its morphologic and clinical features are contrasted with those seen in the leukocytes of the Chediák-Higashi anomaly.

**SUMMARIO IN INTERLINGUA**

Esseva trovate que un puera de sex annos de etate con thrombocytopenia habeva le anormalitate de May-Hegglin, consistente de corpores de Döhle in le leucocytos in association con plachettas gigante. Isto esseva etiam observate in le matre e le fratre del patiente le quales habeva normal numera-\[sic\]tiones plachettal. Se corrobora le natura familial de iste anormalitate. Le pertinente litteratura mundial es revistate. Le characteristicas morphologic e clinic del condition es contrastate con illos vidite in le leucocytos del anor-\[sic\]malitate de Chediák-Higashi.

**ADDENDUM**

At present (September 1962) the patient is clinically very well. Her plate-\[sic\]let count is 240,000/mm\(^3\). The hydrocortisone was discontinued in June.

**REFERENCES**

14. Donohue, W. L., and Bain, H. W.:


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