Anomalous Panleukocytic Granulation

By Luiz Gonzaga Saraiva, Miccio Azevedo, José Mauricio Correa, Gerson Carvalho and José Donato Prospero

This is a report of a girl who exhibited a rare type of alteration in the granulation pattern of the white cells from the peripheral blood, bone marrow and spleen, similar to that described by Béquez César (1943), Steinbrinck (1948), Chediak (1952), Boturão (1953), Higashi (1954), Donohue and Bain (1957), and Maggi et al. (1957). Efrati and Jonas (1958) observed a case showing in addition to the leukocytic anomaly, a leukemic blood picture.

The descriptive name “anomalous panleukocytic granulation” is adopted in this paper to mean that atypical granules were found in every class of leukocyte, although these granules were not identical in their morphology and nature.

Case Report

History.—B. R., a white girl, three years and six months old was admitted to the local Children’s Hospital of the Brazilian Red Cross on November 18, 1957. Her parents, born in Brazil, had consanguinity, as they were first cousins. Both were white. The mother had had five children and one miscarriage. One of the children died of pneumonia at nine months. The father had been an alcoholic and was syphilitic. He showed large achromic spots on the abdominal and scrotal skin. The patient was the fourth child and was born after normal pregnancy and delivery. Her brothers were apparently healthy. The patient had had measles and chicken pox. When four months old she could keep her head erect and two months later she had her first tooth and could sit up. The child was nursed by her mother until seven months of age. She said her first words when she was one year old; her speech progressed little since then. After she was six months old she became irritable and suffered frequent infections of the respiratory tract. When three years old she suffered from daily fever, excessive thirst and profuse perspiration. Four months later, she showed generalized, transitory edema and increase in size of the abdomen. A few days before admission to the hospital, her urine became dark and the sclerae yellowish.

Physical examinations.—The positive physical findings included: malnutrition, dyspnea, cough, altered teeth, drumstick fingers, dilated abdomen and collateral venous circulation of the portacaval type in the thoraco-abdominal region and the aspect and posture of psychomotor underdevelopment. There were dystasia and dysshasia, no paralysis, normal tonus and slight postural kyphosis. The weight was 8,700 grams, height 79 cm., cranial perimeter 45 cm. The skin, of normal turgor and elasticity, was moist and icteric. The hair was brown, thin and of normal distribution. The subcutaneous connective tissue was underdeveloped. Lymph glands were of normal size and consistency. The spleen was...
and liver were hard, non-tender, palpable at 4 cm. and 3 cm. from the thoracic limits, respectively. The cardiovascular findings were: heart, ictus between the 5th and 6th intercostal spaces at the level of the mammary line; pulse 110, arterial pressure 90/40; electrocardiogram, normal. There was stertorous breathing in both lungs. The pupils were isochromic and isocoric; pupillary reflexes to light: normal. There was no photophobia, and the iris was well pigmented. Funduscopic examination revealed normal retina, tortuous vessels, turgid veins, slight diminution of arterioles diameter and papilledema.

Neurologic examination showed symmetric and active deep reflexes on all extremities. Both feet showed very slight clonus but no Babinski reflex. Gesell's development level was between 12 and 18 months. Electroencephalogram indicated bioelectrical cerebral activity showing poor organization for the age and sex of the patient. X-rays study showed lung fields with diffuse shadows, especially on the bases, global increase of cardiac area, and generalized rarefaction with osteogenic underdevelopment of the skeleton. The bone age corresponded to that of a 2 year old child.

Clinical course.—The patient was observed over a period of nine months; during this time she gained 2300 grams. Fever occurred when the patient developed a generalized pyodermatitis (during the second half of January), when antityphoid fever vaccine was administered for a study of antibody development and leukocytes behavior, and when she had bronchopneumonia. After the pyodermatitis some immunohematologic tests became positive, reverting to negative after a lapse of two months. The jaundice which the patient exhibited on admission disappeared after one month (total bilirubin: 0.4 mg. per cent).

In the first two weeks of June she developed rhinopharyngitis with cough, expectoration and vomiting. The respiratory ailments became more pronounced; the child was submitted to bronchoscopy and antibiotics were given locally in several instances. The bronchial mucosa was congested, with abundant mucopurulent exudate rich in polymorphonuclear neutrophils. Staphylococcus aureus was isolated. In August, bronchopneumonia developed, until death ensued. Peripheral blood and bone marrow counts at this time are shown in table 1. The spleen, liver and superficial lymph glands remained unchanged during the entire period of observation. The patient received symptomatic and anti-infectious (vaccines, antibiotics, chemotherapeutic agents) treatment.

LABORATORY INVESTIGATIONS

Laboratory examinations (tables 1 and 2) were repeated frequently during the hospitalization. The electrophoresis data and the erythrocytic osmotic fragility are shown in figures 1 and 2, respectively. Changes were observed in the bilirubinemia, in some immunohematologic tests (see Clinical Course, above), electrophoresis of proteins (fig. 1) and in peripheral blood and bone marrow counts (table 1). The other findings did not depict significant changes.

The preparations of peripheral blood, bone marrow and spleen were stained with Leishman's stain and subjected to cytochemical tests. The morphologic findings were essentially the same in the several material collections. They will be described in detail because of their obvious importance.

Peripheral blood—Neutrophils. The neutrophils exhibited zones resembling Döhle's bodies (figs. 3 and 4) which were oval, round, rectangular, fusiform or irregular in shape, ranging from 0.5 to 3.0 micra. Their number in each cell ranged from 3 to 20. Their distribution in the cytoplasm was variable. They stained greenish gray in variable intensities. Besides these zones, small round granules, from 0.3 to 0.5 micron, were observed in 10 per cent of the neutrophils. The number of these granules varied from 3 to 12;
Table 1

<table>
<thead>
<tr>
<th>A - PERIPHERAL BLOOD</th>
<th>B - MARROW</th>
<th>C - SPLEEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes, millions/mm³</td>
<td>Dec</td>
<td>Jan</td>
</tr>
<tr>
<td>4.30</td>
<td>4.40</td>
<td>4.20</td>
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<tr>
<td>Hemoglobin, grams/100ml</td>
<td>9.3</td>
<td>9.2</td>
</tr>
<tr>
<td>Hematocrit, ml/100ml</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Mean corpuscular volume, µm³</td>
<td>81</td>
<td>79</td>
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<tr>
<td>Mean corpuscular hemoglobin, pg</td>
<td>22</td>
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<tr>
<td>Mean corpuscular hemoglobin conc. %</td>
<td>27</td>
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<td>Leukocytes, thousands/mm³</td>
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<td>340</td>
</tr>
<tr>
<td>Neutrophils %</td>
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</tr>
<tr>
<td>Band forms %</td>
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<tr>
<td>Metamyelocytes %</td>
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<tr>
<td>Eosinophils %</td>
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<td>4.0</td>
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<tr>
<td>Monocytes %</td>
<td>16.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Lymphocytes %</td>
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<td>72.0</td>
</tr>
<tr>
<td>Plasma cells %</td>
<td>1.0</td>
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<tr>
<td>RBC Sedimentation rate (Westergren-mm/hr)</td>
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<td>30</td>
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<tr>
<td>Saline fragility, %</td>
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<td>Hyper</td>
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<tr>
<td>Normoblasts</td>
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<td>Megakaryocytes</td>
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<tr>
<td>Myeloblasts</td>
<td>%</td>
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<tr>
<td>Promyelocytes</td>
<td>%</td>
<td>0.0</td>
</tr>
<tr>
<td>Megakaryocytes</td>
<td>%</td>
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<tr>
<td>Myeloblasts</td>
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<td>Promyelocytes</td>
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<td>Megakaryocytes</td>
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<td>Megakaryocytes</td>
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ANOMALOUS PANLEUKOCYTIC GRANULATION

About half of the neutrophils presented very few intensity. Sometimes seen was incompletely segmented nuclei. The chromatin of neutrophils was sometimes seen concentrated in masses which took the stain with variable intensity.

EOSINOPHILS (fig. 6). The usual granules (20 to 40 per cell) were round or oval, varying from 1.0 to 3.0 micra in diameter. Sometimes the distribution of these granules was not uniform. Nuclei with two and three segments predominated.

BASOPHILS (fig. 7). Basophils were scanty in the preparations. The few usual granules were round and large, from 1.5 to 2.0 micra in diameter.

LYMPHOCYTES. The cytoplasm of 70 per cent of the lymphocytes showed one or more corpuscles, usually round and sometimes oval, whose diameter commonly ranged from 1.0 to 2.0 micra, sometimes more (fig. 10). About 80 per cent of the lymphocytes contained one single corpuscle (figs. 8, 9, 10, 11 and 12). The remaining 20 per cent contained two corpuscles (figs. 13 and 14) or very rarely three (fig. 15). Their localization in the cytoplasm was variable. A clear zone or halo was sometimes observed around the corpuscles. They usually stained in a way similar to or paler than the nucleus.

MONOCYTES. The cytoplasm of 5 to 10 per cent of the monocytes showed

very few cells showed more. They stained dark purple and were usually found at the periphery of the cytoplasm. They were found mostly in the banded-form neutrophils (fig. 5). About half of the neutrophils presented banded or incompletely segmented nuclei. The chromatin of neutrophils was sometimes seen concentrated in masses which took the stain with variable intensity.
small areas where fine lilac-stained granules accumulated (figs. 17 and 18). Other monocytes exhibited dark purple, round corpuscles ranging from 0.3 to 1.0 micron in diameter (fig. 19 and 20).

**Plasmocytes** (fig. 16). In very rare instances plasmocytes with corpuscles similar to those observed in lymphocytes were found.
ANOMALOUS PANLEUKOCYTIC GRANULATION

Bone marrow.—Starting from the more primitive cells we noticed the following deviations from normal in the granulocytic series, Ferrata’s nomenclature being used.

**MYELOBLASTS** (fig. 23). The myeloblasts showed a basophilic cytoplasm, taking the stain more deeply at the periphery and containing granules (30 to 50 per cell), whose diameter ranged between 0.5 to 2.0 micra. The granules were found agglomerated in an area close to the nucleus; a few could be seen scattered in the remaining cytoplasm. The larger granules were surrounded by a clear zone. The granules stained a brilliant reddish purple. The smaller ones stained homogeneously whereas the larger ones exhibited a lighter center. The nucleus was eccentric with 2 to 4 nucleoli.

**PROMYELOCYTES** (figs. 22, 24 and 25). The cytoplasm exhibited the anomalous granules; these were round, smaller and fewer than those observed in myeloblasts. They were more delicate, and usually had a clear center.
Figs. 21–25.—Photomicrographs of bone marrow.

Figs. 26–28.—Spleen preparations. (Leishman, ×900)

Fig. 21, hemohistioblast containing granules larger than usual. A neutrophil shows Döhle’s body-like structures. Fig. 22, transition form of myeloblast-promyelocyte (upper left) with two giant granules (arrow). One neutrophilic promyelocyte-myelocyte (center) with small granules. Fig. 23, myeloblast with anomalous granules. Fig. 24, neutrophilic promyelocyte (above) with anomalous granules. In one of the angles formed by the nucleus and the cytoplasm of the promyelocyte there is condensation of granules. Myelocyte (below) with few anomalous granules. Fig. 25, promyelocyte with anomalous granules. A vacuole with a central granule is also seen. Fig. 26, macrophage containing phagocytized material. Fig. 27, myeloblast (center) with anomalous granules. There is also a neutrophil with Döhle’s body-like structures and a lymphocyte. Fig. 28, pulp cell with a large inclusion.

Their distribution tended to be more peripheral and in many promyelocytes the granules were not found in the archoplasm. They stained to a purple fainter than that of myeloblasts. In some promyelocytes, vacuoles could be observed in the cytoplasm, sometimes containing one round granule (fig. 25).

Myelocytes (fig. 24). These cells exhibited a number of granules smaller than those of promyelocytes. In the more mature cells, the granules were
scanty. From the myelocyte stage on, small round granules were seen, colored light orange.

**Metamyelocytes, Banded and Segmented Neutrophils.** These showed the same characteristics as those found in the peripheral blood.

**Eosinophilic Series.** The irregularity shown by the specific granules of cells from the peripheral blood was also observed in the bone marrow cells. However, these alterations were less frequent the younger the cell was.

**Basophilic Series.** In the few cells observed the findings were similar to those in the peripheral blood.

**Hemohistioblasts.** In some hemohistioblasts, granules larger than usual were observed (fig. 21).

The anomalies observed in the leukocytes were not present in the cells of the red and thrombocytic series. It may also be noted that there were no anomalous granules in epithelial cells from the vagina, mouth and tracheobronchial tree.

**Spleen.—**Associated with Targino and Jamra, we studied material obtained by splenic needle puncture (table 1, C). There was an increase of plasmocytes, pulp cells and macrophages (fig. 26). Some of these latter cells contained inclusions (fig. 28). Very rarely myeloblasts (fig. 27) were found. The granulocytes exhibited the same characteristics observed in the cells from the bone marrow and in the peripheral blood, but the lymphocytes with abnormal corpuscles were less frequent.

**Cytochemical tests.—**The presence of polysaccharides, lipids, desoxyribonucleic acid and peroxidase was investigated by the use of periodic acid-Schiff, Sudan Black B, Feulgen and Washburn technics, respectively.

The reaction of a given type of leukocyte to the cytochemical tests was the same whether it belonged to the peripheral blood, bone marrow or spleen.

**Myeloblasts, Promyelocytes and Myelocytes.** The peculiar granules from these cells gave positive reactions to Sudan Black B and peroxidase (figs. 37, 42, 43 and 44). In the myeloblasts harboring large granules, the peroxidase reaction was more intense at the periphery of the granules, leaving a clear center (fig. 42). The granules positive in Sudan Black B and peroxidase tests exhibited variation in size.

**Metamyelocytes, Banded and Segmented Neutrophils.** The structures taking the Leishman stain reacted positively to Sudan Black B and the peroxidase test. In the banded neutrophils and especially in the segmented ones the peroxidase positive granules appeared very large, having a dark greenish color (figs. 29 and 30). The same appearance was observed with the Sudan Black B test (fig. 33 and 34). The P.A.-S. reaction of the segmented neutrophils was positive in the cytoplasm. However, small, clear negative areas were observed which apparently corresponded to the Leishman-stained structures similar to Döhle's bodies (fig. 38).

**Eosinophils.** The granules were peroxidase-positive and had a swollen appearance (fig. 31). In the young cells, these granules appeared partially superimposed on the nucleus (fig. 43). The eosinophilic granules were Sudan Black B positive, the lipoidic substance being found at the granule's
Figs. 29-44.—Photomicrographs of peripheral blood and bone marrow after cytochemical tests. (X 900)

Figs. 29-32, peroxidase test in the peripheral blood. Neutrophil with giant peroxidase granules (Figs. 29 and 30). Monocyte with peroxidase granules larger than usual (Fig. 31). Fig. 32, Sudan Black B test in the peripheral blood. Neutrophils with giant Sudan Black B granules (Figs. 33 and 34). Eosinophil (Fig. 35) and monocyte (Fig. 36) with larger than usual granules. Fig. 37, giant Sudan Black B granules in a myeloblast (arrow). Fig. 38, P.A.-S. test in a neutrophil. The clear areas apparently are the negative images of the Döhle's body-like structures (hematoxilin counterstaining). Fig. 39, lymphocyte with P.A.-S-positive corpuscle (hematoxilin counterstaining). Figs. 40 and 41, monocyte showing erythropagocytosis (Fig. 40) and two Hargraves cells (Fig. 41; patient's leukocytes incubated with serum from a patient with lupus erythematosus). Fig. 42, positive-peroxidase test in the anomalous granules from a myeloblast (left) and a neutrophilic promyelocyte (right). The myeloblast granules are more deeply stained at their periphery. Fig. 43, positive-peroxidase test in the granules from a neutrophilic promyelocyte (left) and an eosinophilic promyelocyte (right). In the latter, the peroxidase granules are partially superimposed to the nucleus. Fig. 44, giant Sudan Black B positive granules in a neutrophilic promyelocyte.

periphery while the center was sudanophobic (fig. 35). The intensity of the reaction increased as the cell matured. The P.A.-S. test was positive in the cytoplasm and negative in the specific granules.

LYMPHOCYTES. The specific granules did not stain by the Feulgen, Sudan
ANOMALOUS PANLEUKOCYTIC GRANULATION

Black B and peroxidase tests. They were P.A.-S.-positive (fig. 39). This reaction, however, was abolished by previous treatment with saliva. In addition to these large granules, many of the lymphocytes contained small glucogen-containing granules, as is commonly observed.

MONOCYTES. The Feulgen and P.A.-S. tests were negative in the peculiar structures stained by Leishman stain. The peroxidase test was positive and the granules appeared larger than usual. They sometimes agglomerated and were irregularly distributed in the cytoplasm (fig. 32). The picture after the Sudan Black B test was similar to that of peroxidase stain although providing more delicate detail (fig. 36).

Leukocytic activity.—When the child’s leukocytes were incubated with serum from patients with lupus erythematosus, the typical Hargraves cells (fig. 41) were obtained. Rosettes as well as erythro- and nucleophagoctysis by neutrophils and monocytes were verified (fig. 40). The search for L.E. cells in the same child was always negative. Her own leukocytes as well as those from normal individuals were employed. In the cells from the latter, no anomalous granules or corpuscles appeared after their incubation with the serum from our patient.

The patient’s leukocytes when incubated with cultures of Salmonella typhosa and Staphylococcus pyogenes var. aureus exhibited a phagocytic activity similar to that of the controls. After parenteral vaccination with anti-typhoid-paratyphoid vaccine there was an increase in the number of neutrophils showing phagocytosis of the bacilli. Also, after incubation there was a decrease in the number of the corpuscles containing lymphocytes.

Liver needle biopsy.—The portal fields were prominent and contained an excess of collagen infiltrated by a large number of mononuclear cells; the limiting plate, however, was present (figs. 45 and 46). The liver cells were arranged in normally appearing plates, a slight variation in shape and volume being evident (fig. 47). Their nuclei were preserved but a small number of pyknotic nuclei was observed. The hepatic cell cytoplasm was normal. A small degree of focal dilatation of the sinusoids was apparent. The Kupffer cells, with large dense nuclei and scanty cytoplasm, were prominent. In the sinusoids there was focal accumulation of mononuclear cells similar to those found in the portal fields (fig. 47). These cells were lymphocytes, plasmocytes and reticular cells.

The P.A.-S.-positive granules in the liver cells were normal in amount and disposition. Positive granules were also found in the cytoplasm of the Kupffer cells and in some mononuclear cells.

Necropsy.—Grossly the main findings were: hepatosplenomegaly (550 and 160 grams, respectively), enlargement of the heart (140 grams), enlargement of the mesenteric lymph nodes and bilateral bronchopneumonia, which was considered the cause of death.

Histologically the main changes were characterized by intense focal or diffuse cellular infiltration by lymphoid cells, plasma cells and reticular cells in the liver (fig. 48), mesenteric lymph glands (fig. 51) and spleen (fig. 52), and small focal infiltrations by the same cells in the kidney (figs. 49 and 50), soft retroperitoneal tissues and skeletal muscle. In the spleen...
Figs. 45–53.—Histologic picture: liver biopsy (Figs. 45–47) and necropsy (Figs. 48–53) (Hematoxylin and eosin).

Fig. 45, enlarged portal field containing cellular infiltrate. Lobular architecture is maintained. (× 90)  Fig. 46, same field showing with more detail the type of the cells in the infiltrate. There is focal invasion of the limiting plate by the same cells. (× 250)  Fig. 47, same type of cells are seen in and around the intralobular sinusoids. The hepatic cells appear preserved. (× 250)  Fig. 48, necropsy. Liver. The same cell infiltrate is observed. (× 90)  Figs. 49 and 50, kidney. Cellular focal interstitial infiltration. (× 110 and × 250)  Fig. 51, lymph node. The whole architecture is obliterated by cellular infiltrate. (× 220)  Fig. 52, spleen. Diffuse cellular infiltration of the red pulp. A malpighian body is shown. (× 90)  Fig. 53, bone marrow. Hypercellular marrow. (× 90)
ANOMALOUS PANLEUKOCYTIC GRANULATION

and lymph nodes many of the reticular cells exhibited phagocytic activity. The identification of the cells was supported by the study of touch preparations.

In the liver (fig. 48) the picture was similar to that described in the biopsy specimen. However, cellular accumulations in the sinusoids lumini were not conspicuous and hepatocytes showed a moderate degree of fatty degeneration.

In the spleen (fig. 52) there was marked diffuse infiltration of the red pulp associated with small, widely-spaced Malpighian bodies. These presented a central region with reticular hyperplasia, immature lymphoid cells, and, at times, they were surrounded by a layer of mature lymphocytes.

In the mesenteric lymph glands (fig. 51) there was almost complete obliteration of the normal structure by infiltration with the above-mentioned cells.

The lungs revealed hemorrhagic bronchopneumonia with purulent bronchiolitis. A histiocytic reaction in the alveolar septae was observed which was also found occasionally in the blood vessel's adventitial layer.

The rib sections contained a myeloid hyperplastic marrow (fig. 53). The structure of the bone tissue was preserved.

Sections from the central nervous system, pituitary, thyroid, adrenals, pancreas, intestinal tract, genital tract and skin did not show alterations. The thymus was atrophic.

Touch preparations of the spleen and lymph nodes yielded a picture in accordance with the histologic findings. Similar preparations of the bone marrow (sternum, rib and tibia) showed hypercellularity, granulocytic series hyperplasia, plasmocytosis, normal appearance of the erythroid and megakaryocytic series. The cells of the granulocytic series in the touch preparations presented abnormal granules similar to those found during life. Scarcely anomalous granules were seen in cells of the lymphoid series, in the lymph glands and spleen.

COMMENTS

A comparison of the findings made in our case with those of previous reported cases depicts a common morphologic alteration of the granulation in the leukocytic cells from the peripheral blood and bone marrow. The distinction from Alder's anomaly seems clear in view of the morphology and staining behavior of the anomalous granules.

The results of the cytochemical tests employed suggest that the peculiar structures found in neutrophils and lymphocytes are of different constitution. The effect of saliva treatment indicates that the anomalous corpuscles of the lymphocytes contain glucogen. The results of the peroxidase test agree with the previous work of Higashi (cf. also Sato). In addition to anomalous granules in neutrophils and eosinophils Steinbrink also reported nuclear changes in 60 per cent of the cells. The banded forms exhibited constrictions whereas the segmented forms rarely showed
complete segmentation. This was interpreted by the author as Pelger's anomaly. Chediak, Higashi and ourselves also have found an abnormal nuclear structure in leukocytes.

With respect to the development of the granules in the bone marrow white cells, it seems that the peculiar granules of the myeloblasts change in number, size, color and tone according to the degree of maturation of the cell, finally giving rise to the structures observed in the banded and segmented leukocytes from the peripheral blood. The "maturation stages" are specially apparent when they are observed with the phase microscope. In our bone marrow preparations, we could not detect a decreased production of myeloid cells but only the occurrence of the anomalous granules even in the youngest cells. It seems that the bone marrow was able to react since it showed the cytologic changes expected after the pyodermitis rash and the bronchopneumonia, when we found an increase of neutrophils in the capillary blood. As mentioned before, the phagocytic activity of neutrophils and monocytes was not altered, despite the presence of the peculiar structures.

Efrati and Jonas described a case in which a leukemic blood picture as well as granular anomaly of the leukocytes was present.

Another laboratory finding worthy of mention was the electrophoretic behavior of our patient's serum (fig. 1). The increase of the gamma globulin fraction was such that it reached a level higher than that of the albumin. This could suggest the presence of some macroglobulin. Our patient's serum was kindly examined by Dr. U. Kanzow, of the University of Cologne (Germany), who could not detect macroglobulins either by ultracentrifugation or by precipitin investigations. The relatively reduced base of the gaussian curve indicates some homogeneity, which suggests that the hypergammaglobulinemia of the patient may be attributed to a single factor. The increase in the alpha-2 fraction observed between the first and second samples (fig. 1) might be determined by minor infections without greater alterations of the protein metabolism. The patient developed a pyodermitis during this period. The lipidogram depicted a drop in both lipoproteic fractions, which suggests a deficient use of fat metabolism products with low levels of cholesterol and phospholipids. The ultracentrifugation (table 2) showed a decrease of lipoproteins. The protein-bound polysaccharides showed a marked increase of the gamma fraction which disappeared in the second sample. A third analysis performed one month before death revealed that the albumin level was further reduced, that the beta-protein fraction was increased and slight changes in the glycoprotein pattern.

The clinical course as well as several symptoms show variations in the cases reported in the literature, the condition presenting some individual variations in its pathologic picture. However, the common denominator is the anomalous panleukocytic granulation. Death occurred at ages varying between 11 months and 6½ years. There is one exception: Boturão's patient, who is still alive 6 years after the initial observation. He is now 13 years old and is apparently healthy, but has photophobia, albinism of fundus oculi and whitish-gray hair. The leukocyte anomaly persists.

The consanguinity of the parents has not always been found in the above-
ANOMALOUS PANLEUKOCYTIC GRANULATION

1125

reported cases. The findings of healthy parents and healthy as well as unhealthy brothers together with the occurrence of the disease in siblings of either sex suggested a chromosomal origin without sex linkage. It seems that the disease is transmitted by a recessive gene, and that the sick children represent a homozygotic state. We examined the peripheral blood of the parents and brothers of our patient. The blood counts were normal. In smears of the father's blood rare lymphocytes were seen harboring giant corpuscles in their cytoplasm. The structure and segmentation of neutrophils showed no abnormality. Alterations of the leukocytic granulation in the father's blood are also referred by Béguez César1 (lymphocytes) and Efrati and Jonas8 (lymphocytes, neutrophils and eosinophils). In a blond, 6 months old brother, we found very discrete alterations consisting of rare neutrophils exhibiting structures similar to Döhle's bodies as well as some eosinophils with fewer and larger than usual granules; rare lymphocytes showed the anomalous granules. It was not possible to obtain bone marrow specimens. The electrophoretic analysis of the parent's sera is shown in figure 1.

The basic histologic findings described in the literature are focal or diffuse cellular infiltration in the organs, suggesting a systemic disease. These infiltrates possibly represent the anatomicopathologic substratum of the disease, whose seat would be the reticuloendothelial system. The variability of the hitherto reported cellular findings might be due to the fact that the biopsies and necropsy were performed at different stages of the condition. We feel that only careful study of further cases may lead to a fair interpretation of the pathology of the disease. In our case, the histologic picture of the liver, kidneys and lymph nodes showed a distribution—but no cytologic character—similar to that found in leukemia. The findings in the spleen, again, were markedly different from the usual ones in the different phases or types of leukemia. No extramedullary hematopoesis was found. In the touch preparations from lymph nodes, spleen and bone marrow, no tumor cells were present. Tumor cells were not found in many peripheral blood and bone marrow examinations nor in the splenic puncture, all made during life. Donohue and Bain6 ruled out leukemic infiltration. Maggi et al.7 in a liver needle biopsy found infiltration of the portal fields by histiocytes; the adenogram showed lymphoid hyperplasia, but tumor cells were never mentioned. The central nervous system in our patient did not show significant lesions. In the skin histologic changes comparable to the ones described by Pierini and Abulafia12 were not observed.

The clinical history and laboratory findings suggested that the condition has a constitutional and familial origin with cellular and metabolic alterations. The blood changes together with abnormalities of other tissues appear to be manifestations of a systemic process.

SUMMARY

Anomalous panleukocytic granulation is described in the peripheral blood, bone marrow and spleen of a 3 year old girl. Myeloid leukocytes showed giant peroxidase and Sudan Black B-positive granules. Lymphocyte corpuscles were positive in the periodic acid-Schiff test. Deviations in the
structure and segmentation of the neutrophil nuclei were observed. Increase of gamma globulins and decrease of lipoproteins were found in the blood serum.

Hepatosplenomegaly, psychomotor underdevelopment, respiratory tract infections, roentgenologic changes of bones, lungs and heart were also found. The parents were first cousins, and anomalous corpuscles were seen in the father's lymphocytes.

At necropsy diffuse or focal infiltration of the organs by lymphoid, plasma and reticular cells suggested a systemic condition.

**SUMMARIO IN INTERLINGUA**

Es describite anormal granulation panleucocytic, occurrente in sanguine peripheric, medulla ossee, e splen de un puera de 3 annos de etate. Le leucocytes myeloide monstrava granulos gigante con positivitate pro peroxydase e nigro sudanic B. Le corpusculos lymphocytic se monstrava positive in le test a acido periodic de Schiff. Deviationes de structura e segmentation esseva observate in le nucleos neutrophilic. Augmentos de globulinas gamma e reductiones de lipoproteinas esseva constatate in le sero de sanguine.

Esseva etiam trovate hepatosplenomegahia, dysdisveloppamento psychomotori, infectiones del vias respiratori, e alterationes roentgenographic de ossos, pulmon, e corde. Le parentes esseva cosinos del prime grado, e corpusculos anormal esseva constatate in le lymphocytos del patre.

Le constatation necroptic de diffuse o focal infiltration del organos per cellulias lymphoide, plasmocytos, e cellulias reticular pareva indicar que il se tractava in iste caso de un condition systemic.

**REFERENCES**

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ANOMALOUS PANLEUKOCYTIC GRANULATION

Anomalous Panleukocytic Granulation

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