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FAMILIAL SHIFT TO THE LEFT OF THE LEUKOCYTES (PELGER'S NUCLEAR ANOMALY OF THE LEUKOCYTES), WITH REPORT OF A CASE *

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IN 1928 Pelger [6] reported to the Dutch Pathological Society at Amsterdam two cases showing an anomaly of the leukocytes, hitherto undescribed in the literature. The neutrophiles, eosinophiles and basophiles all showed a large percentage with non-segmented nuclei, and the segmented forms were represented almost exclusively by those with only two nuclei. Furthermore, the nuclei differed from those met with in the ordinary shift to the left of infectious diseases, in that they had a remarkably regular shape with even contours. The protoplasm of the neutrophiles on the other hand showed fine even granulations, of the type seen in mature cells. His first case was a woman who suffered from cachexia of obscure origin, and died of a terminal pulmonary infection; there was no autopsy. His second patient was a man with splenomegaly; material obtained by puncture of the spleen was injected into a guinea-pig and caused tuberculosis in the animal. Pelger believed that the anomaly of the leukocytes was pathological, in some manner connected with tuberculosis, and of bad prognostic import.

Three years later Huët [4] discovered a similar hemogram in a niece of Pelger's first patient, and investigating other members of the family, found it in them also. He was therefore the first to recognize the familial character of the anomaly, and since it was present in healthy people, he declared it to be without pathological significance. Huët also reported two other families with this condition; there was no interrelationship between these families.

Other reports soon followed, so that up to the present time there have been recorded five such families in Holland, three in Germany, one each in Switzerland, Czechoslovakia, and the United States. It has been shown that the anomaly is inherited as a dominant Mendelian character, not sex-linked.

The following case, taken from the writer's private practice, seems worthy of record. It is the second to be reported in this country, and the first involving a person of English ancestry, Peterson's [7] publication having concerned a Chinese family.

CASE REPORT

The patient, a lawyer now 73 years of age, has been under the writer's care for the past 26 years. In January 1918 he had an attack of lobar pneumonia of moderate

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severity, with high fever and terminating by crisis; the leukocyte count was 16,600 with 82 per cent neutrophiles. In November 1918 he had influenza, with a temperature of 103 degrees and a leukocyte count of 3,500; no differential count was made. These facts are interesting as indicating a normal reaction to infection on the part of the bone marrow.

For the remainder of this long period he has had no serious illnesses, and is now in good health and active in the practice of his profession.

Five years ago he had an attack of syncope, the cause of which was undetermined, and a routine examination of the blood disclosed the fact that, although there were no signs of infection and the total leukocyte count was normal, more than half of the neutrophiles were non-segmented or staff forms, and that the nuclei of the remainder had, almost without exception, only two lobes. This curious condition has persisted ever since, with little change in the relative proportions (table 1). Most

TABLE I

Date	Red Cells Millions	Hgb. %	Leukocyte Count	Neutrophiles		Lymphocytes	Monocytes	Eosinophiles	Basophiles
				Staff Cells	Segmented Cells				
11–18–31	4.4	70	8,600	34	26	22	9	9	0
12–18–31	4.9	75	7,100	26	16	39	11	8	0
1– 6–32	—	—	—	34	24	17	15	10	0
3–15–32	—	75	6,200	46	16	30	5	3	0
6–13–32	—	75	6,000	43	19	29	4	5	0
12– 5–32	—	70	7,700	47	17	23	4	9	0
5–13–33	—	75	5,300	32	24	36	6	2	0
10–13–33	—	80	5,000	36	15	33	12	3	1
7–31–34	—	80	5,800	32	21	30	10	4	3
4–18–35	—	80	—	36	30	25	4	5	0
11–11–35	—	80	—	36	25	29	8.5	1.5	0
11–11–36	—	80	—	32	22	30	10	5	1
4–28–37	3.4	75	6,100	38	24	27	8	3	0
6– 2–37	4.7	88	7,800	43	21	27	5	3	1

of the smears have shown no nuclei with more than two lobes; rarely one with three lobes has been present (up to 1.5 per cent in the differential count), but never any with more than three lobes.

The appearance of the nuclei of the neutrophiles is unusual, the contours being smooth and regular, in contrast with the irregular shapes seen in the ordinary shift to the left, and in normal blood. A fair number of the non-segmented forms (up to 12 per cent of all neutrophiles) might be classified as "juvenile," by reason of their broad kidney-shaped nuclei; no myelocytes were encountered. The segmented cells have two oval or round nuclei, connected by a fine thread.

The protoplasm of the neutrophiles shows no abnormalities, toxic granulation and vacuolization being uniformly absent.

The eosinophiles are affected in a similar way, but to a less marked degree, a differential count of 100 eosinophiles showing 38 per cent non-segmented, 62 per cent two-lobed, none with more than two lobes. It should be noted that in normal blood segmentation of the eosinophiles is not carried out to the same extent as it is in the case of the neutrophiles, 76 per cent having two nuclei, and only 19 per cent more than two. However, staff cells normally make up only 3 per cent of the total, according to Zündel.[10]

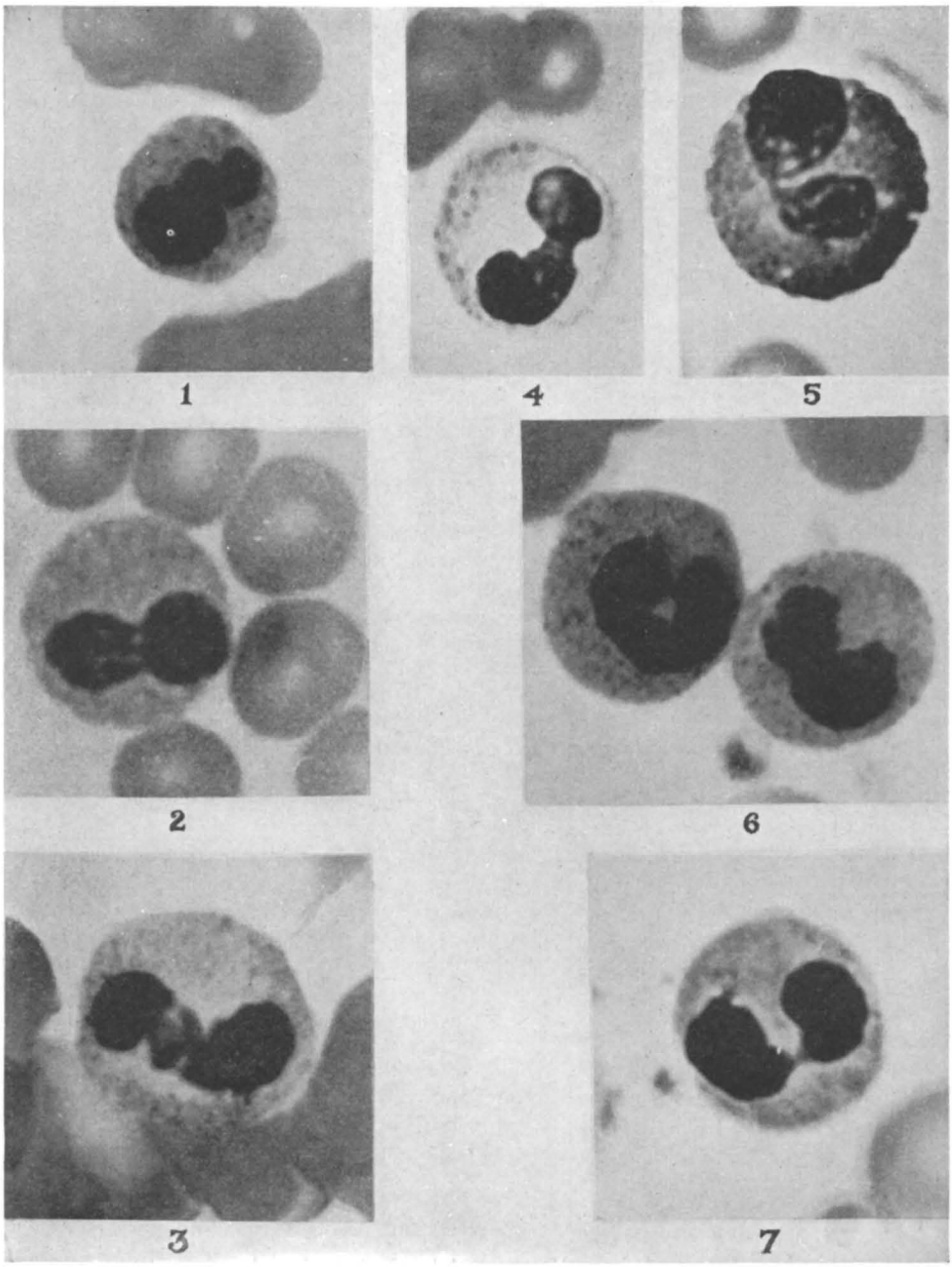

FIG. 1. Photomicrographs of polymorphonuclear leukocytes. No. 5 shows an eosinophile, others are neutrophiles. Leishman stain, magnification approximately 800.

It was difficult to determine whether the basophiles were involved or not, on account of the scarcity of these cells, and their frequent failure in normal blood to show clear-cut segmentation into several nuclei.

When treated with Goodpasture's stain, all of the neutrophiles showed abundant oxidase granules. In a supravital preparation examined by Dr. R. M. Thomas, all of the granulocytes showed motility, and no abnormal granulations were present.

An attempt to estimate the phagocytic activity of the leukocytes, made by Prof. George H. Smith, disclosed an interesting phenomenon, hitherto undescribed in this condition; on centrifugation of the oxalated blood, the leukocytes gathered together into a sticky mass, so cohesive that it was impossible to draw them up into a pipette, or smear them on a slide. No explanation of this curious behavior was forthcoming.

The differential count was normal, so far as lymphocytes, monocytes and basophiles were concerned. A tendency to eosinophilia (up to 10 per cent) was present, for which no cause was apparent; it is interesting to note that a grandnephew of the patient, otherwise healthy and not showing the anomaly, had 18 per cent eosinophiles. In some of the cases reported in the literature eosinophilia has been present but not often enough to suggest any connection with the anomaly.

The red count, hemoglobin, and total leukocyte count were within normal limits, apart from a trifling anemia, and the red cells showed no abnormalities. The platelet count was 240,000, the reticulocytes numbered 0.8 per cent. The coagulation time was 8 minutes, the bleeding time 1½ minutes. The patient's blood group is "A" (international nomenclature). The sedimentation rate was not determined.

Investigation of the relatives of the patient was disappointing. He has had no children, and both his brothers are dead. Examination of smears of all the children and grandchildren of these brothers, to the number of eight, and of two cousins, failed to reveal the anomaly in any of them. It is therefore impossible to state positively whether the condition in this person is familial or not, but since all of the cases reported in the literature have been familial, it may be assumed that it is.

The family history reveals a tendency to arterial disease. One brother died at 50 of a ruptured aneurysm of the iliac artery, the result of atheroma, the other died suddenly, of coronary occlusion, at the age of 57. The only sister was still-born. The father, however, lived to the age of 96.

Physical examination, April 22, 1937. Age 73 years. A tall thin man weighing 148 pounds. Color fair, pupils equal and react to light, arcus senilis present, sclerae faintly yellowish. Mouth and throat negative. Thyroid gland and lymph nodes not enlarged. Heart of normal size, action regular; there is a rather loud systolic murmur in the aortic area, transmitted towards the neck. Pulse rate 56, blood pressure 104 systolic and 58 diastolic; the peripheral arteries are moderately thickened. Abdomen natural, liver and spleen not enlarged. Knee jerks and plantar reflexes normal. On the skin of the neck and upper part of the chest anteriorly there are numerous rounded or flattened papules of a yellowish-white color; a biopsy was done, and a diagnosis of multiple benign cystic epithelioma was made. The urine is negative. Wassermann and Kahn tests of the blood negative. Blood group "A" (international nomenclature). The patient has shown a pronounced arcus senilis and a systolic murmur in the aortic area since the age of 47 years.

Discussion of the Literature

The blood picture as first discovered by Pelger has been verified by all subsequent observers. Unfortunately Pelger's description is not to be found in print, except as quoted by some of the Dutch writers, for the account of his original communication to the Dutch Pathological Society [6] merely alludes to a demonstration of two patients with a rare anomaly of the

leukocytes, without any description of the blood picture; the promised extensive article on the subject never appeared. Staff cells have been present in large numbers in all cases, and have almost invariably exceeded the segmented forms. Cells with more than two nuclei have been found rarely, or not at all. The shift to the left has gone as far as juvenile cells, but myelocytes very seldom have been noted, and then in small numbers (0.5 per cent, Schilling). The proportion of juvenile cells has varied widely, as might be expected on taking into account the element of subjectivity in the classification of this form of cell. Schilling, on examining smears from 11 cases, found the juveniles making up the majority of the non-segmented cells, but Undritz recorded only from 2 to 9 per cent.

All authors are agreed that the eosinophiles are involved in the shift, but as regards the basophiles opinions are divided. No extensive studies of the basophiles have been made.

Toxic granulation of the protoplasm of the neutrophiles has been absent, except in one of Zündel's cases.

The response to infection has been reported only in one instance; in one of Huët's cases during an acute unspecified infection the percentage of staff cells rose from 26 to 44 per cent.

No studies of the bone marrow have been made, nor have any autopsies been performed.

The sedimentation rate has been normal in all the cases in which it has been measured, in contrast to the increased rate met with in the infectious shift to the left.

Blood grouping seldom has been determined; Jordan's patient belonged to group "O," the writer's to group "A."

The familial character of the anomaly has been proved in all the cases reported up to the present time, with the exception of Pelger's second patient, and the case of Chevallier and Ély,[3] in both of which the relatives were not investigated. The trait has been found present in three generations by Huët, Jordans * and Peterson. It has been transmitted by both sexes, and males and females are affected in equal proportions (exactly 50 per cent of each). It is therefore not sex-linked. In no case have the offspring of unaffected members shown the anomaly. The proportion of the affected among the children of affected parents has varied from 50 to 100 per cent; Alieff and Reekers found 7 out of 14 affected, Huët 3 out of 6, Jordans 6 of 9 in the second generation, 3 of 6 in the third, Zündel 4 of 6, and 3 of 4 in the second and third generations respectively. The highest incidence was in the family of Undritz, in which all of 5 living members of the second generation were affected (two had died without investigation), and all of 3 siblings in the third generation. In no instance have both husband and wife been proved to be bearers of the trait.

* Jordans' family is identical with family "Q" of Burger; the family tree is completed in Burger's article.

It is thus apparent that the anomaly is a dominant Mendelian character, not sex-linked.

A large majority of the affected persons have been healthy, and there is no evidence that there is any unusual tendency to disease in these families. Many of them have had members who were tuberculous, but this may be accounted for by the ubiquity of this malady, and by the fact that the anomaly is more likely to be detected in the case of tuberculous patients in sanatoria, because of the periodical examinations of the blood which are made there. The Wassermann test has been negative in all of the cases in which it has been done. The association with hyperthyroidism in Peterson's family (5 cases) is unique in the literature.

The occurrence of this anomaly exclusively as an inherited trait indicates that the segmentation of the nuclei of the neutrophiles and eosinophiles is regulated by a constitutional factor. When this becomes modified by the process of mutation, the anomaly takes place, and is transmitted to the descendants as a dominant character.

Diagnosis. The diagnosis can be made from the stained smear by one who is familiar with the condition, on the following points: (1) The even contour and tendency to kidney shape with rounded ends on the part of the nuclei of the staff cells; (2) the failure to find neutrophiles with more than two nuclei; and (3) the absence of toxic granulation. In all of these respects the blood picture differs from the infectious shift to the left. In case of doubt the absence of signs of infection in the patient, and investigation of the relatives will clarify the situation. Failure to recognize the condition may lead to a serious mistake in prognosis.

The anomaly might be of medico-legal importance, as regards questions of identity and paternity.

Prognosis. From the evidence available, it appears that the health of persons with this anomaly is not adversely affected, and that their leukocytes are adequate so far as function is concerned.

Summary and Conclusions

1. A case of familial shift to the left of the leukocytes is reported, in which no other members of the family were found to be affected, probably on account of the lack of direct descendants.

2. The typical blood picture was present, viz., a high percentage of staff cells, mostly of crescentic or kidney shape; absence or extreme rarity of segmented forms with more than two nuclei; even contour of the nuclei, and absence of toxic granulation.

3. The literature is discussed.

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