

THE OCCURRENCE OF NORMOBLASTS IN THE PERIPHERAL BLOOD IN CONGESTIVE HEART FAILURE: AN INDICATION OF UNFAVORABLE PROGNOSIS

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DURING THE PAST year the authors have observed 9 patients with severe congestive heart failure, all of whom showed a varying number of normoblasts in the peripheral blood. In some of these cases there was a temporary remission of the sequellae of the heart failure; during this remission the normoblasts disappeared from the peripheral blood. However, in all cases the patients died.

CASE REPORTS

Case 1. C. D., a 34 year old woman, was admitted on June 12, 1946, because of decompensated mitral stenosis. She was slightly jaundiced; the liver was greatly enlarged; there were infarcts in both lungs. Five per cent normoblasts were found in the peripheral blood. The patient died on July 2, 1946. The diagnosis was confirmed at autopsy.

Case 2. S. W., a 56 year old woman, entered the hospital on May 9, 1946, because of dyspnea, from which she had been suffering during the previous six months. She was cyanotic, dyspneic, and had slight jaundice. On examination, a mitral insufficiency, stenosis and auricular fibrillation were found. The liver was much enlarged; there was extensive edema. During this period, 10 and 17 per cent, respectively, of normoblasts were found on two occasions in the peripheral blood, but these disappeared within three days when her condition improved. In spite of this remission, the patient died on May 22, 1946. On the day before her death she had another infarction of the lung.

On May 13, a sternal puncture had been performed. The bone marrow was found to be essentially normal, but the presence of a relatively great number of normoblasts and erythroblasts was noted (about 25 per cent of all nucleated cells).

The diagnosis of valvular heart disease was confirmed at autopsy; there were many infarcts in both lungs and a thrombosis of the left auricle of the heart.

Case 3. A. G., a 20 year old woman, entered the hospital on May 4, 1946, with cardiac decompensation, due to insufficiency and stenosis of the mitral valve. She was dyspneic but not cyanotic. There was no jaundice. The liver was enlarged. There was massive edema of the legs. The blood count was as follows:

| | May 6, 1946 | May 7, 1946 |
|------------------------|-------------|-------------|
| Leukocytes..... | 12,800 | 17,000 |
| Erythrocytes..... | 3,640,000 | 3,900,000 |
| Hemoglobin..... | 61 | 63 |
| Normoblasts..... | — | 7 |
| Mycocytes..... | 1 | 0.5 |
| Metamyelocytes..... | 0.5 | 0.5 |
| Stabs..... | 5.5 | 9 |
| Polynuclear cells..... | 54.5 | 69 |
| Eosinophiles..... | 0.5 | — |
| Monocytes..... | 2.5 | 2.5 |
| Lymphocytes..... | 35.5 | 18.5 |

There was a marked anisocytosis, poikilocytosis, polychromasia, anisochromia and macrocytosis. The patient died on May 8, 1946. The autopsy showed a verrucous endocarditis (of the mitral and aortic valves), thrombi in the left auricle of the heart, congestion, fatty degeneration and regeneration of the liver.

Case 4. A. B., a 34 year old man, was admitted on June 28, 1946, with a diagnosis of insufficiency and

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stenosis of the mitral valve and aortic stenosis. He was cyanotic and extremely dyspneic. There was slight jaundice. The liver was palpable. There was no edema. The patient had distinct anginal pain. An electrocardiogram showed changes that were typical of a severe myocardial lesion. The blood picture was as follows: leukocytes, 7,000; erythrocytes, 5,000,000; hemoglobin, 100; normoblasts, 3; stabs, 4; polynuclear cells, 80; monocytes, 1; lymphocytes, 15.

The patient died on July 5, 1946. No autopsy was performed.

Case 5. H. S., a 71 year old man, was admitted on March 4, 1946, with "cardiac asthma." He had been known for years to have suffered from hypertension. The patient was extremely cyanotic. There was slight jaundice and very severe dyspnea. He showed all the signs of congestive heart failure. There was extensive edema of the legs, ascites and hydrothorax. One normoblast was found per 100 nucleated cells. When the signs of heart failure disappeared, normoblasts were no longer seen. The patient died November 4, 1946. Autopsy showed hypertrophy of the heart, multiple emboli in both lungs and chronic glomerulonephritis.

Case 6. P. H., a 48 year old woman, was admitted on November 9, 1946, with mitral insufficiency and stenosis. She was dyspneic and cyanotic. No jaundice was present. There was gangrene of the tip of the nose and of both lower legs. No pulsations were felt in the left femoral and the right popliteal arteries. There was an infarct in the right lung. The blood count was as follows: leukocytes, 22,000; erythrocytes,

TABLE 1.—Blood Picture of S. W. (Case 2)

| | 5/10 | 5/11 | 5/13 | 5/14 | 5/16 | 5/18 | 5/21 |
|------------------------|-----------|------|------|--------|-----------|------|-----------|
| Leukocyte count..... | 12,500 | | | 12,700 | 12,400 | | 26,000 |
| Erythrocyte count..... | 5,250,000 | | | | 5,360,000 | | 5,310,000 |
| Hemoglobin..... | 77 | | | | 80 | | 82 |
| Normoblasts..... | 10 | 17 | 3 | | | | |
| Myelocytes..... | | | 1 | | | | |
| Metamyelocytes..... | 1 | 1 | | | | | |
| Stabs..... | 4 | 7 | 4 | 4 | 4 | 4 | 7 |
| Polynuclear cells..... | 82 | 81 | 86 | 88 | 89 | 79 | 84 |
| Monocytes..... | 1 | 2 | 1 | 4 | 3 | 1 | |
| Lymphocytes..... | 12 | 9 | 8 | 4 | 4 | 16 | 9 |

4,020,000; hemoglobin, 59; normoblasts, 1; stabs, 6; polynuclear cells, 80; eosinophiles, 1; monocytes, 3; lymphocytes, 10.

The patient died on November 16, 1946. The autopsy revealed a thrombus in the left auricle of the heart, an infarct of the lower lobe of the right lung, an embolic obturation of the left iliac artery and congestion of the liver.

Case 7. T. V., a 45 year old woman, was admitted on November 19, 1946. She had a history of chorea twenty-seven years previously. A diagnosis of mitral insufficiency and stenosis was made. The patient had auricular fibrillation and multiple infarctions of both lungs. There was gangrene of the tip of the nose and of the right foot; the latter was caused by an obturation of the right femoral artery. The patient was extremely dyspneic and deeply cyanotic. There was no jaundice. An electrocardiogram showed bundle branch block. The blood count was as follows: leukocytes, 2,800; erythrocytes, 4,500,000; hemoglobin, 78; normoblasts, 4; myelocytes, 1; metamyelocytes, 1; stabs, 1; polynuclear cells, 78; monocytes, 1; lymphocytes, 14.

The patient died on November 20, 1946. At autopsy the clinical diagnosis was confirmed: valvular heart disease, thrombosis of the right auricle, multiple infarctions in both lungs. A small amount of fluid was found in both pleural cavities. Cardiac cirrhosis of the liver with regeneration was also present.

Case 8. T. S., a 40 year old woman, was admitted for the first time on April 24, 1946, because of mitral insufficiency and stenosis, with auricular fibrillation. She had a greatly enlarged liver with ascites. The patient left the hospital on July 6, and was readmitted on August 30. On this second admission she was extremely dyspneic, cyanotic and subicteric. On October 1, a few normoblasts were found in the peripheral blood. The patient died on October 14, 1946. At autopsy, the mitral valve lesions were found;

in addition, she had a tricuspid stenosis and there was a thrombus in the right atrium. The liver was cirrhotic.

Case 9. J. D., a 63 year old woman, was admitted on November 13, 1946, with a diagnosis of mitral insufficiency and stenosis, with auricular fibrillation, and decompensation. She was slightly dyspneic, and deeply cyanotic. There was no jaundice. Infarctions were present in both lungs. The blood count was as follows: leukocytes, 5,600; erythrocytes, 4,300,000; hemoglobin, 88; normoblasts, 2; polynuclear cells, 66; eosinophiles, 2; monocytes, 5; lymphocytes, 27.

The patient died on February 5, 1947. The clinical diagnosis was confirmed at autopsy; there were multiple infarctions in both lungs.

DISCUSSION

The appearance of normoblasts in the blood of patients with congestive heart failure is mentioned only twice in the literature. The standard textbooks of diseases of the blood and of the heart describe the finding of normoblasts in the peripheral blood only in relation to congenital heart disease accompanied by cyanosis. In

TABLE 2a.—*Cabot's cases*

| Patient | Age | Clinical data | Hematologic data | Remarks |
|----------|-----|--------------------------------------|---|---------|
| Case I | 8 | Mitral disease; nephritis | Hb. 35, 2% normoblasts, leukocytes 220,000 | Died |
| Case II | 25 | Mitral disease; aortic insufficiency | Hg. 35, 1% normoblasts, leukocytes 13,000 | Died |
| Case III | 30 | Mitral disease; aortic insufficiency | 1st day: Hb. 10, 8% normoblasts, leukocytes 6,000 7th day: Hb. 10, 4% megaloblasts, 7% normoblasts, leukocytes 4,200 15th day: Hb. 15, leukocytes 10,400 20th day: Hb. 12.5, 1% megaloblasts, leukocytes 5,000 | ? |

acquired valvular disease, and in other forms of congestive heart failure, this sign seems to have been overlooked by the majority of investigators.

Cabot¹ mentions, in the fifth edition of this book, "The Clinical Examination of the Blood," three cases with decompensated mitral disease in which a severe anemia was present. The blood contained nucleated red cells. All three were chronic cases without active endocarditis. He does not give further details, and there are no data regarding the presence of infarcts in the lungs. Two of Cabot's patients died; the fate of the third is not mentioned.

In 1931, Frank and Hartmann² described six patients with various types of "right-sided heart failure" in whom normoblasts were found in the peripheral blood. All cases showed cyanosis and some degree of jaundice, and all of them died. The cases of Frank and Hartmann were not anemic.

Table 2 summarizes the authors' observations, and some of the data on the cases described by Cabot, and Frank and Hartmann. From this table it is evident that all the cases showed a very severe insufficiency of the heart. It is also clear that it was

TABLE 2b.—*Frank and Hartmann Cases*

| Patient | Age | Clinical data | Hematologic data | Remarks |
|----------|-----|---|--|--|
| Case I | 52 | Anginal complaints; dyspnea; pleural transudate; anasarca | Hb. 92, 7% erythroblasts | Autopsy: Coronary sclerosis; myodegeneration of heart; aneurism of left ventricle with thrombosis |
| Case II | 37 | Insufficiency and stenosis of mitral and aortic valves; insufficiency of tricuspid valve; decompensation; enlarged liver; slight jaundice; infarctions in lungs | Hb. 48, 1% macroblasts, 4% normoblasts, leukocytes 25,000 | Died. No autopsy |
| Case III | 39 | 2 years before admission, amputation of leg for gangrene caused by endarteritis obliterans; "pneumonia"; slight jaundice | Hb. 90, 4% erythroblasts, leukocytes 17,200 3 days later: Hb. 88, 14% erythroblasts, leukocytes 19,000 5 days later: Hb. 87, per 100 white cells. 175 erythroblasts, 14 macroblasts, leukocytes 14,800 | Autopsy: Thrombus in left ventricle and right atrium; arteriosclerosis and formation of a thrombus in right coronary artery; myocardial infarction. Thrombangiitis obliterans of abdominal aorta |
| Case IV | 54 | Coronary thrombosis; edema of legs; jaundice | Hb. 67, 4% erythroblasts, leukocytes 10,000 | Autopsy: Coronary thrombosis; aneurism of left ventricle of the heart with a large thrombus |
| Case V | 34 | Strong cyanosis; edema | 2nd day: Hb. 87 per 100 white cells, 64 erythroblasts, 6 macroblasts, leukocytes 21,400 3rd day: Hb. 87 per 100 white cells, 52 macroblasts, 25 erythroblasts, leukocytes 17,700 | Autopsy: Hypertrophy of right ventricle, thrombi in left ventricle, thrombosis of right pulmonary artery |
| Case VI | 42 | Insufficiency and stenosis of mitral valve; insufficiency of tricuspid valve; extreme cyanosis; extreme dyspnea; jaundice; edema | 5th day: Hb. 78, 2% normoblasts, leukocytes 10,500 11th day: 1% macroblasts, 2% erythroblasts 12th day: 7% erythroblasts, 3% macroblasts 13th day: 4% erythroblasts | Autopsy: Chronic endocarditis of mitral and tricuspid valve; atrophy and regeneration of liver; jaundice |

the decompensation and not any specific type of heart disease that caused the normoblastosis. Among the patients showing the phenomenon there were cases

TABLE 26.—*Authors' observations*

| Patient | Age | Clinical data | Hematologic data | Remarks |
|----------|-----|---|--|---|
| Case I | 34 | 6/12: Stenosis and insufficiency of mitral valve; auricular fibrillation; congestion of lungs; orthopnea; cyanosis; edema of legs. 6/15: Jaundice 6/17: Infarction in lung 6/30: Greatly enlarged liver 7/2: Died | 6/19: 5% normoblasts 6/21: 3% normoblasts, Hb. 59 6/25: 1% normoblasts 6/27: 1% normoblasts | Autopsy: Chronic pancarditis; hypertrophy of heart; thrombosis in both ears of heart; infarction in lung; edema of legs |
| Case II | 56 | 5/9: Insufficiency and stenosis of mitral valve; auricular fibrillation; enlarged liver; edema of legs; orthopnea; cyanosis; slight jaundice 5/13: Injection of salyrgan, followed by a large diuresis 5/22: Died | 5/10: Hb. 77, 10% normoblasts, leukocytes 12,500 5/11: 17% normoblasts 5/13: 4 hrs. after injection of salyrgan: 3% normoblasts. From 5/14 onward, no normoblasts | 5/12: Sternal puncture—bone marrow almost normal, 25% of nucleated cells are normoblasts and erythroblasts. Autopsy: Recurrent endocarditis of mitral valve; hypertrophy of heart; infarction in lungs; thrombosis of left heart-ear |
| Case III | 20 | 5/4: Insufficiency and stenosis of mitral valve; enlarged liver; edema of leg. 5/8: Died | 5/6: Hb. 61, no normoblasts, leukocytes 12,800 5/7: 7% normoblasts, leukocytes 17,000 | Autopsy: Verrucous endocarditis (mitral and aortic valves); thrombi in left heart-ear; congestion of the liver with fatty degeneration and regeneration |
| Case IV | 34 | 6/28: Insufficiency and stenosis of mitral valve; stenosis of aortic valves; enlarged liver; cyanosis; extreme dyspnea; slight jaundice; no edema 7/5: Died | Hb. 100, 3% normoblasts; leukocytes 7,000 | No autopsy |
| Case V | 71 | 3/4: Decompensated hypertension; cardiac asthma; extreme dyspnea and cyanosis; slight jaundice; hydrothorax; ascites; gangrene and edema of legs 3/10: Regression of decompensation 8/30: Many attacks of dyspnea; general condition poor 11/4: Died | 3/4: 1% normoblasts, leukocytes 1,300 3/10: no normoblasts | Autopsy: Hypertrophy of heart; emboli of lungs; chronic nephritis |

TABLE 2c.—Continued

| Patient | Age | Clinical data | Hematologic data | Remarks |
|-----------|-----|---|---|---|
| Case VI | 48 | 11/9: Insufficiency and stenosis of mitral valve; dyspnea and cyanosis; gangrene of tip of nose and both legs below knee; obturated left femoral artery and right popliteal artery; infarction in lung 11/16: Died | 11/9: Hb. 59, 1% normoblasts, leukocytes 22,000 | Autopsy: Chronic endocarditis; stenosis of mitral valve; thrombus in left heart-ear; embolic obturation of left iliac artery; infarction in lung; congestion of liver |
| Case VII | 45 | 11/19: Insufficiency and stenosis of mitral valve; auricular fibrillation; decompensation of heart; infarction in lung; gangrene of tip of nose and of right foot; extreme dyspnea and extreme cyanosis; bundle-branch block 11/20: Died | 11/19: Hb. 78, 4% normoblasts, leukocytes 2,800 | Autopsy: Chronic endocarditis; stenosis of mitral valve; thrombus in right auricle of heart; cardiac cirrhosis of liver with regeneration; infarctions in lungs |
| Case VIII | 40 | 4/24: Insufficiency and stenosis of mitral valve; auricular fibrillation; cirrhosis of liver; dyspnea, cyanosis; slight jaundice 10/14: Died | 10/1: Hb. 78, 1% normoblasts, leukocytes 10,600 | Autopsy: Chronic endocarditis of mitral, aortic and tricuspid valves; thrombus in right atrium; cirrhosis of liver |
| Case IX | 63 | 11/13: Insufficiency and stenosis of mitral valve; auricular fibrillation; decompensation of heart; slight dyspnea; extreme cyanosis; infarction of lungs 12/12: General condition poor 2/5 of next year: Died | 11/15: Hb. 88, 2% normoblasts, leukocytes 5,600 | Autopsy: Chronic endocarditis of mitral valve; infarctions in lungs |

of decompensated valvular heart disease as well as cases of heart failure in hypertension or in coronary thrombosis. In Cabot's cases it might be argued that the normoblastosis was a result of the anemia rather than of heart disease, but in all other cases anemia played no role. The predominant factor in these nonanemic cases seemed to be a marked diminution of the oxygenation of the blood in the lungs, as evidenced during life by severe cyanosis. After death this was explained

in many cases by the finding of a thrombus in one of the auricles or ventricles of the heart and/or infarcts of the lungs. Three of Frank and Hartmann's cases had myocardial infarction with secondary formation of a mural thrombus in the left ventricle. One patient had a thrombosis of the right pulmonary artery. Two patients had severe decompensation as a result of mitral stenosis. In all our cases, thrombosis or embolism inside the heart or pulmonary arteries was found; eight times this was verified at autopsy. Apart from thrombi and emboli in the heart and lungs, the postmortem examinations showed no changes which could have caused the normoblastosis. Fatty degeneration of the liver was regularly present, cirrhosis and regeneration of bile ducts were sometimes prominent features. No extramedullary blood formation was found.

Taking into consideration Cabot's anemic cases, the conclusion is justified that peripheral normoblastosis occurs especially in those patients with heart failure who

TABLE 3

| No. | Age | Diagnosis | Normoblasts | Duration of life after first detection of normoblasts | Cyanosis | Dyspnea | Thrombi in heart | Infarcts in lungs |
|-----|-----|------------------------------------|-----------------|---|----------|---------|------------------|-------------------|
| | | | <i>per cent</i> | | | | | |
| 1 | 34 | Mitral disease | 5 | 13 days | + | ++ | + | + |
| 2 | 56 | Mitral disease | 10 | 12 days | + | + | + | + |
| 3 | 20 | Mitral disease | 7 | 1 day | - | + | + | - |
| 4 | 34 | Mitral disease; aortic stenosis | 3 | 7 days | + | ++ | ? | - |
| 5 | 71 | Decompensated hypertension | 1 | 10 months | ++ | ++ | - | + |
| 6 | 48 | Mitral disease | 1 | 7 days | + | + | + | + |
| 7 | 45 | Mitral disease | 4 | 1 day | ++ | ++ | + | + |
| 8 | 40 | Mitral disease; tricuspid stenosis | 1 | 13 days | + | + | + | - |
| 9 | 63 | Mitral disease | 2 | 3 months | ++ | ++ | - | + |

are either markedly cyanotic or strongly anemic, so that it appears as if anoxia is the most important cause of the normoblastosis. We are inclined, therefore, to regard the occurrence of normoblasts in the peripheral blood as an indication of an attempt on the part of the body to increase the number of circulating red cells as a result of the stimulus which anoxia exerts on the blood-forming apparatus. Apparently, normoblasts appear in the peripheral blood only when anoxia is extreme, in a degree that occurs only in the very severe forms of heart failure.

Decompensation alone does not seem to produce the phenomenon; it requires the presence of thrombi and/or infarcts in the lesser circulation. This is probably the reason why Walter, Blumgart and Volk³ did not find normoblasts in the blood in their cases of congestive heart failure, as they excluded all cases with complications from their study. They noted, however, that there was an increase in reticulocytes in the peripheral blood in heart failure, which disappeared when the condition improved.

The presence of normoblasts in the peripheral blood in heart failure thus seems to indicate that the condition is complicated by mural thrombosis in the heart o

pulmonary artery, or by pulmonary emboli, or a combination of these conditions. Hence, it is easily understood why peripheral normoblastosis is a sign of such poor prognosis.

In some, but not in all cases, the normoblastosis was accompanied by a leukocytosis and (or) the presence of young precursors of the myeloid group. Some cases showed not only a peripheral normoblastosis but a distinct leuko-erythroblastic blood picture. This was most pronounced in one of Frank and Hartmann's patients who had a total white count of 21,000 and not less than 70 per cent nucleated red cells.

SUMMARY

The authors recommend the search for normoblasts in the blood of patients with severe heart failure. When normoblasts are found, a marked interference with the oxygenation of the blood, either by pulmonary infarcts or thrombi inside the heart, is most likely to be present. It seems justifiable to consider the prognosis as very grave in these cases. This rule proved to hold even in those cases where, concomitant with an improvement in the heart failure, the normoblasts disappeared temporarily from the peripheral blood.

REFERENCES

- ¹ CABOT, R. C.: *A Guide to the Clinical Examination of the Blood*. 5th edition, New York, 1904.
- ² FRANK, E., AND HARTMANN, E.: Akute Makrocytär-Erythroblastische Blutbilder ohne Anemie bei Hochgradige Schwäche der Rechten Herzkammer. *Klin. Wchnschr.* 10: 15, 1931.
- ³ WALTER, J. V., BLUMGART, H. L., AND VOLK, M. C.: Studies of the blood in congestive heart failure. *Arch. Int. Med.*, 66: 1230, 1940.