The Macrocytosis of Hepatic Disease. II. Thick Macrocytosis

By John Bingham

The macrocytosis of hepatic disease is a baffling and intriguing blood disorder. A macrocytic blood picture is one in which the mean cell diameter of the erythrocytes is 7.60 microns or greater (by the method of measurement used in this study). Of 222 patients suffering from a variety of hepatic diseases, 137 patients (62 per cent) had a macrocytic blood picture. The macrocytic erythrocytes of these patients were of three types: a thin macrocyte, a thick macrocyte, and a target macrocyte. Because the etiology and morphologic characteristics of these three macrocytes were different, three macrocytic blood pictures have been delineated and termed thin macrocytosis, target macrocytosis and thick macrocytosis.

Thin macrocytosis is a condition in which all the macrocytes are thin. Because these cells are flattened their diameter is increased but their volume is unchanged. Target macrocytosis is a condition in which 10 per cent or more of the thin macrocytes have undergone target cell changes. Thick macrocytosis is a condition in which both thick and thin macrocytes are present, the thick macrocytes being present in sufficient numbers to raise the mean cell volume to 110 cubic microns or more. The patients with thick macrocytosis had free hydrochloric acid in the gastric juice.

Of the 137 patients with macrocytosis, 81 patients had thin macrocytosis, 39 patients had target macrocytosis and 17 patients had thick macrocytosis.

Method

The technical methods used in this study have been described in detail elsewhere and will be briefly mentioned. Normal measurements are shown in table 4. The mean cell diameter of the erythrocytes was measured by projecting specially stained blood films onto paper at a magnification of 2000 diameters. The outlines of 200 cells, selected at random, were traced on paper, the diameters measured and the mean cell diameter and standard deviation calculated. Anisocytosis was expressed as the standard deviation of the mean cell diameter. Mean cell thickness was calculated according to the volume/area formula:

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This work was supported by a grant from the National Research Council of Canada.

Submitted Apr. 2, 1959; accepted for publication June 28, 1959.
Bone Marrow and Blood

Bone Marrow

In order to understand the terminology used to discuss the bone marrow of thick macrocytosis it is necessary first to review briefly the bone marrow found in hepatic disease generally.

Iliac marrow aspirations of 87 patients of the total group of 222 patients with hepatic diseases were examined. In these marrow films four separate lines of erythrocytic maturation were observed: normoblastic (15 patients); macronormoblastic (60 patients); atypical megaloblastic (7 patients); megaloblastic (5 patients). The various stages through which a maturing erythrocyte passes are indicated by the prefixes: pro, basophilic and polychromatic. Thus the stages in normoblastic maturation would be pronormoblast, basophilic normoblast and polychromatic normoblast. For macronormoblastic maturation they would be promacronormoblast, basophilic macronormoblast and polychromatic macronormoblast. The stages in atypical megaloblastic and megaloblastic maturation are designated in the same way.

Normoblastic maturation.—This was the normal line of erythrocyte maturation (fig. 1A–D).

Macronormoblastic maturation. Macronormoblastic maturation differed from the normoblastic maturation in both the size and structure of the cell. At all stages of development both the cell and its nucleus were larger than normal. The structure of the nucleus was less compact than was the nucleus of normoblastic maturation. This difference in compactness was best seen in the polychromatic staining cells in which the chromatin was in distinct and widely separated wedges in contrast to the pyknotic nucleus of normal maturation. (fig. 1E–H).

Atypical megaloblastic maturation.—This type of maturation has been described by Jones.² It has been called “intermediate megaloblastic erythropoiesis” by others.³ Compared to megaloblastic maturation to be described, the nuclei were more centrally placed and the threads of chromatin coarser. However, the meshlike structure of the nucleus of the megaloblast was present and there was no clumping of chromatin. The open nuclei persisted into the polychromatic stage and only in the orthochromatic stage did pyknotic nuclei appear (fig. 1I–L).

Megaloblastic maturation.—In this line of erythrocyte maturation the shape of developing erythrocytes tended to be irregular. The amount of cytoplasm was increased proportionately to the nucleus and the nucleus lay eccentrically. The nuclear structure was open and lacy with no hint of clumped chromatin. The threads of chromatin were fine and the nuclei resembled a fine sieve of gossamer-thin mesh. Like a sieve the nucleus appeared convex and stood out from the cytoplasm (fig. 1M–P).

Bone marrow aspirations were studied in 15 of 17 patients with thick macrocytosis. In six patients erythroid maturation was macronormoblastic, in four it was atypical megaloblastic, and in five it was megaloblastic. Bone marrow aspirations were not obtained from two patients, but from the characteristics of their peripheral blood they probably had macronormoblastic maturation.

Blood

The blood picture of the patients with thick macrocytosis varied with each of the three types of erythroid maturation present. The measurements of the erythrocytes accompanying each of these types of maturation are shown in table 1. The blood of the five patients with megaloblastic maturation was characterized by severe...
Fig. 1.—Types of erythrocyte maturation in bone marrows of patients with hepatic disease. *Vertical columns* show lines of development: A–D, normoblastic; E–H, macronormoblastic; I–L, atypical megaloblastic; M–P, megaloblastic.

*Horizontal columns* show stages of development: A, E, I, M, prostage; B, F, J, N, basophilic stage; C, G, K, O, polychromatic (early) stage; D, H, L, P, polychromatic (late) stage. (× 1700).

anemia (erythrocyte count below 2 million), a high mean cell volume and by a bizarre blood picture consisting of large, obese macrocytes whose shapes were round or oval, microcytes, poikilocytes, marked anisocytosis and giant polymorphonuclear leukocytes. Thin macrocytes and even normocytes arising from macronormoblastic and normoblastic lines of maturation were also seen in the blood films.

The blood of the four patients with atypical megaloblastic maturation resembled that just described except that it was less abnormal. The erythrocyte count was higher, mean
Table 1.—Types of Erythrocyte Maturation and Mean Erythrocyte Counts and Measurements of Each Type in Patients with Thick Macrocytosis

<table>
<thead>
<tr>
<th>Type of erythropoiesis</th>
<th>No. of patients</th>
<th>MCD</th>
<th>MCV (μ³)</th>
<th>Anisocytosis (μ)</th>
<th>RBC count (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macronormoblastic</td>
<td>6</td>
<td>8.10</td>
<td>113</td>
<td>0.62</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(8.01-8.35)</td>
<td>(111-120)</td>
<td>(0.55-0.77)</td>
<td>(2.5-4.4)</td>
</tr>
<tr>
<td>Atypical megaloblastic</td>
<td>4</td>
<td>8.12</td>
<td>117</td>
<td>0.72</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7.81-8.29)</td>
<td>(110-127)</td>
<td>(0.62-0.78)</td>
<td>(2.6-3.9)</td>
</tr>
<tr>
<td>Megaloblastic</td>
<td>5</td>
<td>8.41</td>
<td>136</td>
<td>1.04</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(8.03-8.91)</td>
<td>(115-160)</td>
<td>(0.79-1.25)</td>
<td>(1.3-2.0)</td>
</tr>
</tbody>
</table>

cell volume lower and the blood picture less bizarre. Abnormalities of the white cell could still be seen.

The blood picture of the six patients with macronormoblastic maturation and of the two patients in whom marrow films were not obtained was even less abnormal. The predominant macrocyte was the thin macrocyte, but sufficient thick macrocytes were present to raise the mean cell volume to 110 cubic microns or more. The shape of the macrocytes was round. Poikilocytes were rare and the leukocytes normal.

**Etiology**

**Type of Hepatic Disease**

The frequency of thick macrocytosis in the various types of hepatic disease is shown in table 2.

Thick macrocytosis occurred only in patients with cirrhosis—Laennec’s, postnecrotic or biliary. Fifteen of the 17 patients with thick macrocytosis suffered from Laennec’s cirrhosis and two from subacute yellow atrophy (postnecrotic cirrhosis). Thick macrocytosis was also found in the blood of three patients with biliary cirrhosis and one other patient with subacute yellow atrophy. However, as these last four patients also had target macrocytosis, they will be described with this disorder. Thick macrocytosis did not occur in patients with hepatitis, primary or secondary cancer of the liver or of biliary passages, obstructive jaundice due to cholecodocholithiasis, or to variety of benign noncirrhotic disorders of the liver.

**Dietary Deficiency**

In an attempt to determine why some patients with cirrhosis developed thick macrocytosis and others did not, studies were carried out to determine the relationship between the presence of thick macrocytosis and the following: the severity of the hepatic disease, the various clinical signs of hepatic disease, the biochemical tests of hepatic function and the diet. The only positive correlation found was with diet. Thick macrocytosis occurred in two groups of patients with dietary deficiency; (a) those who had a long history of severe food deprivation prior to admission to hospital and (b) patients with subacute yellow atrophy who, without eating, lingered for long periods between life and death.

The relationship between diet and thick macrocytosis was demonstrated in a group of 35 patients suffering from Laennec’s cirrhosis and chronic alcoholism in whom an accurate assessment of dietary intake was made. A dietary and drinking index (DDI) was devised in which the nutritional value of
Table 2.—The Frequency of Thick Macrocytosis in the Various Types of Hepatic Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of patients</th>
<th>No. of patients with thick macrocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laennec's cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Alcoholic</td>
<td>96</td>
<td>14</td>
</tr>
<tr>
<td>B. Nonalcoholic</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Subacute yellow atrophy (postnecrotic cirrhosis)</td>
<td>7</td>
<td>2*</td>
</tr>
<tr>
<td>Biliary cirrhosis</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoma of liver, pancreas or biliary tract</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Dialedocholithiasis</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Other benign obstruction</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous hepatic disorders</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>222</strong></td>
<td><strong>17</strong></td>
</tr>
</tbody>
</table>

*One other patient with subacute yellow atrophy had both thick and target macrocytosis and has been included under the latter.

†Three other patients with biliary cirrhosis had both thick and target macrocytosis and have been included under the latter.

Table 3.—Relationship Between Dietary Deficiency and the Type of Macrocytosis

<table>
<thead>
<tr>
<th>DDI</th>
<th>Thin macrocytosis (no. patients)</th>
<th>Target macrocytosis (no. patients)</th>
<th>Thick macrocytosis (no. patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9–18</td>
<td>12</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>27–81</td>
<td>11</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

The diet and the amount of alcohol consumed were estimated (table 3). The quantity of alcohol drunk, the duration of drinking, the inadequacy of the diet, and the duration of the poor diet were graded 1, 2 and 3. Multiplication of the scores for the quantity of alcohol and the duration of drinking gave a drinking factor. Multiplication of the scores for the diet and duration of the diet gave a dietary factor. The drinking factor multiplied by the dietary factor gave the dietary and drinking index (DDI). An index of 18 or less indicated minimal dietary deficiency (50 per cent of normal diet) and minimal alcohol (less than 6 ounces of distilled spirits or equivalent daily). An index above 18 indicating increasing dietary deficiency and alcohol excess, with 81 indicating maximal dietary deficiency and alcohol excess. From inspection of table 3 it is apparent the macrocytosis of the thick type occurred only in those patients with severe dietary deficiency or alcohol excess, whereas in the other two types of macrocytosis dietary deficiency and alcohol excess were unrelated to macrocytosis.

Concentrated liver extract (40 units or more weekly by parenteral injection) was administered to five patients with the following results:
Patient 1. Initial erythrocyte count was 1.7 million; the reticulocytes rose in 14 days to 30 per cent.

Patient 2. Initial erythrocyte count was 2.7 million; the reticulocytes rose in 7 days to 16.4 per cent.

Patient 3. Initial erythrocyte count was 1.3 million; the reticulocytes rose in 9 days to 30 per cent.

Patient 4. Initial erythrocyte count, 2.2 million. Liver was administered after the blood counts had started to improve from the food alone. There was no rise in reticulocyte count but there was a slight drop in cell diameter.

Patient 5. When liver was administered a reticulocyte response to food had already occurred. A further slight rise in the reticulocyte count followed administration of the liver.

Vitamin B₁₂ (100 micrograms or more weekly by parenteral injection) was administered to three patients.

Patient 1. The erythrocyte count rose from 2.0 million to 3.7 million in 8 weeks but the cell diameter increased from 8.43 microns to 9.27 microns in the same period.

Patient 2. The erythrocyte count rose from 3.2 to only 3.7 million in 9 weeks and there was no significant decrease in cell diameter during this period (8.24 microns to 8.01 microns). There was no rise in reticulocyte count.

Patient 3. Initial erythrocyte count of 1.9 million; the reticulocytes rose in 5 days to only 6.5 per cent.

The ingestion of a normal hospital diet without drugs produced reticulocyte responses of 12, 12 and 11 per cent, respectively, in patients whose erythrocyte counts were 1.6 million, 2.6 million and 1.3 million.

The hematologic responses to liver, vitamin B₁₂ and diet were not those expected in patients who had a primary deficiency in "liver factor" such as occurs in pernicious anemia. When liver was administered the peak reticulocyte responses were delayed and they fell off gradually; with the administration of vitamin B₁₂ there was a poor reticulocyte response and no decrease in macrocytosis; with diet alone there was a satisfactory rise in reticulocytes and disappearance of thick macrocytosis.

Comparison with Pernicious Anemia

In pernicious anemia the morphologic characteristics of the blood and bone marrow vary with the erythrocyte count. When the erythrocyte count is low (i.e., 2 million or less) the classic blood picture and megaloblastic marrow are present. With a higher erythrocyte count (2 to 3.5 million), the blood picture is still macrocytic but not as bizarre; the mean cell volume is lower although still above 110 cubic microns, and the bone marrow picture is atypical megaloblastic. When the erythrocyte count is above 3.5 million, as found in patients who have received inadequate treatment (i.e., sufficient to correct the anemia but not to eliminate macrocytosis) or in patients in early relapse, the blood picture is again different. These patients have broad, thin macrocytes, very little anisocytosis, a mean cell volume below 110 cubic microns and a macronormoblastic marrow.
A comparison was made between blood and bone marrow films of patients with thick macrocytosis of hepatic disease and of patients with pernicious anemia whose mean cell volume was 110 cubic microns or more. Had the films been unlabeled it would not have been possible to differentiate the two disorders. Both sets of films had bizarre blood pictures with thick, obese macrocytes, microcytes, poikilocytes, marked anisocytosis, giant leukocytes, and, depending on the severity of the anemia, erythrocyte maturation of the macronormoblastic, atypical megaloblastic or megaloblastic type. The average diameter and volume of the erythrocytes were the same (table 4). However, when the films were selected according to the same erythrocyte levels and compared, a distinct difference was found. At the same erythrocyte level, patients with pernicious anemia showed greater immaturity in the blood and bone marrow than did patients with hepatic disease. For instance, the blood and bone marrow of a patient with pernicious anemia at 2 million erythrocyte count was comparable to that of a patient with hepatic disease at 1.5 million erythrocyte count. One expression of this difference capable of measurement was anisocytosis. The greater degree of anisocytosis in pernicious anemia compared to hepatic disease is shown in figure 2.

No patient with hepatic disease had the extreme blood and bone marrow changes found in a patient with pernicious anemia and a very low erythrocyte count, such as 1 million or less.

The blood and bone marrows of patients with the thin macrocytosis of hepatic disease (described previously) were also compared with the blood and bone marrows of patients with pernicious anemia who were either in early relapse, or who had received inadequate treatment and who had thin macrocytes and a mean cell volume below 110 cubic microns. On inspection of individual unselected blood and marrow films no difference could be detected between the two. Both had thin macrocytes, moderate anisocytosis, a normal or only slightly elevated mean cell volume, no change in leukocytes and macronormoblastic maturation. The average erythrocyte diameter and volume of the two disorders were approximately the same (table 4). However, when the blood and bone marrow films of the two disorders were compared at the same level of erythrocyte count, once again the greater immaturity of the marrow of pernicious anemia was seen (fig. 2).

DISCUSSION

The cause of thick macrocytosis of hepatic disease appears to be a dietary factor. The disorder developed only in patients whose type of hepatic disease was accompanied by dietary deficiency. It was seen in patients with Laennec's cirrhosis and alcoholism for whom alcohol had been substituted for other food and in patients with subacute yellow atrophy who lingered for long periods between life and death without eating.

The missing dietary factor causing thick macrocytosis was not vitamin B12. The administration of large doses of liver produced only suboptimal response. Folic acid was not tested but Jandl has reported a hematopoietic response to folic acid in four patients with this disorder. However, no figures were given.
A dietary deficiency is not the only factor involved in the etiology of thick macrocytosis; some patients with severe dietary deficiency do not develop thick macrocytosis. In searching for the explanation of this phenomenon, the importance of pre-existing thin macrocytosis was recognized. It appears that a patient who has already developed thin macrocytosis is predisposed to develop thick macrocytosis should a sufficiently severe dietary deficiency occur. If thin macrocytosis has not developed, the same degree of dietary deficiency might produce cirrhosis with resultant thin macrocytosis.
Table 4.—Erythrocyte Measurements and Counts of Thick and Thin Macrocytosis of Hepatic Disease and of Pernicious Anemia

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C*</th>
<th>D†</th>
<th>E‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cell diam. (μ)</td>
<td>7.14</td>
<td>8.17</td>
<td>7.94</td>
<td>8.00</td>
<td>7.79</td>
</tr>
<tr>
<td></td>
<td>(6.80-7.49)</td>
<td>(7.60-8.91)</td>
<td>(7.60-8.90)</td>
<td>(7.60-8.39)</td>
<td>(7.61-8.16)</td>
</tr>
<tr>
<td>Mean cell thickness (μ)</td>
<td>2.30</td>
<td>2.27</td>
<td>2.01</td>
<td>2.42</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td>(1.9-2.6)</td>
<td>(2.0-2.7)</td>
<td>(1.6-2.3)</td>
<td>(2.2-2.6)</td>
<td>(1.8-2.1)</td>
</tr>
<tr>
<td>Anisocytosis (μ)</td>
<td>0.45</td>
<td>0.85</td>
<td>0.60</td>
<td>0.96</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>(0.34-0.56)</td>
<td>(0.55-1.25)</td>
<td>(0.40-1.07)</td>
<td>(0.76-1.18)</td>
<td>(0.53-0.78)</td>
</tr>
<tr>
<td>Mean cell volume (μ³)</td>
<td>95</td>
<td>123</td>
<td>99</td>
<td>122</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>(96-100)</td>
<td>(110-160)</td>
<td>(75-110)</td>
<td>(110-140)</td>
<td>(85-110)</td>
</tr>
<tr>
<td>Mean erythrocyte count (millions)</td>
<td>4.80</td>
<td>2.67</td>
<td>3.62</td>
<td>1.79</td>
<td>4.65</td>
</tr>
<tr>
<td></td>
<td>(4.10-5.60)</td>
<td>(2.74-4.40)</td>
<td>(1.60-5.40)</td>
<td>(1.36-3.01)</td>
<td>(4.24-5.11)</td>
</tr>
</tbody>
</table>

A. Normal erythrocytes (22 healthy subjects); B, thick macrocytosis of hepatic disease (17 patients); C, thin macrocytosis of hepatic disease (81 patients); D, thick macrocytosis of pernicious anemia (18 patients); E, thin macrocytosis of pernicious anemia (14 patients).

*The measurements of the 81 patients with hepatic disease and thin macrocytosis were taken from a previous report.†

†The measurements of 14 of the 18 patients with thick macrocytosis of pernicious anemia were obtained from Mogensen’s monograph.‡

‡The measurements of the 14 patients with thin macrocytosis of pernicious anemia were kindly supplied by Dr. J. G. Watt of Toronto.

All the measurements were made by the same technic.

The etiology and characteristics of thin macrocytosis have been described in detail elsewhere. Briefly, thin macrocytosis, produced by a macronormoblastic type of erythrocyte maturation, develops in about one-half of patients with damage to hepatic parenchymal cells. The type of hepatic disease causing this damage is unimportant, provided parenchymal cells are damaged. The disorder is seen in cirrhosis, hepatitis, neoplastic and obstructive types of hepatic disease. It does not occur in patients with fatty liver or with simple obstructive jaundice of short duration in which hepatic cells are not damaged. Thin macrocytosis is not corrected by the administration of vitamin B₁₂, liver, folic acid or a normal diet, and it only disappears with the healing of the underlying hepatic disease.

The two stages in the development of thick macrocytosis may be summarized as follows:

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Development of Thick Macrocytosis

Hepatic parenchymal cell damage from any cause
↓
Macronormoblastic maturation
↓
Thin macrocytosis
+ Severe protein deficiency
↓
Atypical megaloblastic or megaloblastic maturation
↓
Thick macrocytosis
```

There is another macrocytic anemia which has many features in common with the macrocytosis of hepatic disease—the anemia of protein malnutrition in African natives. From the published reports two types of macrocytic anemia may be distinguished.
The first type has hepatosplenomegaly, thin macrocytes, macronormoblastic marrow maturation and absence of response to folic acid, liver or vitamin B₁₂. This type seems to be the same as the thin macrocytosis of hepatic disease described in an earlier report.¹

The second type of macrocytic anemia in Africans has thick macrocytes, megaloblastic marrow maturation and disappears with the ingestion of a good diet, folic acid, liver³ and vitamin B₁₂.⁶ It seems to be the same as the thick macrocytosis of hepatic disease described in this report except for the response to vitamin B₁₂.

**Conclusions**

1. Three types of macrocytic blood pictures have been found in patients with hepatic disease. These have been called thin, thick and target macrocytosis.

2. Thick macrocytosis, the subject of this report, was the least common of the three types. It was found in 17 of 222 patients suffering from a variety of hepatic disorders, of whom 137 had a macrocytic blood picture.

3. The blood and bone marrow of patients with thick macrocytosis closely resembled, but were not identical to, those of pernicious anemia. They appeared to be the same as those occurring in protein malnutrition.

4. The thick macrocytosis of hepatic disease was found only in patients with cirrhosis. It was caused by protein starvation in patients already susceptible by reason of pre-existing hepatic parenchymal cell disease and thin macrocytosis. The course of development was progressively as follows: hepatic parenchymal cell disease, macronormoblastic type of erythrocyte maturation, thin macrocytosis, severe protein malnutrition, atypical megaloblastic type of erythrocyte maturation, and thick macrocytosis.

**Summario in Interlingua**

1. Tres typos de macrocytosis esseva notate in patientes con morbo hepatic. Ilios esseva designate como leptomacrocytosis, pycnomacrocytosis, e macrocytosis a cellulæs de oculo de ave.

2. Pycnomacrocytosis, le thema del presente reporto, esseva le minus commun del tres typos. Ilo esseva incontrate in 17 ex 222 patientes con diverse disorders hepatic. Macrocytosis (del un o del altere typo) esseva presente in 137 del 222 patientes.

3. Le sanguine e le medulla ossee de patientes con pycnomacrocytosis esseva muto simile sed non idenit a illos vidite in patientes con anemia perniciose. Ilo esseva esser le mesmes como illos occurrente in malnutrition proteinic.

4. Le pycnomacrocytosis de morbo hepatic esseva incontrate solmente in patientes con cirrhosis. Ilo esseva causat per malnutrition proteinic in patientes predisponite per le pre-existentia de morbo de cellulæs parenchymal hepatic e leptomacrocytosis. Le curso del disveloppamento del morbo sequava iste ordine de stadios: Morbo de cellulæs parenchymal hepatic, typo macronormoblastic de maturation erythrocytic, leptomacrocytosis, sever malnutrition proteinic, typo megaloblastic atypic de maturation erythrocytic, e pycnomacrocytosis.
REFERENCES

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JOHN BINGHAM