

Myeloid Metaplasia of Spleen in Hookworm Disease (*)

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(With plates LVI–LVIII)

DISCUSSION

The only uniform verification was that of the absence of myeloid metaplasia in liver. In spleen, proliferation of connective tissue from aged individuals was found, in four cases (Cases 5, 8, 9 and 10); presence of pigment in three cases (Cases 4, 6 and 8), in one of which iron had been administered one day before his death, and same may have been given in the other two. In the majority of cases, a complete absence of pigments in splenic pulps was observed, thus confirming what already was known about the slight blood destruction in ankylostomotic anaemia. With the exception of two cases (Cases 3 and 4), a numerical increase, at times a remarkable one, of *plasmazellen* was observed. The presence of haemocytogenic cells, normally not to be met with in spleen, was verified in various cases. We observed megakaryocytes in Cases 1, 2, 5 and 9; numerous eosinophilous myelocytes in Cases 1 and 5, and erythroblasts of advanced evolutionary stage in almost all cases (with the exception of Cases 8, 9 and 10). In no case was the presence of basophilous or polychromatic erythroblasts actually ascertained.

There is no general consensus of opinion about volume changes of spleen in ankylostomiasis. Some authors report a slight enlargement, whilst others state this organ is of normal volume in this disease. The findings here presented, gathered from 23 cases of ankylostomiasis, without association of any other disease, show that, on an average, spleen of adults does not appear to be increased in weight. Yet, such is not the case in individuals under 15 years, in which this organ is found to be evidently enlarged.

We were not given the chance of examining the spleen of young individuals, save one case alone, but we believe it to be most likely that in them this organ always shows myeloid metaplasia. We are in-

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duced in this belief by the fact that only in individuals of over 50 years did we not meet with this type of regeneration. It is of evidence that such regression to the fetal stage will be met with more easily in children, a circumstance which suggests, for the explanation of the spleen enlargement observed in them, the existence of an intense proliferation of medullary cells.

These verifications in the haemolyticopoietic organs in ankylostomiasis, seemingly common to all hypochromic and iron-sensitive anaemias, have a great elucidative significance, not only for the pathogenesis of these anaemias but also for the process of blood regeneration due to treatment. As the clear understanding of this relationship will, most likely, disclose new ways for more detailed investigations, we will give a short account of all these facts as follows.

As it is known, the elements on the red series of the haematopoietic organs, in their normal state, are not excited by an exaggerated administration of substances acting on them. In the same manner, in pernicious anaemia the administration of haematopoietic principles of liver, or in hypochromic anaemias the administration of iron salts, after normalizing the blood figures, does not occasion an exaggeration in the production of blood cells and haemoglobin. The excitation of these organs is due essentially to deficiency of substances, like we can observe in acute hemorrhages, where the outflow of blood from the organism produces, in normal cases, a strong haemogenic regeneration.

For the better understanding of the facts observed in nature, concerning blood disturbances, it must be admitted that the haemocytopoietic organs are normally under a constant checking action of determinate substance existing in the organism. As soon as the quantities of these substances decrease, the haematopoietic organs immediately proliferate, and they proliferate the more in accordance with the greater quantity of substances that is eliminated from the economy. The larger the hemorrhage, the larger the regeneration, and the greater the severity of anaemia of a deficiency cause, (it is observed in hookworm disease at least) and also the greater the hyperplasia of immature medullary elements.

As far as our question is concerned, i. e. iron deficiency, the hyperplasia of the haematopoietic organs seems to proceed in a specific manner as compared with the proliferated cellular type. In bone marrow there is a marked predominance of the normoblast over the other cells. Sabin and Doan (11) verified that in normal bone marrow from rabbits there are to be found normally 70 % of granulocytes, 25 % of nucleated red cells and 5 % of other varieties. These authors verified more-

over, among the elements of the red series, that normoblasts exist in the percentage of 69 %, or, when considered in proportion to all other medullary cells, of 17 %. In bone marrow of hookworm disease, when the medullary eosinophilous reaction is not very intense, there is a percentage of normoblasts clearly above 50 %, just the same as may be easily verified by the photographic documentation of an earlier paper of ours (10). Consequently, there is an increase from 17 % to 50 % or approximately of 30 % of normoblasts in ankylostomotic marrow.

Morphologically, the normoblast met with at such great extent in the haemoliticpoietic organs of hookworm patients, closely resembles the normal normoblast. The fundamental change of the disease seems to take place in the following evolutionary stage for the formation of the young red cell (reticulocyte). Witts (12) already remarks that iron is, most likely, an indispensable substance for the process of normal maturation from normoblast to erythrocyte. We believe it is so indeed, and we hope to give in the future a more direct contribution to this matter.

Normoblastosis, called forth by iron deficiency, is a fact of constant observation. In man, as Witts foreshadows it, normoblastosis is always present in all iron-sensitive anaemias and, lately, we may draw the same conclusion from the paper of Keith and Miller (13), on nutrition anaemia of rats. These authors say: — « Hematopoietic 'centers' appear in the liver and spleen, while fat tends to disappear from bone marrow, being replaced by erythroblastic tissue ».

As these authors do not describe any anomaly in the erythroblastic tissues examined, we believe that the normoblasts, as far as their number is concerned, predominate over the other cells of the red series, just the same as it is observed in normal rabbits.

We previously reported, and here we insist upon, the point regarding the significance of this fact for the haemoglobin metabolism. The strong normoblastic regeneration in this anaemia indicates, first and foremost, a remarkable quantity of haemoglobin synthesis. Iron deficiency in the organism seems not to exert any influence upon the formation of blood pigment, but it does exert its influence upon a process of a particular oxydation in the normoblasts. It is noted in other anaemias, and we also verified it in hookworm disease, that there is an exaggerated elimination of uric acid in the urine, during the period of blood regeneration due to iron administration.

The maturation process of the normoblast is nothing else but the disappearance, or rather the transformation, of the nucleus of this cell. One of the final products of nucleine is uric acid, and this transformation is essentially an oxydation. This deficiency of oxydation

conveys a disturbance in the metabolism of haemoglobin, since the normoblasts, in spite of their exaggerated proliferation, are retained in spleen and bone marrow. The neoformation of red cells in hookworm disease, in proportion to the progression of anaemia, proceeds in a manner qualitatively insufficient until it reaches the degenerative features which characterise these cells, when observed in the peripheral blood circulation in this anaemia. Therefrom results the paradoxical appearance of a bone marrow rich in erythroblasts with haemoglobin and, on the other hand, blood with red cells (at times in normal ratio), poor in this substance.

The verification, even a superficial one, of a post mortem examination in a case of ankylostomiasis is a very curious fact indeed. On the one hand, we note blood poor in respiratory pigment which, on account of an oxygenation deficiency of the tissues, conveys a degeneration of nearly all organs, whilst, on the other hand, we observe in spleen and mainly in the bones this pigment there retained in great abundance.

Owing to these findings, the stupendous blood regeneration observed in hookworm disease after iron administration becomes quite comprehensible. Although this substance, most likely, induces a neo-production of haemoglobin, it is essentially to the normal discharge of erythroblastic cells already laden with this pigment that a quick blood recomposition is due and, therewith, the return to the normal state in a relatively short time.

SUMMARY AND CONCLUSIONS

We investigated, in the liver and the spleen of ten pure cases of ankylostomiasis, haemocytopoietic elements. We verified the weight of spleen in 23 cases of individuals from 3 to 60 years old. In no case did we meet with haemopoietic cells in liver. In seven cases we found in spleen elements of the red series at an advanced evolutionary stage (orthochromatic erythroblasts with pyknotic nucleus). In some of these cases we observed megakaryocytes and numerous eosinophilous myelocytes. The three cases which did not show any myeloid metaplasia in spleen were from individuals of over 50 years. Nevertheless, in another case of an individual 59 years old this metaplasia was verified. In individuals of over 20 years, the average weight of spleen in nine cases appeared to be equal to the normal weight. In 14 other cases, between 3 and 14 years of age, the weight of this organ was always sensibly higher than in normal individuals of the corresponding age.

These results suggest the possibility of the myeloid metaplasia being the fact responsible for the weight increase of spleen in young individuals victimatized by hookworm anaemia.

The remarkable proliferation of orthochromatic erythroblasts shows that the degree and quickness of blood regeneration after iron administration are due, essentially, to the great quantity of haemoglobin previously formed in the spleen and bone marrow of ankylostomized organisms.