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BONE AND MARROW: OSTEO-HAEMATOPOIETIC ENTITY

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Haematopoietic red marrow being located in bone is a fact to which we are so accustomed that the relationship between bone and red marrow is often regarded as a merely topographic one.

Our recent investigations, together with some previous data have shown that bone and haematopoietic marrow are connected not only topographically but they represent an anatomical, physiological, pathological and even a therapeutical unit.

In our investigations on rickets we observed that young rats fed on a rachitogenic diet generally became anaemic as soon as the signs of severe rickets manifested themselves. It is well known that anaemia occurs in association with severe rickets, but it still seemed interesting to carry out experiments for studying the anaemia developing in rickets (Krompecher, G. Lelkes, B. Galamb, E. Kerner [6]).

One group (10 animals) of young rats (4 weeks old, weighing 30 g each) were fed on a rachitogenic diet (modified McCollum's diet, containing 75% corn-grits, 15% delubricated wheat bran, 3% $CaCO_3$, 1% salt, mixed with distilled water).

A similar group of rats received the same diet. They were kept in a similar cage in the same room as the previous group. The only difference was that this second group instead of 3 g of $CaCO_3$ received 3 g of fresh powdered eggshell. The antirachitic effect of eggshell has been previously demontrated [5, 1, 6].

The third group served as control (normal diet). The curve of the body-weight showed a significant increase in the eggshell group.

As regards the behaviour of red blood corpuscles it has to be mentioned that in our climate in rats 4 weeks old the average red blood corpuscle count is 4 700 000. In four weeks this normally rises by $^3/_4$ million, to increase later to above 6 million per cu. mm. In contrast with this physiological increase of the red blood corpuscle count, no increase was observed in rats fed on McCollum's rachitogenic diet (2 in Fig.). Moreover, after 4 weeks, when the signs of severe rickets had already manifested themselves, the red blood corpuscle count showed a remarkable decrease to 3 and half million. On the other hand, the group which received eggshell and was thus protected from rickets, showed as early as in the fourth week of treatment an increase of the red blood corpuscle count to over 6 millions (1 in Fig.) surpassing not only the $CaCO_3$ group, but even that of the normal controls (3 in Fig.) Repeating twice this experiment similar significant differences were obtained.

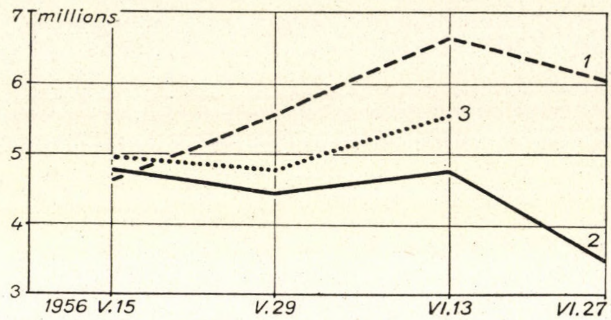

Fig. 1

Protection against rickets in the rats in the eggshell group was verified by experiments performed in 1952—53 involving the line-test, the histologic picture of the epiphyseal cartilage, body weight, bone length and weight, Ca and P content, bone tenacity, general aspect, behaviour and movement of animals. An increase on the red blood corpuscle count was in every experiment connected with the successful protection from rickets. We made investigations to find out the cause of the increase in the red blood corpuscle count and also to determine whether eggshell would contain any haematopoietic factor (Vitamin B_{12}, etc.) These attempts, however, failed and the only constant finding was the connection of good haematopoietic function with the healthy and well-built bone system.

It seemed thus necessary to study the anatomical, physiological and pathological connections between bone and haematopoietic red marrow.

It is the merit of RÖHLICH—(VEREBÝ) to have demonstrated in a series of publications the anatomical, vascular connection between the compact bone substance and the underlying red marrow. RÖHLICH—VEREBÝ showed (1939) that the red marrow has a double vascular supply one through the arteria nutritia and another, indirect one, through the bone (= "portal" blood-supply). He demonstrated a considerable number of veins of the compacta to enter the sinuses of red marrow. The compact bone substance and the underlying red bone marrow are thus anatomically connected (anatomical unity). This connection was demonstrated in a scheme by WALTHER (1948) and was confirmed in rats by FLIEDNER, SANDKÜHLER and STODTMEISTER (1956). It may be mentioned that RÖHLICH—VEREBÝ (1939) made his observations in young humans, dogs and cats.

Having found the anatomical connection, RÖHLICH—(VEREBÝ) (1941—42) made experiments to obtain physiological proof of the connection between bone and red marrow. After destroying the blood supply coming through the bone (by carving the compacta, leaving a layer of 1 mm) so that the red marrow received arterial blood only through the arteria nutritia, the haematopoietic activity of the red marrow was not only disturbed but even stopped in the respective area. The arteria nutritia by itself did not prove sufficient to maintain haematopoiesis. This was direct proof of the red marrow being dependent on the blood supply which passes through the bone.

As we know, bone building and bone resorption are continually occurring. It seems probable that substances liberated during bone resorption are essential in haematopoiesis. Röhlich—(Vereby) carried out further experiments transplanting tubular bones into muscles ; very soon granulation tissue entered into the medullary cavity from both ends of the tubular bone. The formation of new bone trabecules and that of haematopoietic red marrow, however, occurred only after the perforating vessels had passed through the bone wall and had thus entered the marrow ; another evidence of the importance of the vascular connection between bone and bone marrow. Röhlich—Vereby postulated the existence of a substance deriving from bone inducing haematopoiesis. The nature of this substance is not known. Levander, Annersten, Lacroix and Roth [12] suggest it to be alcohol-soluble. Dobi and Cseppentő (1955), having repeated the experiments of Röhlich (Vereby), confirmed his findings modifying the implantation of bone tubes — keeping the bone before implantation in alcohol for 72 hours — this osteopoietic and haematopoietic agent seemed not to be present in the bone any more. This unknown substance — originating from the bone, carried through the vessels to red marrow and exerting there a haematopoietic activity — was found to be soluble in alcohol.

These few data demonstrate physiologically and experimentally the intimate connection between compact bone and red marrow.

In spongious bone where bone building and resorption and haematopoietic activity occur at the very same place, their intimate connection is obvious.

This anatomical and physiological connection between bone and haematopoietic bone marrow clearly explains the pathological and therapeutical interrelation observed in our experiments on rickets. Besides rickets the anaemia occurring in Albers-Schönbergs (marble bone) disease and in cases of osteitis deformans (Paget) affirms the significance of this unitiy.

Regarding this osteo-haematopoietic entity, we can summarize its essence by stating that in healthy bone there is a healthy red marrow with good haematopoiesis, whereas in diseased bone (e. g. rickets) there is a diseased marrow with disturbed haematopoiesis.

Summary

Bone and red marrow are anatomically connected by their blood supply, since vessels of the compact bone enter the sinuses of red marrow [7, 13, 3].

By the vessels some not yet identified substance is physiologically transported from the bone to the marrow. This substance is necessary for haematopoiesis. Destroying in any way the connection between bone and marrow in which case the arteria nutritia alone has to supply the marrow with blood, makes haematopoiesis to stop [8 11, 2]. In experimental rickets the disturbance of bone formation caused a disturbance of haematopoiesis (anaemia): pathological connection [6]. If by therapeutic means bone disease (rickets) was prevented anaemia did not develop: therapeutic connection [6].

Bone and marrow can thus be regarded as an osteohaematopoietic entity connected anatomically, physiologically, pathologically and therapeutically.

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