The origins of bone marrow as the seedbed of our blood: from antiquity to the time of Osler

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The marrow is currently well defined as the seedbed of our blood, producing 200 billion red cells, 10 billion white cells, and 400 billion platelets on a daily basis. Yet, the role of the marrow was unknown in antiquity and only first experimentally defined during the latter 19th century. Hippocrates (460–375 BC), who used observation and reasoning rather than mysticism to reach his conclusions, considered the marrow the nutrient source for bone, an opinion shared by Galen (130–200). Aristotle (384–322 BC) took the opposite view and considered the marrow to be an osseous waste product *(excrementum ossium)* (1). Impressed by the vascularity of the marrow, anatomists in the 18th century also expounded Hippocrates' view and considered the marrow the vascular component of bone. Yet, it was noted in 1700 by the French anatomist Duverney that many bones, like those of the middle ear, have no marrow, and hence it would be unlikely that the marrow was essential for the nutrition of bone (2). It was also noted by Charles Robin in 1872 that in the course of development, the marrow was formed after the bone, again suggesting the unlikelihood that it was a source of bone nutrition (1).

Literature through the ages often alluded to marrow as the essence or central part, considered rich and nutritious as a food source, possessing warmth, energy, and inner heat, as well as being the seat of vitality and manliness. The Greek playwright Euripides (480–406 BC) noted: "Love must not touch the marrow of the soul. Our affections must be breakable chains that we can cast them off or tighten them." A quote from Shakespeare's Macbeth: "Avaunt! And quit my sight! Let the earth hide thee! Thy bone is marrowless. Thy blood is cold; thou hast no speculation in those eyes which thou dost glare with." Yet, in his chapter entitled "Bone Marrow: the Seedbed of Blood" in Wintrobe's *Blood: Pure and Eloquent* published in 1980, Tavassoli noted: "For centuries, poets, healers, and philosophers saw and described the close link between blood and life. Not so the marrow. Its role as the seed bed of blood lay hidden, like a seed in the soil" (3).

While red cells were first described in the 17th century, it was not until the 19th century that a search for their origin could begin. The concept of red cell production could not be formulated until cell theory was postulated in 1838 by Schleiden and Schwann, identifying the cell as the fundamental unit of life (4, 5). Schleiden proposed that cells were formed by a process analogous to crystal formation with confluence of granules. He did not conclude that living cells were necessary for the formation of new cells. Scholars of this period also were not cognizant that blood formation was a continuous process. There was no recognition of a finite life span for red cells necessitating continuous replenishment. The focus was on embryonic life, with the assumption that blood cells, once formed in the embryo, remained in the body throughout life.

Neumann and Bizzozero, both contemporaries of Osler, are credited with making the initial observations leading to the recognition of the marrow as the seat of blood formation. Ernst Neumann (1834–1918) was a lifelong citizen of Konigsberg, capital of former eastern Prussia, where he was appointed professor of pathology in 1866 *(Figure 1).* He had done postgraduate studies in Prague and trained with Virchow in Berlin. In his report published in October 1868, Neumann described the presence of nucleated red blood cells in the bone marrow sap of humans and rabbits by squeezing bone (6). He was the first to conclude that during postembryonic life, erythropoiesis was taking place in the marrow. Translation from this text is as follows:

> In the so-called red bone marrow of man as well as the rabbit, one can regularly find, in addition to the well-known marrow cell, certain other elements which have not been mentioned until now; namely nucleated red blood cells, in every respect corresponding to embryonic stages of the red blood cells. . . . It is possible to trace the origin of these elements to the marrow cells. The high content of colorless elements in the blood of the marrow makes it likely that there is a migration of contractile marrow cells into the vessels.

One year later he noted:

> The present work intends to demonstrate the physiologic importance of the bone marrow and that it is an important organ for blood formation which has not been recognized. It operates continually in the de novo formation of red blood cells (7).

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Figure 1. Franz Ernst Christian Neumann (1834–1918).

Figure 2. Giulio Bizzozero (1846–1901).

However, Neumann concluded erroneously that the proliferation of marrow cells occurred inside the blood vessels of the marrow; the concept of marrow sinusoids was not coined until Minot's description in 1901 (8).

Neumann also recognized that leukocytes were formed in the marrow and later postulated a common stem cell for all hematopoietic cells. This may have been his most prescient observation. He noted that a continuing transformation of lymphoid cells into colored blood cells takes place in the bone marrow throughout life. This lymphoid marrow cell forms not only erythropoiesis but is capable (in itself) of self-regeneration. He published an illustration in 1912 showing an embryonic liver containing the "great lymphocyte stem cell" that he postulated was also present in the marrow. Neumann advocated that all blood cells were descendants of the postembryonic stem cell, representing the unitarian point of view. This contrasts with the view of dualists such as Ehrlich, who asserted that some lymphocytes were separate cell lineages and that some lymphocytes originated in the lymph nodes and spleen and others in the bone marrow. Neumann concluded that "a final decision will only arrive if it is possible to isolate the individual colourless cells and to study its life events in vitro culture for some time, as Robert Koch demonstrated with bacteria." He considered the source of these stem cells to be reticulum cells originating in the marrow. It was not until the 20th century that the concept of "hematopoietic inductive microenvironment" was postulated, in which stem cells may migrate to the marrow and begin to proliferate and produce blood cells (9, 10).

Neumann also made observations to distinguish between "red marrow," which is the blood-producing marrow, and "yellow marrow," which consists mostly of fat. In 1882, a phenomenon referred to as "Neumann's law" was defined, where at birth bones contain red marrow but with age blood production contracts toward the center of the body, leaving peripheral bones to produce primarily fatty marrow (11). Years later, Huggins maintained that the higher thermal temperature in the central part of the body was more conducive to the production of blood cells.

Giulio Bizzozero (1846–1901) studied medicine at the University of Pavia, graduating in 1866 at the age of 20 *(Figure 2).* After working in Pavia, he was appointed professor of general pathology in Turin. Like Neumann, he also studied with Virchow in Berlin. At age 22 in 1868, he published two articles confirming that nucleated red blood cells in the marrow evolved into nonnucleated red cells and extended these observations to include the formation of white blood cells (12, 13). Bizzozero also concluded that the marrow was the site not only of blood formation but also of blood destruction, based on the erroneous assumption that large cells containing pigment granules were scavenger cells containing red cell debris. He later coined the term *blutplatchen*, or platelet, and added to Osler's observations that platelets were independent cellular elements that played a role in coagulation (14). He popularized the concept that this new cell represented an independent cell line with the specialized function of hemostasis, or arresting the flow of blood. He also concluded that hemostasis and blood coagulation were not synonymous.

The proposal of the cellular origin of red cells contrasted with a great number of divergent theories in the latter 19th century. Erb maintained that red cells were the product of disintegration of white cell nuclei (15). Wharton Jones espoused that nuclei of precursor cells swelled, acquired hemoglobin, and evolved into red cells (16). Pouchet noted that red cells may be derived from white cells by "hemoglobinic degeneration" (17). Weber considered fat globules the origin of red cells (18). Hayem thought that platelets were the source of red cells and stated:

> There exists in the blood of all vertebrates tiny structures which are not erythrocytes and not leucocytes; destined in their ultimate development to become erythrocytes, they represent a very young form of those elements, and are a varied precursor of the red cell. Thus, we have proposed to name these cells hematoblastes (19).

Ranvier postulated that large scavenger cells in the marrow produced hemoglobin with budding and ultimately release of red cells (20). While all these theories now seem bizarre, at the time the viable nature of red cells had not been established since fixatives often leached the hemoglobin out of red cells until stains were introduced by Ehrlich and Romanowsky.

All of these discoveries occurred at a time when Osler was making his experimental observations identifying platelets as an independent cellular element in the blood. Perhaps Osler's observation that platelets were a normal and independent component of blood linked to thrombus formation represented his most significant original scientific contribution. His initial description of platelets was published in 1874:

> Careful investigation of the blood proves that, in addition to the usual elements, there exist pale granular masses, which on closer inspection present a corpuscular appearance. In size they vary greatly from half or quarter that of a white blood corpuscle, to enormous masses. . . . They have a compact solid look, . . . while in specimens examined without any reagents the filaments of fibrin adhere to them (21).

A drawing by Osler in the paper noted individual platelets as distinct cellular elements in a blood vessel. He did credit earlier drawings by Schultze's "granular masses" and Addison's particles that were not identified as independent cellular elements. Much to Osler's chagrin, his early reports on these elements were ignored by Bizzozero, whose monograph was published 8 years after Osler's drawings. In 1883, in an article entitled "The Third Corpuscle of the Blood," Osler noted: "The origins of the corpuscles remain a problem—one of many connected with the blood which await solution at the hand of the histologist" (22). His prediction was finally borne out in 1906, when James Homer Wright, using his famous stain, determined that megakaryocytes in the marrow shed cytoplasm that were platelets.

In view of Osler's interest in blood cellular elements, it is somewhat surprising that in his first edition of *The Principles and Practice of Medicine,* published in 1892, the bone marrow was mentioned briefly only three times in discussions of smallpox, leukemia, and pernicious anemia (23). He noted marrow hemorrhages in smallpox. In leukemia, "instead of fatty marrow, the medulla of the long bones may resemble the consistency of matter which forms the core of an abscess." In pernicious anemia, the marrow resembles that of a child, predominantly red marrow secondary to cellular hyperplasia. Nowhere in the text does the assumption appear that the marrow is the seedbed for production of red cells, although the observations of Bizzozero and Neumann had been known for 25 years.

Yet, 6 years before publishing *The Principles and Practice of Medicine,* Osler gave a series of three Cartwright Lectures in New York, reviewing his own work and that of others on blood platelets, coagulation, and thrombosis (24). The first lecture was titled "The Blood Plaque or Third Corpuscle," in which he focused on platelet morphology and number and speculated concerning their origin. He also discussed the role of these "plaques" in disease and referred to his own observations. He stated that these plaques were increased in chronic wasting diseases, possibly the initial description of reactive thrombocytosis. He also noted that they may be elevated in some cases of leukemia and Hodgkin's disease. In the third lecture, "The Relation of the Corpuscles to Coagulation and Thrombosis," Osler reviewed his work and that of Bizzozero and others, indicating that platelets, not leukocytes, were the initial cellular element of thrombosis.

In his second lecture he discussed the degeneration and regeneration of corpuscles and noted:

> The corpuscles present a remarkable sameness, and we cannot pick out with readiness the old elements ready to die, or the new ones which have just made their appearance. This it is which makes the blood such a puzzle, for the corpuscles, so far as observation goes, neither die nor are born in the circulating fluid, but appear to enter it as perfect elements and are removed from it before they are so changed as to be no longer recognizable.

He further noted that the red corpuscles in health are constantly degenerating and constantly being reproduced. He commented that there can be no doubt that nucleated red cells originate in the bone marrow, crediting both Neumann and Bizzozero, and stated, "It would be unreasonable in the highest degree to suppose that in the red marrow of the adult it was present for any other purpose." He speculated on the process used by these cells to convert into the ordinary red disk, as he noted the "transformation of the nucleated red into the ordinary forms . . . by the gradual disappearance of the nucleus." He also commented on the controversy about other possible origins of red cells, noting that the "colorless corpuscles (white blood cells) constitute separate elements with important functions quite apart from the regeneration of red cells" (24).

These lectures were Osler's most definitive discussion of bone marrow function. Towards the end of the 19th century, rapid advances in morphologic methods took place, especially Paul Ehrlich's introduction of aniline dyes and of heat-fixed films of blood smears and the bone marrow. This led to further expansion of our knowledge of blood production and eventual confirmation of the hematopoietic stem cell, as postulated by Neumann. With the application of bone marrow transplantation in the latter 20th century, we now replace the seedbed of our blood to combat fatal disorders of the bone marrow. As noted by Tavassoli, it would also now seem that the Hippocratic postulate has been subtly reversed (3). Rather than the marrow being the nutrient source for bone, the bone provides an environment essential for the marrow. Certainly, the hematopoietic stem cell requires the microenvironment of the marrow to proliferate. In conclusion, the role of the marrow as the seedbed of our blood has been clearly delineated, based in large part on observations by Osler and his contemporaries, especially Neumann and Bizzozero, in the latter 19th century.

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