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Title: **What is a Platelet?**

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What is a platelet? All of the articles, notes, and letters in this newsletters are about ITP. And ITP is all about too few platelets. One topic that has never been directly addressed is to actually describe blood platelets; to understand all about blood platelets is important for patients with ITP. Here we will describe the structure of platelets, their circulation in the blood, and their normal function. In the next issue we will describe how platelets develop in the bone marrow and the hormone that regulates their normal number in the blood.

Platelets are produced from the largest cells of the bone marrow, which are called megakaryocytes. The process of platelet production is unique: as the megakaryocyte grows larger, its substance is divided into tiny segments, each surrounded by its own membrane. At the completion of this process these tiny segments all break loose, each becoming a platelet. Therefore individual platelets are not truly complete cells. They have none of the machinery that can make new proteins and other molecules. They are merely fragments of their parent megakaryocyte. Yet they have a wonderful array of abilities to stop bleeding. No one knows this better than a patient with ITP!

Most platelets travel through the circulation for a week to ten days. Since they are tiny cells, much lighter than the larger red blood cells, they are pushed to the side of the blood vessels. This has a purpose, because as platelets roll along the surface of the vessel wall, they can immediately detect gaps and injuries, and this is where they do their work. The surface of the platelet is studded with many different adhesive molecules. Each of these molecules recognizes a specific component of the blood vessel wall. They do not recognize the endothelial cells, the cells which line the inside of the blood vessel. Endothelial cells have specific properties to prevent platelets from sticking to them. But platelets do recognize the complex structure of fibers that surround the vessel forming an envelope just outside the endothelial cells. So when there is a break in the endothelial cell lining, these fibers are exposed to the blood, and then platelets immediately stick. This is the first reaction to stop bleeding.

As soon as platelets stick to these fibers that surround the blood vessel, they are stimulated to change shape, and this shape change is associated with the appearance of new sticky adhesion molecules on the platelet surface. These secondary adhesive reactions cause platelets to stick to each other, forming a clump. This clump of platelets is sufficient to stop bleeding from small cuts. This is why a patient with severe hemophilia does not bleed excessively from small cuts, because they are normal and his platelets can stop the bleeding on their own. However when a wound is larger, such as when a tooth is pulled, platelets alone cannot stop the bleeding. This is when the proteins of the blood plasma are required to provide additional clotting support, and it is one of these plasma proteins that is abnormal in patients with hemophilia. This plasma clot forms among and around the platelets, stabilizing the platelet clump.

In addition to these platelet surface adhesive reactions, platelets are full of tiny granules that secrete material important for clot formation. Platelets are also full of muscle-type proteins which contract, just as a muscle contracts, to make the clot firm. It is surprising how much that these tiny fragments of cells can do. But we all know how important they are!

Above we described platelet structure and function. Now we will describe how platelets develop in the bone marrow and what regulates their normal number in the blood.

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All of the circulating blood cells (platelets, red blood cells, and white blood cells) originally develop from a single ancestor cell called a 'stem cell'. In response to a variety of hormones, these stem cells develop and divide; with each division the number of cells doubles. In response to specific hormones, these stem cells acquire features that commit them to ultimately become either platelets, red cells, or white cells. Cells that will produce platelets first become giant cells, the largest in the marrow, called megakaryocytes. Each megakaryocyte produces several thousand platelets by a process that is unique in the human body: platelets are simply tiny pieces of this giant cell. Imagine the shattering of a 'Lego' toy: the big structure is a megakaryocyte; each individual piece is a platelet.

When a bone marrow aspiration is done to determine the cause of thrombocytopenia, the objective is to determine whether a normal number of megakaryocytes is present in the marrow. If megakaryocytes are absent or few, it is concluded that the thrombocytopenia is due to poor platelet production. If the number of megakaryocytes is normal, it is concluded that the thrombocytopenia is due to increased destruction of platelets that are being produced normally. In most patients with ITP, a bone marrow aspiration is not necessary to make the diagnosis, because everything else in the patient exam is normal except for increased bruising and bleeding, and everything else in the blood tests is normal except for low platelets.

The hormone that controls platelet production, called thrombopoietin and abbreviated as TPO, was identified in 1994. In patients who have too few megakaryocytes (for example, aplastic anemia, in which the marrow appears empty) TPO levels in the blood are extremely high, conveying the body's attempt to stimulate greater platelet production. In patients with ITP, TPO levels are not increased to such high levels because TPO is regulated not by the number of circulating platelets but rather by number of megakaryocytes in the bone marrow. This suggests platelet production may not be maximal in ITP and also raises the question whether TPO therapy would be beneficial to some patients with ITP.

Currently all treatments, such as prednisone, splenectomy, and other drugs, are focused on controlling the increased platelet destruction caused by antibodies which are being formed against platelets. An alternative idea is that platelet production could be increased by TPO. Since it is not necessary to achieve a normal platelet count for a treatment to be effective, a drug that can maintain a safe platelet count for example greater than 20-30 may be an effective alternative to current treatments.

No matter how good the idea in theory, most ideas for new treatments never actually lead to availability of useful drugs. Even when they do, the process takes several years. TPO therapy seems like a good idea, so we hope it may eventually become a good treatment for ITP.