A Perspective on Living with Low Platelet Counts: The Big Three - Lifestyle, Diet and Surveillance

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Note: This is a DRAFT document in process of completion.

> "Our minds and bodies are political – they frequently promise more than they deliver and are difficult to measure against precise numbers. Rather than attempting to control them, we need to determine the limit settings."

1. One User's Perspective.

The information below is drawn largely, but not exclusively, from the Platelet Disorder Support Association website[1]. Some additions relate to personal experience over five years with thrombocytopenia (ITP). In that period, my platelet counts have risen steadily from unsafe levels (~35,000 cu/ml) to low but safe ranges (~100,000 cu/ml), now counting as a mild case of chronic ITP. At the same time, the ability of my blood to clot has been improved markedly – all this without any overt intrusion such as removing my spleen, IVIG and prednisone therapy or rituximab therapy[2]. Very many drugs and substances are detrimental to one's platelets – something we each need to understand. Some almost routine medications like Ibuprofen and Tylenol need to be used with caution, as we will see below. Prescribed medications for blood pressure (Accupril / quinapril) and cholesterol control (Lipitor) can reduce the platelet count significantly, yet we need to take prescriptions necessary for general management of our health. Overall the best approach in my view is continued avoidance of drugs so far as reasonable, along with careful diet control and strict lifestyle choices. The philosophy is simply that a healthy body has best chances of mounting its own defenses and making repairs that are required.

RISKS YOU MIGHT FACE

It is important to understand the risks and simple exposures presented by diminished platelet count and NOT rush into medical intrusion unless that is warranted. In my personal view, it is more important to ensure that the clotting function is unaffected than to be concerned about platelet count – provided you have a chronic case of ITP only. A useful framework is;[3]

Normal Platelet Count	150,000 - 400,000 cells/mm3
	Note: Normal values will vary from laboratory to laboratory.

Risk of Bleeding is based on the Platelet Count	
100,000 - 149,000 cells/mm3	Little to no risk of bleeding
50,000 - 99,000 cells/mm3	Increased risk of bleeding with injury
20,000 - 49,000 cells/mm3	Risk of bleeding increased without injury
10,000 - 19,000 cells/mm3	Risk of bleeding greatly increased
Less than 10,000	Spontaneous bleeding likely

So you say to yourself; "If I had plenty of platelets, then I would be safe!" But that is not a valid thought at all. Our bodies are like any other machine – designed and refined to operate with a narrow operating range of all the relevant fuels and lubricants. Everything needs to fall within the

[1] http://www.pdsa.org/itp-information/itp-warnings.html and http://www.itpscience.com/about/about_ITP.html
[2] http://www.itpscience.com/treatment_goals/therapeutic_overview.html
[3] http://www.chemocare.com/managing/low_blood_counts.asp

ranges that evolution has equipped us to tolerate. We have to accept that the wisdom of ages did not rest on nonsense alone. Our generation might have more powerful tools with which to play, but is fundamentally no smarter than the scholars of a millennium or more ago. Contemporary Western medicine relies on compartmental description of bodily functions and has its roots in the work of the Muslim physicians[4] who broke away from earlier philosophical approaches of Greco-roman schools. Subdivision allows more specific depth to knowledge but introduces the peril of isolation of which we alone are the architect. We must look out the window from time to time.

In fact, you do not find the best indications for event-free survival by achieving a high platelet count within the normal range. An adequate supply of platelets is essential to repair the minute vascular damage that occurs with daily life, and to initiate thrombus formation in the event of overt vascular injury. Accumulating evidence also indicates vital roles for platelets in wound repair and the innate immune response. While platelet count in the range 150K to 400K is considered "normal" within groups of "healthy" individuals, the level for any individual is maintained within fairly narrow limits from day to day. A substantial movement is reason for analysis, whether that is upward or downward since high counts are not ideal either. Epidemiological evidence indicates that individuals who display platelet counts in the highest quartile of the normal range have a 2-fold increased risk of adverse cardiovascular events. Also, higher platelet levels carry an unfavorable prognosis for individuals with metastatic cancer and tumors.

Being normal does not necessarily give you the best position. It simply means you are average in the population being surveyed and running the same risks according to the measure at hand. Driving down a crowded highway – you are abnormal and taking a huge risk if you elect to drive at the speed limit or below. But if the traffic is sparse and safety is of some concern, it would be entirely normal for you to proceed within the legal limit. Perhaps you might even follow the advisory speed signs. Every individual measure has a bias and *that is built into your stem cells*.

Hematopoietic Stem Cell **HSC :** $CD34^+$, $CD59^+$, $Thy1/CD90^+$,$CD38^{lo/-}$, C-kit/$CD117^+$, lin^-				
	Myelo-Erythroid Progenitor Cell **CFU-GEMM**			
Lymphoid Progenitor	Erythroid Progenitor	Myeloid Progenitor		
CFU-L	**CFU-E / BFU-E**	**CFU-GM**	**CFU-GM**	**CFU-Meg**
$CD34^+$	$EPO\text{-}R^+$	$GCSF\text{-}R^+$	$GCSF\text{-}R^+$	$TPO\text{-}R^+$
lymphocytopoiesis	erythropoiesis	granulocytopoiesis	monocytopoiesis	thrombocytopoiesis
Lymphoblast	Proerythroblast	Myeloblast	Monoblast	Megakaryoblast
Prolymphocyte	Polychromatophilic erythrocyte	Promyelocyte	Promonocyte	Promegakaryocyte
	Normoblast	ENB myelocyte		Megakaryocyte
Large lymphocyte	Reticulocyte	ENB metamyelocyte, ENB band cell	Early monocyte	
Small lymphocyte	Erythrocyte	Granulocytes ENB = Eosinophil Neutrophil Basophil	Monocyte	Thrombocytes (Platelets)

Table 1 Lineage of blood cells and progenitors commencing with hematopoietic stem cells HSC in the bone marrow: CFU = 'colony forming unit'; BFU = 'burst-forming unit'; ENB = eosinophilic / neutrophilic / basophilic; EPO-R = erythropoietin receptor; GCSF-R = G-CSF receptor; TPO-R (aka Mpl) = TPO receptor. Progenitor cells CFU-GEMM express $TPO\text{-}R^+$, $EPOR^+$, $CD41^+$, $GCSF\text{-}R^+$. The CFU-L are $CD34^+$. CFU-Meg and platelets are $TPO\text{-}R^+$, $EPO\text{-}R^-$, $CD41^+$.

The cells of the blood originate with hematopoietic stem cells HSC and these normally produce daughter cells that repopulate peripheral white blood cells in the ratio 85% lymphoid cells to 15% myeloid cells. However, HSC cells can be My-bi or Ly-bi, meaning biased toward myeloid or lymphoid cells in a mixture that is preserved through successive generations. The gene

[4] Ibn Sina (Avicenna) 980-1037CE; Ibn al-Nafis1213-1288CE.

expression involved in this mixture is fixed by environmental factors and not by underlying DNA factors. (It is epigenetically fixed.) As a result, individuals will have characteristic bias in the peripheral lymphoid to myeloid cell balance unless some major disturbance to the HSC population takes place. Equally, there will be some characteristic balance in differentiation to myeloid versus erythroid progenitors according to the individual features of the hematopoietic stem cell lineage. Then, peripheral blood count data must be expected to show a wide range across the population and no single person is likely to sit mid-way for all counts.

SOME OF THE FACTORS AT PLAY

The hematopoietic stem cells (HSC) in the bone marrow are responsible for the lifelong production of all circulating blood cells and they have the ability to self-duplicate. Problems of platelet insufficiency arise by any of three downstream effects;

- Platelet underproduction
- Platelet destruction, or
- Platelet dysfunction.

Most therapies are directed toward problems of excessive clearance or destruction of the platelets. The conceptual model involves platelet autoantibody production from B-cells, followed by clearance of the antibody coated platelets by macrophages in the spleen or liver.

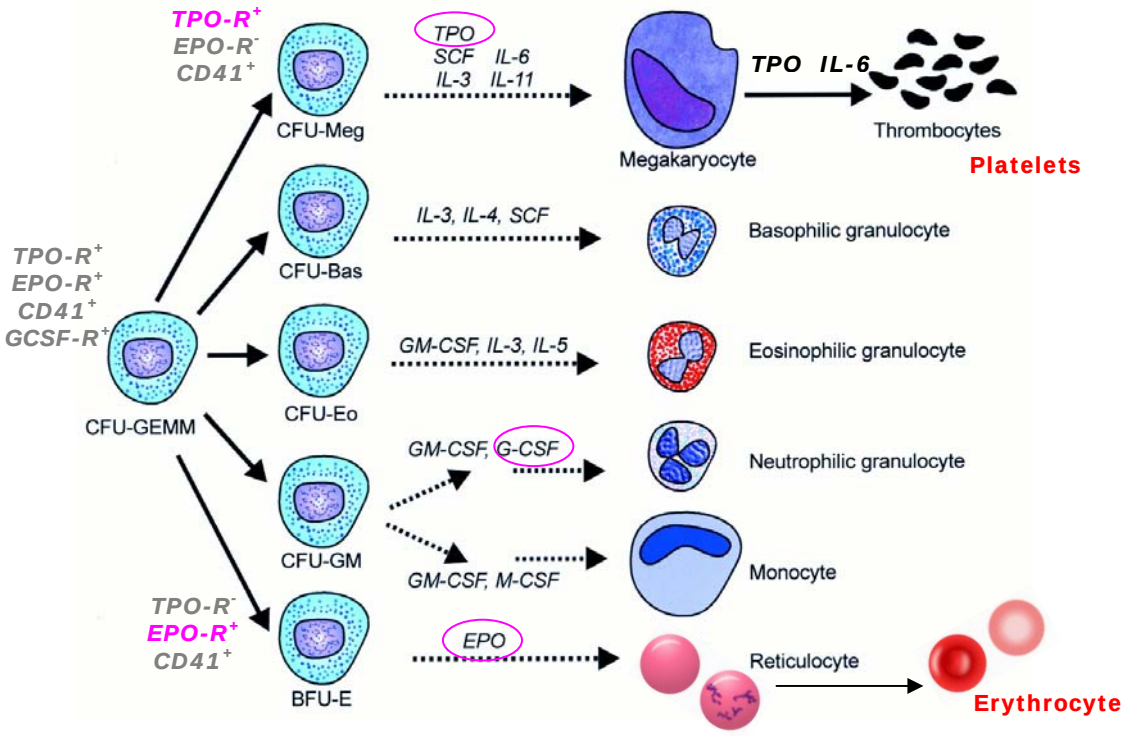

Figure 1. Simplified model of hematopoiesis; adapted from Wolber & Jelkman[5] and also Pang et al[6]. Growth factors controlling viability, proliferation, and differentiation of hematopoietic stem and progenitor cells (CFU, colony-forming unit; BFU, burst-forming unit) of megakaryocytes (Meg), granulocytes (G), monocytes (M), and erythrocytes (E). Bas, basophils; Eo, eosinophils; GEMM, granulocytes, erythrocytes, monocytes and megakaryocytes.

Key: TPO, thrombopoietin; SCF, stem cell factor; IL, interleukin; CSF, colony stimulating factor; EPO, erythropoietin; EPO-R, EPO receptor; TPO-R, TPO receptor; GCSF-R, G-CSR receptor.

[5] E-M Wolber and W. Jelkman; News Physiol. Sci. (2002) 17: 6-10

[6] J. Pang et al; J. Clin. Invest. 115: 3332–3338 (2005).

The process is depicted as commencing with binding of the "prongs" or variable Fab region of the antibody to thrombopoietin (TPO) bound to the platelets, with subsequent attachment of the constant "stem" region to the FcγR receptors on macrophages. Despite the nice simplicity of such a model, its weakness is in presuming that the platelet population simply sits around and is not deployed except for the purpose of stemming the loss of blood. Nature is not so wasteful, nor reliant on single passage mechanisms. So platelets have other things to do – and these alter their fortunes. After all, the developed mammalian system originated in a single organism and discrete functions have not located exclusively to disparate offspring.

The literature tells you platelets are created from megakaryocytes (Megs) that come from myeloid stem cells. Each Meg can form several thousand platelets in a fragmentary process regulated by thrombopoietin (TPO) acting on its receptor TPO-R (Mpl). TPO is a hormone originating primarily in the liver and to a lesser extent in the kidney. It is also made by stromal cells in the bone marrow, as well as other sources in the spleen, lung and brain. Production in the liver is augmented by Interleukin-6 (IL-6). The importance of TPO in the physiological control of platelet homeostasis has been demonstrated in mutant mice. Platelet counts are reduced to ~10% of normal in mice deficient in either the TPO gene or the TPO receptor gene. The animals show no apparent physical abnormalities. They do not bleed spontaneously, but their bleeding times are prolonged when tested by the tail clip assay. Blood cell counts other than platelets are normal.

The growth factors responsible for the baseline rate of platelet production in the absence of TPO action are still to be identified. Factors that also stimulate proliferation and differentiation of Megs are IL-3, IL-6, IL-11 and stem cell factor (SCF). None as single components can substitute for TPO. Notably, the TPO receptor is present mainly on hematopoietic stem cells, megakaryocytic progenitors, and Megs. Research studies in humans and experimental animals have shown that the administration of recombinant human TPO (rhTPO) results in a dose-dependent stimulation of thrombopoiesis and thus increases the concentration of circulating platelets[7].

Looking at Figure 1, notice how differentiation of the CFU-GEMM progenitor between lineages that end in platelets, erythrocytes and neutrophils is determined strongly by the balance of TPO, EPO (erythropoietin) and colony stimulating factors G-CSF & GM-CSF. The lymphocyte population is stimulated in response to CD34 signaling received from bone marrow stromal cells. The primary source of TPO is the liver and that of EPO is the kidney. Fibroblasts and macrophages produce G-CSF while endothelial cells, macrophages fibroblasts and T-cells provide GM-CSF. Given an established HSC population with its inbuilt biases, the peripheral blood should be populated by the different cell categories in abundances set by the steady-state levels of their specific chemical signaling agents *within the volume of the bone marrow*. Two additional factors then have to be addressed:

1) What gradients exist in chemical signaling molecule concentrations between the region of their creation and their place of action in the bone marrow, and
2) What are the feedback processes that establish quasi-steady state (homeostasis)?

But just before we look at regulatory mechanisms; there are special features of TPO that we need to understand. The receptor for thrombopoietin is CD110 (TPO-R), a member of the hematopoietin receptor family. It is expressed on hematopoietic stem cells, a sub-fraction of hematopoietic precursor and on cells of the megakaryocytic lineage and platelets. Megakaryocyte proliferation and differentiation is induced upon binding of thrombopoietin to CD110 and the stem cells are protected from apoptosis.[8] Also, CD110 is not a substrate for enzymes, nor are there any commercial monoclonal antibodies available.

[7] Also occurs with recombinant human megakaryocyte growth and development factor (rhMGDF)

[8] http://mpr.nci.nih.gov/prow/guide/11586825_g.htm

Regulatory Mechanisms

There are not only similarities in the molecular structures but also in the production sites for EPO and TPO. However, although there is a postnatal switch in the main site of EPO synthesis from the liver to the kidneys, the liver remains the principal site of TPO synthesis throughout mammalian life. The liver accounts for 95% of the total body TPO mRNA in human fetuses. Study of adult human tissues has shown that the TPO mRNA-expressing cells are mainly hepatocytes in the liver and proximal tubular epithelial cells in the kidneys. While the kidneys are the principal source of EPO, the liver is a supplementary producer. Also the spleen contributes to the supply of both molecules EPO and TPO. The methods of regulation are also mirror imaged. The interactions are depicted in Figure 2.
The production of TPO is constitutive. It is independent from the actual platelet concentration in blood. Regulation of the plasma TPO concentration, and thus platelet production, is accomplished by megakaryocytes and platelets metabolizing the hormone and consuming it. Accordingly, the rate of platelet production reflects the rate of perfusion of TPO into the bone marrow volume occupied by the CFU-Meg units. In contrast, erythropoiesis is regulated through pO_2-dependent EPO gene expression. That is, it is controlled by the concentration of oxygen in the vicinity of the source cells. CFU-E units respond to the EPO arriving from the kidneys while the kidneys are controlled by the amount of oxygen arriving in the circulation. The liver, on the other hand, sits to the side of TPO transport and consumption and virtually acts as a constant supply pump. While the possibility exists for the secondary production of both TPO and EPO in bone marrow, it is not yet established if this has some distant (paracrine) mediation of the principal supply.

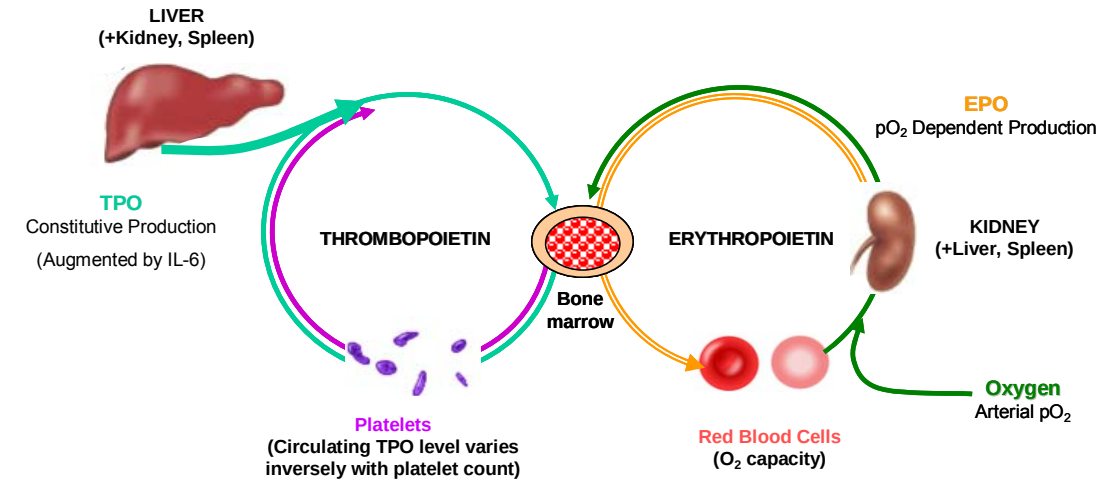

Figure 2. Feedback control circuit of the plasma TPO concentration *(left)* compared with that of EPO *(right)*. Adapted from Wolber & Jelkman. TPO is mainly produced in liver and to a minor degree in kidney, spleen, and other organs at a rate independent of the concentration in blood and bone marrow. The circulating level of TPO is regulated by Meg and platelet absorption. Erythropoiesis is regulated through oxygen concentration (pO_2) dependent EPO gene expression.

If the populations of CFU-Meg units and CFU-E units are at quasi-static levels sufficient to match the available TPO and EFO, then the rates at which platelets and red blood cells are produced will simply be a matter of the supply reaching inner regions of the marrow volume. In my own case of chronic thrombocytopenia, the white blood cell count is typically low while the red cell count and hemoglobin levels are essentially normal. Within that, the ratio of absolute neutrophils to absolute lymphocytes is typically about 2.5 to 1. As the ratio rises, in my case, so does the platelet count (interestingly, my mother shows the same pattern). Even though the bone marrow is not abnormal in microscopic detail, platelets are depressed in the peripheral blood. This correlates with evidence of increased erythropoiesis. By implication, my problem arises from imbalance of the TPO / EPO control loops – something we will look at in the next section.

When the erythroid and myeloid units are in shortage, there is likely to be a competition for differentiation of the common progenitors CFU-GEMM. It is reasonable to expect as a result that the products will show a teeter-totter effect as the competition plays out. But additional players may enter, such as neutrophils. These come from CFU-GM stimulated mainly by G-CSF. When a shortage of these progenitors occurs, there will be an added competition for CFU-GEMM differentiation. Now we are likely to find imbalances between red blood cell, neutrophil and platelet counts in a complete blood assay, reflecting the population prevalence of the progenitors as well as the supply of stimulatory medium.

Lymphocytes are created by lymphoid stem cells CFU-L as a result of L-selectin binding to the CD34 receptors, the source being stromal cells. This process involves signaling over short distances and so should not be subject to variability in the transport of the chemical agent. But if the lymphocyte population has been depleted seriously by chemotherapy designed for example to eliminate the B-cell population, one can easily imagine a heavy draw down on the grandparent stem cells, the HSC's. In result, the rebuilding of a lymphocyte population that has been largely destroyed is likely to work adversely against the levels of the other blood cells. Some of the therapies for thrombocytopenia are designed to consume red blood cells as a sacrificial offering to offset the consumption of platelets targeted by auto-antibodies. The same principle is likely to occur here, just driven by a different heavy demand on the progenitor cell population. In conclusion, then, it is quite understandable that the balance of blood cell counts can get out of sway when seriously intrusive therapies are used with the effect of reducing one population within the community. Experience says that recovery to the final balance will take time – measured in months where large excursions have been imposed.

Regulation of Thrombopoietin Levels

This is an interesting and complicated subject ably described in a paper by Kaushansky[9]. But such is the effect of time that additional data about chemical signaling is available, while new medication in the form of a TPO-R agonist "Nplate" has received FDA approval.

a) Regulation of thrombopoietin production

Investigators have found that blood and marrow levels of thrombopoietin are inversely related to platelet count. Patients with aplastic anemia or thrombocytopenia secondary to myelosuppressive therapy display high levels of the hormone. However, there are some notable exceptions to this relationship. The first is seen in states of platelet destruction, where levels of the hormone are not as high as would be anticipated from the degree of thrombocytopenia. Such instances, seen in most patients with idiopathic thrombocytopenic purpura, are characterized by megakaryocyte hypertrophy, which likely contributes to thrombopoietin regulation. A second instance in which thrombopoietin levels are not accurately predicted by blood platelet count is in patients with inflam- matory, reactive thrombocytosis, where levels of the hormone are higher than expected. However, an important unanswered question is whether alterations in thrombopoietin production explain the thrombocytosis associated with iron deficiency.

A major component of thrombopoietin regulation is achieved by receptor-mediated uptake and destruction (Figure 3), a mechanism of hematopoietic growth factor regulation first established for M-CSF. Platelets bear high-affinity thrombopoietin receptors that remove the hormone from solution, thereby establishing an autoregulatory loop; as platelet counts rise, they remove more of the hormone from the circulation, driving levels down, whereas in thrombocytopenic states there are less platelets to adsorb thrombopoietin, allowing levels to rise and drive increased thrombopoiesis. However, not all thrombopoietin receptors contribute to this effect; while endothelial cells display c-Mpl receptors and some endothelial cell types proliferate or migrate in

[9] K. Kaushansky; *J. Clin. Invest.* 115:3339–3347 (2005). doi:10.1172/JCI26674.

response to the hormone, transplantation studies have shown that endothelial cell c-Mpl does not materially affect thrombopoietin levels despite a 100-fold more expansive cell surface (and predicted greater c-Mpl mass) than that displayed by the totality of megakaryocytes and platelets. Therefore, the mere presence of c-Mpl does not guarantee that it is involved in regulating thrombopoietin blood levels.

A second exception to the relatively simple platelet-adsorption and- destruction model of platelet homeostasis is illustrated by the physiological response to severe thrombocytopenia; studies in both mice and humans show that while marrow stromal cells display very little thrombopoietin mRNA under normal conditions, transcripts for the cytokine greatly increase in the presence of thrombocytopenia (Figure 3). The precise humoral or cellular mediators of this effect are under intense study. For example, in one report, the platelet α-granule proteins PDGF and FGF-2 increased, but platelet factor 4, thrombospondin, and TGF-β decreased thrombopoietin production from primary human BM stromal cells. However, others have reported that HGF is responsible for thrombopoietin production from hepatocytes.

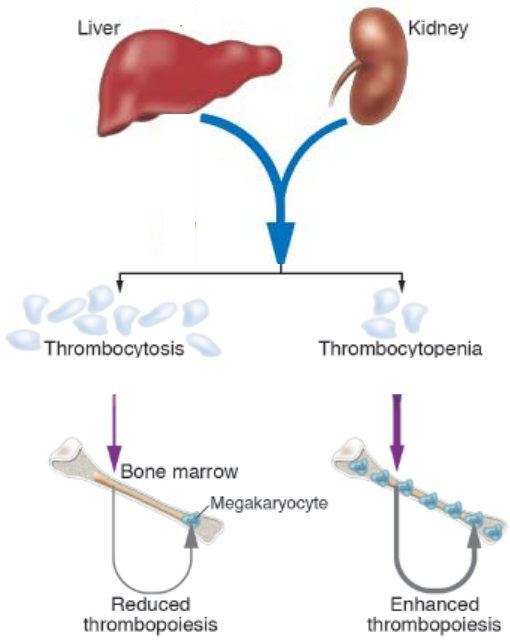

Figure 3 The regulation of thrombopoietin levels: A steady-state amount of hepatic thrombopoietin (TPO) is regulated by platelet c-Mpl receptor (TPO-R) – mediated uptake and destruction of the hormone. Hepatic production of the hormone is depicted. Upon binding to platelet c-Mpl receptors, the hormone is removed from the circulation and destroyed, which reduces blood levels. In the presence of inflammation, IL-6 is released from macrophages and, through TNF-α stimulation, from fibroblasts and circulates to the liver to enhance thrombopoietin production. Thrombocytopenia also leads to enhanced marrow stromal cell production of thrombopoietin, although the molecular mediator(s) of this effect is not yet completely understood.

A third mechanism of thrombopoietin regulation occurs in states of reactive thrombocytosis, where hormone concentrations are higher than that predicted by the degree of thrombocytosis. For example, inflammatory stimuli affect thrombopoietin production, with the acute-phase response mediator IL-6 increasing thrombopoietin transcription from the liver. These in vitro effects are also seen in vivo; administration of IL-6 to mice or cancer patients increases thrombopoietin-specific mRNA in the liver and levels of the hormone in the blood. Since an anti-thrombopoietin antibody neutralizes the thrombopoietic effects of administered IL-6, it is now clear that thrombopoietin is the final mediator of inflammation- induced thrombocytosis.

b) Additional modes of thrombopoietic regulation

In addition to thrombopoietin, additional factors likely influence thrombopoiesis, as the genetic elimination of thrombopoietin or its receptor leads to profound but not absolute thrombocytopenia (the platelet counts in these settings are about 10% of a normal level). In order to determine whether any of the known hematopoietic cytokines contributes to the residual thrombopoiesis in the *c-Mpl*–null state, such mice have been crossed with other cytokine- or cytokine receptor–deficient animals; from these studies it is clear that IL-3, IL-6, IL-11, and LIF are not basal, physiological mediators of thrombopoiesis. However, the chemokine stromal cell–derived factor-1 (SDF-1) exerts numerous influences on megakaryopoiesis, and studies indicate that it may be responsible for thrombopoiesis not related to thrombopoietin. For example, SDF-1 acts alone and in synergy with thrombopoietin to enhance megakaryocyte colony formation in serum-free culture. The chemokine also affects the motility of megakaryocytes, driving their migration toward stromal cells, with which they productively interact in an integrin $\alpha_4\beta_1$–dependent manner. The administration of SDF-1, along with FGF-4, can nearly normalize the platelet count of c-Mpl–deficient mice and can enhance platelet recovery following myelosuppression. Thus, accumulating evidence points to SDF-1 and marrow stromal cells as important influences on thrombopoiesis, but whether levels of the chemokine or surface expression of integrins can be modulated in response to thrombocytopenia remains unknown.

Chemical Signals: IL-6, NPY and others

It is interesting that IL-6 has an active role on thrombopoietin regulation, but then IL-6 has an active role in most things. The information gets confusing because of the signaling mechanisms of IL-6 itself. Serum IL-6 measurements only tell you half the story since the receptor for this cytokine can be shed from cell membranes under various circumstances and circulates as the soluble receptor sIL-6R. The soluble receptor forms a complex with serum IL-6 and so negates the signals that are meant to transmit via this chemical – the more so, the greater the transmission distances and the more proteolytic shedding of IL-6R from cells that express this target. Distant (paracrine) communication, such as we see in Figure 3 is thus susceptible in this way to influence by cellular kinetics driven from elsewhere. It is also susceptible to neuroimmune and neuroendocrine mechanisms, particularly involving sympathetic nervous responses. These alter the amount of IL-6 in circulation and change its association with other cytokines such as Il-1 and TNF-α.

Another unusual fact about Il-6 is that it follows a diurnal variation, just like the cortisol cycle although offset slightly in time. Still further, it is influenced strongly by exercise and obesity as smooth contractile muscle and also adipose cells secrete IL-6. Finally, the tendency to obesity or not depends on the way your body stores or consumes energy derived from dietary intake. How you sense satisfaction or hunger depends in part on neuropeptide Y (NPY) which operates on the other side of the blood brain barrier --- so convention of dividing the body into distinct little compartments would have you believe. But in fact, NPY is a true neuro-immune transmitter and is secreted from post-ganglionic nerves of the sympathetic nervous system (SNS) directly into the immune circulation. Here we are seeing a steady accumulation of hard science that binds events in the immune and endocrine spheres with consequences of SNS activity; with diet, obesity, exercise level, attitude, psychological stress and sleep patterns.

Current technical description places IL-6 as a true hormone, like TPO and the conventional list. Rather than simply being signaling molecules, they are part of the bodily process of systemic self-regulation. So; lifestyle, diet and surveillance are more than relevant to the current topic although specific research may still be limited. There is one further aspect of platelets that we might consider. Another key component of the platelets is serotonin. Serotonin is a mood elevating neurotransmitter, but 99% of the serotonin in the blood (2% of all that in your body) is held within the platelets. It is required to promote vascular constriction around damage sites to which platelets are attracted. In addition to serotonin, your platelets also carry its 'parent' or precursory

chemical L-tryptophan. While serotonin can't pass through the blood brain barrier, L-tryptophan can. Once again we have a linkage, although I must point out that studies suggest that the serotonin level in the serum is far more stable than it oft may be across the border in the brain.

The role of neuropeptide Y (NPY) on serum IL-6 levels has its own levels of interest. NPY is the most abundant neuropeptide in the brain. It is a true neuro-endocrine transmitter, secreted by the hypothalamus and it enters the blood directly. The mechanics go as follows. Both cellular and humoral functions of the immune system are modulated by the sympathetic nervous system (SNS). This interaction is mainly mediated by the release of catecholamines (CA) and their receptor-specific action on immune cells. However, neuropeptide Y (NPY), also present in sympathetic nerve terminals, is released upon SNS-stimulation. NPY modulates potent immunological effects in vitro and in vivo, such as differentiation of T helper cells, monocyte mediator release, NK cell activation, and immune cell redistribution. In addition to this direct action within the neuroimmune crosstalk, NPY is also able to modulate the immunomodulatory effects of other neurotransmitters, thereby acting as a neuroimmune co-transmitter. However it is depleted in concentration while being secreted from the nerve cells and is arguably a short term stimulant of the immune system. Its abundant period appears to be matched to the lag time for epinephrine to appear in the circulation. Their immune modulation effects are similar.

Be Observant

We should notice also that crash repair specialists are typically not fascinated by eliminating accidents; highway designers cannot overcome human inattention; and no-one really understands why so many are gripped by road rage, seeing every traveler nearby as an object to defeat and overtake. Controlling attitude and impulse is an essential for survival on any highway, including the highway of life. When you suffer from low blood platelet count or inadequate platelet function, you may notice: increased bruising; petechiae (red dots on your skin); bleeding from nose, gums, and rectum. These are ready signals if you are observant. They are markers you can watch to understand the progression of your condition. You need to keep a mental tally of lifestyle or other factors that might time with any significant change. Platelets can escape from the circulation without mechanical bleeding or by agglomeration and clearance. Your platelets might adhere to neutrophils under the influence of C-reactive protein or epinephrine (adrenaline) or they might be stuck together in a number of ways. Also, the platelets may be direct targets for destruction by the immune system. Platelets may be coated with an antibody and then removed as a result of infections, as a side-effect of medicines like quinine or in conjunction with specific diseases in which abnormal production of other antibodies may occur (for example, rheumatoid arthritis). Finally the adequacy of platelet function depends on their surface chemistry and the amount of agents such as serotonin held within them. As a result, a low platelet count does not transcribe to simple Rx response. It also seems safe to generalize that we have more things at hand to reduce platelet count in total than we have to increase it.

So it is really important to watch the signs and any trends that occur; manage yourself in the light of those signals; don’t expect an abrupt chemically-driven conquest over the dynamics within, and; be willing to invest in a process of steady improvement. For example, be observant and notice whether there are any changes in visible signs and if there is a noticeable change in the way that a scratch on your skin will show blood, form droplets and then clot over. Be especially careful about pain relieving medication such as aspirin and ibuprofen – not just which ones you use, but how much and how frequently. Yet, some improvements come along unexpectedly and you have to think about their root cause in order to build on them. However smart the doctors, they are in the hands of the patient. Be a smart patient.

2. About ITP: The Platelet Disorder Support Association

From the PDSA website[10]: ITP, idiopathic thrombocytopenic purpura, also known as immune thrombocytopenic purpura, is classified as an autoimmune disease. In an autoimmune disease the body mounts an attack toward one or more otherwise normal organ systems. In ITP, platelets are the target. They are marked as foreign by the immune system and eliminated in the spleen, or sometimes the liver.

Researchers have identified more than eighty autoimmune diseases. The National Institutes of Health (NIH) estimates that 5% to 8% of the United States population, between 14 and 24 million people, suffer with autoimmune disease. The number of individuals in the United States with ITP has been estimated to be approximately 200,000. In adults, about three times more women have the disease than men. In children, the ratio is about even. It affects all age and ethnic groups. There are about 100 new cases of ITP per million people per year. Approximately half of the new cases are in children.

All blood cells originate and mature in the bone marrow. They begin in 'stem' cells, then differentiate into the red cells, white cells, and platelets. The white blood cells include three varieties, granulocytes, monocytes (macrophages) and lymphocytes. Normal platelet counts range from 150,000 to 400,000 per cu/ml. Those with ITP have a lower platelet count. It can range from severe cases that hover close to zero to more mild cases where the counts stay in closer to 100,000. It is important to understand that 30,000 is often considered a 'safe count,' one that is high enough to protect against cerebral hemorrhage. In people with ITP the platelets are often enlarged. They stay in the blood stream from a few hours to close to the normal eight to ten days depending on the severity of the disease.

Platelets play a crucial part in the blood clotting process by forming a platelet plug. This is a two step process. First, single platelets bind to the site of the wound (adhesion). Next, the platelets bind to each other (activation). Activation can be stimulated by components released when the blood vessel is damaged and by thrombin, released during the blood clotting process. When platelets become activated they change. They release agents which recruit and activate the surrounding platelets. The result of these two processes is the formation of fibrin which stabilizes the platelet plug, stops bleeding and allows injuries to heal.

Below are lists of drugs and other substances that may reduce blood platelet counts in some individuals. Reactions vary between individuals. According to PDSA information, "Quinidine, quinine, sulfonamides, nonsteroidal anti-inflammatory drugs, and gold compounds were among the most frequently reported drugs that cause thrombocytopenia. Another list of adverse side effects is maintained by the FDA. The Blood Center of Southeastern Wisconsin has a laboratory that can test for drug-induced thrombocytopenia and other platelet problems.

SUBSTANCES THAT REDUCE PLATELET COUNTS

Common Drugs that can significantly reduce platelet counts

Inflammation/Pain	
acetaminophen	(Tylenol, Panadol, others) - considered safe by many, however, some incidences of platelet reduction were found in journal articles.
aspirin	(acetylsalicylic acid, ASA) relief of mild to moderate pain and inflammation. Decreases white blood cells and platelet counts.
ibuprofen	NSAID
diclofenac	analgesic NSAID, (Apo-Diclo, Arthrotec, Cataflam, Novo-difenac,Voltaren)
meclofenamate sodium	NSAID (Meclomen)
morphine	analgesic, opioids
naproxen	NSAID, (Naprosyn)
piroxicam	NSAID, analgesic, (Apo-Piroxicam, Feldene, Novopirocam, Nu-Pirox)
sulfasalazine	bowel anti-inflammatory (Azaline, Azulfidine, Salazopyrin)

http://www.pdsa.org/itp-information/itp-warnings.html

[10] http://www.pdsa.org/itp-information/itp-warnings.html

Drugs that can significantly reduce platelet counts

Anxiety/Depression	
diazepam	antianxiety, tranquilizer (Valium, among others)
chlorpromazine	antipsychotic, tranquilizer (Chlorpromanyl, Largactil, Thorazine)
imipramine	antidepressant (Antipress, Apo-imipramine, Impril, Janimine, Tipramine)
thiothixene	(Navane)
Arthritis	
penicillamine	antiarthritic, heavy metal poisoning, (Cuprimine, Depen)
Attention Deficit Disorder	
methylphenidate hydrochloride	(Ritalin) thrombocytopenia purpura is listed as a side-effect
Cancer	
levamisole	(Ergamisol)
interferon alpha	(Roferon A, Intron A)
tamoxifen	(Nolvadex)
Cholesterol	
atorvastatin calcium	(Lipitor) - binds to plasma proteins
See: M L Gonzalez-Ponte:, 'Atorvastatin-induced severe thrombocytopenia. (Research Letters): Oct 17, 1998 - Lancet	
Diabetes	
chlorpropamide	antidiabetic, (Apo-Chlorpropamide, Chloronase, Diabinese, Glucamide)
Fungus Infection	
amphotericin	(Amphocin, Fungizone)
Gout	
allopurinol	(Alloprin, Lopurin, Novopurol, Purinol, Zurinol, Zyloprim)
Hair Loss	
minoxidil	antihypertensive, hair growth stimulant (Minodyl, Minoximen, Rogaine)
Heartburn	
cimetidine	Heartburn Tagamet, also Zantac, Pepcid
ranitidine	H-2 Receptor blocker (Zantac)
Heart Conditions	
acetazolamide	Used for glaucoma, seizures, retention of fluid in congestive heart failure, mountain sickness
amiodarone	(Cordarone)
amrinone	(Inocor)
diltiazem	antianginal, antihypertensive, calcium channel blocker (Apo-Diltiaz, Cardizem)
digoxin	digitalis preparations, congestive heart stimulant and treatment of heart rhythms. (Lanoxicaps, Lanoxin, Novodigoxin.)
procainamide	antiarrhythmic (Apo-Procainamide, Procamide, Procanbid, Promine, Rhythmin)
quinidine	antiarrhythmic (Apo-Quinidine, Cardioquin, Duraquin, Quinora)
High Blood Pressure / water retention	
chlorothiazide	diuretic, antihypertensive (Aldoclor, Diachlor, Diupres, Didudrigen, Diuril, Supres)
chlorthalidone	antihypertensive, diuretic (Apo-Chlorthalidone, Combipres, Hygroton-Reserpine, Thalitone, Uridon)
furosemide	antihypertensive, diuretic (Lasix, Lo-Aqua, Luramide)
quinapril hydrochloride	(Accupril)
Infections	
ampicillin	antibiotic used to treat infections (Amcill, Ampicin, Ampilean, Omnipen, Polycillin, Penbritin, Principen)
cephalosporins	anti-infectives cefaclor (Ceclor), cefadroxil (Duricef, Ultracef), cefamandole (Mandol) cefazolin (Ancef, Kefzol, Zolicef) cefixime (Suprax) cefmetazole (Zefazone), cefonicid (Monocid) cefoperazone (Cefobid) ceforanide (Percef) cefotaxime (Claforan), cefotetan (Cefotan) cefoxitin (Mefoxin) cefprozil (Cefzil) ceftazidime (Fortaz, Tazidime, Tazicef) ceftizoxime (Cefizox), ceftriaxone (Rocephin) cefuroxime (Ceftin, Kefurox, Zinacef) cephalexin (Keflex, Keftab) cephalothin (Keflin) cephapirin (Cefadyl) cephradine (Anspor, Velosef) moxalactam (Moxam) Omnicef
nalidixic acid	(Negram)
penicillin	antibiotic causes abnormal bleeding or bruising
pentamidine isethionate	(Pentam, NebuPent, Pentacarinate)
rifampin	antibiotic (Rifadin, Rifamate, Rofact)
sulfamethoxazole	anti-infective (Apo-Sulfatrim, Bactrim, Comoxol, Septra, etc.)
trimethoprim/sulfamethoxazole	anti-infective (Apo-sulfatrim, Bactrim, Coptin, Septra)
vancomycin	anti-infective (Vancocin, Vancoled, Vancor)
Malaria	
chloroquine	used to treat malaria and amebic infection , causes bone marrow depression (Aralen, Kronofed-A-JR)
hydroxychloroquine	(Plaquenil) - antimalarial, immunosuppressant, used in lupus, rheumatoid arthritis,

	causes bone marrow suppression
Premenstrual Distress	
Sarafem	
Seizure Disorders	
acetazolamide	anticonvulsant (Ak-Zol, Dazamide, Diamox, Storzolamide)
carbamazepine	anticonvulsant , reduced formation of all blood cells (Apo-carbamazepine, Epitol, Mazepine, Tegretol).
phenytoin	anticonvulsant (Dilantin, Ekko JR, Mebroin, Phelantin)
topiramate	anticonvulsant (Topamax)
valproic acid	anticonvulsant (Depakote, Epival)
zonisamide	(Zonegran) also used for migraine and weight loss
Tuberculosis	
isoniazid	antituberculosis (Isotamine, Laniazid, Vitamin B-6)
ethambutol	(Myambutol)

http://www.pdsa.org/itp-information/itp-warnings.html

Products that Contain phenylpropanolamine (PPA) can reduce the number of Platelets

Acutrim Diet Gum Appetite Suppressant Plus Dietary Supplements
Acutrim Maximum Strength Appetite Control
Alka-Seltzer Plus Children's Cold Medicine Effervescent
Alka-Seltzer Plus Cold medicine (cherry or orange)
Alka-Seltzer Plus Cold Medicine Original
Alka-Seltzer Plus Cold & Cough Medicine Effervescent
Alka-Seltzer Plus Cold & Flu Medicine Effervescent
Alka-Seltzer Plus Cold & Sinus Effervescent
Alka Seltzer Plus Night-Time Cold Medicine Effervescent
BC Allergy Sinus Cold Powder
BC Sinus Cold Powder
Comtrex Deep Chest Cold & Congestion Relief
Comtrex Flu Therapy & Fever Relief Day & Night
Contac 12-Hour Cold Capsules
Contac 12 Hour CapletsCoricidin D Cold, Flu & Sinus
Dexatrim Caffeine Free
Dexatrim Caffeine Free
Dexatrim Extended Duration
Dexatrim Gelcaps
Dexatrim Vitamin C/Caffeine Free
Dimetapp Cold & Allergy Chewable Tablet
Dimetapp Cold & Cough Liqui-Gels
Dimetapp DM Cold & Cough Elixir
Dimetapp Elixir
Dimetapp 4 Hour Liquid Gels
Dimetapp 4 Hour Tablets
Dimetapp 12 Hour Extentabs Tablets
Naldecon DX Pediatric Drops
Permathene Mega-16
Robitussin CF
Tavist-D 12 Hour Relief of Sinus & Nasal Congestion
Triaminic DM Cough Relief
Triaminic Expectorant Chest & Head Congestion
Triaminic Syrup Cold & Allergy
Triaminic Triaminicol Cold & Cough
Triaminic Orange 3D Cold & Allergy, Cherry (Pink) 3D Cold & Cough, Berry 3D Cough Relief, Yellow 3D Expectorant

Go to the FDA website for more information: www.fda.gov/cder/drug/infopage/ppa/

Other substances that can reduce the number of platelets

alcohol
alfalfa sprouts (if likely to harbor salmonella)
allicin (in Kwai, Kyolic & other garlic supplements)
chlorine
dong quai (angelica sinensis)
echinacea
gold and gold salts
Metabalife (contains Ma Huang and other substances that interfere with blood clotting)
niacin (by causing liver problems)
pesticides
quinine (found in tonic water and bitter melon)
salicylates

http://www.pdsa.org/itp-information/itp-warnings.html

PRESERVING THE PLATELET PRODUCTION

Not everything in life that can cause harm is wished onto us by lawmakers, taxation agents and drug companies. In fact the greatest devil we face individually is ourselves. Alcohol is a personal choice about which the whole society tends to operate in denial – not by disputing its effects, but by failing to observe the recommendations regarding daily intake, how they differ between the sexes, and how it changes as we age. It has / can exert an adverse effect on the platelet count. Seemingly, everything that arouses the taste and jars excitement has to be moderated continually as we age. And that does not come as a surprise really since our systems are increasingly slower to return to whatever our quasi-normalcy might be – and we have accrued a steadily growing level of burden simply by virtue of the exposures our bodies have endured over the years. There is, however, a question of balance and judgment as we proceed from this point to look at

things that reduce the ability of platelets to clot. Some of these will include food choices that are desirable from other viewpoints.

And it seems to me that we cannot simply decide to avoid decisions concerning the platelet clotting ability while focusing on those rather less personal choices that apparently degrade the actual platelet count. The reason, simply, is that the miles of arteries, veins and pathways along which the platelets perambulate are not impermeable things. If they were, the body could not sustain the muscle and tissue. Platelets are small things, the smallest elements in the blood, and we do not want them to climb out of the space where they belong by processes of non-mechanical bleeding. We might never see such bleeds, but we will lose platelets and other things as a result. So yes, the fort is guarded best by ensuring that the platelets are not spread freely into places they belong. Several dietary decisions impinge here alone. One of which is the level of available serotonin to act as vascular constrictor. But in addition, we have auto-antibodies that could attack the platelets and encourage macrophages to consume them. Even T-cell balance is now seen as important to preserving the platelets that are created. Interestingly, then, a recommended diet to combat thrombocytopenia merges seamlessly with diets designed to guard against rheumatoid arthritis. My personal experience again has shown a sudden major increase in platelet count following basic dietary trends in the household as my wife started to combat rheumatoid arthritis through diet. So we will look at the additional changes coming from that direction in the following sections.

Substances that reduce the ability of platelets to clot

- aspirin
- aspartame (can also cause thrombocytopenia)
- beer (especially dark beer)
- blueberries
- chocolate (dark)
- chondroitin sulfate (can act like heparin)
- vitamin E
- feverfew
- heparin (can also cause thrombocytopenia)
- garlic/onions
- gingko biloba (can also reduce platelet count)
- ginger
- ginseng
- goldenseal
- green tea
- guarana
- red/purple grape products (grape juice, red wine, raisins)
- pycnogenol
- Omega 3 fatty acids
- SSRI's (Prozac, etc.)
- Quercetin, rutin, and related bioflavonoids
- ticlopidine (ticlid) used to prevent blood clots
- tomatoes
- wood ear mushrooms

http://www.pdsa.org/itp-information/itp-warnings.html

3. ITP Diet Suggestions: The Platelet Disorder Support Association

In the PDSA Survey of Non-Traditional Treatments in ITP[11] about 40% of the responders reported some improvement in their bleeding symptoms and their platelet count with either the macrobiotic diet or the diet recommended in Eat Right for Your Type by Dr. Peter J. D'Adamo. Less success was reported for the Atkins and Zone diets, high protein, low carbohydrate diets. The recommendations listed below are based on principals from the macrobiotic and "Eat Right" diet, general nutritional research and research linking the impact of diet changes on other diseases that have common features with ITP.

If you would like to implement some of the diet changes listed in this article, please make the changes slowly so your body can adjust. Sometimes diet changes can cause withdrawal and detoxification symptoms as your body adjusts to the new foods and eliminates the old.

These suggestions are guidelines only. Be sure to discuss any diet changes with your physician.

1. **Eat a wide variety of fresh food**
   Maximize the value of each bite. Eat food from as close to the source as possible and as soon as possible. Avoid canned and frozen foods and leftovers. The nutritional value of food deteriorates with time. A wide variety of food assures your body gets the variety of nutrients it needs.

[11] www.itppeople.com/survey/2001/index.html

2. **Eat whole foods**
   Eat whole grain cereals, brown rice, and whole wheat products. Reduce the amount of white flour, white rice and processed foods. Processed grains are stripped of their natural nutrient-rich coating.
3. **Eat organic foods**
   Eat un-sprayed foods grown using natural fertilizers. Some pesticides and herbicides have been shown to exacerbate autoimmune diseases and lower platelets. Additives and preservatives can increase the disease-causing free radicals in your body.
4. **Reduce sugar**
   Reduce the amount of white refined sugar as well as fructose, corn syrup, honey and other sweeteners. Limit fruit and fruit juice. Sugar contributes to an acidic disease-promoting body condition.
5. **Reduce dairy products**
   Reduce or eliminate milk, cheese, ice cream, and yogurt from your diet based on your reaction to these foods and other dietary needs. Dairy foods have been shown to contribute to mucus formation and exacerbate some autoimmune diseases.
6. **Eat healthy fats**
   Use cold pressed oils such as olive or canola in cooking and baking. Avoid hydrogenated, partially hydrogenated or trans-fats. These contribute to free radical damage. Reduce the amount of deep fried food which also adds to the free radical load.
7. **Eat green**
   Eat as many leafy greens as possible, especially kale and collards. Add sea vegetables (sea weed) to your diet. These choices contain large amounts of calcium, minerals, and vitamin K to help clotting.
8. **Limit meat**
   Rely on lean, white fish, whole grains and beans and some nuts for protein. Meat is often laced with residual antibiotics, hormones, and saturated fat.
9. **Avoid problem foods**
   Avoid alcoholic beverages which can damage bone marrow. Reduce the amount of blueberries, red/purple grape products, garlic, onions, ginger, ginseng, and tomatoes. These foods can interfere with blood clotting. Avoid food and drinks containing quinine[12]:
10. **Avoid allergic foods**
    Many people have delayed food allergies that produce vague and difficult-to-diagnose symptoms. If you don't feel well, consider having a food allergy test.
11. **Chew your food well**
    Chewing each bite until it is liquid can aid digestion, aid the passage of nutrients into your blood stream, and promotes healthy alkaline blood chemistry.
12. **Drink pure warm water**
    Drink plenty of filtered or bottled water at room temperature or above. Taking periodic sips of hot water can cleanse impurities from the body. Ice water can slow and hinder the digestive process. Tap water may contain small amounts of chemicals that are harmful.

4. My further Diet Suggestions

Luckily for my sanity, diets tailored to reduce rheumatoid arthritis are built around the traditional Mediterranean diet that has been shown through numerous studies to be a desirably basis for healthy living. Key features include:

- High consumption of breads, pasta, rice, couscous, polenta, bulgur and potatoes
- High consumption of fruits (3-4 pieces a day), legumes and vegetables (5 different varieties)
- Moderate amounts of grilled and steamed fish
- Moderate amounts of olive oil - consumed with fresh vegetables and on salads
- Small portions of lean red meat with no visible fat and lean pork
- Alcohol in small amounts, but take the time to understand what "small" and "average" mean.

[12] www.itppeople.com/warnings.htm

There are several variations to the principles[13], summarized under the following headings;

Eliminate nightshades. One of the most common diet claims is that eliminating nightshades, which include potatoes, tomatoes, eggplants, and most peppers, relieves arthritis.

Alkaline diet. The alkaline diet presumes both OA and RA are caused by too much acid. Among the foods it excludes are sugar, coffee, red meat, most grains, nuts, and citrus fruits. This diet eliminates most vitamin C sources, a factor one needs to understand

Dong diet. This restrictive diet relies heavily on vegetables, except tomatoes, and eliminates many of the same foods as the alkaline diet.

Vegetarian diet. Some people report improvement in symptoms, but evidence is mixed.

Switching fats. One of the known correlations between food and arthritis is that omega-6 fatty acids increase inflammation, and omega-3 fatty acids reduce it. Limit intake of meat and poultry, and increase your intake of cold-water fish, such as sardines, mackerel, trout, and salmon. For salad dressings and cooking, substitute olive, canola, and flaxseed oils for corn, safflower, and sunflower oils.

Gin-soaked raisins. Lots of people claim it works, but experts say there's no evidence. Grapes and raisins do contain anti-inflammatory compounds, but not in amounts that would be therapeutic.

Green tea. Drinking three to four cups of green tea a day could help people with RA.

Although I have followed the recommended diet for ITP patients with some revisions, as follows;

Eat more
- Cold water fish such as salmon, tuna, herring, mackerel and halibut for their beneficial omega 3 fatty acids
- Salmon, tuna, shrimp, sunflower seeds, eggs and (provided no dairy allergy is present) vitamin-D fortified milk products for their vitamin D
- Organically grown fruits and vegetables
- Extra virgin olive oil

Eat Less
- dairy, if allergy is suspected or confirmed
- wheat, if allergy is suspected or confirmed
- meat, particularly high-fat cuts
- saturated fat, including partially hydrogenated oils

Restrict
- nightshades (potatoes, tomatoes, eggplants, and most peppers)
- sugars and alcohol (preferably none)
- highly spiced foods (Mexican cuisine, curries etc)

1. **Eat a wide variety of fresh food**
   Avoid restaurant or other dining that relies on prepared foods which, although they might appear fresh, are frequently liberated by use of various preservative approaches.
2. **Eat whole foods**
   Reduce the use of flour where possible. Consider arrowroot in cooking. Don't use breads as alternative to other grain sources that have reduced salt and sugar content.
3. **Eat organic foods**
   Many of the 'problems' associated with non-organic foods can be eliminated by thorough preparation.
4. **Reduce sugar**
   Hold the line as firmly as possible with sugar elimination, being sure to achieve energy requirements through suitable carbohydrate and protein sources. Beware of sugar content in breakfast cereals.

[13] http://www.medicinenet.com/script/main/art.asp?articlekey=46269. See also http://www.whfoods.com/foodadvisor.php

5. **Reduce dairy products**
   Limit the fat intake from dairy products but treat cheese as a valuable protein source.
6. **Eat healthy fats**
   Reduce the amount of fried food and fatty choices.
7. **Eat green**
   Eat as many greens as reasonable, but ensure full quotas of different colored vegetables.
8. **Limit meat**
   Limit meat to one meal per day only, at a standard serving size of 145gm / 5oz. At least one day should be entirely vegetarian and two days should be fish meals, chosen for omega 3 fatty acids.
9. **Avoid problem foods**
   Zero alcoholic beverages and minimal vegetables / fruits of the nightshade family. Highly spiced meals such as Mexican cuisine and curries re reserved for special occasions. Fresh red/purple grapes are eaten almost daily at a serving size of about 200gm / 7oz per day. I do savor that 25gm or so of chocolate at night.
10. **Avoid allergic foods**
    Have a food allergy test if you have an allergic symptoms; especially look for dairy and wheat allergies.
11. **Chew your food well**
    Make each meal a pleasant relaxed time.
12. **Drink pure warm water**
    Ensure you do not become dehydrated. The level of hydration is measured by the amount you urinate, not by what you consume. Beware of diuretics in sodas and similar drinks.