

# Idiopathic Thrombocytopenic Purpura: Pathophysiology and Management

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## Abstract

Our understanding of the pathophysiology of ITP owes to pioneering work of W J Harrington in 1951, delineating the immunologic nature of platelet destruction. In ITP, antibody-coated platelets are destroyed by macrophages of RES. However, other mechanisms are also implicated: C-mediated platelet lysis and newly described C-independent peroxide injury. Both induce platelet fragmentation and lysis, generating procoagulant platelet microparticles (PMP). A third mechanism of platelet consumption in the microvasculature is proposed, based on overlapping syndromes of ITP and TTP in some patients. In assessing hemostasis in ITP, platelet counts alone is not sufficient. Evaluation of platelet clumping, giant platelets, and platelet activation, marked by increased PMP is useful. Patients with platelet activation or giant platelets bleed less and detection of clumping prevents unwarranted therapy. Thrombotic complications may develop in ITP. A syndrome, characterized by recurrent TIA-like symptoms, progressive memory loss due to ischemic small vessel disease is described. The management of ITP should include the search for and elimination of underlying causes and careful evaluation of hemostasis. Therapy is divided into definitive vs symptomatic measures. The former including splenectomy, danazol, chemotherapy offers lasting remission after therapy was stopped, while the later including glucocorticoids, gammaglobulin, antiD antibodies and others increases platelet counts but seldom sustains remission upon withdrawal. Danazol therapy is up-dated since it is an effective and safe definite measure in ITP.

*Key Words:* ITP;Platelet microparticles;Danazol

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## 1. Historical Background on ITP

Idiopathic thrombocytopenic purpura (ITP) is the most common autoimmune blood disorder. In this disease, autoantibodies interact with platelets to render them susceptible to rapid clearance from the circulation. In adults, it is usually a chronic and life-long condition but in children it is often self limiting. Many reviews of ITP have been published. This review emphasizes developments made at our institution and is limited to adult ITP.

In the early 20th century, two conflicting theories for the cause of thrombocytopenia in ITP were debated. One group believed that thrombocytopenia in ITP is caused by peripheral destruction of platelets while the other proposed that impaired platelet production was the main pathology.

This controversy was resolved by a paper by Dr.

William J Harrington, published in 1951, based on self-experimentation: he injected himself with plasma from his ITP patients and documented a rapid fall in his platelet counts, within several hours. His platelet counts plummeted below 10,000 as he developed chills, fever, headache, confusion and petechiae. After one week, his platelet counts returned to normal [1]. He performed similar experiment on volunteers, confirming his original finding, and concluded that some factor in the plasma of ITP patients was destroying the platelets. He later provided evidence that the plasma factor resided in the gamma-globulin fraction, and suggested that it was in fact an antibody against platelets [1-3].

Through this seminal observation, he resolved the controversy of pathogenesis of ITP at the young age of 28. A few years later he had written a comprehensive review on the pathogenesis of ITP, appearing in *Progress in Hematology* [3]. In that review, he predicted that the

spleen would turn out to be the major site of platelet destruction as well as antibody production and furthermore, that antibody directed against megakaryocytes and could pass the placenta to cause neonatal thrombocytopenia. His review of 1956 correctly anticipated most of our present-day knowledge of the pathogenesis of ITP. See the brief biography of Dr. William J Harrington at the last page.

In 1965, Schulman et al extended the observation of Dr. W.J. Harrington, further delineating the plasma factor in the pathogenesis of ITP [4] and showing that the degree of thrombocytopenia following infusion of ITP plasma depended on the dose of plasma infused. With high-dose of ITP plasma, platelets were mainly destroyed in the liver while at low-dose they were destroyed in the spleen. Removal of the spleen negated development of thrombocytopenia, and administration of glucocorticoids (GC) minimized thrombocytopenia. In addition, reticulo-endothelial blockade by red cell stroma completely inhibited sequestration of platelets sensitized with ITP plasma [4]. These pioneering works, by Dr. Harrington in the 1950s [1-3] and Dr. Schulman in the 1960s [4], provided unequivocal evidence for, and delineation of, the basic pathophysiology of ITP.

Recent studies reveal that thrombopoietin (TPO) levels in ITP are low compared to those with thrombocytopenia from aplastic anemia, suggesting inappropriate thrombopoiesis in most patients with ITP [5]. Thus, it is now fair to say that both sides of the early 20th century controversy had been partly right, although we now know that platelet destruction is the major cause of thrombocytopenia in ITP. Chromium-labeled platelet survival in normal healthy controls is 8 days, while in severe ITP, the 50%-disappearance time (T1/2) of labeled platelets is extremely short, ranging from 2 - 9 minutes [6]. This indicates the overwhelming power of platelet destruction in severe ITP.

## 2. Mechanisms of Thrombocytopenias in ITP

Since all therapies of ITP are aimed at preventing platelet destruction, it is essential to understand the mechanisms of platelet destruction in order to design rational therapy. However we do not yet fully understand them.

### 2.1. Phagocytosis by Macrophages

It is widely believed that platelets are destroyed by the mononuclear phagocytic system in ITP [1-4]. The Fc portion of antibodies on the surface of platelets binds to Fc receptors (FcR) of macrophages, triggering phagocytosis. Under this assumption, the interaction of macrophages with opsonized platelets is the key event determining platelet destruction and influences the severity of thrombocytopenia. Accordingly, three factors will determine the severity of platelet destruction in ITP: (1) amount of antibodies coating the platelets, (2) activity of Fc receptors of macrophages, and (3) micro-environment facilitating this interaction, the spleen being

the optimum milieu. Most present therapies act to (i) block or down-regulate Fc receptors of macrophages (GC, danazol, IV gammaglobulin, antiD antibodies). Other strategies include (ii) suppression of antibody production by B cells (chemotherapy, Ritoxan) or (iii) elimination of optimal milieu (splenectomy), or others considered below.

However, it is now increasingly recognized that additional mechanisms are also operating, at least in some subsets of ITP patients.

### 2.2. Platelet Lysis

Complement-mediated platelet lysis has long been suggested in ITP, though it has not been well documented clinically. In vitro, ITP antibodies fix complement to platelets and cause lysis, suggesting that this mechanism may operate also in vivo in some patients with ITP [7,8]. Platelet lysis in vivo has been reported in a patient with ITP associated with monoclonal IgM antiplatelet antibodies [9]. Horstman et al demonstrated that in the presence of fresh serum, antiplatelet antibodies induced fragmentation and lysis of platelets in vitro and generated procoagulant platelet microparticles (PMP) [10]. This effect was abolished if the serum was heated, indicating a role of complement in antibody-mediated fragmentation and lysis of platelets [10].

Recently, a completely different mechanism has come to light. Wentworth et al demonstrated that virtually all antibodies can generate hydrogen peroxide to damage and fragment cells without complement, and proposed that this represents a built-in killing function [11]. Nardi et al reported that antibodies specific to epitopes of GPIIIa 49-66 from patient with HIV-associated ITP generated peroxide-induced platelet damage, leading to platelet fragmentation, release of procoagulant PMP, and thrombocytopenia [12]. This new mechanism of platelet lysis remains to be explored in ITP.

### 2.3. ITP/TTP Overlapping Syndromes: Platelet Consumption in the Microvasculature?

It has been well documented that some patients with ITP may develop TTP, or TTP may relapse as ITP [13-15]. These overlapping syndromes are not yet well recognized but are more frequently described in patients with HIV and HTLV-1 infection [16]. When manifesting ITP, they respond well to GC, much like classic ITP; but when manifesting TTP, GC is ineffective while exchange plasmapheresis/plasma infusion is required, as in classical TTP.

It is not yet clear if this overlap represents a spectrum of one disorder or a transformation from one to the other. One possibility is that antibodies may cross-react between platelets and endothelial cells, with endothelial injury occurring only at the higher concentrations of antibodies. By this hypothesis, concentration of antibodies could determine the courses of ITP/TTP and their inter-conversion. Microangiopathies may be present in many patients with ITP. Dr. Zucker-Franklin et al

described red cell fragmentation in most patients with ITP when examined by electron microscopy [17], indicating that subclinical microangiopathy is common in ITP. Microangiopathic platelet consumption may occur in ITP, but its frequency and extent remains to be elucidated.

### 3. Hemostasis in ITP

Platelet count has been the major parameter for predicting severity of ITP and risk of bleeding. But most hematologists are well aware that this is not true in many patients with ITP. Some with severe ITP (platelets less than 10,000) do not bleed while others with higher platelet counts bleed excessively.

Platelet dysfunction in ITP has been well described in the literature, indicating that antiplatelet antibodies can and do influence platelet function [18-22]. Antibodies may bind to adhesion molecules or other receptors on platelets to alter platelet function. They may impair adhesion and aggregation of platelets, inducing features of Glanzmanns thrombasthenia [20] or inducing Bernard-Soulier-like syndromes [21] or various other platelet dysfunctions. These patients bleed even with normal platelet counts. In contrast, some antibodies may activate platelets, promoting thrombotic complications in ITP [22].

#### 3.1. Other Related to Hemostasis in ITP

Platelet clumping (Pseudothrombocytopenia). Platelet counts can be factitiously low due to platelet clumping in vitro (following blood drawing). Failure to recognize pseudothrombocytopenia can lead to erroneous diagnosis of ITP, subjecting patients to unwarranted, potentially dangerous, and expensive therapy. In addition, platelet clumping makes it difficult to assess the degree of thrombocytopenia in ITP patients.

Clumping is a rather frequent laboratory finding, seen in 15-17% of thrombocytopenic patients at two clinics [23,24]. It is most often seen in blood drawn in EDTA, less with ACD or citrate. However, it is not restricted to EDTA [25]. Among anticoagulants, EDTA and heparin were worst [26]. Supplementation with aminoglycosides, either before or after blood drawing, prevented clumping [27,28], while use of iloprost was only partially effective [27].

Mechanisms of platelet clumping may be diverse. EDTA and other anticoagulants including ACD partially but immediately activate platelets, upregulating expression of CD62, CD63, and inducing platelet aggregation [25,26]. IgG antibodies [29] or cold reacting IgM autoantibodies [30] against GP IIb were responsible for clumping in many reported cases, and EDTA induced conformational changes to make antigenic binding sites accessible to antibodies [29]. Two-thirds of patients with platelet clumping with EDTA were positive for anticardiolipin antibodies in one study [31]. Pseudothrombocytopenias due to platelet clumping was observed following infusion of abciximab (Fab fragment of a

chimeric monoclonal antibody to Gp IIb/IIIa) for acute coronary ischemias [32].

Platelet clumping occurs with ITP patients and factitiously lowers platelet counts. Correct platelet counts are difficult to obtain with automated blood counters. It is important to examine blood smears and count platelets manually in ammonium oxalate.

Giant platelets are young platelets, more active metabolically and functionally [33]. They are the platelet counterparts of reticulocytes (young red cells) and are prominent in conditions of increased platelet production with rapid turnover, such as ITP [34]. Patients with giant platelets bleed less, implying they are hemostatically active. Some giant platelets may not be counted as platelets by automatic blood counter, therefore true platelet counts may be much higher than indicated by automated platelet count.

Platelet microparticles (PMP) and platelet activation in ITP. We described increased PMP in patients with ITP [35]. Those with high PMP bled less compared to those with similar platelet counts but low PMP. Those with higher PMP seldom bled in spite of severe thrombocytopenia. On the contrary, we described a group of ITP patients with unusually high PMP who suffered from subtle recurrent TIA from ischemic small-vessel disease in CNS. They presented with recurrent weak spells, dizzy spells, memory loss and progressive cognitive dysfunction, leading to vascular dementia. MRI of brain revealed subcortical lesions consistent with ischemic small vessel diseases. We suggested that high concentration of procoagulant PMP promoted thrombosis in small vessels in CNS.

In vitro studies showed that anti-platelet antibodies induce complement-mediated platelet fragmentation and release of PMP. However, incubation of opsonized platelets with phagocytic cells did not release PMP. This suggests that the high PMP seen in some ITP patients could be due to autoantibody-induced platelet fragmentation with complement [10]. PMP are procoagulant, exhibiting platelet factor 3 (PF3) activity and capacity to bind annexin V. Although procoagulant PMP appear to protect against bleeding in thrombocytopenic states, they may also promote thrombotic occlusions of small subcortical vessels, leading eventually to vascular dementia in later life [35-38]. The efficiency of PMP detection may vary with different flowcytometers [37] but ELISA methods are available [39].

Increased platelet microparticles are often associated with markers of platelet activation. These include increased expression of CD62P, and functional PF3. Patients with marked platelet activation seldom bleed even in thrombocytopenic state.

Thrombotic complications in ITP. In addition to ischemic small vessel diseases described above, other thrombotic complications may occur in ITP. We reported acute coronary syndrome (ACS) developing in ITP patients despite limited risk factors and relatively young ages [40], as well as venous thrombosis and mesenteric vein thrombosis, especially following splenectomy [41]. Several investigators have described throm-

bosis in patients with ITP. In one case study, antiplatelet antibodies activated platelets in vitro, suggesting that platelet activating autoantibodies were responsible for the observed thrombotic complications [22]. In most of these patients, laboratory indicators of platelet activation were positive.

These findings indicate that some ITP patients may suffer from both bleeding and thrombotic complications. They are not necessarily protected from thrombotic complications by low platelet counts.

#### 4. Therapy of ITP [42-44]

Selection of therapy of ITP may be seen as a 3-step process.

Step 1 is to search for and eradicate the cause of thrombocytopenia. This should not be based solely on initial evaluation but must continue throughout the course of patient care. The search should include the following considerations:

1) Infections: Bacterial (H Pylori), viral (HIV, HTLV-1, hepatitis C, EB virus infections, etc.), or other infections.

2) Underlying other autoimmune diseases such as collagen vascular diseases, cryoglobulinemia, anticardiolipin antibody syndromes, etc.

3) Underlying neoplasms, especially lymphoproliferative disorders. ITP associated with low-grade neoplasms present a difficult challenge. However, eradication of such underlying causes will cure the ITP.

Step 2 is to determine whether or not to treat low platelet counts. In this regard, the hemostatic setting discussed above should be carefully considered. We do not treat low platelet counts in completely asymptomatic patients with ITP.

Step 3 is to select the appropriate therapy among many therapeutic options.

Therapy of ITP can be classified into definitive vs. symptomatic measures. Definitive therapies may be defined as treatments which induce lasting remissions, i.e., years, even after therapy is discontinued. Symptomatic therapies, on the other hand, are those which increase platelet counts transiently but seldom offer sustained remission, especially after therapy is stopped.

ITP is a life-long disease in most patients, and transient elevation of platelet counts by expensive therapies have little impact on patient wellness except in certain situations where life-threatening bleeding may occur (as in surgical or other invasive procedures).

##### 4.1. Definitive Measures in ITP

i. Search for and eradicate the cause. This constitutes the best definitive therapy. As our knowledge advances, the list of causes for ITP will doubtless increase. The most recent addition to the list is H Pylori [45]. Although the original report suggested that eradication of H Pylori eliminated ITP, such a strict causal relationship was not supported in other studies [46]. Nonetheless, the search for cause should be continued through the entire

course of management of patients with ITP.

ii. Splenectomy. Splenectomy as a treatment for disease was initially suggested by a medical student in the 18th century. It is now the most definitive measure for chronic ITP. However, nearly half of patients fail to achieve lasting remission by this surgery. Recently, laparoscopic splenectomy has made the procedure easier. Immunization with pneumococcal vaccine, Hemophilus influenza vaccine, and meningococcal vaccine 2 weeks prior to surgery is recommended.

The long-term effects of splenectomy have not been fully addressed. There has been some concern about high incidence of infection and thrombosis among splenectomized patients in later years. Study of non-splenectomized vs splenectomized veterans found a higher incidence of early death in splenectomized veterans, attributed to infections and thrombotic cardiovascular diseases [47]. Cognitive dysfunctions and dementias in subgroups of ITP patients appeared to progress faster in splenectomized patients [38].

iii. Danazol was introduced for ITP in 1983 [48-51]. Autoimmune diseases including ITP are far more common in women than men, and sex hormones play a critical role [52]. In general, androgens inhibit and estrogens accelerate manifestations of autoimmunity [52]. Danazol is an attenuated synthetic androgen, created to be tolerable by women. Our original report on the use of danazol in ITP has been confirmed and danazol is now widely employed in ITP. It is easy to administer and appears safe for long-term therapy. Some have achieved long-lasting remissions for many years even after its discontinuation [49,50]. It is one of the few definitive non-surgical treatments and should be offered to all patients with ITP. However, therapy should be continued for at least 6 months, preferably a full year, since delayed responses are seen [50]. We start with danazol 200mg twice a day, with or without prednisone. Danazol is absorbed poorly in fasting states, therefore must be taken after meals. Depending on responses or side effects, the dosage can be decreased or increased to 200 mg TID, rarely QID. In some patients, high doses appear to have adverse effects and low dosage is more effective [49]. In those patients the dosage can be reduced to 50mg per day, or 200mg 2-4 times per week. Once remission is sustained, the dosage is decreased to 1- 3 times a week under close titration. With this schedule, we have not seen seriously adverse effects in almost two decades and more than 200 patients.

Since danazol works slowly, we start with danazol and prednisone. Once improvement is evident and sustained, prednisone is tapered off and danazol continued for extended periods as the dosage is gradually reduced.

We do not yet know the optimum dosage (which may vary with individual patients) of danazol for ITP, or its relevant mechanism of benefit. Further studies are needed to address these important questions. (See below for more about danazol therapy.)

iv. Chemotherapy. Although low oral daily doses of azathioprine and cyclophosphamide for ITP were re-

ported in the early 1970s, overall responses were low, and its mutagenic potential deterred its application, especially in young patients. Vincristine and vinblastine have been widely used. They act more rapidly (usually by 1 week) than other chemotherapies and appear free from mutagenic risk. They induce thrombocytosis in animal models and humans, another advantage. Three modes of drug administrations have been employed: IV injection, slow infusion, and loading to platelets. Some patients in our original studies appeared completely cured of ITP [53-56]. More recently, however, high-dose pulse cyclophosphamide or combination chemotherapy have been shown to induce lasting remission in ITP, as demonstrated in patients with SLE. On the other hand, the potentially serious side effects of these agents, such as bone marrow suppression and mutagenicity, demand weighing the benefits of therapy against risks, particularly among women of child bearing age. High-dose of Dexamethasone is free from mutagenicity. Recently, Rituxan has been employed. Complete response was seen in 5 of 25 patients (20%) with some sustained remission. It is a limited but valuable agent in some patients [57].

#### 4.2. Symptomatic Measures [41-43]

i. Glucocorticoids (GC) [42-44] are the most widely used first-agent in ITP but long-term side effects discourage their prolonged use. In general, the benefits of GC wane when the drug is reduced or discontinued. Recently, high dose pulse of Decadron was proposed.

ii. I.V. Gammaglobulins [42-44] are often used in patients with severe ITP but response is seldom sustained. Since platelet counts increase promptly, it is well suited for preparation for major surgery or other procedures but not for long-term maintenance. Its side effects include renal failure and possible transmission of blood-borne diseases.

iii. Anti-D antibodies [43,44]: AntiD-coated RBC saturate Fc receptors of macrophages, thereby ameliorating binding of opsonized platelets, improving platelet counts in ITP. Responses are similar to IV gammaglobulins, and are transient in most responders. It is also very expensive, and often causes hemolysis. Its long-term side effects are not clear.

iv. Removal of antibodies or immune complexes [43, 44]: Removal of circulating antibodies in ITP is a rational means for ameliorating the ITP disease process. This can be accomplished by (a) plasmapheresis or (b) absorption of immune complexes and antibodies on Staphylococcal protein A column.

Although initial reports were promising, neither approach has well withstood the test of time, and consequently are seldom employed in the treatment of ITP. However, in severe refractory cases with high titers of antibodies, they may be worth trying.

v. Immune modulations [44]: Many new approaches which attempt to modulate immunity in ITP are emerging. These include Interferon, Cyclosporin, and monoclonal antibodies such as anti-CD20 (Rituxan) and

anti-CD154. Bone marrow transplant has been added for severe ITP. Use of Interferon and cyclosporin showed some benefit in a minority of patients with refractory ITP. Rituxan showed early promise but benefitted less than half of patients [57].

vi. Other Measures [42-44]: The benefit of large doses of ascorbate (vitamin C) for ITP was reported in the 1980s. This therapy is inexpensive, has few side effects, and may be useful in some mild cases of ITP. There is no clear rational basis for its benefit. In-depth study of this therapy deserves attention. Colchicine was reported helpful in ITP but the response rate was low. However, it is convenient to administer and has minimal side effects. Dapsone has also been used in some cases.

### 5. More on Danazol Therapy

Danazol (Danocrine<sup>®</sup>) is a synthetic attenuated androgen, initially formulated for the treatment of endometriosis and subsequently found useful in angioneurotic edema and other disorders [58]. Our experiences over decades has reinforced its value as a primary therapy, even before (or in conjunction with) glucocorticoids (GC). Splenectomy can often be avoided in patients receiving long-term danazol therapy.

Advantages of danazol over other agents are well recognized. Danazol is better tolerated than GC in long term use. It does not increase risk of infection nor osteoporosis. It is effective in those who failed on other therapies; it is effective in about 1/3 of patients who failed on GC.

Remissions induced by long-term danazol have frequently lasted for years, up to decades, even after discontinuance of danazol. Such long-term remissions are unusual with other therapies such as GC, IV gammaglobulin, or antiD antibodies. Early withdrawal (prior to 6 months) usually resulted in relapse.

Review of literature on danazol therapy. There have been twenty-five publications on danazol therapy in ITP [48-50,59-80]. Twenty-one reported favorably on the value of danazol in ITP while 4 reported negative outcomes [59,60,67,69]. In most negative studies, danazol was used in a small number of patients as a single agent, and was discontinued after 2-4 months. In our studies, danazol was initially added to prednisone and, after remission was obtained, prednisone was tapered off. In some patients, response was delayed as long as 10 months (3), therefore it is recommended to continue therapy for at least 6 months or preferably 1 year, if no serious side effects occur. It is difficult to assess the efficacy of danazol in these negative studies because of premature withdrawal of the drug.

Pharmacokinetic studies indicates that danazol concentrations in plasma and in blood cell membranes are extremely variable [81,82]. Some patients who failed on standard dosage (400-800 mg a day) responded to low dose (50 mg a day) [49], suggesting that excessively high blood concentrations may have adverse effects on platelets. Better knowledge of its pharmacokinetics, mechanisms of action, and cause of indi-

vidual variation would improve danazol therapy in ITP.

Mechanisms of action of danazol in ITP is not known. Platelet antibodies specific to platelet glycoproteins were measured before treatment and in remission induced by danazol: antibody persisted in remission [83]. We found similar results in patients with AIHA: Coombs test remained positive in years of remission by danazol therapy. Danazol decreased Fc receptor expression on circulating monocytes [73]. We reported alteration of T cell subsets in patients with danazol therapy [84]. These data indicate that the main action of danazol is not to eliminate antibody production in ITP, but rather, modulation of the efferent arm of immune responses. Danazol may induce some form of immune tolerance.

We reported that danazol is incorporated into membranes of red cells, lymphocytes, platelets and possibly other cells, altering membrane properties [85]. Altered membrane properties could modify expression of antigens or receptors (such as Fc) critical to the autoimmune reaction. In red cells, danazol induced shape change and rendered them resistant to osmotic lysis. In vitro, danazol inhibited autoantibody binding to RBC at physiologic concentrations [86]. These protean actions of danazol remain to be elucidated.

Long-term safety. Since ITP is a chronic illness, long-term safety is an important issue. Long-term study on patients with angioneurotic edema confirmed the safety of danazol therapy given over a 10 years period [87]. Several cases of hepatic peliosis and hepatomas have been reported [88,89]. These are very rare complications. We have confirmed the safety of danazol therapy in ITP patients. In our study, danazol dosage was reduced once remissions were sustained. We have not seen any serious side effects in two decades of clinical experience.

In other disorders. Danazol is a drug of choice in autoimmune hemolytic anemia (AIHA), a disorder similar to ITP. In this disorder antibodies are directed to red cells instead of platelets. In fact, responses and durations of remissions in AIHA of warm antibody type were better than for ITP; and the spleen can be spared in such responders [51,90]. As in ITP, remissions often lasted for years, even after danazol was stopped, though Coombs test remained positive.

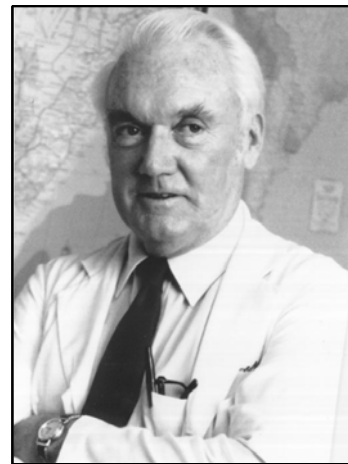
Efficacy of danazol was also documented in patients with paroxysmal nocturnal hemoglobinuria (PNH). Many who failed on GC responded to danazol and maintained remission for many years. However, unlike ITP and AIHA, withdrawal of danazol in PNH was associated with relapse in most cases, and low dose maintenance therapy was required [51,91].

In summary, the benefit of danazol for treatment of ITP is increasingly appreciated. However, the optimal dosage regimen and mechanism of action remain to be clarified. Particular attention should be addressed to long-lasting unmaintained remissions induced by danazol therapy in ITP. Future investigation on its pharmacokinetics and mode of immune modulation will improve and optimize danazol therapy. Furthermore, under-

standing the mechanism of danazol could lead to development of better drugs. Danazol therapy should be offered to all patients with ITP, as well as AIHA and PNH.

## 6. Concluding Remark

ITP is a good model for the general study of autoimmune diseases: it is a common disorder and can be monitored objectively by platelet count to assess disease activity and effects of therapy. Immune alterations can be tracked by well-defined antigen-antibody interactions. Knowledge gained from study of ITP can be applied to other autoimmune disorders.



### Biography: Dr. William J Harrington, Sr. (Sept. 21, 1923 - Sept 4, 1992)

Dr. William J Harrington earned international reputation at the youthful age of 28 through his seminal paper delineating the pathogenesis of ITP. Dr. Wintrobe described him as a rising star in the new generation of hematologists. The most prestigious schools offered him leadership positions as dean or chairman, but to everyone's surprise, he chose a new medical school in Miami, Florida. He envisioned the school as a center for research, education, and patient care, with reach into Latin American nations. He wished to build in the then-new tradition of excellence in research as well as patient care, rather than following the old authoritarian tradition.

Dr. Harrington became Chief of Hematology at the University of Washington in St. Louis at age 31, and at age 40 took over at Miami, the youngest Chairman of any Department of Medicine. He began to build the department with strong research orientation and high standards of patient care. He created many innovative programs in the department and school. Among them were the PhD-MD program, established to educate scientists to earn the MD degree in 18 months; research programs to foster collaboration between the University

of Miami and Latin America; and the Latin American Training Program, recruiting elite graduates from schools in Latin America for training as medical leaders in their countries.

He was a truly altruistic and inspiring leader, deeply admired by students, faculty, and research scientists. He was a mentor to numerous researchers and physicians in the USA and abroad. He would often advise his students, Be an architect, not a custodian.

But he was most beloved by his patients. His dedication to patients was unconditional. His inspirations in research always sprang from his commitment to their well-being. To illustrate, his seminal observations on ITP sprang from the tragic death of a teenage girl with ITP whom he met as a medical student. She was hospitalized with profuse vaginal bleeding and was falsely accused of having miscarriage by the physicians on call in the presence of her embarrassed parents. He cared for his patients with devotion every day, including weekends and holidays, and even on the day when Hurricane Andrew destroyed his house and paralyzed Miami, the very day he died.

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