RAPID COMMUNICATION

Human Thrombopoietin Levels Are High When Thrombocytopenia Is Due to Megakaryocyte Deficiency and Low When Due to Increased Platelet Destruction

By Robert V.B. Emmons, Diane M. Reid, Robert L. Cohen, Gloria Meng, Neal S. Young, Cynthia E. Dunbar, and N. Raphael Shulman†

Thrombopoietin (TPO), the ligand for c-mpl, stimulates proliferation of committed megakaryocytic progenitors and induces maturation of megakaryocytes. To better understand factors regulating TPO levels, we measured blood levels of TPO in patients with impaired platelet production due to aplastic anemia (AA) and with platelet destructive disorders, including idiopathic thrombocytopenic purpura (ITP), posttransfusion purpura (PTP), drug purpura (DP), and X-linked thrombocytopenia (XLTP). The TPO receptor capture enzyme immunoassay (EIA) used had a detection limit of ~150 to 200 pg/mL. TPO was undetectable in 88 of 89 normal individuals. Eighteen of 19 patients with AA and a mean platelet count (MPC) of 18,000/μL (2,000 to 61,000/μL) had markedly elevated TPO levels (mean, 1,467 pg/mL; range, 597 to 3,834 pg/mL). Eight AA patients who responded to immunosuppressive therapy with their MPC increasing to 140,000/μL (92,000 to 175,000/μL) had substantial decreases in TPO (mean, 440 pg/mL; range, 193 to 771 pg/mL). Initial TPO levels did not differ significantly between responders and nonresponders. In contrast, all 21 patients with ITP and an MPC of 16,000/μL (1,000 to 51,000/μL) had undetectable TPO levels, as did 6 patients with acute PTP or DP and 2 patients with XLTP. Megakaryocyte mass, reflected in the rate of platelet production, appears to be the major determinant of TPO levels in thrombocytopenic patients rather than circulating platelet levels per se. Measurement of serum TPO may be useful in differentiating thrombocytopenias due to peripheral destruction from those due to thrombopoietic failure. *This is a US government work. There are no restrictions on its use.*

THROMBOPOIETIN (TPO), also known as c-mpl ligand or megakaryocyte growth and development factor (MGDF), has been isolated and cloned by several groups.[1-6] It promotes proliferation of committed megakaryocytic precursors and differentiation of immature megakaryoblasts in vitro and in vivo.[1-4,6-8] Expression of c-mpl in humans is restricted to nonlymphoid hematopoietic tissues including CD34$^+$ cells, megakaryocytes, and platelets, with lower levels detected in endothelial cells.[9,10] The predominant sites of TPO production are liver and, to a lesser degree, kidney, although the specific cell(s) responsible for production is not known.[1,2] Many lines of evidence indicate that TPO acting through c-mpl is essential for normal thrombopoiesis. For example, c-mpl antisense oligodeoxynucleotides inhibit synthesis of c-mpl mRNA in CD34$^+$ cells and prevent them from forming megakaryocytic colonies.[9] In addition, both c-mpl–deficient mice and homozygous TPO-deficient mice have markedly reduced megakaryocytes and circulating platelets.[11,12]

The homeostatic factors that maintain relatively constant platelet mass in normal individuals have yet to be clearly defined. Recent studies of experimental thrombocytopenia induced in animals by chemotherapy, radiation, or antiplatelet antibodies indicate an inverse relationship between circulating platelet mass and TPO levels.[3,13-15] However, other observations, particularly in humans, indicate that megakaryocyte mass may be the principal regulator of TPO levels.[16-21] To understand this apparent inconsistency, we measured TPO by receptor capture enzyme immunoassay (EIA) in patients with equivalent degrees of thrombocytopenia due to two different mechanisms: decreased platelet production with megakaryocytic hypoplasia (AA) and increased platelet destruction with normal or increased megakaryocyte mass and documented or presumed normal platelet production (idiopathic thrombocytopenic purpura [ITP], posttransfusion purpura [PTP], drug purpura [DP], and X-linked thrombocytopenia [XLTP]).

MATERIALS AND METHODS

Patient selection. Patients were referred to the Clinical Center for diagnosis and/or treatment of thrombocytopenia or AA. Serum or plasma anticoagulated with EDTA or citrate was collected using a single syringe technique during periods of thrombocytopenia or after recovery and stored at $-20°C$. AA patients had moderate or severe disease by standard criteria[22] and received immunosuppressive therapy with antithymocyte globulin (ATG) or ATG/cyclosporine under NHLBI Institutional Review Board-approved research protocols.[23] ITP was diagnosed clinically as thrombocytopenia with normal or increased marrow megakaryocytes and no concurrent abnormality that could otherwise explain thrombocytopenia. In all cases, diagnoses of PTP and DP were serologically confirmed. Congenital microthrombocytopenia and eczema, with (Wiskott-Aldrich syndrome) or without immunodeficiency, were the bases for diagnosis of XLTP. [111]In autologous platelet survivals were performed according to general guidelines,[24] with the modification that apheresis rather than phlebotomy was performed to ensure ample red blood cell (RBC)-free platelets for labeling.

EIA for TPO. A full description of our TPO assay is in preparation (G. Meng, personal communication). Briefly, microtiter wells were incubated overnight with 2 mg/mL rabbit F(ab')$_2$ antihuman Fc (Jackson Immuno Research, West Grove, PA) and then for 2

hours with 100 ng/mL of a chimeric mpl-IgG.[1] Twofold dilutions of samples (starting at 1:5) and standards were added to wells and incubated for 1 hour. Bound TPO was quantitated colorimetrically by addition of biotinylated affinity-purified polyclonal rabbit anti-TPO (Genentech, South San Francisco, CA) followed by streptavidin-conjugated peroxidase. Recombinant full-length TPO produced in mammalian cells was used to generate a curve that was subjected to a four-parameter nonlinear regression curve-fitting program. The working range of the assay, representing only data points on the linear portion, was 150 pg/mL to 10 ng/mL. The performance characteristics of the assay are similar in serum and plasma (independent of anticoagulant). TPO was below limits of detection in 88 of 89 normal individuals. The assay preferentially detects active full-length TPO yielding similar values to bioassays performed at Genentech.

RESULTS

Table 1 provides clinical data and TPO levels on each patient studied. TPO levels in AA patients were threefold to 19-fold above the minimum detectable amount of 200 pg/mL. Ten patients unresponsive to immunosuppressive therapy had a mean platelet count (MPC) of 14,000/μL (2,000 to 34,000/μL) and a mean TPO level of 1,511 pg/mL (597 to 3,834 pg/mL). Eight patients who subsequently responded to immunosuppressive therapy had an initial MPC of 23,000/μL (5,000 to 61,000/μL) and a mean TPO level of 1,517 pg/mL (710 to 2,880 pg/mL). After recovery, when their MPC was 134,000/μL (92,000 to 175,000/μL), TPO levels were substantially decreased but still greater than controls (mean, 440 pg/mL; range, 193 to 771 pg/mL). Pretreatment bone marrow cellularity was severely depressed, with absent megakaryocytes in all but one AA patient. TPO was not detectable in 1 pancytopenic AA patient who had a platelet count of 19,000/μL and relative sparing of megakaryocytes on bone marrow biopsy. The patients responding to therapy had significant improvement in marrow cellularity, although megakaryocyte numbers, not quantitated precisely, appeared subnormal.

All 28 patients with acute and chronic thrombocytopenias resulting from platelet destruction had undetectable TPO levels. TPO levels in patients with ITP and those with aplastic anemia (before response to therapy) were significantly different ($P < .0005$) despite equivalent platelet counts ($P = .54$). Of the 21 ITP patients, 14 had undergone splenectomies and none had ever received cytotoxic chemotherapy. Survival of autologous ^{111}In-labeled platelets in ITP patients no. 1, 3, 7, 13, 15, and 21 was decreased approximately proportionally to decreases in platelet levels, indicating that production was normal (data not shown). An allogeneic platelet survival on patient no. 1 with XLTP was 8 days and autologous survival approximately 2 days, consistent with the diagnosis.[25,26]

DISCUSSION

Our data corroborate findings of others that TPO levels are characteristically high in humans and experimental animals with insufficient platelet production secondary to megakaryocytic hypoplasia. However, studies limited to those particular thrombocytopenias have not clearly distinguished whether elevated TPO levels correlate inversely with megakaryocyte or platelet mass. Our findings of undetectable TPO levels in a second group of patients with equal degrees of

Table 1. Specific Data on Patients Included in This Study

Diagnosis	Patient No.	Age (yr)/Sex	Platelet Count ($\times 10^{-3}$/μL)	TPO Level (pg/mL)
AA responders pre/post therapy	1	51/F	12/156	1041/193
	2	63/M	5/175	1492/271
	3	19/M	17/175	1722/251
	4	6/F	61/92	1149/732
	5	35/M	37/115	710/257
	6	63/M	32/140	1391/499
	7	4/M	17/116	2880/771
	8	18/F	16/154	897/548
AA nonresponders	1	49/F	3	2407
	2	29/F	15	1812
	3	64/M	6	1374
	4	47/M	8	787
	5	34/F	2	1137
	6	69/M	11	3834
	7	11/M	34	887
	8	15/M	24	597
	9	28/M	19	1213
	10	26/F	19	1070
	11	23/M	15	<200
ITP	1	57/F	51	<200
	2	54/M	18	<200
	3	23/M	5	<200
	4	50/F	15	<200
	5	33/F	6	<200
	6	34/M	2	<200
	7	54/F	28	<200
	8	64/F	2	<200
	9	39/F	14	<200
	10	53/F	10	<200
	11	62/M	40	<200
	12	48/M	19	<200
	13	55/F	11	<200
	14	36/F	32	<200
	15	52/F	10	<200
	16	71/F	38	<200
	17	27/M	1	<200
	18	64/M	10	<200
	19	32/F	13	<200
	20	30/F	7	<200
	21	25/F	10	<200
PTP	1	81/F	5	<200
	2	76/F	2	<200
	3	44/F	1	<200
DP	1	45/F	70	<200
	2	64/F	2	<200
	3	61/F	8	<200
XLTP	1	8/M	40	<200
	2	8/M	11	<200

The mean duration of illness of ITP patients was 13.8 years (range, 1 month to 41 years); of PTP patients, 6 days (2 to 12 days); of DP patients, 4 days (1 to 7 days); and of XLTP patients, 8 years.

thrombocytopenia, but plentiful megakaryocytes and normal platelet production, help clarify this issue. Megakaryocyte mass, platelet turnover, or some parameter of megakaryocytic function, not circulating platelet number, appears to be the major regulator of TPO levels.

Before the isolation of TPO, bioassay measurements of

serum megakaryocyte colony-stimulating activity (Meg-CSA) also correlated with megakaryocytic mass.[16,17] Patients with AA or amegakaryocytic thrombocytopenia had increased levels of Meg-CSA compared with normals, whereas a small number of patients with ITP did not. More recently, MGDF was elevated in 11 patients after myeloablative therapies and marrow or autologous peripheral stem cell transplants, at a time when marrow cellularity was likely suppressed, but before platelet counts decreased to less than 100,000/μL.[18] There is compelling evidence from animal experiments that platelet mass alone does not control TPO levels. Meg-CSA in plasma collected from sublethally irradiated rats was elevated even when platelets were transfused to maintain normal levels after irradiation.[20] Additionally, mice lacking the p45 subunit of erythroid transcription factor NF-E2 have unelevated endogenous TPO levels despite absolute thrombocytopenia due to maturation arrest of megakaryocytes.[21]

Studies of immunologically mediated thrombocytopenias have yielded some conflicting data between humans and rodents with respect to relationships between TPO levels and fluctuations in platelets or megakaryocytes. Acute thrombocytopenia induced by antiplatelet serum was associated with transitory markers of enhanced megakaryocytic stimulating activity in several early animal experiments.[27-31] More recently, specific increases in TPO were detected in mice and rabbits within 3 to 24 hours of precipitous decreases in platelets caused by antiplatelet sera.[3,14,32] The duration of TPO elevations ranged from hours to several days. Comparable acute measurements on humans have not been reported. However, 2 of our patients with PTP and DP had undetectable TPO levels as early as days 1 and 2. If megakaryocyte mass or function is the major modulator of TPO in all species, one might postulate that hyperimmune antisera used experimentally injured megakaryoctytes. However, this is unlikely because the same antisera, administered repeatedly or in great excess to rodents did not maintain thrombocytopenia.[15] Rodents have more rapid platelet turnover[33,34] than humans and marked compensatory platelet production that precludes induction of experimental chronic immune thrombocytopenia.[15] Humans are highly susceptible to antibody-induced thrombocytopenia and have limited compensatory platelet production.[35,36] Perhaps regulation of TPO levels in rodents reflects responsiveness to factors not operable in humans.

Regardless of whether TPO expression is constitutive[12,13,19] or inducible,[37] free TPO levels are regulated to some extent by receptor-mediated uptake. Platelets, whether transfused or incubated in vitro, lower plasma TPO through binding and possible metabolism.[14,38] Larger platelets, often present in immune thrombocytopenias, may have increased receptor numbers that could account for greater uptake per platelet. However, platelet size would not explain low TPO levels in the XLTP patients who have microthrombocytes. Marrow CD34$^+$ progenitors and megakaryocytes are also a part of the cellular pool bearing c-mpl, but may be less accessible to plasma TPO than circulating platelets. Perhaps transient TPO elevation can be caused by rapid diminution of the circulating platelet c-mpl pool, which is promptly corrected by continued platelet production at a normal rate. If so, increases of TPO in PTP, DP, or acute ITP may be elevated very early, during the period TP is developing, as in animal models, but not when it is established. Low TPO values with severe thrombocytopenia are not limited to immune-mediated disorders, for this association occurred in XLTP syndromes in which megakaryocyte mass is normal but congenitally defective platelets are prematurely destroyed.

TPO levels undetectable by our assay, yet slightly above normal, may have been missed. Nevertheless, there was essentially no overlap between the two groups of thrombocytopenic patients under study. Furthermore, there is no available data to suggest that putative inhibitors of the TPO EIA, including anti–c-mpl, anti-TPO, microparticulate, or soluble c-mpl, would have explained the uniformly low TPO levels in patients with destructive thrombocytopenias.

TPO measurements may be helpful to differentiate decreased platelet production from increased peripheral destruction in rare instances of thrombocytopenia with borderline marrow hypoplasia. Our single AA patient with residual megakaryocytes and a low TPO level may have had peripheral destruction contributing to his thrombocytopenia. There are reports suggesting that a minority of ITP patients have low rather than characteristic normal or increased platelet production.[39] Measurement of TPO levels may help determine whether this subset of ITP patients truly exists.

Our observations raise the possibility that exogenous TPO might speed recovery from acute immune thrombocytopenias and elevate platelet counts in those patients with chronic ITP in whom the rate of platelet destruction can be overcome by physiologically attainable increases in production.

REFERENCES

1. de Sauvage FJ, Hass PE, Spencer SD, Malloy BE, Gurney AL, Spencer SA, Darbonne WC, Henzel WJ, Wong SC, Kuang W-J, Oles KJ, Hultgren B, Solberg LA, Goeddel DV, Eaton DL: Stimulation of megakaryocytopoiesis and thrombopoiesis by the c-Mpl ligand. Nature 369:533, 1994

2. Lok S, Kaushansky K, Holly RD, Kuijper JL, Lofton-Day CE, Oort PJ, Grant FJ, Heipel MD, Burkhead SK, Kramer JM, Bell LA, Sprecher CA, Blumberg H, Johnson R, Prunkard D, Ching AFT, Mathewes SL, Bailey MC, Forstrom JW, Buddle MM, Osborn SG, Evans SJ, Sheppard PO, Presnell SR, O'Hara PJ, Hagen FS, Roth GJ, Foster DC: Cloning and expression of murine thrombopoietin cDNA and stimulation of platelet production in vivo. Nature 369:565, 1994

3. Wendling F, Maraskovsky E, Debili N, Florindo C, Teepe M, Titeux M, Methia N, Breton-Gorius J, Cosman D, Vainchenker W: c-Mpl ligand is a humoral regulator of megakaryocytopoiesis. Nature 369:571, 1994

4. Bartley TD, Bogenberger J, Hunt P, Li Y-S, Lu HS, Martin F, Chang M-S, Samal B, Nichol JL, Swift S, Johnson MJ, Hsu R-Y, Parker VP, Suggs S, Skrine JD, Merewether LA, Clogston C, Hsu E, Hokom MM, Hornkohl A, Choi E, Pangelinan M, Sun Y, Mar V, McNinch J, Simonet L, Jacobsen F, Xie C, Shutter J, Chute H, Basu R, Selander L, Trollinger D, Sieu L, Padilla D, Trail G, Elliott G, Izumi R, Covey T, Crouse J, Garcia A, Xu W, Del Castillo J, Biron J, Cole S, Hu MC-T, Pacifici R, Ponting I, Saris C, Wen D, Yung YP, Lin H, Bosselman RA: Identification and cloning of

a megakaryocyte growth and development factor that is a ligand for the cytokine receptor Mpl. Cell 77:1117, 1994

5. Sohma Y, Akahori H, Seki N, Hori T, Ogami K, Kato T, Shimada Y, Kawamura K, Miyazaki H: Molecular cloning and chromosomal localization of the human thrombopoietin gene. FEBS Lett 353:57, 1994

6. Kuter DJ, Beeler DL, Rosenberg RD: The purification of megapoietin: A physiological regulator of megakaryocyte growth and platelet production. Proc Natl Acad Sci USA 91:11104, 1994

7. Kaushansky K, Lok S, Holly RD, Broudy VC, Lin N, Bailey MC, Forstrum JW, Buddle MM, Oort PJ, Hagen FS, Roth GJ, Papayannopoulou T, Foster DC: Promotion of megakaryocyte progenitor expansion and differentiation by the c-Mpl ligand thrombopoietin. Nature 369:568, 1994

8. Banu N, Wang JF, Deng B, Groopman JE, Avraham H: Modulation of megakaryocytopoiesis by thrombopoietin: The c-Mpl ligand. Blood 86:1331, 1995

9. Methia N, Louache F, Vainchenker W, Wendling F: Oligonucleotides antisense to the proto-oncogene c-mpl specifically inhibit in vitro megakaryocytopoiesis. Blood 82:1395, 1993

10. Debili N, Wendling F, Cosman D, Titeux M, Florindo C, Dusanter-Fourt I, Schooley K, Methia N, Charon M, Nador R, Bettaieb A, Vainchenker W: The Mpl receptor is expressed in the megakaryocytic lineage from late progenitors to platelets. Blood 85:391, 1995

11. Gurney AL, Carver-Moore K, de Sauvage FJ, Moore MW: Thrombocytopenia in c-mpl-deficient mice. Science 265:1445, 1994

12. de Sauvage FJ, Luoh S-M, Carver-Moore K, Ryan A, Dowd M, Eaton DL, Moore MW: Deficiencies in early and late stages of megakaryocytopoiesis in TPO-KO mice. Blood 86:255a, 1995 (abstr, suppl 1)

13. Ulich TR, del Castillo J, Yin S, Swift S, Padilla D, Senaldi G, Bennett L, Shutter J, Bogenberger J, Sun D, Samal B, Shimamoto G, Lee R, Steinbrink R, Boone T, Sheridan WT, Hunt P: Megakaryocyte growth and development factor ameliorates carboplatin-induced thrombocytopenia in mice. Blood 86:971, 1995

14. Kuter DJ, Rosenberg RD: The reciprocal relationship of thrombopoietin (c-Mpl ligand) to changes in the platelet mass during busulfan-induced thrombocytopenia in the rabbit. Blood 85:2720, 1995

15. Kuter DJ, Rosenberg RD: Appearance of a megakaryocyte growth-promoting activity, megapoietin, during acute thrombocytopenia in the rabbit. Blood 84:1464, 1994

16. Hoffman R, Mazur E, Bruno E, Floyd V: Assay of an activity in the serum of patients with disorders of thrombopoiesis that stimulates formation of megakaryocytic colonies. N Engl J Med 305:533, 1981

17. Mazur EM, de Alarcon P, South K, Miceli L: Human serum megakaryocyte colony-stimulating activity increases in response to intensive cytotoxic chemotherapy. Exp Hematol 12:624, 1984

18. Nichol JL, Hokom MM, Hornkohl A, Sheridan WP, Ohashi H, Kato T, Li YS, Bartley TD, Choi E, Bogenberger J, Skrine JD, Knudten A, Chen J, Trail G, Sleeman L, Cole S, Grampp G, Hunt P: Megakaryocyte growth and development factor. Analyses of in vitro effects on human megakaryopoiesis and endogenous serum levels during chemotherapy-induced thrombocytopenia. J Clin Invest 95:2973, 1995

19. Chang M, Suen Y, Meng G, Buzby J, Williams S, Shen V, Knoppel A, Fernandez G, Cairo MS: Regulation of TPO mRNA expression and protein production: TPO gene regulation appears post transcriptional, and endogenous levels are inverseley correlated to megakaryocyte mass and circulating platelet count. Blood 86:368a, 1995 (abstr, suppl 1)

20. Miura M, Jackson CW, Steward SA: Increase in circulating megakaryocyte growth-promoting activity (Meg-GPA) following sub-lethal irradiation is not related to decreased platelets. Exp Hematol 16:139, 1988

21. Shivdasani RA, Rosenblatt MF, Zucker-Franklin D, Jackson CW, Hunt P, Saris CJM, Orkin SH: Transcription factor NF-E2 is required for platelet formation independent of the actions of thrombopoietin/MGDF in megakaryocyte development. Cell 81:695, 1995

22. Young NS, Alter BF: Aplastic Anemia, Acquired and Inherited. Philadelphia, PA, W.B. Saunders, 1994

23. Rosenfeld SJ, Kimball J, Vining D, Young NS: Intensive immunosuppression with antithymocyte globulin and cyclosporine as treatment for severe acquired aplastic anemia. Blood 85:3058, 1995

24. Heyns AduP, Badenhorst PN, Wessels P, Pieters H, Kotze HF, Lotter MG: Indium-111-labelled human platelets: A method for use in severe thrombocytopenia. Thromb Haemost 52:226, 1984

25. Pearson HA, Shulman NR, Oski FA, Eitzman DV: Platelet survival in Wiskott-Aldrich syndrome. J Pediatrics 68:754, 1966

26. Grottum KA, Hovig T, Holmsen H, Abrahamsen AF, Jeremic M, Seip M: Wiskott-Aldrich syndrome: Qualitative platelet defects and short platelet survival. Br J Haematol 17:373, 1969

27. Kalmaz GD, McDonald TP: Effects of antiplatelet serum and thrombopoietin on the percentage of small acetylcholinesterase-positive cells in bone marrow of mice. Exp Hematol 9:1002, 1981

28. Evatt BL, Shreiner DP, Levin J: Thrombopoietic activity of fractions of rabbit plasma: Studies in rabbits and mice. J Lab Clin Med 83:364, 1974

29. Hill RJ, Levin J: Regulators of thrombopoiesis: Their biochemistry and physiology. Blood Cells 15:141, 1989

30. McDonald TP, Cottrell M, Clift R: Hematologic changes and thrombopoietin production in mice after X-irradiation and platelet-specific antisera. Exp Hematol 5:291, 1977

31. Ebbe S, Phalen E, Threatte G, Londe H: Modulation of radiation-induced hemopoietic suppression by acute thrombocytopenia. Ann NY Acad Sci 459:179, 1985

32. Hunt P, Li Y-S, Nichol JL, Hokom MM, Bogenberger JM, Swift SE, Skrine JD, Hornkohl AC, Lu H, Clogston C, Merewether LA, Johnson MJ, Parker V, Knudten A, Farese A, Hsu RY, Garcia A, Stead R, Bosselman RA, Bartley TD: Purification and biologic characterization of plasma-derived megakaryocyte growth and development factor. Blood 86:540, 1995

33. Odell TT Jr, McDonald TP: Life span of mouse blood platelets. Proc Soc Exp Biol Med 106:107, 1961

34. Ebbe S, Baldini M, Donovan J: Comparative studies of platelet survival by different methods in the rabbit. Blood 25:548, 1965

35. Shulman NR, Marder VJ, Weinrach RS: Similarities between known antiplatelet antibodies and the factor responsible for thrombocytopenia in idiopathic purpura. Physiologic, serologic, and isotopic studies. NY Acad Sci 124:499, 1965

36. Aster RH, Keene WR: Sites of platelet destruction in idiopathic thrombocytopenic purpura. Br J Haematol 16:61, 1969

37. McCarty JM, Sprugel KH, Fox NE, Sabath DE, Kaushansky K: Murine thrombopoietin mRNA levels are modulated by platelet count. Blood 86:3668, 1995

38. Fielder PJ, Hass P, Nagle M, Stefanich E, Widmer R, Keller G, Eaton D: Human platelets as a model for the binding, internalization, and degradation of thrombopoietin (TPO). Blood 86:365a, 1995 (abstr, suppl 1)

39. Ballem PJ, Segal GM, Stratton JR, Gernsheimer T, Adamson JW, Slichter SJ: Mechanisms of thrombocytopenia in chronic autoimmune thrombocytopenic purpura. Evidence of both impaired platelet production and increased platelet clearance. J Clin Invest 80:33, 1987

1996 87: 4068-4071

Human thrombopoietin levels are high when thrombocytopenia is due to megakaryocyte deficiency and low when due to increased platelet destruction

RV Emmons, DM Reid, RL Cohen, G Meng, NS Young, CE Dunbar and NR Shulman

Updated information and services can be found at:
http://www.bloodjournal.org/content/87/10/4068.full.html

Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml