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Telephone: +86-10-85381891
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Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjhematol@wjgnet.com
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REVIEW

# Current viewpoints on platelet contribution to inflammation

Julia Etulain, Mirta Schattner

Julia Etulain, Mirta Schattner, Laboratory of Experimental Thrombosis, Institute of Experimental Medicine, CONICET-National Academy of Medicine, Pacheco de Melo 3081, 1425, Buenos Aires, Argentina
Author contributions: Etulain J contributed to acquisition and interpretation of the literature information and drafting the article; Schattner M contributed to conception and design of the article, critical revision for important intellectual content and final approval of the version to be published.
Correspondence to: Mirta Schattner, PhD, Laboratory of Experimental Thrombosis, Institute of Experimental Medicine, CONICET-National Academy of Medicine, Pacheco de Melo 3081, 1425, Buenos Aires,
Argentina. mschattner@hematologia.anm.edu.ar
Telephone: +54-11-48055759 Fax: +54-11-48050712
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## Abstract

Inflammation is an underlying feature of a variety of human diseases. Because inflammatory diseases are a major cause of morbidity and mortality in developed countries, understanding the interaction of the most important factors involved is an important challenge. Although platelets are widely recognized as having a critical role in primary hemostasis and thrombosis, basic and clinical evidence increasingly identifies these enucleated cells as relevant modulators, as both effector and target cells, of the inflammatory response. The cross-talk between platelets, endothelial cells and leukocytes in the inflammatory milieu mat be seen as a double-edged sword which functions not only as an effective first-line defense mechanism but may also lead to organ failure and death in the absence of counter-regulation systems. The molecular mechanisms involved in the reciprocal activation of platelets, endothelial cells and leukocytes are beginning to be elucidated. In the light of the existing data from experimental and clinical studies it is conceivable that platelet adhesion molecules and platelet mediators provide promising targets for novel therapeutic strategies in inflammatory diseases. The potentially adverse effects of these approaches need to be carefully addressed and monitored, including alterations in hemostasis and coagulation and particularly the impairment of host defense mechanisms, given the recently identified pivotal role of platelets in pathogen recognition and bacterial trapping. In this review we discuss the most important recent advances in research into the cross-talk between platelets and vascular cells during inflammation and the clinical consequences of these interactions.



**Key words:** Platelets; Inflammation; Leukocytes; Endothelial cells; Inflammatory diseases

**Peer reviewer:** Rory R Koenen, PhD, Assistant Professor, Institute for Cardiovascular Prevention, Klinikum der LMU München, Pettenkoferstrasse 9, 80336 München, Germany

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## INTRODUCTION

Inflammation is an underlying feature of a variety of human diseases. Although platelets are widely recognized as having a critical role in primary hemostasis and thrombosis, increasing basic and clinical evidence identifies these enucleated cells as relevant modulators, both as effector and target cells, of the inflammatory response. Here we discuss the most important recent advances in research into the cross-talk between platelets and vascular cells during inflammation and the clinical consequences of these interactions.

## CROSS-TALK BETWEEN PLATELETS, LEUKOCYTES AND ENDOTHELIAL CELLS IN THE INFLAMMATORY MICROENVIRONMENT

A traditional concept in vascular biology was, that under

normal conditions, platelets circulate without interacting with the intimal endothelial lining of the vessel wall, and only after endothelial injury do they firmly adhere to adhesive proteins exposed on the subendothelial matrix, thereby allowing thrombus formation. In this sense, the endothelium comprises several mechanisms that prevent platelet adhesion to the intact endothelium and maintains platelets in a resting state. These include the release of nitric oxide and prostacyclin, potent inhibitors of platelet function[1]. However, during the last decade, substantial experimental and clinical data have revealed that even in the absence of any apparent morphological damage but during inflammatory states, platelets can bind to the intact endothelium, partly because the physiological inhibitory mechanisms are impaired, and partly because new adhesion molecules are expressed on the surface of activated endothelial cells[2-4]. These findings have not only created a new paradigm in vascular biology but also opened a new, growing and extensive research area concerning the physiological and pathophysiological consequences of platelet-endothelial cell interaction.

Platelet adhesion to the intact endothelium is coordinated by a sequence of events that comprise initial tethering of platelets, followed by rolling and subsequent firm adhesion. Whereas the tethering and rolling of platelets to activated or injured endothelium is primarily mediated by selectins, firm adhesion depends on the activation of platelet integrins and expression of adhesion molecules on the endothelial surface. During the sequential steps of the adhesion process, platelets become activated and eventually secrete an arsenal of potent inflammatory molecules from their α-granules. In fact, platelets contain numerous chemokines [CCL5 (RANTES), CXCL4 (PF-4), CXCL12 (SDF-1α), CCL2 (MCP-1), CCL3 (MIP-1α), CXCL5 (ENA-78), CXCL2 (GROβ), CXCL8 (IL-8)], cytokines (IL-1β), and surface molecules (CD40L and P-selectin) that can be released or exposed on the cell surface after platelet activation by rolling over inflamed endothelium[5,6].

In the adjoining endothelial cells, the platelet-secretory mediators alter the chemotactic, adhesive and proteolytic properties of endothelium, further promoting the switch to an inflammatory endothelial phenotype. In sum, firm adhesion of platelets to the endothelium causes platelets to spread and secrete the platelet releasate, promoting the activation of inflammatory signaling cascades not only in endothelial cells but also in platelets. This, in turn, accelerates the recruitment and activation of leukocytes, a fundamental event in the inflammatory response[5-9].

Similar to the multistep paradigm underlying platelet adhesion to endothelium, leukocyte adhesion to the intact endothelium is coordinated by a sequence of events that comprise initial tethering of leukocytes, followed by rolling, activation, adhesion, and transmigration of leukocytes across the endothelium[8]. Activated platelets adhered to an activated endothelium, further promote each of these local recruitment steps by inducing "secondary capture" of leukocytes (mainly polymorphonuclear and monocytes) which induces interaction of platelets with leukocytes first, followed by leukocyte-endothelial interaction[10]. The initial ligation between platelet P-Selectin and leukocyte PSGL-1 induces activation of integrin αMβ2 (CD11b/CD18 or Mac-1) through a molecular cascade that includes downstream effectors such as tyrosine kinases belonging to the Srk family, PI3 kinases, and small GTPases[11-15]. Leukocyte Mac-1 can interact with platelets directly or indirectly. In the first scenario, Mac-1 binds to both GPIb[16] and JAM-C[17] constitutively expressed on platelets. In the second setting, fibrinogen acts as a bridge between Mac-1 and its platelet surface receptor, integrin αⅡbβ3[13,18]. In addition to fibrinogen, Mac-1 also binds to high molecular weight kininogen which in turn recognizes GPIb on the platelet surface[19]. Bridging by thrombospondin and CD36 antigens (present in monocytes and platelets) has also been shown to mediate platelet interaction with leukocytes[20].

The numerous chemokines and cytokines that can be released or exposed on the cell surface of activated platelets can bidirectionally stimulate leukocytes and endothelial cells[5,6,8]. These molecules can accumulate on the luminal-endothelial surface and interact with the leukocytes through specific G-protein-coupled chemokine receptors expressed on the leukocyte surface[6,7] initiating on leukocytes a second wave of intracellular signaling cascades which eventually lead to further up-regulation of Mac-1 expression and activity, and to the activation of other[21-23] integrins such as α4β1 (VLA-4) and αLβ2 (LFA-1)[8,14]. These interactions also induce delayed activation responses including the activation of the nuclear translocation of the transcription factor κB (NF-κB), which triggers the synthesis of key pro-inflammatory molecules and endows leukocytes with an inflammatory phenotype. Simultaneously, platelets stimulate the expression of counter-receptors for leukocyte integrins on the endothelial cell surface. These include the intercellular adhesion molecule 1 and vascular cell adhesion molecule 1[24,25] that recognize LFA-1 or Mac-1 and VLA-4 respectively, contributing to consolidate the firm adhesion of leukocytes to the endothelium[21]. Activated leukocytes generate reactive oxygen species (ROS), release serinoproteases, myeloperoxidase and pentraxin 3, all molecules that are able to stimulate platelets and endothelial cells thus assuring and strengthening the cross-talk between the vascular cells at the inflammatory site[15,21,26,27].

Upon binding of leukocytes to the vessel wall, chemokines from the underlying intima stimulate them to migrate through the endothelial monolayer into the subendothelial space. The endothelial cells participate actively in the transmigration event. During transendothelial migration, the cell-cell junctions disengage transiently and locally to allow the leukocyte to cross[28,29]. Platelet-leukocyte complexes show increased transmigration by two mechanisms, when compared with leukocytes alone. First, platelet-leukocyte association could induce endothelium permeability through the inflammatory molecules released after platelet-mediated leukocyte activa-

tion. These proinflammatory mediators may trigger ROS production from circulating and adherent leucocytes, which strongly increases vascular permeability inducing morphological and molecular responses of endothelial cells[30]. The second mechanism involves the attachment of platelets and leukocytes mediated by P-selectin and its ligand, PSGL-1[31]. Interestingly, van Gils *et al*[32] demonstrated that although platelets facilitate monocyte transmigration, dissociation of the platelet-leukocyte complex during transmigration occurs due to both mechanical stress and a PSGL-1 redistribution-mediated platelet translocation towards the trailing end of the migrating monocytes. Whether migrated monocytes from the mixed cell aggregate are additionally different due to the platelet interaction, as compared to migrated platelet-free monocytes, is an intriguing question that remains to be studied. The platelet mediated leukocyte migration process could also be enhanced by microenvironment inflammatory conditions such as low pH. In this context, it was recently reported that platelet P-selectin expression is increased under extracellular acidosis. This phenomenon not only results in promotion of platelet-neutrophil aggregate formation, but also enhances the neutrophil migration process[33]. Moreover, during the inflammatory response neutrophil death can be delayed by, several cytokines, bacterial products such as LPS, low pH of the media and platelets[34-36]. Although the mechanisms by which platelets promote leukocyte survival are still not clear, the release of soluble mediators, as well as platelet-leukocyte contact appears to be involved in this phenomenon[37-39]. Interestingly platelets under acidic conditions prevent neutrophil apoptosis to a higher degree than platelets or low pH alone, reinforcing the notion that conditions of the inflammatory milieu further enhance the inflammatory response mediated by platelets[33]. However, our group has also shown that unlike low pH values, exposure of platelets to high temperatures results in a decrease of P-selectin expression on the platelet surface[40]. These data suggest that hyperthermia may dampen the proinflammatory activity of platelets. Therefore, since the inflammatory focus is characterized not only by the low pH values but also by several other features including swelling, heat and high levels of cytokines, experiments using a combination of the inflammatory stress signals or *in vivo* approaches are necessary to further understand the influence of the inflammatory milieu on platelet-mediated inflammatory responses.

Besides intracellular phagocytosis, a novel mechanism in pathogen killing by neutrophils has been recently described. This involves the extracellular release of nuclear DNA and microbicidal protein content upon activation with different stimuli such as PMA, IL-8, bacterial and fungal species. These DNA structures, named neutrophil extracellular traps (NETs), provide a highly effective antimicrobial mechanism, which results in neutrophil death and contributes to pathogen control and elimination of several pathogens[41-43]. Remarkably, Clark *et al*[44] described that *in vivo*, bacterial trapping through NET formation is dependent on the expression of TLR4+ on the surface of platelets, allowing them to sense and recognize bacteria. These fascinating findings unveiled a novel mechanism wherein platelets, acting as sentinels, have the ability to interact with bacterial molecules, allowing the activation of the innate immune system during sepsis. However, much research still remains to be done to elucidate the mechanisms and mediators through which platelets are able to spur neutrophils to release these extracellular traps.

Overall, this extensive experimental and clinical evidence leaves little doubt about the contribution of platelets to the inflammatory response. This phenomenon is not surprising if we consider that from an evolutionary point of view, platelets are related to hemocytes which in arthropods are nucleated cells responsible for immunity as well as for coagulation. It is clear that, in higher order species, these functions have diverged into more specialized cells, the platelets. These have retained some of the features of innate immunity, in particular their ability to cooperate with neutrophils and monocytes in the initiation, progression and resolution of inflammation[45]. In this context, platelets not only have all the cell adhesion molecules and cytokines necessary to interact and activate leukocytes, but also have the machinery to recognize and present pathogens to the effector cells[46,47]. Moreover, platelets express all the components of NF-κB, a key transcription factor responsible for the synthesis of the main proinflammatory molecules[48,49]. Interestingly, although platelets are enucleated cells, activation of platelet NF-κB appears to be another mediator of platelet activation[48,50]. It has recently been shown that treatment of platelets with specific inhibitors of NF-κB results in the inhibition of several platelet responses, including platelet adhesion and spreading, αIIbβ3 integrin activation, platelet aggregation, the release of dense and α granules, and a decrease in clot retraction times and thrombus stability[48,50]. In addition, the joint action of NF-κB activation and p38 phosphorylation appears to be a key molecular mechanism for the expression of P-selectin on the membrane of activated platelets under inflammatory conditions[40]. These novel non-genomic activities of platelet NF-κB suggest that the blockade of platelet function by NF-κB inhibitors might be relevant in those clinical situations where these drugs are being considered for anti-tumor and/or anti-inflammatory therapy.

## PLATELET-ENDOTHELIAL-LEUKOCYTE INTERACTION: A "DOUBLE-EDGED SWORD"

In general, amplification of the leukocyte activation state by platelets appears to have a positive and beneficial physiologic role in both the inflammatory and innate immune response. However, we should bear in mind that a failure in the regulatory mechanisms of these cellular responses may contribute to persistent vascular inflam-

mation, and in this context, platelets contribute to the enhancement of the physiopathology of chronic inflammatory diseases.

## ATHEROSCLEROSIS

Although, for several decades, hypercholesterolemia and lipid deposit on the vessel walls were considered major events in the pathogenesis of atherosclerosis, abundant recent data support the concept of atherosclerosis as a chronic inflammatory disease of a multifactorial nature[4,51,52]. The contribution of platelets to the process of atherosclerosis was unclear for decades, mainly because the availability of conclusive data obtained in humans is very limited. However, the beneficial effect of platelet anti-aggregating therapies in secondary prevention of cardiovascular diseases left no doubts about the major role of platelets, at least in advanced atherosclerotic disease states[4]. We now know that platelets not only are major contributors to the final phases of atherosclerosis, but also that platelet interaction with the intact endothelium and leukocytes are critical events in the initiation and progression of this inflammatory disease[51,53,54]. Activated platelets and platelet–leukocyte aggregates adhere to the endothelium at sites that are prone to plaque formation and deliver diverse chemokines, which in turn amplify the transmigration of monocytes and other mononuclear cells into the arterial wall[55,56]. Besides chemokines, platelets also express functional chemokine receptors including CCR1, CCR3, CXCR4 and $CX_3CR1$[57,58]. Interestingly, it has recently been reported that $CX_3CR1$ expression is upregulated in platelets from hyperlipidemic mice and promotes platelet-monocyte complex formation. The detection of platelet-bound CX3CL1 on smooth muscle cells from these mice suggests that the CX3CR1-CX3CL1 axis might have a relevant role in platelet accumulation and monocyte recruitment at sites of arterial injury in atherosclerosis[58].

Platelets not only promote monocyte differentiation into macrophages[59], but also induce CD34+ progenitor cells to migrate and differentiate into foam cells[60,61]. Interestingly, a range of data give biological plausibility to the epidemiological evidence of a significant association between leukocyte count and the incidence of coronary heart disease[27]. These findings highlight the necessity for clinical studies that evaluate the efficacy of a long-term antiplatelet strategy for primary prevention in high-risk patients at an early stage of atherosclerotic disease.

The observation that NETs act as a scaffold for thrombus formation has given NETs a previously unrecognized role, linking inflammation with thrombosis in both infectious and non-infectious clinical settings. Although, NETs were initially shown to be involved in venous thrombosis[62-64], they have also been recently observed in murine and human atherosclerotic lesions, suggesting that exploring the functionality of NETs in atherosclerosis will lead to novel insights into the pathogenesis of this inflammatory disease[65]. In this context, histones and defensins are some of the proteins exposed on the NETs scaffold. These molecules have been shown to be inducers of platelet activation and fibrin formation[66-68]. Furthermore, extracellular histones are known to be cytotoxic toward endothelium[69,70]. Therefore, it is conceivable that activation or even apoptosis of the different cell types of the atheroma plaque, mediated by histones or defensins, could be one of the mechanisms through which NETs contribute to atherosclerosis development and progression[67].

## SEPSIS

Probably the best example of platelet contribution to the pathophysiological inflammation response is sepsis and multiple organ failure. Adhesion of activated platelets within the microcirculation and formation of platelet aggregates contributes to vascular hyperpermeability as well as hypoperfusion[71,72]. During systemic inflammation and infection platelets become activated, as indicated by an increase in the number of CD62P-positive (P-selectin) platelets and platelet-leukocyte conjugates which are thought to contribute to disease pathogenesis, potentially through the occlusion of organ microvasculature[73,74]. Moreover, in patients with severe inflammatory response syndrome, it was observed that activated platelets release platelet microparticles (PMP) that express functional surface receptors which allow them to adhere to leukocytes[75]. However, the relative contribution of PMP, compared with intact platelets, in mediating enhanced platelet–neutrophil adhesion in sepsis is unknown.

Similar to atherosclerosis, platelet-mediated NET formation, is an exciting newly-identified cellular event that could account for the tissue damage during sepsis. In fact, although the formation of NETs may be beneficial to the host for the isolation and prevention of spreading of the invading bacteria, uncontrolled or persistent DNA traps may form at the expense of injury to the host[42]. It appears that when LPS-activated neutrophils bind endothelium little damage occurs, but if the bound neutrophils encounter LPS-bearing platelets they become significantly activated and release NETs that damage the underlying endothelium[44].

## ARTHRITIS

Rheumatoid arthritis is a chronic inflammatory and autoimmune disorder that typically affects the synovial joints of the hands and feet. Relationships between platelet activation and rheumatoid arthritis have been shown in many studies. Using a combination of pharmacological and genetic methods Boilard *et al*[76] recently demonstrated that platelets amplify inflammation in rheumatoid arthritis *via* collagen-dependent microparticle production. The microparticles are pro-inflammatory, and bring about cytokine responses from synovial fibroblasts *via* IL-1α and -1β. Taken together, these results suggest that platelets and their microparticles may have an impor-

tant role in promoting the joint pathology observed in patients with rheumatoid arthritis. However, the role of platelets in this inflammatory disease still needs further investigation since experiments using a porcine model of arthritis demonstrated that platelet-rich plasma can attenuate arthritic changes, as assessed histologically, based on protein synthesis of typical inflammatory mediators in the synovial membrane and cartilage[77].

## LUNG DISEASES

In several lung diseases, neutrophil accumulation into the lungs is the most important contributor to pulmonary destruction. However, there is evidence that platelets also have an important role in the pathogenesis of inflammation. In particular, platelets play a critical role in the recruitment of leukocytes. Moreover, circulating platelet–leukocyte aggregates have been detected in patients with allergic asthma, cystic fibrosis, and experimental lung injury[2,78-80].

Increased expression of P-selectin appears to be a major event involved in the interaction of platelets and leukocytes both on the activated pulmonary endothelium and in the formation of mixed cell aggregates[80,81]. The critical role of platelets in the initiation of lung injury was substantiated by studies showing that, in experimental models of acid aspiration and sepsis-induced acute lung injury, platelet depletion reduces neutrophil infiltration and protein leakage[80]. In addition, disruption of platelet-derived chemokines prevents neutrophil extravasation in LPS and sepsis-induced acute lung injury[82].

NET generation as a result of non-infectious inflammatory processes has been recently associated with the pathogenesis of cystic fibrosis and transfusion-related acute lung injury[83]. Moreover, targeting platelet activation with either aspirin or integrin αIIbβ3 inhibitors decreases NET formation and lung injury[84].

## INFLAMMATORY BOWEL DISEASES

The two major forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Patients with IBD are at increased risk for thromboembolism, which is one of the causes of death in this population. As genetic factors do not explain the greater risk of venous thrombosis in CD or UC patients, a pathogenesis-oriented approach has suggested that coagulation abnormalities are very probably the result of the cells and cytokines involved in the inflammatory nature of the diseases[85]. In this context, platelets from these patients exhibit enhanced homotypic and heterotypic (platelets-leukocytes) aggregation responses[86,87]. Both platelets and neutrophils are recruited to postcapillary venules in inflamed colons, with each recruitment process influencing the other[88]. Cell-cell interactions supported by selectins and both platelet-associated CD40L and platelet-derived soluble CD40L, are critical to the subsequent endothelial barrier dysfunction[89,90]. Interestingly, it appears that the interaction between platelets and neutrophils does not end at the vessel wall, because in IBD patients platelets have been observed to infiltrate the colon interstitium and move into the gut lumen along with neutrophils. Whether the extravasation of platelets potentiates the inflammatory response remains unclear, although there is evidence suggesting that this process may exacerbate the fluid secretion and diarrhea associated with IBD[91].

## CONCLUSION

Circulating blood cells are increasingly perceived as critical mediators of sustained vascular inflammation. The cross-talk between platelets and endothelial leukocyte cells in the inflammatory milieu may be seen as a double-edge sword, which functions not only as an effective first line defense mechanism but may also lead to organ failure and death in the absence of counter regulation mechanisms.

The molecular mechanisms involved in the reciprocal activation of platelets, endothelial cells and leukocytes are beginning to be elucidated. Defining the specific, fine regulation of their interaction is likely to yield novel targeted approaches and therapeutic strategies to modulate vascular inflammation, which will hopefully prove more effective and less toxic than those that are currently available.

The era of genomics and proteomics has recently been introduced in platelet research and will continue to offer major tools to help understand platelet pathology in the course of inflammation.

Because inflammatory diseases are a major cause of morbidity and mortality in developed countries, understanding the interaction of their most important components is an important challenge. In light of the existing data from experimental and clinical studies it is conceivable that platelet adhesion molecules and platelet mediators provide promising targets for novel therapeutic strategies in inflammatory diseases. Given the recently identified pivotal role of platelets in pathogen recognition and bacterial trapping, there is a need to carefully address and monitor the potentially adverse effects of these approaches, including alterations in hemostasis and coagulation and particularly the impairment of host defense mechanisms.

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Singapore

April 23-26, 2102
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Amman, Jordan

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34th World Congress Of The International Society Of Hematology 2012
Quintana Roo, Mexico

May 8-11, 2013
12th International Symposium on Myelodysplastic Syndrome
Berlin, Germany

May 9-12, 2012
American Society of Pediatric Hematology/oncology 25th Annual Meeting 2012
New Orleans, United States

June 27-30, 2012
SSC 2012 - 58th Scientific and Standardization Committee meeting of the ISTH
Liverpool, United Kingdom

June 28-30, 2012
MASCC/ISOO 2012 - International Symposium--International Symposium on Supportive Care in Cancer
New York, NY, United States

August 8-10, 2012
Coagulation Testing Quality Conference and Wet Workshop
Rochester, MI, United States

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

*No author given*

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

*Volume with supplement*

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

**Books**

*Personal author(s)*

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

*Conference proceedings*

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

*Conference paper*

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal** (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

**Patent** (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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