The enhancement of blood clotting associated with stress was caused by the liberation of adrenaline in plasma.6,7 In 1957, a possible mechanism for faster clotting after adrenaline was provided by Marciniak,8 who found a transient increase in coagulation factor VIII after injection in rabbits. Reports of raised factor VIII after adrenaline infusion in humans soon followed: the average increase was to about twice the starting level, with no measurable change in other clotting factors.9 In patients with mild hemophilia the magnitude of the factor VIII increase induced by adrenaline was similar to that elicited in healthy individuals.9,10

These findings stimulated further research, with the goal to identify a factor VIII–increasing agent that would be free of the side effects of adrenaline and could be administered to hemophilic patients as autologous replacement therapy. Vasopressin and insulin also induced an increase of factor VIII, but their side effects were not milder than those of adrenaline, making clinical use unrealistic. An important step forward was made with the observation that desmopressin, a synthetic analogue of vasopressin, increased factor VIII and vWF in healthy individuals.12,13 Unlike the natural antidiuretic hormone, desmopressin produced little or no vasoconstriction, no increase in blood pressure, and no contraction of the uterus or gastrointestinal tract, so that it was well tolerated when administered to humans.12,13

A big step forward was taken when desmopressin was used in patients for the prevention and treatment of bleeding, first during dental extractions and then during major surgical procedures with mild hemophilia A or vWD.1 Surgery was performed without blood products, demonstrating that autologous factor VIII and vWF increased in patient plasma by desmopressin could effectively replace homologous factors contained in blood products.1 These clinical results were soon confirmed.14-16

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MECHANISMS OF ACTION OF DESMOPRESSIN

Despite 20 years of clinical use of desmopressin, mechanisms of action are still not completely understood. The increases in the plasma levels of factor VIII and vWF occur not only in deficient patients, but also in healthy individuals and in patients who already have high levels of these factors. Desmopressin shortens the prolonged activated partial thromboplastin time and the bleeding time.17 These effects probably result from the increases in factor VIII and vWF, which play a rate-accelerating role in these global tests of intrinsic coagulation and primary hemostasis. Desmopressin has no effect on platelet count or aggregation, but enhances platelet adhesion to the vessel wall.18,19 Release into plasma of large amounts of tissue plasminogen activator is another short-lived effect of desmopressin.12,13 Plasminogen activator generates plasmin in vivo, but most of the plasmin is quickly complexed to α2-antiplasmin and does not produce fibrinogenolysis in circulating blood.20 Accordingly, it is usually unnecessary to inhibit fibrinolysis when desmopressin is used for clinical purposes.

How do factor VIII and vWF increase in plasma? Because these factors increase rapidly and transiently, it is most likely that desmopressin causes them to be released from storage sites. The storage site(s) of factor VIII and the interaction between released factor VIII and concomitantly released vWF are not well established. The vascular endothelium is presumably the main source of vWF. This view is supported by the observation that in rats injections of desmopressin elicit biological responses that are clearly related to the activation of endothelial cells, like surface expression of P-selectin and subsequent margination of leukocytes.21 In normal individuals, desmopressin infusion produces important changes in the content and localization of vWF in vascular endothelial cells.22 There is a reduction in the amount of the protein and a change in its localization, which causes a tendency for the protein to move abuminally toward the cellular basement membrane.22 Notwithstanding these data focusing on the endothelial cell as the most likely source of vWF, addition of desmopressin to cultured endothelial cells in vitro does not release vWF.23 Even though cultured cells may not be identical to native cells and might have lost specific receptors during culture, these observations suggest an indirect action of desmopressin through a second messenger. In the search of such a second messenger, it was shown that release of vWF from endothelial cells occurred after the addition of desmopressin to monocytes.24 These data, and those implicating monocyte-derived platelet activating factor as the second messenger acting upon endothelial cells,25 need confirmation. Desmopressin acts on storage sites via its strong V2 agonist activity, since patients with nephrogenic diabetes insipidus, who are unresponsive to V2 agonists, do not have increased factor VIII and vWF levels after treatment with desmopressin.26 Anephric patients respond normally,13 indicating that the site of the V2-like receptors involved in the hemostatic properties of desmopressin is not in the kidney. Their location is currently unknown.

A puzzling, unresolved question is how desmopressin is efficacious in bleeding disorders other than hemophilia and vWD, in patients who have normal or even high levels of factor VIII and vWF. The favorable effects of the compound may be mediated by increased platelet adhesion to the vessel wall,18,19 due not only to the rise of plasma vWF but also to the abluminal secretion of the protein toward the subendothelium20; by heightened coagulability, due to supranormal levels of factor VIII, a rate-accelerating factor in the process of fibrin formation21; and by the fresh appearance in plasma of ultralarge vWF multimers.28 These are hemostatically very effective because they support to a higher degree platelet adhesion to the vascular subendothelium and induce platelet aggregation under conditions of high shear.29 Other putative mechanisms or mediators have been proposed to explain the hemostatic efficacy of desmopressin. For instance, the compound induces the adhesion of erythrocytes to the endothe- lium20 and decreases the endothelial production of 13-hydroxyoctadecadienoic acid (HODE), a derivative of linoleic acid that powerfully inhibits platelet adhesion to the vessel wall.31 The role of these mechanisms is uncertain and the search for additional or alternative mechanisms of action has been unfruitful so far.

DESMOPRESSIN IN THE MANAGEMENT OF CONGENITAL BLEEDING DISORDERS

In hemophilia and vWD, desmopressin is efficacious because it provides a form of autologous replacement therapy. Table 1 summarizes the routes of administration, the recommended dosages, and the pharmacokinetic properties of desmopressin-induced factor VIII and vWF.

The prototypes of patients who respond to desmopressin and avoid the use of coagulation factor concentrates are those with measurable levels of factor VIII and vWF, ie, patients with mild hemophilia A and type 1 vWD,1,14-16 whereas patients with unmeasurable levels do not respond at all.17 In mild hemophilia A the efficacy of desmopressin usually correlates with the postinfusion plasma levels of factor VIII.1,14-16 Accordingly, therapeutic indications are defined by the nature of the bleeding episode, the baseline factor VIII levels, and the levels that must be attained and maintained for hemostasis. Clinical failures of desmopressin can usually be explained by the attainment of factor VIII levels in plasma that are insufficient to control bleeding.1,14-16 For instance, a major surgical procedure in a patient with factor VIII levels of 10 U/dL may not be successfully managed with desmo-

### Table 1. Recommended Dosages of Desmopressin and Factor VIII

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Intravenous and subcutaneous: 0.3 μg/kg</th>
<th>Intranasal: 300 μg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean factor increase</td>
<td>3-5 times (range: 1.5-20 times)</td>
<td></td>
</tr>
<tr>
<td>Time to peak levels</td>
<td>30-60 min after intravenous injection</td>
<td>90-120 min after subcutaneous injection and intranasal application</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>5-8 hours for factor VIII</td>
<td>8-10 hours for vWF</td>
</tr>
</tbody>
</table>
Subcutaneous and intranasal desmopressin are at least as efficacious as intravenous desmopressin and can be self-administered. Although intravenous desmopressin is recommended before surgery or for treating severe hemorrhages, because very consistent responses are required in these situations, subcutaneous desmopressin can be used at home to prevent or treat minor bleeding episodes and in women with vWD who have excessive bleeding at menstruation. Others prefer to use intranasal desmopressin as spray in these situations, even to handle major bleeding episodes and surgical operations.

Despite the fact that neither in vitro nor in vivo studies have clearly proved a direct stimulatory effect of desmopressin on platelets (reviewed by Wun et al.3), the drug shortens or normalizes the bleeding time of some patients with congenital defects of platelet function.39,40 Defects associated with normal dense granule stores benefit more from the compound.40 Accordingly, there is usually a good response in patients with defects of the release reaction, with cyclooxygenase deficiency, and in those with isolated and unexplained prolongations of the bleeding time. Most patients with storage pool deficiency respond to desmopressin but a few do not,40 so a test dose is recommended to select responders. Whether the effect on a laboratory test such as the bleeding time corresponds to a hemostatic effect is not well established. On the other hand, these levels should be sufficient for the patient to have a minor procedure, such as circumcision or dental extractions.

Many patients with type 1 vWD respond to desmopressin with increases in factor VIII and vWF that are larger than those seen in hemophilias.32 In addition to factor VIII, in these patients a determinant of the clinical efficacy of the compound is its capacity to shorten or normalize the bleeding time. Although in type 1 vWD this effect is usually achieved in proportion to the levels of normally functioning vWF attained in plasma,28 the bleeding times of patients with type 3, characterized by complete deficiency of vWF, and of those with dysfunctional molecules are usually not shortened.17,28 There are, however, a few patients with type 2A vWD in whom desmopressin does shorten the bleeding time.33 The reasons for these different behaviors are not clear and a test dose is the only way to differentiate responders from nonresponders. In theory, the administration of desmopressin to patients with heightened interactions between platelet glycoprotein Ib and vWF (type 2B and platelet-type or “pseudo” vWD) might be potentially dangerous, because it is followed by platelet aggregation and, in most instances, by thrombocytopenia.34 Although there is some evidence that desmopressin is clinically efficacious in these patients (reviewed by Castaman and Rodeghiero33), most hematologists would be reluctant to use it. Table 2 summarizes the indications for desmopressin in patients with different types of vWD.

Patients treated repeatedly with desmopressin may become less responsive, perhaps because stores are exhausted.33 Some experimental data support this hypothesis because repeated infusions of desmopressin lower the amount of vWF contained in vascular endothelial cells.23 The average factor VIII responses obtained when desmopressin is repeated three to four times at 24-hour intervals are approximately 30% less than those obtained after the first dose.32 The clinical implications are that the efficacy of desmopressin may be limited when factor VIII levels must be maintained above the baseline levels for a prolonged period of time. In these situations, which occur relatively seldom in the clinical management of mild hemophilia and type 1 vWD, it may become necessary to use plasma-derived or recombinant factors, or to supplement desmopressin with them.
philadelphia A to the corresponding patients from other countries where the compound was used later. In the United States, for instance, where in the period 1977-1985 mild hemophiliacs were mainly treated with plasma concentrates because desmopressin was not licensed until 1984, anti-HIV prevalence is 18.4%, nine times higher than in Italy. 41

DESMOPRESSIN IN ACQUIRED AND DRUG-INDUCED BLEEDING DISORDERS

The hemostatic defect in uremia is characterized by a prolonged bleeding time, a laboratory abnormality that correlates strongly with the hemorrhagic symptoms of these patients, mainly epistaxis and bleeding from the gastrointestinal tract. Dialysis may improve the bleeding time and the bleeding tendency, but this is not always the case. In the search for pharmacological agents that could improve hemostasis in uremia, intravenous desmopressin was considered, despite the fact that factor VIII and vWF are normal in uremic patients. 42 The postinfusion bleeding time became normal in about 75% of them, and returned to baseline values after approximately 8 hours. 43 Well-conducted but uncontrolled clinical studies have shown that desmopressin can be used successfully to prevent bleeding before invasive procedures (biopsies and major surgery) and to stop spontaneous bleeding. 42 Conjugated estrogens are a long-acting alternative to desmopressin, because they shorten the bleeding time with a more sustained effect lasting for 10 to 15 days. 43 The two products can be given together, exploiting the different timings of their maximal effects. Currently, most patients with chronic renal insufficiency are regularly treated with erythropoietin. This practice has led to the sustained improvement not only of anemia but also of the hemostatic defect, 44 so that short-acting compounds such as desmopressin and conjugated estrogens are now less frequently needed.

The bleeding time is prolonged in some patients with liver cirrhosis. There is usually mild or moderate thrombocytopenia, but platelet counts do not correlate negatively with the bleeding time. Factor VIII and vWF are in the high normal range, or even higher, yet intravenous desmopressin shortens the bleeding time of cirrhotic patients. 45,46 However, a controlled clinical trial has shown that desmopressin is not useful in the management of acute variceal bleeding in cirrhotic patients. 47 Because this is the most frequent and serious hemorrhagic problem the overall clinical impact of desmopressin in liver cirrhosis is relatively small.

Desmopressin counteracts the effects of hemostasis measurements of some antithrombotic drugs. It shortens the prolonged bleeding time of individuals taking widely used antiplatelet agents such as aspirin and ticlopidine, 48 the prolonged bleeding time and activated partial thromboplastin time of patients receiving heparin, 49 and the bleeding time of rabbits treated with streptokinase 50 or hirudin 51 (without corresponding human data). It also counteracts the antihemostatic effects of dextran, with no apparent impairment of the antithrombotic properties. 51

In summary, in chronic renal disease desmopressin remains indicated only for those patients with renal failure not treated or unresponsive to erythropoietin. Desmopressin is a possible treatment for patients with liver cirrhosis and prolonged bleeding time who need invasive diagnostic procedures such as liver biopsies. There is as yet little clinical evidence that desmopressin prevents or stops bleeding complications that develop in association with the use of antithrombotic agents. The compound may provide an opportunity to control drug-induced bleeding without stopping treatment and perhaps avoiding recurrence or progression of thrombosis.

DESMOPRESSIN AS A BLOOD-SAVING AGENT

The broadening indications of desmopressin, since the first use in hemophilia and vWD in 1977, led several investigators to evaluate whether the compound was beneficial during surgical operations in which blood loss is large and for which multiple blood transfusions are needed.

Open heart surgery with extracorporeal circulation is the epitome of operations that warrant the adoption of blood-saving measures. In addition to techniques such as presurgical removal of autologous blood for postsurgical retransfusion, returning all oxygenator and tubing contents to the patient, and autotransfusion of the mediastinal shed blood, prophylaxis with pharmacological agents might help reduce blood transfusion further. Since 1986, desmopressin has been evaluated for this purpose. In the first controlled randomized study carried out in patients undergoing complex cardiac operations associated with large blood losses, results were impressive. 52 Given at the time of chest closure, desmopressin reduced dramatically perioperative and early (12 hours) postoperative blood loss and transfusion requirements by about one third. 52 On the other hand, in two subsequent large studies of patients undergoing less complex operations with lesser blood loss, there were no significant differences between desmopressin- and placebo-treated patients in either total blood loss or transfusion requirements. 53,54 Other studies, mainly in patients undergoing coronary artery bypass grafting and uncomplicated valve replacement, failed to find any benefit of desmopressin. 55,56

The conflicting results of desmopressin in open heart surgery might be due to the fact that most studies were of small size and had insufficient statistical power to detect true differences in blood loss. A meta-analysis of 17 randomized, double-blind, placebo-controlled trials, which included 1,171 patients undergoing open heart surgery, has attempted to overcome this pitfall. 57 Overall, desmopressin reduced postoperative blood loss by 9%, a value that is statistically significant but of little clinical impact. Although desmopressin had no blood-saving effect when the total blood loss in placebo-treated patients decreased in the lower and middle thirds of distribution (687 to 1,108 mL), the compound reduced blood losses by 34% when blood loss was larger. 58 Therefore, desmopressin seems beneficial only in cardiac operations associated with large blood loss (>1 L). It is not easy to predict which patient will bleed more, but situations such as reoperation, presurgical use of antiplatelet agents, preexising coagulation defects, and sepsis might help to identify the cases suitable for prophylaxis. Lower preoperative plasma levels of factor VIII and vWF may also help to
identify patients most at risk of bleeding. However, the overlap of values is so large that it is not possible to use these measurements to select patients with the most to gain from the use of desmopressin.

Desmopressin is not the only blood-saving agent that can be used in cardiac surgery. The synthetic antifibrinolytic amino acids epsilon-aminocaproic acid (EACA) and tranexamic acid and the broad-spectrum protease inhibitor aprotinin have also been used, particularly after the recognition that acquired immunodeficiency syndrome (AIDS) could result from blood transfusions contaminated with HIV. A few direct comparison studies and a meta-analysis have shown that the order of efficacy of these hemostatic agents (greatest to least) is aprotinin, tranexamic acid, EACA, and desmopressin. On the other hand, the order of drug cost is also the same. Cost-effectiveness analysis is necessary to help the clinicians in making a choice that currently would be directed to aprotinin, but with formidable costs.

The efficacy of desmopressin has also been evaluated in noncardiac surgical operations characterized by large blood loss. When administered to hemostatically normal children before spinal fusion for idiopathic scoliosis, desmopressin reduced their average operative blood loss by about one third, but these favorable results were not confirmed in a subsequent study. Desmopressin did not reduce blood loss or transfusion requirement after total hip or knee arthroplasty. Preoperative desmopressin failed to reduce blood loss in patients undergoing debridement and grafting of burn wounds, a procedure in which extreme blood loss is a frequent occurrence.

In summary, the efficacy of desmopressin as a blood-saving agent in cardiac and noncardiac surgical operations appears doubtful at the moment.

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Desmopressin (DDAVP) in the Treatment of Bleeding Disorders: The First 20 Years

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