Erectile Dysfunction As a Marker for Vascular Disease

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A body of evidence from basic science and clinical research is emerging to provide a compelling argument for endothelial dysfunction as a central etiologic factor in the development of atherosclerosis and systemic vascular diseases (hypertension, dyslipidemia, diabetes, ischemic heart disease, stroke, or claudication). Erectile dysfunction (ED) is another prevalent vascular disorder that, like cardiovascular disease, is now thought to be caused by endothelial dysfunction. In fact, a burgeoning literature is now available that suggests that ED may be an early marker for atherosclerosis, cardiovascular risk, and subclinical systemic vascular disease. The emerging awareness of ED as a barometer for vascular health and occult cardiovascular disease represents a unique opportunity for primary prevention of vascular disease in all men. Although the implications of this relationship for primary and secondary prevention of cardiovascular disease are not fully appreciated, the available literature makes a strong argument for the role of ED as an early marker for the development of significant cardiovascular risk factors and cardiovascular disease.

Introduction

Cardiovascular disease remains a source of significant morbidity and mortality despite advances in prevention, diagnosis, and treatment. According to the findings of the Global Burden of Disease study that was funded by the World Health Organization, the World Bank, and Harvard University, ischemic heart disease and cerebrovascular disease were the fifth and sixth most common causes, respectively, of disability worldwide in 1990. By the year 2020, ischemic heart disease is projected to be the leading source of global disability and cerebrovascular disease will be the fourth most common cause [1]. Improved strategies for the prevention and treatment of vascular disease clearly are urgently needed.

Erectile dysfunction (ED) is defined as the persistent inability to maintain or achieve a penile erection sufficient for satisfactory sexual performance. There are a number of underlying (obesity, sedentary lifestyle, atherogenic, diet), traditional (age ≥ 45 years, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, hypertension, diabetes, smoking), and emerging (insulin resistance/metabolic syndrome) risk factors that are shared between ED and cardiovascular disease [2–4]. Evidence is emerging that endothelial dysfunction is an important common denominator between these two conditions [5,6]. In fact, a burgeoning literature is now available that suggests that ED indeed may be an early marker for atherosclerosis, cardiovascular risks, and subclinical systemic vascular disease [7,8]. Recognizing ED as a sign of early endothelial dysfunction could have a huge impact on preventive health care by providing a clinical tool for physicians to identify men at an early stage prior to the development of atherosclerosis or an adverse vascular event.

This paper reviews the relationship between ED and cardiovascular disease, including the role of endothelial dysfunction as a common etiologic factor for both. New evidence from clinical studies showing that ED precedes the development of cardiovascular disease also are reviewed and placed into perspective.

Erectile Dysfunction and Cardiovascular Disease: The Past

Erectile dysfunction is a remarkably common condition [2]. Difficulty attaining or sustaining a firm erection is the earliest and most common symptom of ED. As many as 30 million men in the United States are estimated to have ED [9]. The Massachusetts Male Aging Study (MMAS) surveyed 1290 primarily white men between the ages of 40 and 70 years and found that ED was present in 52% of this large community sample [10]. Data from the National Health and Social Life Survey, which included a national probability sample of 1410 men, indicate that 16% of men younger than 40 years of age have ED. In addition, black men are 20% more likely than white men to have ED [11].

Although the pathophysiology of ED is multifactorial and includes arterial, neurogenic, hormonal, cavernosal, iatrogenic, and psychogenic causes [9], it is now widely accepted that organic ED in a substantial majority of men is due to underlying vascular causes, especially atherosclerosis [8,12–14]. Numerous clinical epidemiology studies have demonstrated that ED is highly prevalent in

men with vascular risk factors for cardiovascular disease. Diabetes [15,16], hypertension [17], dyslipidemia [18], cigarette smoking, obesity, and sedentary lifestyles [3,10,19] are associated with an increased incidence of ED. The concept of ED being an outcome of cardiovascular disease is well accepted today.

Atherosclerosis, Endothelial Dysfunction, Erectile Dysfunction, and Cardiovascular Risk

An emerging basic science and clinical database provides a strong argument for endothelial and smooth muscle dysfunction as a central etiologic factor in systemic and peripheral vascular diseases, including ED. The endothelium, which is the layer of epithelial cells that lines the structures of the cardiovascular system, is pivotal to the regulation of vasomotor tone. Endothelial cells are a primary source of nitric oxide (NO), which is a nonadrenergic-noncholinergic vasodilatory neurotransmitter involved in the regulation of vascular wall function. Endothelial dysfunction, which is associated with impaired vasodilatation, precedes the development of atherosclerotic lesions [4] and can be caused by vascular insults, such as diabetes, cigarette smoking, hyperlipidemia, and hypertension [20]. At the cellular level, endothelial dysfunction results in impaired release of NO. Oxidative stress (*ie*, free radical damage), which interferes with the NO pathway and also is directly toxic to the endothelium, is a causal factor in clinically evident occlusive cardiovascular disease and the vascular damage associated with preclinical disease. Free radical damage and impaired function and availability of NO also result in increased adhesion and aggregation of platelets and neutrophils and the release of vasoconstrictor substances [6,7].

Many men will note the onset of ED, specifically difficulty being able to maintain a firm erection, before they are diagnosed with cardiovascular disease (hypertension, dyslipidemia, diabetes, coronary artery disease, or peripheral vascular disease). The anatomic structure of the penis and the physiology of getting and maintaining an erection provide clues as to why the penile vascular bed has some unique properties that facilitate early detection of systemic vascular disease.

The penis is a richly vascularized organ and penile erections are, in large part, a vascular event. The penile anatomy consists of the two corpus cavernosa and the ventral corpus spongiosum that surrounds the urethra. The corpora cavernosa are supplied by the dorsal and cavernous arteries, with venous return occurring through the subtunical venular plexus, the deep dorsal vein, and others (Fig. 1). Penile erection is the result of a complex and coordinated series of events involving vascular response, neuronal pathways, and psychosomatic stimulation. The NO pathway is activated upon sexual stimulation and NO is released into penile smooth muscle from the vascular endothelium of the penis and the autonomic, cavernous nerve terminals. Within the penile smooth muscle, NO activates guanylyl cyclase, which increases the concentration of the second messenger, cyclic guanosine monophosphate (cGMP). The elevated concentrations of cGMP result in relaxation of arterial smooth muscle in the penis and a marked increase in penile blood pressure. In addition, cGMP relaxes trabecular smooth muscle, which facilitates engorgement of the sinusoidal spaces, lengthening and enlargement of the penis, and compression of the subtunical venules (Fig. 1). The net result is complete occlusion of penile venous outflow and trapping of blood within the corpus cavernosa. NO from autonomic nerve endings in the penile tissue are thought to initiate smooth muscle relaxation and the erectile response, whereas NO from penile vascular and sinusoidal endothelial cells is thought to play an important role in maintaining a firm erection. Detumescence or flaccidity occurs following the release of norepinephrine and contraction of the intracorporeal smooth muscle [9,21].

A functioning NO pathway therefore is a primary determinant of smooth muscle tone, arterial inflow, and restricted venous outflow in the physiology of erection. Disruption of any of these factors can lead to ED. Endothelial dysfunction, which is associated with impaired release and activity of NO, underlies the pathophysiology of vascular ED [5,6,22].

The penis as a vascular organ may be very sensitive to changes in oxidative stress and systemic NO levels for several reasons. The small diameter of the cavernosal arteries and the high content of endothelium and smooth muscle on a per-gram tissue basis (compared with other organs) may make the penile vascular bed a sensitive indicator of systemic vascular disease. Therefore, ED can be the result of any number of structural or functional abnormalities in the penile vascular bed. For example, ED may result from occlusion of the cavernosal arteries by atherosclerosis (structural vascular ED), impairment of endothelial dependent or independent smooth muscle relaxation (functional vascular ED), or a combination of these two factors. ED caused by functional vascular factors occurs early and is likely linked to oxidative stress and decreased availability of NO. These functional factors initially result in poor relaxation of penile endothelium and smooth muscle that presents clinically as ED, particularly difficulty maintaining a firm erection. This early clinical symptom of poor maintenance caused by functional endothelial cell dysfunction likely occurs before the development of structural, occlusive penile arterial disease and may be one of the earliest signs of systemic cardiovascular disease. Over time, these systemic functional factors can lead to the development of chronic cardiovascular disease [7].

Erectile Dysfunction: An Early Marker for Vascular Disease

Recently conducted studies that measured early markers of cardiovascular disease and endothelial dysfunction

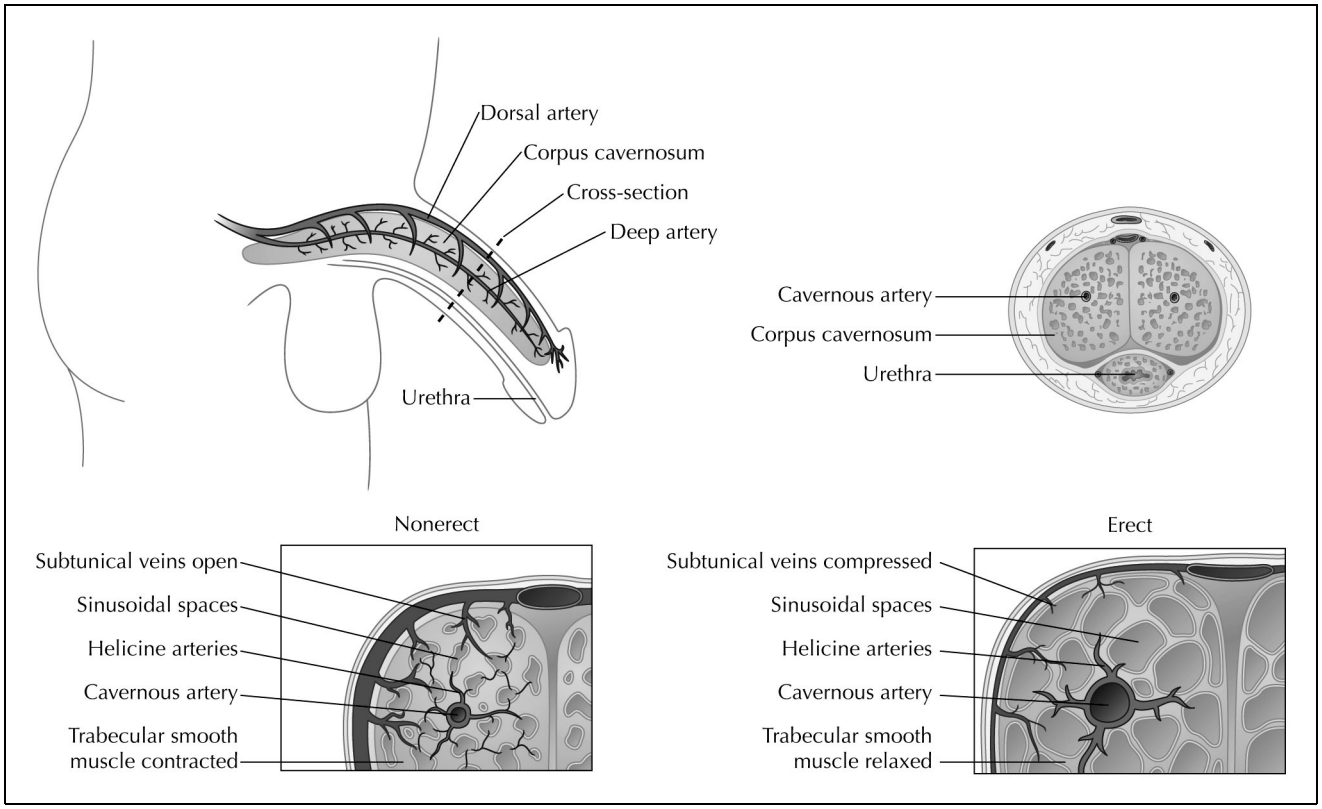

Figure 1. Anatomy of penile erection and detumescence. (*From* Billups, with permission).

demonstrate that damage to the penile vascular bed occurs before systemic vascular illness becomes clinically apparent [23••,24•,25]. In one study that assessed disease in vascular beds other than the penis, 30 men with Doppler-proven ED and no clinical evidence of cardiovascular disease (mean age, 46 years) did not differ from 27 healthy age-matched control subjects across a number of measures for peripheral vascular structure and function (*ie*, rapid CT imaging for coronary calcification, aortic pulse wave velocity, and carotid intima media thickness), except those that assessed systemic endothelial function using flow-mediated brachial artery vasodilatation studies. When compared with control subjects, men with ED exhibited significantly lower brachial artery flow-mediated, endothelium-dependent vasodilation ($P \leq 0.05$) and endothelium-independent vasodilation (*ie*, blunted response to 0.4 mg sublingual nitroglycerin; $P = 0.02$), which suggests the presence of a peripheral vascular abnormality in the NO pathway [23••] (Figs. 2 and 3).

In another study, biochemical markers of endothelial cell activation were used to compare 45 men with ED and no clinical cardiovascular disease with 25 age-matched healthy control subjects. All but two men with ED had penile blood flow Doppler results that were normal. Biochemical and structural markers compared between the men with ED and the control subjects included carotid intima-media thickness (IMT), soluble P-selectin, ICAM-1, VCAM-1, and endothelin-1. Results revealed no difference in carotid IMT scores between the two groups, but soluble P-selectin, ICAM-1, VCAM-1, and endothelin-1 levels were significantly higher in the men with ED and no cardiovascular disease [24•]. Results from these two studies support the theory that symptoms of erectile difficulty precede overt structural occlusion of larger vessels, suggesting that ED is an early manifestation of systemic vascular disease.

Another recent study examined the incidence of significant carotid arterial disease based on carotid ultrasonography in men with ED [25]. This study correlated carotid IMT with cardiovascular risk factors and severity of ED in a group of 270 men. The men were divided into those who had ED with no known cardiovascular risk factors and those who had ED and multiple cardiovascular risk factors. Only one man out of 50 with ED and no cardiovascular risk factors (mean age, 40 years) had a carotid IMT study that was indicative of significant vascular disease (IMT measurement of ≥ 1.0 mm). Of the 220 men with ED and multiple cardiovascular risk factors, 18% (39 of 220) showed a carotid IMT score indicative of significant vascular damage. Men with abnormal carotid IMT scores had more severe ED. The authors concluded that men with ED and known cardiovascular risk factors may benefit from a carotid IMT ultrasonography test. The carotid IMT test has been shown to correlate with increased risk of a future adverse vascular event by detecting subclinical carotid artery disease. Those men who are found to have a carotid IMT consistent with significant vascular disease are likely

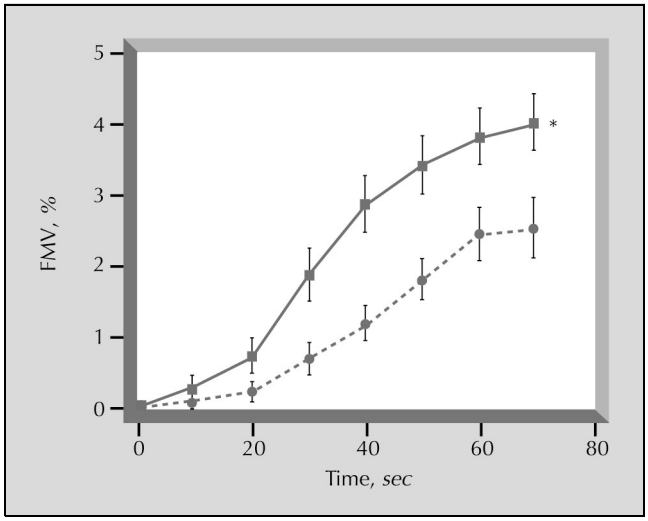

Figure 2. Brachial artery flow-mediated vasodilation was significantly reduced in men with erectile dysfunction (•) versus healthy control subjects (■) over the whole time period ($P = 0.014$). The difference also was significant when comparing the percent dilation from baseline with 60 seconds after cuff release ($P = 0.05$).

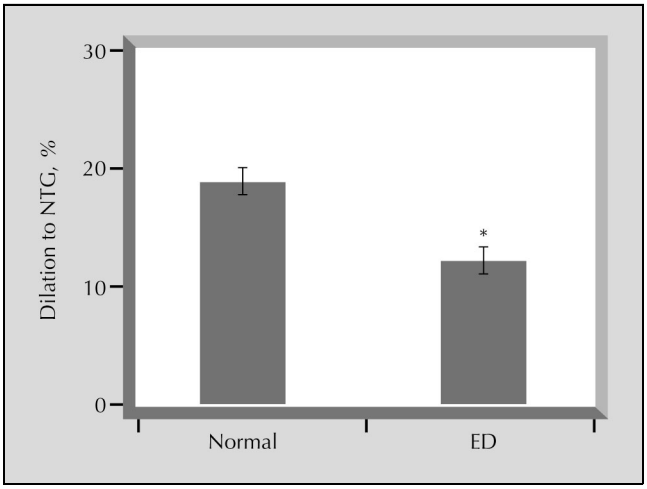

Figure 3. The vasodilator response to 0.4 mg of sublingual nitroglycerin (NTG) was significantly impaired in men with erectile dysfunction (ED) versus healthy control subjects (13.0% ± 1.4% vs 17.8% ± 1.4 %; $P = 0.02$).

good candidates for aggressive management of the associated cardiovascular risk factors to decrease the chance of a future acute vascular event.

Another recent study went a step further by providing evidence that ED may be an independent risk factor for a stroke. The study investigators followed 1209 men from the MMAS over a 15-year period. None of these men had any history of stroke, transient ischemic attack, or known disease of the carotid arteries. ED was detected by self-reported questionnaires. The study results showed that within the group of 1209 men, those who had ED were approximately 3 times more likely to have a stroke during the 15-year follow-up compared with those men who did not have ED. Even after adjusting for age and other cardiovascular risk factors, the men with ED still had a 150% increased risk of having a stroke during the 15-year period [26].

Erectile dysfunction should be considered as an early symptom of cardiovascular disease and as an emerging risk factor that should lower the threshold to obtain additional screening studies for coronary artery and peripheral vascular disease (*ie*, carotid IMT ultrasonography, ankle-brachial index, and penile Doppler ultrasonography). There may be a new role for penile Doppler ultrasonography as a technique to identify men with arterial, vasculogenic ED who may benefit from early aggressive management of cardiovascular risk factors in addition to our standard ED treatments. Such a fundamental shift in thinking could profoundly affect preventive vascular medicine.

Conclusions

Erectile dysfunction is highly prevalent and for many years, has been viewed as a complication of cardiovascular disease, diabetes, and hypertension. ED and systemic vascular disease share many common risk factors. However, a robust, emerging database offers convincing evidence that ED is more than a serious quality-of-life issue for sexually active men, particularly those with cardiovascular disease. Penile erection is a vascular process and the small vessels of the penis are very sensitive to occlusive changes. Endothelial dysfunction, in which damage to the lining of the arterial walls impairs the NO pathway and vasodilation, is an important pathophysiologic factor underlying ED and cardiovascular disease. As studies of men who have ED but no overt cardiovascular disease have shown, ED indeed may be one of the first clinical manifestations of atherosclerosis, which begins as a nonobstructive, functional process. This evidence cannot be ignored. ED now must be considered as an early marker of subclinical or undiagnosed cardiovascular disease.

The recognition of ED as a harbinger of systemic cardiovascular disease represents a remarkable opportunity for prevention. Unfortunately, misinformation and stigma continues to prevent many men from discussing ED with their physicians and many physicians from aggressively asking men about erectile difficulty in the office setting. I firmly believe that all men who are 25 years of age and older should be screened for ED, regardless of their clinical presentation and level of sexual function. Patients who are discovered to have ED must be thoroughly and aggressively assessed for cardiovascular risk and occult systemic vascular disease.

Clinical studies are beginning to show that treatment of risk factors for cardiovascular disease can improve erectile function. Smoking cessation results in a rapid improvement in erections [3,27] and response rates to sildenafil therapy are higher among men with fewer vascular risk factors compared with men who have multiple risk factors [28]. A recent study has shown that aggressive intervention with diet and exercise improves ED and endothelial cell function while decreasing systemic inflammatory

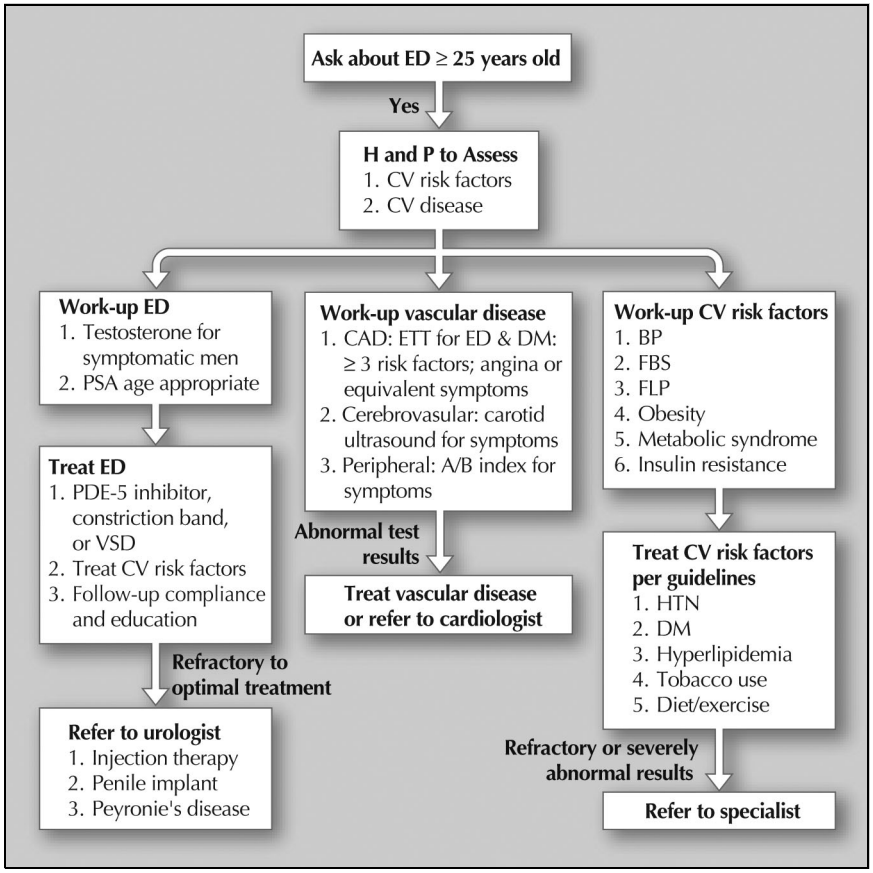

Figure 4. Cardiovascular risk assessment and management algorithm for men with erectile dysfunction seen in a primary care clinic setting. BP—blood pressure; CAD—coronary artery disease; CV—cardiovascular; DM—diabetes mellitus; ETT—exercise treadmill testing; FBS—fasting blood sugar; HTN—hypertension; PDE—phosphodiesterase; PSA—prostate-specific antigen. (*From* Billups, with permission).

mediators and the severity of other traditional cardiovascular risk factors [29]. One clinical study revealed that in men with ED caused primarily by elevated low-density lipoprotein cholesterol levels, treatment with atorvastatin over a 3-month period resulted in significant improvements in penile rigidity and ED questionnaire scores [30]. Physicians should begin to consider aggressive management of cardiovascular risk factors as part of the overall evaluation and treatment process for ED. A recent expert advisory panel review article focused on ED as an early marker of systemic atherosclerosis and introduced an algorithm for aggressive management of cardiovascular risk factors in men with ED in the primary care setting [31] (Fig. 4).

Much stills needs to be done to improve our understanding of the relationship among ED, systemic vascular disease, and endothelial dysfunction. The implications of this relationship for primary and secondary prevention of cardiovascular disease are not fully appreciated. The available literature makes a strong argument for the role of ED as an early marker of cardiovascular disease and the results of these studies should not be ignored. Future evidence-based data and large-scale prospective studies of young men with ED that longitudinally monitor cardiovascular risk and emergent disease ultimately will validate current aggressive treatment decisions by clinicians and change reimbursement strategies by health care policy makers and insurers.

Education of patients and physicians is another critically underserved area. The importance of ED as a predictor of serious systemic disease must be emphasized in medical school curricula, residency training programs, and continuing medical education programs. Efforts at educating the public through television, radio, print media, and the Internet are needed. The role of an individualized therapeutic alliance among the patient, his spouse or partner, and the physician should not be underestimated. Patients who understand that ED is an early warning signal for the onset of serious heart disease will be more likely to follow risk-modification strategies, adhere to treatment plans, and achieve positive therapeutic outcomes. Perhaps it is time to elevate the discussion of ED to the level of a public health concern that is associated with prevention of cardiovascular disease.

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