Fibromuscular dysplasia

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Fibromuscular dysplasia is an uncommon angiopathy that occurs in young to middle-aged, predominately female individuals. The disease consists of a heterogeneous group of histologic changes, which ultimately lead to arterial narrowing. Clinical manifestations reflect the arterial bed involved, most commonly hypertension (renal) and stroke (carotid). Fibromuscular dysplasia is a pathologic diagnosis, but the characteristic changes seen on an angiogram can be used to make the diagnosis in the appropriate clinical setting. This noninflammatory disease is a common mimic of vasculitis. A very limited amount of new literature has been published in the past year about this relatively uncommon condition. Curr Opin Rheumatol 2000, 12:41–47 © 2000 Lippincott Williams & Wilkins, Inc.

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Abbreviations

FMD   fibromuscular dysplasia
PTA   percutaneous transluminal angioplasty

Fibromuscular dysplasia (FMD) is a vascular disease affecting small to medium-sized vessels. It is a noninflammatory, nonatherosclerotic condition occurring more frequently in younger individuals and women. The presence of FMD has been demonstrated in almost every vascular bed. Renal artery involvement is most common (60–75%), followed by the cervicocranial arteries (25–30%), visceral arteries (9%), and the arteries in the extremities (5%) [1]. At least two vascular beds are involved in up to 28% of patients [2•]. The diagnosis is most often made by the characteristic angiographic appearance. Although the pathologic specimen is diagnostic, it is rarely obtained.

Pathologic classification

A uniform classification system to describe fibromuscular dysplasia of the renal artery was proposed by Harrison and McCormack in 1971 [3••]. Three main types were identified, according to the dominant arterial wall layer involved. These are intimal fibroplasia, medial dysplasia, and adventitial (periarterial) fibroplasia (Table 1). Medial FMD is further divided into medial fibroplasia, perimedial fibroplasia, and medial hyperplasia. Dissection, initially described as a subgroup of medial dysplasia, is now recognized as a complication of this disease [4]. Although a simplified approach has been proposed [5], the original classification system is still used and is also applicable to extrarenal arterial involvement.

Intimal fibroplasia accounts for less than 10% of all fibrous lesions. Histologically, there is circumferential or eccentric deposition of collagen in the intima without a lipid or inflammatory component. The internal elastic lamina is identifiable but may be fragmented or duplicated. This appearance can be mimicked by endarteritis due to inflammation or trauma. Angiographically a smooth focal stenosis (concentric band) (Figs. 1,2) or a long smooth (tubular) stenosis (Figure 1) may be present [4]. Intimal fibroplasia can occur as a generalized disorder involving the renal, carotid, upper and lower extremity, and mesenteric vasculature simultaneously [6,7], mimicking a multisystem disease such as necrotizing vasculitis.

Medial fibroplasia, a subtype of medial FMD, is the histologic finding in 75–80% of all cases of fibrous dysplasia. Microscopically there are alternating areas of thinned media and thickened fibromuscular ridges containing collagen. Some areas of the internal elastic

Table 1. Classification of fibromuscular dysplasia

Classification	Frequency	Pathology	Angiographic appearance
Medial dysplasia			
Medial fibroplasia	75–80%	Alternating areas of thinned media and thickened fibromuscular ridges containing collagen Internal elastic membrane may be lost in some areas	"String of beads" appearance where the diameter of the "beading" is larger than the diameter of the artery
Perimedial fibroplasia	10–15%	Extensive collagen deposition in the outer half of the media	"Beading" in which the "beads" are smaller than the diameter of the artery
Medial hyperplasia	1–2%	True smooth muscle cell hyperplasia without fibrosis	Concentric smooth stenosis (similar to intimal disease)
Intimal fibroplasia	<10%	Circumferential or eccentric deposition of collagen in the intima No lipid or inflammatory component Internal elastic lamina fragmented or duplicated	Concentric focal band Long smooth narrowing
Adventitial (periarterial) fibroplasia	<1%	Dense collagen replaces the fibrous tissue of the adventitia and may extend into surrounding tissue	

membrane are lost. A "string of beads" is used to describe its angiographic appearance, where the "bead" diameter is larger than the proximal vessel (Figs. 3,4). It involves the distal two-thirds of the main renal artery, occasionally extending into its branches. It is also commonly encountered in the internal carotid artery at the level of the C-1 and C-2 vertebrae. Whereas atherosclerosis typically occurs at the carotid bifurcation, medial fibroplasia is found several centimeters distal to the bifurcation.

The second subtype, perimedial fibroplasia, occurs in 10–15% of all lesions and is found in young girls. Extensive collagen deposition is located in the outer half of the media and can replace it entirely, but does not extend beyond the external elastic lamina. Perimedial fibroplasia may also appear as arterial beading on an angiogram. However, unlike medial fibroplasia, the caliber of the beads does not exceed that of the proximal artery and the beads are usually less numerous. This dysplastic lesion results in severe stenosis and may be associated with collateral circulation.

Medial hyperplasia, the last subtype, is the only lesion in which there is true smooth muscle hyperplasia without fibrosis. It is found in only 1–2% of all lesions and appears as a concentric, smooth stenosis on an angiogram, making it difficult to differentiate from intimal fibroplasia. The location of vessel involvement is similar to that of medial fibroplasia but does not affect the branches of the renal artery as often.

Adventitial fibroplasia is rarely seen (<1%). Dense collagen replaces the fibrous tissue of the adventitia and may extend into the surrounding tissue. The other arterial layers and elastic laminae remain intact.

Etiology

The etiology of FMD is not known despite a variety of theories. In part, it is thought to be a genetic disorder due to the higher incidence of FMD in certain families and in the white population. Rushton [8] studied 20 families and found that in 60% of the cases the inheritance pattern suggested an autosomal dominant trait with variable penetrance. He speculated that the remaining 40% developed disease due to new mutations. Subsequent case reports of disease among family members also suggest a genetic cause [9]. The higher prevalence of disease among women implies that hormonal factors are important [10]. Reported associations include use of ergotamine preparations, methysergide, the rubella syndrome, and heterozygous alpha-1-antitrypsin deficiency [10,11]. There is evidence that cigarette smoking may be a risk factor [12]. Lastly, a variety of diseases have been linked with FMD. These are pheochromocytoma, neurofibromatosis, Ehlers-Danlos syndrome type IV, Alport's syndrome, cystic medial necrosis, and coarctation of the aorta [1].

Fibromuscular dysplasia and the kidney

Approximately 40% of renovascular disorders are due to FMD, of which the most common histologic lesion is medial fibroplasia [13]. However, the age of our population is increasing and atherosclerotic renal artery stenosis is being recognized much more frequently now than in the past. Therefore, FMD may account for a significantly lower percentage of patients with renovascular diseases than several decades ago. These patients present with hypertension when symptomatic. Stenosis infrequently results in deterioration of renal function, as opposed to patients with underlying atherosclerosis. This reflects the natural history of these lesions. Medial fibroplasia was thought to be a stable lesion, whereas other dysplasias (intimal fibroplasia, medial hyperplasia,

Figure 1. Aortogram demonstrating the classic arteriographic appearance of intimal fibroplasia
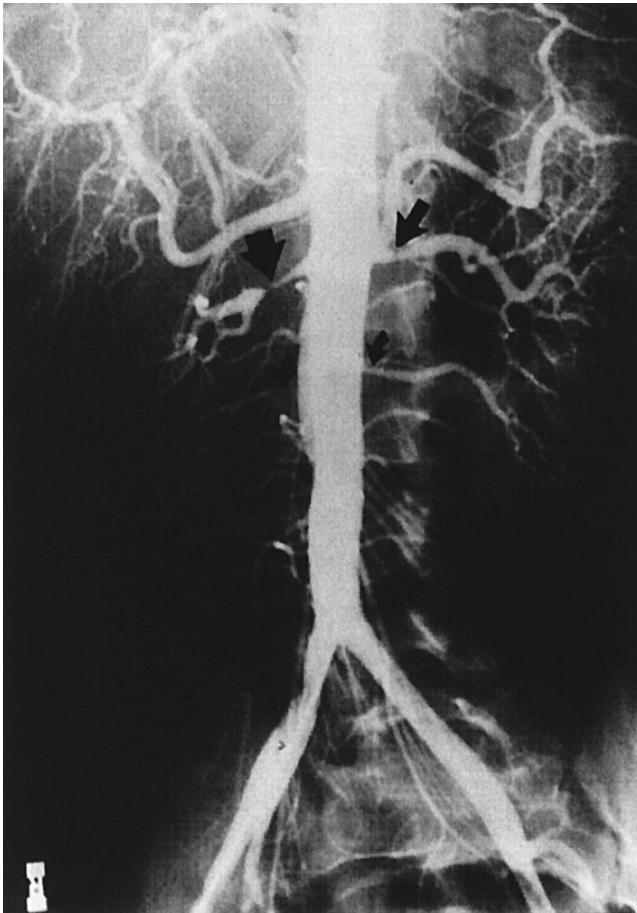
The left renal artery stenosis demonstrates a focal area of narrowing, simulating a band around the renal artery (arrow). The right renal artery demonstrates a long smooth area of narrowing (large arrow). From [13], with permission.

and perimedial fibroplasia) were known to cause progressive disease [14], resulting in ischemic renal atrophy and chronic renal failure [13]. More recent studies have shown that this is not completely accurate. Goncharenko *et al.* [15] studied 42 patients angiographically and demonstrated disease progression in all of them. This included 12 patients with medial fibroplasia, of whom 75% had bilateral disease. Schreiber *et al.* [16•] used serial angiograms to look at 66 patients with lesions due to medial fibroplasia. They documented progressive disease in 33% of their patients. However, none of the lesions progressed to complete occlusion. Only 2 of these 22 patients had a rise in serum creatinine (greater than a 20% increase over baseline), and 6 of the 22 exhibited a decrease in the size of the involved kidney.

The mechanism by which renovascular disease results in hypertension is complex. It depends, in part, on

whether the stenosis is unilateral (renin-dependent hypertension) or bilateral/unilateral with a single functioning kidney (volume-mediated hypertension) [13]. Ultimately, there is increased production of angiotensin II resulting in vasoconstriction and stimulation of aldosterone, resulting in salt and water retention. A variety of diagnostic modalities are available to evaluate renal blood flow and vascular anatomy, including captopril renography, duplex ultrasonography, magnetic resonance angiography, and spiral computed tomography scanning [17–19]. Arteriography remains the gold standard and is especially useful in the diagnosis of branch vessel disease.

Medical management is indicated for the treatment of hypertension. The guidelines of the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure should be followed [20]. An angiotensin-converting enzyme inhibitor or an angiotensin II antagonist should be part of the regimen if the disease is unilateral. Other therapies include the use of antiplatelet agents and risk factor modification, in particular smoking cessation. Endovascular therapy or surgery is indicated when the hypertension is poorly controlled despite maximum doses of three antihypertensive medications, the patient is unable to tolerate the medications or is noncompliant, and as an alternative to lifelong medication in this relatively young population.

Percutaneous transluminal angioplasty (PTA) is a very successful technique for treating renovascular hypertension due to fibromuscular dysplasia. Sos *et al.* [21•] treated 31 patients with PTA and had a technical success rate of 87.1%. Of these patients, 59.3% were "cured" and an additional 33.3% had improved blood pressure control. Only 7.4% did not demonstrate a significant change. Other studies have reported similar success [22,23]. Complications occur infrequently and include vessel dissection, thrombosis, perforation, groin hematoma, and contrast-induced renal failure. *It is not necessary or indicated to stent fibrous lesions, because the recurrence rate after PTA is low, especially for medial FMD.*

Angioplasty is effective for the treatment of disease in the main renal arteries; however, FMD frequently involves the arterial branches. Percutaneous transluminal angioplasty may be useful for lesions in this location. Surgery is a viable option for these patients as well. Several techniques have been described, but the most common approaches are aortorenal bypass and extracorporeal reconstruction and autotransplantation. Studies show a 43–63% cure rate, improved blood pressure control in 30–50% of patients, and a failure rate of less than 10% [24,25]. Morbidity and mortality are signifi-

Figure 2. Angiographic appearance of carotid artery intimal fibroplasia
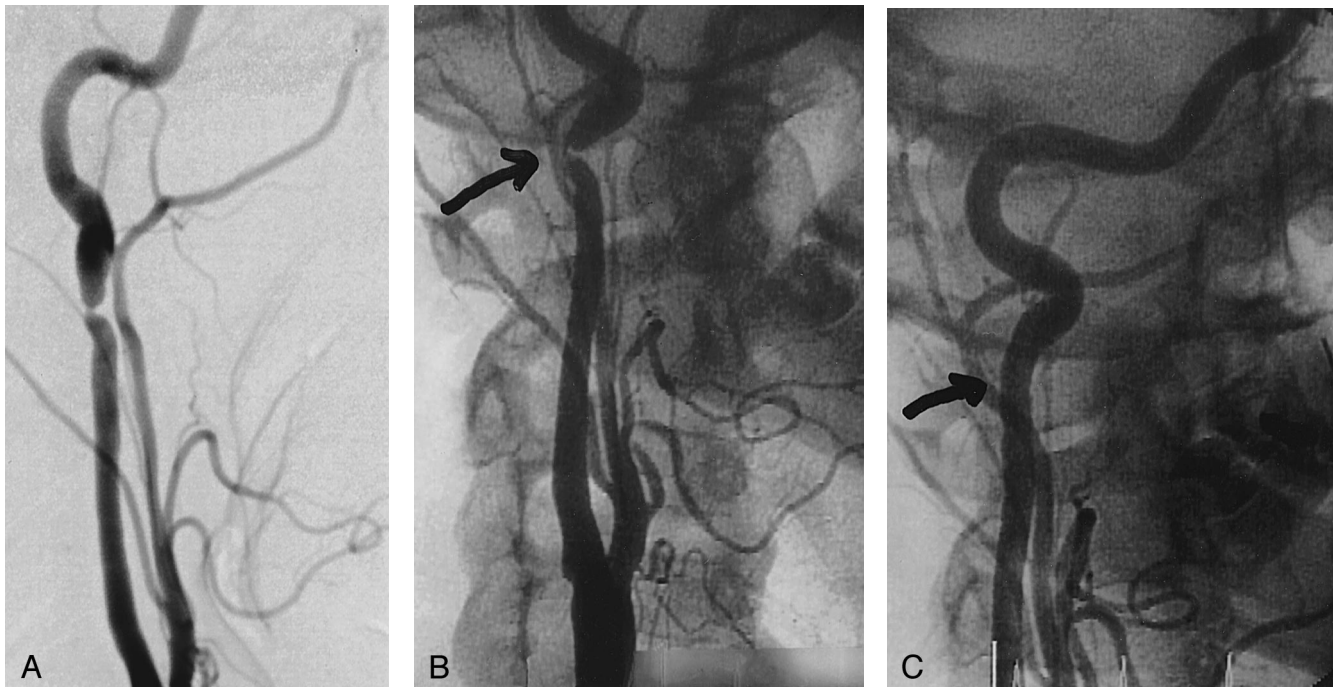
(A,B) A very severe concentric stenosis (intimal fibroplasia) (arrow) is present in the distal right internal carotid artery in this 36-year-old woman presenting with right hemispheric transient ischemic attacks. (C) After percutaneous transluminal angioplasty of the severe stenosis, the internal carotid artery has a normal appearance on angiography (arrow).

cantly lower compared with patients with atherosclerotic lesions. Currently, there are no good controlled, prospective, randomized trials comparing these therapeutic modalities for renovascular disease due to FMD.

## Fibromuscular dysplasia and the central nervous system

Fibromuscular dysplasia can be found throughout the cervicocranial arterial system. The majority of cases involve the internal carotid arteries (95%), often bilaterally (60–85%) [26]. Vertebral artery involvement is less common and frequently coexists with carotid disease [27]. An association exists between intracranial "berry" aneurysms and cervicocranial FMD. The majority are located in the internal carotid artery and the middle cerebral artery [28]. Multiple aneurysms are found in some cases. The frequency of intracranial aneurysms among cases of cervicocranial FMD is reported to be between 21% and 51% [26]. A recent meta-analysis suggests that this is an overestimate and that the true incidence is closer to 7% [29]. All patients with cervicocranial FMD should have a magnetic resonance angiography of the Circle of Willis to rule out an intracranial aneurysm.

Fibromuscular dysplasia may or may not cause symptoms. The diagnosis of FMD in asymptomatic individuals is made when angiography is performed for unrelated reasons. In some patients, FMD is discovered incidentally during evaluations for dizziness, headache, or an asymptomatic cervical bruit. Symptoms occur when these lesions: (1) are tightly stenotic, producing hypoperfusion, (2) embolize, (3) thrombose, (4) dissect, or (5) when an associated aneurysm ruptures. Presenting symptoms vary depending on the severity of disease and its location. Nonspecific symptoms include headache, altered mentation, tinnitus, vertigo, and neck pain. Transient ischemic attack, cerebral infarction, subarachnoid hemorrhage, syncope, Horner's syndrome, and cranial nerve palsies are more specific neurologic symptoms [28]. Of the latter specific diagnoses, the first three are the most frequent [30].

Several techniques can be used to diagnose cervicocranial FMD. Carotid duplex ultrasonography accurately detects stenotic lesions when administered by well-trained personnel. However, because the lesion is typically at the level of the C1-C2 vertebral bodies and not at the proximal origin of the internal carotid artery, it can be missed [31]. It is important for the ultrasound technologist to scan the carotid artery as distally as possible so that this is not overlooked. Magnetic resonance angiography is also a very good noninvasive option [32]. Angiography remains the diagnostic method of choice.

Figure 3. Renal arteriogram demonstrating typical medial fibroplasia of the right renal artery
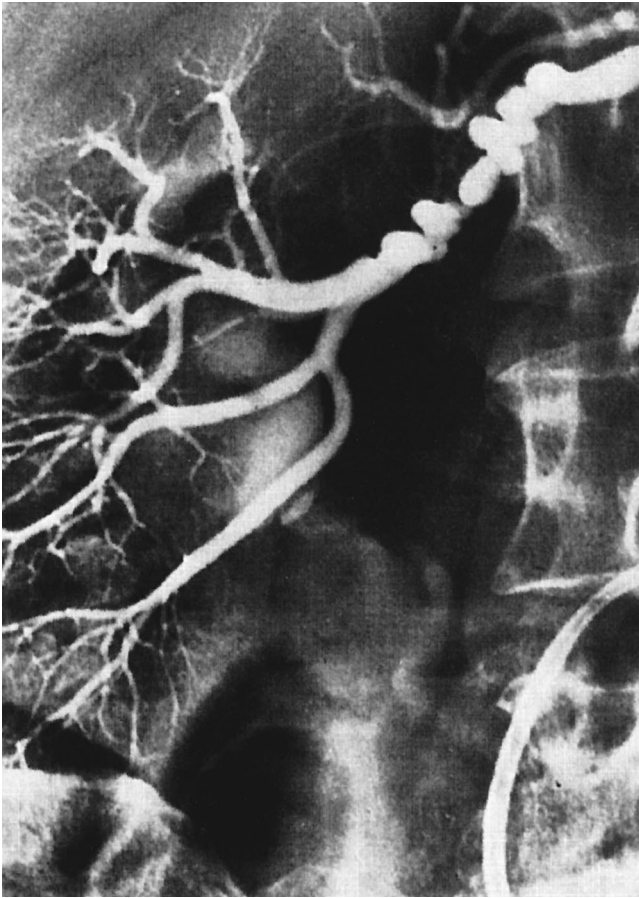
The "string of beads" appearance of the renal artery involves the distal portion of the main renal artery, and the "beads" are larger than the normal diameter of the artery. From [13], with permission.

Management decisions reflect the clinical experience and expertise available at one's institution, the presence or absence of symptoms, and, to an extent, our lack of knowledge concerning disease progression. Asymptomatic patients without associated aneurysms should be treated with antiplatelet agents. The presence of an aneurysm requires surgical consideration. In the past, for stenotic lesions, intraoperative graduated intraluminal dilatation had been most frequently used with good outcomes in symptomatic patients with progressive ischemia [33,34]. However, with smaller balloons and better catheter techniques, PTA is the treatment modality of choice in most patients who are symptomatic. Other methods of treatment are resection with end-to-end anastomosis (or interposition graft) and bypass grafting between the carotid artery and the middle cerebral artery. There are no randomized, controlled, prospective studies comparing these various therapies.

Fibromuscular dysplasia and extrarenal viscera

Fibromuscular dysplasia has been reported in other visceral arteries, including the celiac, superior and inferior mesenteric, hepatic, splenic, and coronary arteries [35•]. The disease usually involves more than one vessel. The angiographic appearance is often smooth and tubular instead of a "string-of-beads" in these vascular beds [10]. Although typically asymptomatic, patients can present with mesenteric ischemia (postprandial abdominal pain, weight loss, and an epigastric bruit). However, due to extensive collateral circulation, infarction is rare. Surgery is indicated if the patient is symptomatic despite conservative management. There are a few cases in which percutaneous balloon angioplasty has been successful. Coronary artery involvement is now more common than initially thought [36].

Fibromuscular dysplasia and extremities

Fibromuscular dysplasia can occur in the arterial circulation of the extremities. In the legs, external iliac arteries

Figure 4. Angiographic demonstration of medial fibroplasia

This angiogram demonstrates medial fibroplasia ("string of beads") in the internal carotid artery several cm distal to the carotid bifurcation. The topographic location is next to C1-2.

are most often involved, but there have been case reports of disease in the femoral, popliteal, tibial, and peroneal arteries. Patients may present with symptoms of intermittent claudication, cold legs, or have evidence of embolic disease distally [37]. Upper extremity symptoms such as arm weakness, paresthesias, claudication, and subclavian steal syndrome are usually due to disease in the subclavian artery. Axillary, brachial, radial, and ulnar arterial involvement have also been described. Symptomatic disease can be treated with graduated intraluminal dilatation, surgical bypass/resection, or percutaneous transluminal angioplasty [37].

Differential diagnosis of fibromuscular dysplasia

Fibromuscular dysplasia is usually easy to differentiate from atherosclerosis. As a general rule, atherosclerosis occurs proximally and FMD (especially medial fibroplasia) occurs in the mid or distal portion of the blood vessel. Patients with atherosclerosis often have multiple atherosclerotic risk factors, whereas most individuals with FMD are younger and have fewer risk factors. There are times, however, when a patient has FMD at a young age and then develops atherosclerosis as he or she gets older. In these instances, one may see angiographic features of both diseases in the same patient.

There have been reports of Ehlers-Danlos Type IV being associated with medial fibroplasia. This should be suspected in patients who have multiple aneurysms in addition to the usual angiographic findings of FMD. Ehlers-Danlos may occur in the absence of any prior bleeding manifestations. If this disease is suspected, a skin biopsy should be obtained and sent for fibroblast culture.

There may be instances when it is difficult to differentiate FMD from vasculitis. There should not be a problem in differentiating medial fibroplasia (string of beads) from vasculitis, but it may be very difficult to differentiate diffuse intimal disease from vasculitis. Fibromuscular dysplasia is by definition a noninflammatory process and therefore not associated with anemia, thrombocytopenia, or abnormalities in acute phase reactants except when it occurs in the face of acute infarction. Large vessel vasculitis may occur in the absence of changes in acute phase reactants in up to 40% of cases. If histologic proof of FMD or inflammation is not available, distinguishing these entities may at times be difficult because the angiographic appearance can be similar. This is most often the case in the disseminated form of intimal fibroplasia. While MRA may be useful in showing wall thickening in patients with giant cell arteritis or Takayasu's arteritis, it is not useful in patients with renal or intestinal FMD because of the propensity to involve branch vessels. To our knowledge, there is no enhancement on T2 or gadolinium magnetic resonance images in FMD, whereas there is in the large artery vasculitides. Intravascular ultrasound may be helpful in distinguishing FMD from vasculitis in some cases. When difficulty in diagnosis exists, the most experienced resources in the medical community should collaborate to distinguish these illnesses. Whereas active vasculitis is usually treated with corticosteroids with or without cytotoxic agents, there is no place for such therapy in FMD.

Conclusions

Fibromuscular dysplasia is an uncommon disease, although it has been demonstrated in nearly every arterial vascular bed. It is frequently confused with vasculitis, atherosclerosis, and congenital vascular diseases, especially when there is diffuse involvement. It can present with hypertension, renal infarction, dissection, transient ischemic attack, and stroke, thus simulating vasculitis. However, it is an important diagnosis to make because there are several relatively safe therapeutic options that have excellent outcomes. Prospective studies are needed to determine the optimal management of FMD for each major vascular bed.

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