Insights into the pathogenesis of acute ischemic syndromes

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OVER THE LAST few years clinical/pathologic observations and experimental investigation have led us to a better understanding of the pathogenetic factors leading to the acute coronary syndromes: unstable angina, myocardial infarction, and ischemic sudden death. The elegant pathologic studies of Falk and Davies and Thomas have emphasized that thrombus formation secondary to plaque rupture and fissuring in the atherosclerotic coronary artery play a major and frequent role in the acute coronary syndromes. Indeed, their observations and the observations of others have established that this pathologic phenomenon is a common link between the three acute coronary syndromes in man. This review focuses on three areas of recent progress: (1) the interaction between platelets, thrombosis, and blood rheology in experimental vessel wall injury, (2) the relevance of these blood vessel interactions to the acute coronary syndromes in man, and briefly (3) the usefulness of antithrombotic therapy in reducing morbidity and mortality due to the acute coronary syndromes.

Interaction of platelets, thrombosis, and blood rheology in experimental vessel wall injury

Platelet adhesion in experimental mild superficial vessel wall injury (figure 1). After removal of the endothelial lining of a normal blood vessel by a mild or superficial injury, the subendothelium becomes coated by a layer of adherent platelets. Adhesion, the process by which platelets attach to the exposed subendothelium, is dependent on platelet receptors and adhesive membrane glycoproteins, and on exposure of activating sites in the subendothelium (figure 1). Glycoprotein Ib in the platelet membrane appears to be important for normal initial contact of platelets with von Willebrand factor in the subendothelial surface. Glycoprotein Ia, which binds directly to exposed subendothelial collagen, may also be important. Glycoprotein IIb/IIIa in the platelet membrane is the receptor for a variety of circulating proteins, including von Willebrand factor and fibronectin, and aside from being important in platelet aggregation (see later), it indicates platelet adhesion.

In the clinical context, subtle injury of the endothelial cell layer, for example that produced by flowing blood at arterial branch points or through stenoses, may trigger platelet adhesion. The release of platelet-derived growth factors after platelet adhesion may contribute to the slow process of atherogenesis.

Platelet aggregation and thrombosis in experimental deep vessel wall injury (figure 1). Severe injury exposes components of the arterial media, particularly fibrillar collagen (with type I being more prevalent in diseased vessels and type III in normal vessels), which in addition to other mediators, induces platelet aggregation. Superimposed on the layer of adhesive platelets, platelet aggregation is triggered by either of three pathways — arachidonate, ADP, and/or the collagen-thrombin-dependent third pathway. Any or all of these pathways may trigger the exposure of the platelet membrane receptor GPIIb/IIIa. Subsequently, fibrinogen, von Willebrand factor, and presumably fibronectin bind to GPIIb/IIIa and bridge activated neighboring platelets, thereby playing a key role in aggregate formation (figure 1). In addition, during platelet adhesion and aggregation, the clotting mechanism may be activated by means of exposure of the blood to the negatively charged damaged subendothelial and medial surfaces (intrinsic clotting system) and to the released tissue factor (extrinsic clotting system) (figure 1). Thrombin is then generated, which further promotes platelet aggregation (probably through the same pathway as collagen); most importantly, thrombin leads to the formation and polymerization of fibrin, which stabilizes the platelet mass and allows the arterial thrombus to resist dislodgement by the high intravascular pressure and shear forces.

In the clinical context, atherosclerotic plaques are
particular rich in fibrillar collagen (the same collagen that is exposed in the model of deep wall injury) and fatty gruel. That is, in the acute coronary syndromes, sudden plaque rupture may trigger platelet aggregation, activation of the coagulation system, and thrombosis, in a fashion similar to that seen with the deep injury model.

Effects of blood rheology in experimental mild/superficial vessel wall injury (figure 2). The number of platelets attaching to an injured vessel wall is determined not only by the degree of injury as described above but also by their transport to the injured area. This transport is determined by the wall shear rate, which is a measure of the difference in blood velocity between the center of the vessel and along the wall. Shear rate increases with decreasing vessel diameter and with increasing flow. We have explored the relationship between shear rate and platelet deposition using a perfusion chamber in which different vessel wall substrates can be exposed to circulating blood at various shear rates mimicking those developed within coronary stenoses in medium-sized arteries.\(^7\)\(^-\)\(^9\) Mimicking mild injury to the vessel wall, the exposure of deendothelialized aortic wall to blood flow at low shear rates characteristic of large arteries and veins results in adhesion of only a single layer of platelets. At higher wall shear rates, characteristic of medium-sized stenotic arteries, initial platelet deposition rate and maximal extent of deposition is significantly higher; maximum platelet deposition or thrombus formation is observed after 10 to 20 min (figure 2). However, with longer exposure the thrombus is dislodged from the exposed surface by the flowing blood. Thus, the platelet deposition is relatively transient, suggesting labile thrombosis of 10 to 20 min duration.

This transient thrombotic phenomenon in the higher shear rate experiment, mimicking mild vessel injury within a stenosis, may have clinical implications in the

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**FIGURE 2.** Left. Platelet deposition on deendothelialized vessel wall against exposure time at different wall shear rates (sec\(^-1\)): \(\Delta = 1690; \bullet = 212; \circ = 106\). Note that with this mild thrombogenic stimulus, at the highest shear rate platelet deposition is labile, the maximum platelet deposition reached at about 10 min being transient. Right, Platelet deposition on type I collagen (strips of pig tendon) against exposure time at different wall shear rates (sec\(^-1\)): \(\bullet = 3380; \circ = 1690; \Delta = 212\). Note that there is no loss of platelets with time up to 30 min; the thrombus is fixed. (Modified from Badimon et al.)
context of episodic chest pain at rest in patients with unstable angina, as discussed later.

Effects of blood rheology in experimental deep vessel wall injury (figure 2). Platelet deposition on collagen type I (from pig tendon), a model for the platelet-vessel wall interaction seen with deep vessel wall injury, has also been studied.\(^8,9\) In contrast to subendothelium, platelet deposition on collagen is much greater at low and also at high shear rates mimicking medium-sized stenotic arteries. Platelet thrombi are then occlusive and remain adherent to the collagen surface. Similar observations have recently been made at higher shear rates induced directly by stenoses of exposed aortic tunica media.\(^10\) Therefore, in the presence of a more powerful thrombogenic stimulus, collagen type I or exposure of the arterial tunica media, the thrombus remains fixed (figure 2). In addition, blood flowing through a vessel is not only suddenly accelerated as it passes through a stenosis, but it is also immediately decelerated distal to the stenosis. This deceleration induces flow separations and recirculation zones (vortices) downstream from the stenosis. The combination of a high shear rate area (the stenosis) activating platelets and a low shear rate area (poststenotic recirculation zones) leading to deposition of fibrin contributes to the "head" of the fixed thrombus being composed mainly of platelets and the "tail" containing a larger amount of fibrin in a meshwork, trapping a large number of red cells.

The permanent or fixed thrombotic occlusion in a high shear rate region of a deeply damaged vessel wall may have clinical implications, as discussed later in the context of Q wave infarction.

Relevance to the acute coronary artery syndromes in man. Recent clinical/pathologic data allow us to speculate on the significance of these experimental observations to the acute coronary syndromes in humans. It is now recognized that plaque disruption is the underlying event that frequently precedes all the acute coronary syndromes.\(^1,3\) Plaques that undergo disruption tend to be soft with a high concentration of cholesterol at the base of the plaque; thinning of the fibrous cap overlying the lipid core precedes its rupture.\(^2\) Pathologic analysis at the site of disruption shows a large number of macrophages (probably monocytes with high content of fat uptake from the interstitium) infiltrating the fibrous cap and the lipid core at the site of the fissure. It has been suggested that enzymes in these cells, which digest collagen and elastin, may weaken the cap and precipitate plaque disruption.\(^11\) The increased shear forces at the level of the stenosis, acute changes in coronary pressure related to exercise and/or changes in coronary tone, and bending and twisting of an artery with each heartbeat may also predispose a plaque to disrupt.\(^3\) Atherosclerotic coronary arteries are highly vascular\(^12\); thus, in a few cases it is possible that hemorrhage within a plaque may contribute to plaque disruption.

Recent technical advances, including quantitative and qualitative coronary arteriography, postmortem coronary arteriography with serial reconstruction of the microanatomy of obstructive lesions, intraoperative coronary angioscopy, and biochemical studies at the time of chest pain, have all underlined the importance of thrombosis superimposed on plaque disruption in unstable angina, as well as in myocardial infarction and sudden death.\(^13\)

Unstable angina (table 1). In patients who underwent sequential coronary arteriography before and after the onset of unstable angina, progression of stenosis was commonly found in studies after the onset of unstable angina.\(^14,15\) In contrast, this progression was not seen in patients with sequential arteriograms whose symptoms remained stable. This increase in stenosis severity may occur secondary to an acute change in the plaque, with or without overlying thrombus formation. Arteriography has also revealed that eccentric stenoses with scalloped or overhanging edges occur in the majority of patients with unstable symptoms, but not in patients with stable symptoms.\(^16\) These complicated lesions were also seen by Levin and Fallon\(^17\) using postmortem arteriography and histologic examination of these lesions revealed plaque disruption.

The Cedars-Sinai group in Los Angeles\(^18,19\) has used angioscopy to examine the coronary arteries of patients undergoing surgery for unstable angina. Patients with progressive symptoms, but without pain at rest, had disrupted plaques without mural thrombosis. This finding might suggest that rupture per se, with a change in the geometrical configuration of the plaque but without overlying thrombus, can increase the degree of stenosis, thus producing exertional ischemia. The angiographic data showing progression of lesion

| TABLE 1 |

| Proposed hypothesis of pathogenesis of the acute and subacute coronary syndromes |
|----------------------------------|-----------------|-----------------|-----------------|
| Syndrome                        | Plaque damage   |                |                |
| Unstable angina                 | +               | +               | + +             |
| Non-Q wave MI                   | + +             | + + A           | + +             |
| Q wave MI                       | + + +           | + + + B         | +               |

+ = mild; ++ = moderate; +++ = severe.
*Vasocconstriction (may contribute to coronary occlusion).
*Collaterals (may decrease extension of infarction).
severity\textsuperscript{14, 15} suggest that this rupture may occur within a relatively minor preexisting lesion. Indeed, we postulate that in unstable angina, the increase in exertional symptoms is due to rupture of fissuring of a relatively small, soft “fatty” plaque, resulting in a more severe intraluminal obstruction.

There is increasing evidence that in unstable angina, chest pain at rest may be produced by intermittent thromboses on the lesion. As suggested by the previously described experimental observations, perhaps the plaque rupture or fissure is less severe in those patients who develop unstable angina and therefore thrombosis is transient or labile, as opposed to that accompanying non–Q or Q wave infarction, in which (see later) we postulate deeper plaque rupture on which thrombosis is more firmly fixed. Indeed, according to most investigators, frequent angiographic detection of thrombus occurs only if the angiogram is obtained soon after an episode of pain at rest. In addition, as per our experimental observation, the body of the thrombus is usually distal to the most severe stenosis. Angioscopy has also shown thrombosis, specifically in patients with a history of angina at rest.\textsuperscript{18, 19} Histopathologically, thrombi of different ages have also been identified at autopsy.\textsuperscript{20} Furthermore, two recent studies\textsuperscript{21, 22} suggest a close temporal relationship between episodes of chest pain at rest and platelet and clotting activation, as assessed by prostanoid and fibrinopeptide A measurements in urine and plasma. All of these studies emphasize the lability of thrombus in patients with unstable angina and chest pain at rest.

Vasoconstriction may also contribute to attacks of transient pain at rest. Abnormalities in coronary tone have been demonstrated in patients and experimental animals by coronary arteriography after the intracoronary injection of acetylcholine, suggesting a defect in endothelial vasodilator function, presumably a decrease in endothelial relaxing factor.\textsuperscript{23, 24} Most pertinent to the acute coronary syndromes, recent experimental evidence reveals that during arterial thrombosis, aggregated platelets may contribute to vasoconstriction\textsuperscript{25} by releasing prostanoids, serotonin, and platelet-derived growth factor.

In summary, an evolving concept for unstable angina is as follows.\textsuperscript{13} A relatively mild stenosis undergoes a change, with minor injury or fissure. Plaque disruption occurs. This leads to an increase in the degree of stenosis resulting in exertional symptoms. In some cases, superimposed thrombosis occurs. As the original injury was minor, a portion of the thrombus is labile, in parallel with the previously discussed experimental data showing lability of thrombus with mild injury. The lability of the thrombus results in only intermittent arterial occlusion perhaps lasting for 10 to 20 min, explaining transient episodes of pain at rest. Additionally, deposited platelets release vasoconstricting compounds that contribute to episodes of reduced coronary caliber and ischemia. This proposal does not exclude the possibility that other factors may stimulate ischemic episodes in patients with unstable angina, for example intermittent vasoconstriction related to endothelial dysfunction with deficiency in endothelial relaxing factor, or transient increases in myocardial oxygen demand.

Non–Q wave infarction (table 1). The precise pathophysiology of non–Q wave infarction is not clear. About one-fourth of patients with non–Q wave infarction have a completely occluded infarct-related vessel at angiography soon after infarction, with the distal territory usually being supplied by collaterals.\textsuperscript{26} In three fourths of patients, the infarct-related artery is patent. The angiographic morphology of the responsible stenosis is the same as that seen in unstable angina, confirming the role of plaque fissuring in non–Q wave infarction as well.\textsuperscript{27} According to experimental data previously discussed, we speculate that in non–Q wave infarction there is a greater degree of atherosclerotic plaque damage than in unstable angina, with a longer persistence of thrombus with or without vasoconstriction. However, the thrombotic occlusion is of insufficient duration to provide Q wave infarction. Indeed, the earlier rise in peak creatine kinase, and the spontaneous resolution of ischemic dysfunction seen early in non–Q wave infarction as compared with Q wave infarction, support the hypothesis that occlusion causes severe transmural ischemia, followed by early reperfusion within the first 2 hr.\textsuperscript{28}

Q wave infarction (table 1). In what way does a Q wave infarction with occlusive thrombus on a ruptured plaque differ from unstable angina? Lack of lability of thrombus may be crucial. According to the experimental data previously discussed, we postulate that in Q wave infarction the initial event is deeper plaque rupture than in the other coronary syndromes, an ulcer as it has been frequently observed.\textsuperscript{2, 29} and the thrombus anchored to a large ulcer is more fixed, lasting at least for several hours. Observations with highly magnified angiographic images of coronary stenosis morphology by Brown et al.\textsuperscript{30} suggest that the lesion responsible for the infarction may be relatively mildly stenotic in over 50% of the patients; in these cases the damage or ulcer may be significant. In about 25% of patients, thrombosis related to a severely stenotic plaque without rupture has been observed.\textsuperscript{2} It is conceivable that in these pa-
Patients with severe stenosis before infarction, well-developed collaterals might prevent extensive infarction, or even result in a non-Q wave infarction.

Finally, an enhanced tendency toward thrombus formation due to increased platelet aggregability or toward increased activation of the coagulation system should also be considered as factors favoring persistent occlusion and infarction. Thus, smoking and increased circulating catecholamines enhance platelet activation; furthermore, the findings of Meade et al. showing a strong association between elevated fibrinogen concentration and factor VII activity and ischemic heart disease mortality are of particular interest.

Postthrombolysis reocclusion. After thrombolysis significant residual thrombus contributes to the residual stenosis visualized at angiography. Based on our observations in the porcine preparation, the high shear rate at the stenosis contributes to increased platelet deposition, which is also enhanced by the highly activated surface of the residual thrombus (figure 3). In humans, both of these mechanisms may contribute to the high incidence of postthrombolysis reocclusion. Indeed, we postulate that the recently observed increase in platelet activation in vivo after thrombolysis may be more closely related to the residual stenosis and surface of the residual thrombus activating platelets than to direct platelet activation by various thrombolytic agents.

Ischemic sudden death. In a high proportion of cases of sudden coronary death, the pathologic process probably involves a rapidly evolving coronary artery lesion in which plaque fissure and resultant thrombus formation lead to an ischemic and fatal electrical instability of the heart. Whether complete absence of collaterals to the territory distal to the thrombotic obstruction or platelet microemboli to the distal myocardium also contribute to ischemic sudden death is thus far uncertain.

Antithrombotic therapy for the acute coronary syndromes. The evidence is strong that thrombus formation at the site of a disrupted atherosclerotic plaque is a mechanism common to acute coronary syndromes. We will briefly review the role of antithrombotic therapy—platelet inhibitors, heparin, oral anticoagulants—in each of the acute coronary syndromes. The role of thrombolytic therapy for Q wave infarction is outside the scope of this review.

Unstable angina

Aspirin. The value of antithrombotic therapy in unstable angina has been conclusively demonstrated by two randomized, placebo-controlled, double-blind trials of aspirin. The Veterans Administration Cooperative Study tested the effect 324 mg aspirin vs placebo on the 3 month incidence of death and acute myocardial infarction in 1266 men with unstable angina. Death or acute myocardial infarction occurred in 5.0% of the aspirin-treated patients vs 10.1% of the placebo group (p = .0005). Benefit persisted to 1 year. There was no increase in gastrointestinal side effects from the relatively low dose of aspirin used in the study. The Canadian Multicenter Trial tested the effect aspirin and sulfinpyrazone in 555 patients with unstable angina over a mean follow-up of 18 months. Patients were randomly allocated to one of four treatment regimens: aspirin (325 mg four times a day), sulfinpyrazone (200 mg four times a day), the combination of aspirin (325 mg four times a day) plus sulfinpyrazone (200 mg four times a day), or a matching placebo. By 2 years, death or acute myocardial infarction occurred in 8.6% of the aspirin-treated patients vs 17% of the group not receiving aspirin, for a risk reduction of 51% (p = .008). Sulfinpyrazone had no beneficial effect. With the higher dose of aspirin used in this study, gastrointestinal side effects were more common than in the Veterans Administration Cooperative Study.

FIGURE 3. Blood derived from a catheterized carotid artery in the pig is perfused through a chamber containing injured arterial tissue with various degrees of eccentric stenosis. A. The percentage of platelets deposited (PD), on the peak of the stenosis (s) when compared with total PD in the exposed tissue. B. The continuous scintigraphic image, from 0 to 50 min, of the events taking place during perfusion of an area with 80% of stenosis (line corresponds to peak of the stenosis [s] and is expressed as indium excess activity with respect to blood).
HEPARIN AND ORAL ANTICOAGULANTS. Intravenous heparin therapy has also been shown to reduce morbidity and mortality in a small group of patients with intermediate coronary syndrome or a severe form of unstable angina randomly assigned to placebo, atenolol, heparin, or a combination of heparin and atenolol. There was an 80% reduction in the combined incidence of death and acute myocardial infarction in the heparin-treated group over the 8 day study period. Many advocate the use of intravenous heparin rather than aspirin during hospitalization for unstable angina to avoid the risk of aspirin-related bleeding if coronary artery bypass surgery is needed. However, the relative efficacy of this agent has to be confirmed.

THROMBOLYSIS. The results of several sequential angiographic studies of thrombolysis in unstable angina suggest that lysis is only useful in those patients who present with partial or total thrombotic occlusion of the ischemia-producing vessel.

Non–Q wave infarction. Since in patients with this syndrome the incidence of Q wave myocardial infarction and sudden death is as high as in those with unstable angina, the role of antithrombotic therapy needs to be tested. Indeed, treatment with aspirin and dipyridamole in the PARIS II study produced a 53% reduction in coronary events in patients with non–Q wave myocardial infarction.

Q wave infarction. In patients with unstable angina and non–Q wave infarction, antithrombotic therapy may prevent coronary occlusion. Indeed, both of these syndromes are associated with a high frequency of subsequent events, Q wave myocardial infarction, and sudden death (high sensitivity end points) that are usually thrombotic (high specificity for antithrombotic therapy). The ability to discern a beneficial effect of aspirin in patients with unstable angina is partly due to these two factors. On the other hand, in Q wave infarction, leaving aside the issue of thrombolytic therapy, the rationale for antithrombotic therapy is the prevention of another thrombotic occlusion in the same coronary artery (reoclusion), or in another coronary artery, leading to ischemic sudden death or a subsequent infarction (secondary prevention). Deaths occurring within the first month after Q wave infarction may be related to infarct extension or reinfarction (reoclusion). Later deaths (within the first year) are usually due to left ventricular failure with a predisposition to ventricular arrhythmias. Thus, within the first year, since most deaths are probably not due to thrombotic events, it is unlikely that antithrombotic therapy would have much impact (low specificity for antithrombotic therapy). Thus, studies of antithrombotic therapy suffer from having an insensitive end point. Nevertheless, there is considerable data regarding antithrombotic therapy after myocardial infarction.

PLATELET INHIBITORS. There is no good evidence that platelet inhibitors other than aspirin are effective after myocardial infarction. The pooled results of studies of aspirin at doses of 300 to 1500 mg daily, usually started after the first month of infarction, suggest that the rates of reinfarction and death are reduced by about 15% to 20%. Of interest, the ISIS-2 preliminary results of aspirin alone at a dose of 160 mg/day started within 24 hr of infarction revealed a significant benefit within the first month when compared with placebo.

ORAL ANTICOAGULATION. The pooled results of several studies suggest that long-term anticoagulant therapy may reduce the rate of recurrence of infarction by about 20%. In addition, the Dutch Sixty Plus Reinfarction Study showed a significant reduction in myocardial infarction and total mortality in patients over the age of 60 in whom anticoagulants were continued compared with rates of these events in those in whom anticoagulants were replaced by placebo. The greater benefit from the use of anticoagulants in this trial over that in previous trials may be related to two factors: (1) anticoagulation therapy was more rigidly controlled, and (2) randomization into treatment groups was made a median of 6 years after a previous myocardial infarction. Therefore, in this relatively stable group of patients, thrombotic events rather than myocardial factors dictated long-term prognosis, so the specificity for thrombosis was higher.

Postthrombolysis reoclusion. The best therapies for the prevention of reoclusion after thrombolysis appears to be: (1) thorough lysis of residual thrombus, (2) immediate anticoagulant therapy with intravenous heparin plus low-dose aspirin, and (3) daily aspirin after discharge. Recently, the ISIS-2 preliminary results of aspirin at a dose of 160 mg/day added to intravenous streptokinase and started within 24 hr of infarction revealed a very significant benefit when compared with placebo.

Two pharmacologic approaches appear promising for the prevention of postthrombolysis reoclusion: (1) use of more effective fibrin-specific thrombolytic agents to decrease the thrombus-related residual stenosis, and (2) transient inhibition of von Willebrand factor or of the specific platelet membrane GPIIb/IIIa receptors with monoclonal antibodies or of thrombin-mediated platelet activation with recombinant peptides. This is currently under investigation and may offer a lower risk of bleeding than inhibiting receptors responsible for platelet adhesion.
Ischemic sudden death and primary prevention. The beneficial role of antithrombotic therapy in the prevention of ischemic sudden death has been described in patients with unstable angina and in patients late after Q wave infarction. Whether antithrombotic agents prevent sudden death or myocardial infarction when given to patients with stable angina or in individuals at high risk for coronary disease is presently being tested.

Recently, preliminary results of studies testing the role of aspirin in the primary prevention of death or infarction in healthy adults have become available. In one study of 22,000 male U.S. physicians receiving either buffered aspirin (325 mg every other day) or placebo for 5 years, there was a significant reduction in rates of myocardial infarction from approximately 0.4% to 0.2% per year. In advising the wide use of aspirin for primary prevention for apparently normal people there are three concerns: (1) the incidence of hemorrhagic stroke was slightly increased in the aspirin group, (2) a randomized primary prevention British study that involved 5000 doctors taking 500 mg aspirin daily or placebo found no significant reduction in myocardial infarction but an increase in disabling stroke, and (3) the very long-term effects of aspirin in blocking the prostaglandin metabolic pathway in various tissues (i.e., central nervous system) is unknown. Therefore, in our view, use of aspirin for primary prevention should only be advised for individuals at very high risk of coronary disease, perhaps excluding those with hypertension because of increased risk of hemorrhagic stroke.

In conclusion, we are on the threshold of an exciting era in the treatment of coronary disease in which the critical role of thrombosis in the production of the major life-threatening clinical syndromes has become recognized. A fuller understanding of the importance of the role of blood flow, of thrombogenic substrate exposure by plaque rupture, and the mechanism of the latter is developing. The continuing manipulation of the hemostatic system by known antithrombotic agents, as well as by newer antithrombotic drugs with a different locus of attack (i.e., peptide-receptor blockers and monoclonal antibodies), together with the results of ongoing clinical trials, promise to improve the future for our patients until the goal of primary prevention can eliminate the disease.

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