The pathogenesis of Raynaud’s phenomenon is not fully understood. However, the last 20 yr have witnessed enormous increases in our understanding of different mechanisms which, singly or in combination, may contribute. A key point is that Raynaud’s phenomenon can be either primary (idiopathic) or secondary to a number of underlying conditions, and that the pathogenesis and pathophysiology vary between these conditions. This review concentrates upon those subtypes of Raynaud’s phenomenon of most interest to rheumatologists: systemic sclerosis-related Raynaud’s phenomenon, primary Raynaud’s phenomenon and Raynaud’s phenomenon secondary to hand–arm vibration syndrome. In this review, I shall discuss the main mechanisms thought to be important in pathophysiology under the three broad headings of ‘vascular’, ‘neural’ and ‘intravascular’. While these are false distinctions because all interrelate, they facilitate discussion of the key elements: the blood vessel wall (particularly the endothelium), the neural control of vascular tone, and the many circulating factors which can impair blood flow and/or cause endothelial injury. Vascular abnormalities include those of both structure and function. Neural abnormalities include deficiency of the vasodilator calcitonin gene-related peptide (released from sensory afferents), ø2-adrenoreceptor activation (possibly with up-regulation of the normally ‘silent’ ø2-adrenoreceptor) and a central nervous system component. Intravascular abnormalities include platelet activation, impaired fibrinolysis, increased viscosity and probably oxidant stress. As our understanding of the pathophysiology of Raynaud’s phenomenon increases, so do our possibilities for identifying effective treatments.

**Key words:** Raynaud’s phenomenon, Pathophysiology, Endothelium, Nervous system, Platelet aggregation.
primarily functional. In contrast, structural vascular abnormalities of both the microvasculature (Fig. 1) and digital artery (Fig. 2) are well recognized in SSc [7–9]. Vascular structure and function in patients with SSc are interdependent. There is no doubt that blood flow in the digits of the patients shown in Figs 1b and 2 is going to be severely compromised, even at ambient temperature, and that any superimposed vasospasm, for example as a result of cold exposure, increases the risk of irreversible tissue damage.

The pathogenesis of the structural vascular abnormalities in SSc is not fully understood and is outside the scope of this review; however, it is well discussed elsewhere [9–11] and includes endothelial cell apoptosis, up-regulation of adhesion molecules, and the interplay of a large number of cytokines and growth factors, and pericyte activation [12]. Endothelial abnormalities occur early [13], but it is not understood how these progress to the florid changes demonstrated in Fig. 2 with pronounced intimal thickening, changes so severe as to lead to almost complete vessel occlusion.

Structural vascular abnormalities have also been reported in hand–arm vibration syndrome. Takeuchi et al. described arterial smooth muscle hypertrophy and periartherial fibrosis in a study of digital biopsies [14] and minor structural abnormalities have been reported on nailfold microscopy [15].

**Functional abnormalities**

This section concentrates upon those functional abnormalities which primarily reflect defects in the endothelium. It is now well recognized that the endothelium is not an inert barrier, but a highly sophisticated layer of cells which reacts to, and produces, a variety of vasoactive substances, including vasoconstrictors and vasodilators. When the endothelium is activated/injured, as in patients with SSc, the balance between vasodilation and vasoconstriction may be disturbed in favour of vasoconstriction (in addition to the endothelium becoming procoagulant and proinflammatory). While it is possible that endothelial activation occurs also in PRP (some investigators have reported raised levels of von Willebrand factor, although others have not [16]), endothelial abnormalities are less likely to be major players in the pathogenesis of PRP.

**Impaired vasodilation.** This may result from a defect in the endothelium, or reduced concentrations of endogenous vasodilators acting on the endothelium.

**Impaired endothelial-dependent vasodilation.** In recent years, there has been considerable interest in the hypothesis that in SSc (and possibly also in PRP) endothelial-dependent vasodilation (i.e. vasodilation requiring an intact endothelium) is compromised at an earlier stage of disease than endothelial-independent vasodilation. This area of research has been facilitated by the development of non-invasive techniques for measuring vasodilation in both small and large vessels. Iontophoresis, a method of driving chemicals into the skin using a small electric current, together with measurement of blood flow responses with laser Doppler, assesses the microcirculation. Iontophoresis with acetylcholine chloride is ‘endothelial-dependent’ because it is dependent upon nitric oxide (NO) production within the endothelium. Iontophoresis with sodium nitroprusside is ‘endothelial-independent’ because the nitroprusside acts as an NO donor and the endothelium is effectively bypassed. Ultrasound studies using the technique described by Celermajer et al. [17] assess endothelial-dependent and -independent responses in large vessels (usually the brachial artery).

While studies examining small and large vessel function in SSc have given conflicting results, with some studies showing no impairment of endothelial function even in patients with...
SSc [18, 19], there is now a considerable weight of evidence from studies using a variety of methods to support a defect in endothelial-dependent vasodilation in SSc [20–26]. Some investigators have reported a defect of endothelial-dependent vasodilation in patients with PRP [27, 28] and Khan et al. reported impairment of both endothelial-dependent and endothelial-independent responses in PRP [29]. Endothelium-dependent and -independent vasodilation have been little studied in hand–arm vibration syndrome.

**Reduced production of vasodilators.** The endothelium produces a large number of vasodilator substances, including NO and prostacyclin. If the endothelium is damaged, these may be underproduced. It has been suggested that NO deficiency contributes to the pathogenesis of Raynaud’s phenomenon, and this has therapeutic relevance because topical application/delivery of NO is known to increase blood flow [30–33]. However, the situation is complex as NO may be overexpressed in SSc [34, 35], and it is possible that NO status in SSc depends on the stage of the disease. A recent study of 20 patients with PRP and 20 with secondary Raynaud’s (seven had SSc) reported higher circulating levels of asymmetrical dimethylarginine (an endogenous inhibitor of endothelial NO synthase) and of endothelin-1 in the secondary Raynaud’s group [36]. This is an interesting finding which, if confirmed, may further implicate NO in the pathophysiology of Raynaud’s phenomenon.

With respect to prostacyclin, a study of rat aortic rings suggested that prostacyclin production is reduced on cold exposure [37]. However, Belch et al. reported that patients with SSc demonstrated increased circulating levels of stable metabolites of prostacyclin, speculating that patients with SSc might be resistant to prostacyclin, although this resistance could be overcome by pharmacological doses [38]. At present, it is not known whether reduced endogenous prostacyclin contributes to the pathogenesis of Raynaud’s.

**Increased vasoconstriction.** The endothelium produces vasoconstrictors as well as vasodilators and the one which has attracted most recent interest in Raynaud’s phenomenon is endothelin-1, especially now that it is possible to block its action therapeutically with receptor antagonists. Endothelin-1 is an extremely potent vasoconstrictor with effects on vascular remodelling [39], and also relevant to SSc is that it is profibrotic.

Although a recent study suggested that endothelin-1 levels, at baseline and after a cold challenge, were no different in patients with PRP or SSc and in healthy controls [40], it seems likely that endothelin is implicated in SSc. This is because endothelin-1 is overexpressed in sclerodermatous skin [41] and endothelin-binding density is increased in skin biopsies from patients with SSc [42]. In addition, bosentan (an endothelin-1 receptor antagonist) has been shown to confer benefit in studies of pulmonary arterial hypertension, which included patients with SSc [43, 44] and in a recent preliminary study of SSc-related digital ulceration [45]. There is also some evidence that endothelin-1 may have a role in PRP. Zamora et al. reported that endothelin-1 levels (as well as being elevated at baseline) rose more in patients with PRP than in controls in response to a cold challenge [46], and although Leppert et al. [47] (similarly to Smythe et al. [40]) found that basal endothelin-1 levels were similar in healthy controls and PRP patients, levels rose after whole-body cooling in the PRP but not in the control group. However, Knock et al. did not find any increase in endothelin-binding in biopsies from patients with PRP [42]. Endothelin-1 may also be implicated in hand–arm vibration syndrome [48].

**Angiotensin is another vasoactive peptide that has both vasoconstrictor and profibrotic effects.** Despite the well-established use of angiotensin-converting enzyme (ACE) inhibitors in scleroderma renal crisis, the exact contribution of the renin–angiotensin system to primary and secondary Raynaud’s phenomenon remains...
unknown. A recent study reported increased circulating levels of angiotensin II in patients with diffuse cutaneous SSc (although not in limited cutaneous SSc) [49]. It is now recognized that ACE inhibitors have effects on endothelial function [50]. The next few years will most likely see increasing research into the role of the renin–angiotensin system in Raynaud’s phenomenon, especially now that angiotensin II receptor antagonists are available and reduced both frequency and severity of attacks in both primary and SSc-related Raynaud’s phenomenon in an open-label, randomized study [51].

One of the key issues in Raynaud’s phenomenon is why vasoconstriction is cold-induced. New insights are provided by a recent series of studies by Furspan et al. [52], who investigated the role of the protein tyrosine kinase signal transduction pathway in PRP by examining responses in dermal arterioles isolated from forearm skin from patients with PRP and healthy control subjects. Responses to three vasoconstrictors—an α2-adrenergic agonist, serotonin and angiotensin II—were increased in PRP patients but only on cooling, and were reversed by protein tyrosine kinase inhibitors. Tyrosine phosphorylation was increased in PRP patients on cooling to 31°C [52]. The role of this signal transduction pathway in the pathophysiology of Raynaud’s phenomenon therefore deserves further study in both primary and secondary Raynaud’s.

Conclusions
In SSc and hand–arm vibration syndrome, abnormalities in both vascular structure and function interrelate to compromise digital blood flow, whereas in PRP abnormalities are most likely purely functional. In the blood vessel wall, the vasoconstriction versus vasodilator balance is tipped in favour of vasoconstriction by (i) impaired endothelial-dependent vasodilation in SSc, and possibly also in PRP and hand–arm vibration syndrome; and (ii) a mismatch between endothelium-derived vasoconstrictors (primarily endothelin-1) and vasodilators (primarily NO and prostacyclin) (Fig. 3). However, there is at present little direct evidence to support this claim other than increased expression of endothelin-1 in SSc and probably also in PRP and hand–arm vibration syndrome.

Further research into signal transduction mechanisms should provide increased insight into the mechanism of cold-induced vasospasm.

Neural abnormalities
Peripheral mechanisms
The sympathetic nervous system is a major player in thermoregulation [53] and it therefore seems likely that the autonomic nervous system contributes to the pathogenesis of both primary and secondary Raynaud’s phenomenon via both central and peripheral (local) mechanisms. Until recently, the nervous system in SSc was a neglected area of research. However, autonomic [54, 55] and peripheral [56] neuropathy are being increasingly recognized in SSc [reviewed in 57]. The situation is complex and a variety of neurotransmitters and their receptors are likely to be involved, relating to small sensory nerve fibres as well as to sympathetic vasoconstrictor and vasodilator nerves. Neuropathy is well described in hand–arm vibration syndrome, and paraesthesia is common [14, 58].

Impaired vasodilation
Nerves supplying blood vessels produce a number of vasodilatory substances. Calcitonin gene-related peptide (CGRP),
released from sensory afferents, has been most studied: others include substance P, neurokinin A and vasointestinal peptide. Immunohistochemical studies have shown a reduction in the number of CGRP-immunoreactive nerve fibres in biopsies of finger skin from patients with SSC and with PRP (changes in the SSC patients were more marked) [59], and hand–arm vibration syndrome [60]. In the biopsies from patients with hand–arm vibration syndrome (and in a subpopulation of nerves in patients with SSC and PRP [61]) there was also a reduction in the pan-neuronal marker protein gene product 9.5, suggesting that the CGRP depletion might be a consequence of damage to peripheral nerve. Although intravenous CGRP has been reported to improve blood flow in patients with severe Raynaud’s phenomenon secondary to connective tissue disease [62], the numbers of patients studied have been small.

Increased vasoconstriction
Several investigators have examined adrenergic function in both primary and secondary Raynaud’s phenomenon [63–69]. Our understanding about the different adrenoreceptors has greatly expanded in recent years; there are at least nine subtypes [70]. Vasoconstriction to noradrenaline is mediated via α1 and α2-adrenoreceptors, but the α2-adrenoreceptors are thought to be more important in the regulation of digital vascular tone [65, 66, 71, 72]. Cold augments smooth muscle α2-adrenoreceptor function [73]. There are three subtypes of α2-adrenoreceptors (α2A, α2B and α2C), and it has been recently shown from work in animal models that it is probably the α2C-adrenoreceptor which is the most important in thermoregulation [73]. In a cell model, in response to cooling, the normally ‘silent’ α2C-adrenoreceptors relocate from the Golgi compartments to the cell surface [74]. Therefore, the α2C-adrenoreceptors may be responsible for cold-induced augmentation of α2-adrenoreceptor activity. However, the interrelationships between the different receptor subtypes are highly complex, with the result that it is not yet known whether selective α2C blockage might be an appropriate line of therapy [11]. The balance between α1- and α2-adrenoreceptors differs between proximal and distal arteries: α2-adrenoreceptor responsiveness was increased in digital arteries compared with more proximal vessels [75]. This further supports the hypothesis that increased peripheral expression of α2-adrenoreceptors could contribute to Raynaud’s phenomenon. Recent support for the α2-adrenoreceptor playing a key role in the pathogenesis of SSC-related Raynaud’s comes from a study of dermal arterioles from uninvolved skin from patients with diffuse SSC; arteriolar smooth muscle demonstrated increased α2-adrenoreceptor reactivity compared with controls, and this increased reactivity was endothelium-independent [69]. α2-Adrenoreceptors may also be implicated in hand–arm vibration syndrome [63].

Central mechanisms
Many patients with Raynaud’s report stress-induced vasospasm, and it therefore seems intuitive that even if neural abnormalities are primarily local to the digits, there must also be a central nervous component. However, this is a difficult area of research, and there is little direct evidence in support of central mechanisms. Edwards et al. showed that patients with PRP do not habituate in the same way as healthy controls to the components of the ‘alerting response’ evoked by acute emotional stress (a sound stimulus) [76, 77]. This alerting response includes vasodilation in forearm muscle and vasoconstriction in the cutaneous circulation of the digits. Digital cutaneous vasoconstriction in response to a cool stimulus was prolonged in the PRP patients and was associated with a rise in endothelin-1 levels in venous blood taken from the dorsum of the cooled hand [77]. The authors suggested that while central nervous mechanisms prolonged vasoconstriction, there was a superimposed effect of locally released endothelin-1.

Conclusions
Release of neurotransmitters from both autonomic and sensory afferent nerves contributes to digital vascular tone. In patients with primary and secondary Raynaud’s phenomenon, key factors in neural control mechanisms that are likely to be tipping the vasoconstriction vs vasodilator balance in favour of vasoconstriction are: (i) impaired vasodilation, including that due to CGRP deficiency; (ii) increased vasoconstriction mediated by activation of α2-adrenoreceptors (Fig. 3). This activation is augmented by cold exposure. It may be that in patients with Raynaud’s phenomenon there is a lower (i.e. higher temperature) threshold for α2C-adrenoreceptors to become activated than in healthy controls.

Central mechanisms may contribute to vasospasm but in most situations peripheral neural mechanisms are the more important.

Intravascular abnormalities
Many circulating factors have been implicated in the pathogenesis of Raynaud’s phenomenon, especially in patients with SSC. These include platelet activation, impaired fibrinolysis, white blood cell activation, reduced red blood cell deformability and oxidative stress, all of which have been described in subsets of patients with Raynaud’s. Often it is not clear whether the abnormality is a primary or a secondary event. However, there is no doubt that in some patients circulating factors are all important, evidenced by cryoglobulinaemia being a ‘cause’ of Raynaud’s phenomenon.

Below are discussed some of the intravascular factors implicated in the pathophysiology of Raynaud’s. Other possible contributors include shear stress (which could equally well be considered under the ‘vascular’ heading) [78] and antiendothelial cell antibodies (via endothelial cell activation) [79]. However, these will not be described further—at present their roles in the pathophysiology of Raynaud’s phenomenon are unclear.

Platelet activation
Platelet activation is well recognized in SSC [80–84] and PRP [16, 81, 83, 84], and vibration may cause platelet activation in both healthy controls and patients with hand–arm vibration syndrome [85]. Platelet activation can be demonstrated by increased circulating levels of thromboxane and of β-thromboglobulin, released from platelet α-granules. Synthesis of thromboxane, a potent vasoconstrictor as well as a platelet aggregator, is increased in patients with SSC, especially on cooling [86], and so may contribute to vasospasm in SSC, and expression of the gene encoding thromboxane synthase was recently found to be increased in leukocytes from patients with SSC [87]. Serotonin, another vasoconstrictor produced from platelets, has also been implicated in the pathophysiology of Raynaud’s [88].

Fibrinolysis
In patients with PRP, fibrinolysis is probably normal [16, 89]. However, defective fibrinolysis has been reported in SSC
Picart was increased in patients with PRP at low temperatures [96].

Vascular pathology of SSc comes from the finding of Bruckdorfer to endothelial injury through peroxidation of cell membrane that oxidative stress may also occur in PRP [102].

Levels of ascorbic acid, an antioxidant, in both groups, suggesting PRP showed some elevation of free radical markers and reduced SSc, but a cross-sectional study including patients with SSc and above. Oxidative stress has been less studied in PRP than in 

Free radicals may be produced by a variety of mechanisms, including the hypoxanthine–xanthine oxidase system and activation of polymorphonuclear leucocytes, as already mentioned above. Oxidative stress has been less studied in PRP than in SSc, but a cross-sectional study including patients with SSc and PRP showed some elevation of free radical markers and reduced levels of ascorbic acid, an antioxidant, in both groups, suggesting that oxidative stress may also occur in PRP [102].

In SSc, it seems likely that oxidative stress contributes to endothelial injury through peroxidation of cell membrane lipids. Further support for a role for oxidative damage in the vascular pathology of SSc comes from the finding of Bruckdorfer et al. that low-density lipoproteins (LDL) in patients with SSc demonstrate increased susceptibility to oxidation compared with LDL from healthy controls or from patients with PRP [103]. Also, increased concentrations of antibodies to oxidized LDL have been reported in SSc [104, 105]. Therefore, a vicious cycle of vasospasm (perhaps against the background of a structurally abnormal vessel), free-radical generation, endothelial injury and more vasospasm can be envisaged.

Conclusions

A wide variety of intravascular or circulating factors has been implicated in the pathophysiology of Raynaud’s phenomenon, especially when this is associated with SSc or hand-臂 vibration syndrome, in which platelet activation, defective fibrinolysis, reduced red blood cell deformability and increased blood viscosity have all been reported. White blood cell activation and oxidant stress have been reported in PRP as well as in SSc and hand-臂 vibration syndrome.

We do not understand how these different factors might interrelate with each other or with the vascular and neural abnormalities already described. It is likely that intravascular factors compromise basal blood flow, especially in the microcirculation, and this is then further compromised by digital vasospasm.

White blood cell activation

White blood cell activation has been reported in patients with SSc, PRP and hand-臂 vibration syndrome [92, 93] and may contribute to oxidative stress, described below.

Reduced red blood cell deformability

This has been reported in SSc, but not in PRP [38, 94] and may reflect damage to the erythrocyte membrane by free radicals [95]. Those familiar with the very low capillary flow rates in many patients with SSc on nailfold video microscopy will be able to envisage easily how any reduction in red blood cell deformability might further compromise the microvasculature.

Increased viscosity

Increased blood viscosity has long been recognized in patients with Raynaud’s phenomenon. Goyle et al. found that viscosity was increased in patients with PRP at low temperatures [96]. Picart et al. reported that increased blood viscosity in patients with SSc was associated with low flow rates, but that viscosity did not differ between patients with PRP and healthy controls [97]. Increased viscosity has also been implicated in hand-臂 vibration syndrome [98, 99].

Oxidative stress

Episodes of Raynaud’s phenomenon, if severe, might be expected to cause repeated episodes of ischaemic reperfusion injury, and oxidative stress (mediated by free radicals) has been implicated in the pathogenesis of Raynaud’s phenomenon and SSc [100, 101]. Free radicals may be produced by a variety of mechanisms, including the hypoxanthine–xanthine oxidase system and activation of polymorphonuclear leucocytes, as already mentioned above. Oxidative stress has been less studied in PRP than in SSc, but a cross-sectional study including patients with SSc and PRP showed some elevation of free radical markers and reduced levels of ascorbic acid, an antioxidant, in both groups, suggesting that oxidative stress may also occur in PRP [102].

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Other factors

Smoking

In patients with SSc, there is an association, between cigarette smoking and the severity of digital ischaemia [106], and although the mechanisms behind this association are not clear, they are likely to include endothelial damage caused by smoking, increased viscosity, impaired fibrinolysis and the high free radical content of cigarette smoke. Smoking may influence hand-臂 vibration syndrome: in a study of 601 subjects, smoking was associated with lower finger systolic pressures [107]. In contrast, a large epidemiological study suggested that there was no association between Raynaud’s phenomenon and cigarette consumption [108]. It may be that smoking is associated with the severity of Raynaud’s (especially in those with underlying vascular disease) rather than susceptibility.

Hormonal factors

Raynaud’s phenomenon is much more common in women than in men and it is likely that hormonal factors are important, especially as variations in blood flow with the menstrual cycle have been described: during the immediate preovulatory period, healthy controls demonstrated digital vascular reactivity similar to that of patients with Raynaud’s phenomenon [109]. At present we do not fully understand the hormonal contribution to vascular tone.

Genetic factors

These have been implicated in both PRP [110, 111] and SSc [112, 113]. The recent developments in the genetics of pulmonary artery hypertension [114, 115] are of interest. Patients with SSc-related pulmonary arterial hypertension often have severe Raynaud’s and therefore understanding the molecular mechanisms whereby mutations lead to vascular pathology may provide insights into Raynaud’s phenomenon as well as into pulmonary hypertension.

Implications for treatment

While this review is concerned with pathophysiology rather than treatment, included is a brief consideration of how greater insights into the pathogenesis of Raynaud’s phenomenon are directing new avenues of treatment (Fig. 4).
Inhibiting vasoconstriction

As already mentioned above, the endothelin-1 receptor antagonist bosentan has recently been shown to confer benefit in patients with SSc-related digital ulceration [45] and further clinical trials are under way. ACE inhibitors have so far been studied little in Raynaud’s phenomenon, but there is currently increased interest in ACE inhibitors [116], especially now that their effects on endothelial function [50] and vascular remodelling are recognized [117], and also in angiotensin II receptor antagonists [51]. The action of serotonin can be blocked by serotonin reuptake inhibitors and results from an open study suggest that fluoxetine, a selective serotonin reuptake inhibitor, may be beneficial in both primary and secondary Raynaud’s [118]. It is possible that in the future selective blockade of α2-adrenoreceptors could be a potentially exciting new avenue of therapy [73].

Increasing vasodilation

Intravenous prostanoid therapy is well established in severe digital ischaemia [119, 120] and oral prostanoids require further evaluation, especially as prostanoids are now thought also to have vascular remodelling effects [121]. Supplementation of the L-arginine/NO pathway is being explored in several ways, including with transdermal NO [31–33], oral administration of L-arginine, and via phosphodiesterase inhibition (which enhances the effect of NO by inhibiting the degradation of cyclic guanosine monophosphate).

Antithrombotics

This is a neglected area of therapeutics in patients with Raynaud’s and more research is required, especially into antiplatelet agents in patients with SSc. Prostanoids, already mentioned, have antiplatelet effects.

Endothelium protection

Several of the above strategies should protect the endothelium. In addition, we need to continue to research antioxidant therapies [122, 123]. Smoking cessation should be actively promoted. Therefore the next 10–15yr should witness increased understanding of how best to treat Raynaud’s phenomenon, possibly using different classes of drug in combination.

Conclusions

Studying Raynaud’s phenomenon presents major challenges for several reasons. First, it must be recognized that Raynaud’s is a symptom complex of a variety of different conditions which themselves have different pathogeneses. Secondly, vascular physiology is itself tremendously complex, and there is considerable intra- as well as interindividual variation in the control of vascular tone even in healthy subjects.

Many different mechanisms have now been implicated in the pathophysiology of Raynaud’s phenomenon. Many of these support the ‘local fault’ hypothesis of Lewis, but others, including intravascular factors and a central nervous component of vasoconstriction, are more in favour of ‘central’ mechanisms, depending upon how these are defined. Contributors to Raynaud’s phenomenon include increased vasospasm and reduced vasodilation, structural abnormality of large and small vessels, and coagulopathy. In turn, the major players influencing these mechanisms include endothelin-1, NO, CGRP (and the balance between these), the α2-adrenoreceptor, free radicals (causing oxidant stress) and platelet activation/aggregation. Progress in unravelling the pathophysiology of Raynaud’s phenomenon is driving new approaches to treatment.
The author undertakes consultancy work for Actelion.

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