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CKJ REVIEW

Unravelling the pathophysiology of chronic kidney disease-associated pruritus

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ABSTRACT

For decades, itch related to chronic kidney disease (CKDaP) has been a clinical problem, but the aetiology and pathophysiology of CKDaP are still not yet fully understood—currently the underlying pathophysiological mechanisms are thought to be multifactorial. As new therapeutic targets have recently been identified and clinical trials have shown promising results, our current understanding of the interrelationships has expanded significantly. Here we review the pathophysiology and recent findings on modulation and sensitization of itch contributing to the development of CKDaP, covering hypothesis regarding immune system dysfunction, metabolic changes, uremic toxin deposition, peripheral neuropathy and imbalances in the endogenous opioid system.

Keywords: CKD, dialysis, inflammation, opioid dysbalance, pathophysiology, pruritus, skin

INTRODUCTION

Itch is normally an alarm signal indicating environmental disturbances of the skin barrier [1]. As this signal is related to pain, primarily nerve C-fibres conduct those signals [1, 2]. Thus pain and itch signalling are closely related [3]. It is important to understand that even in healthy individuals, these sensory nerves are part of an interdependent and communicating system of mediators that are produced by neighbouring sensory neurons and other neighbouring immune and epithelial cells [2]. Figure 1 shows an overview of the connections and signalling pathways generally involved.

Since any itch is a very unpleasant sensation, in particular, pruritus related to chronic kidney disease (CKDaP) can have a major impact on quality of life and sleep quality and is associated with worse outcomes [4–8]. In the pathogenesis of CKDaP, it is postulated that the normal balance is disturbed by various dermatological (e.g. cutaneous barrier dysfunction and xerosis), systemic (e.g. immune system dysfunction and elevated pro-inflammatory cytokines), neurological (e.g. neuropathy, μ-opioid overexpression and κ-opioid downregulation), psychogenic/psychosomatic changes and metabolic alterations (e.g. increased levels of uremic toxins and metabolic by-product accumulation, changed concentrations of ions such as calcium and phosphate) that promote or exacerbate the development of itching [2, 3, 6, 9–12]. Table 1 summarizes discussed pathways and hypothesis.

Nevertheless, the precise molecular relationships in the pathophysiology of uremic pruritus remain unclear. In the absence of convincing experimental models to study uremic pruritus, a large number of clinical studies have been performed that in turn have led to many alternative hypotheses regarding the origin of CKDaP. Encouragingly, some of the therapeutic approaches have recently been shown to have effects on patients' symptoms and quality of life, providing *ex juvantibus* support for the modulated mechanisms previously described. In this regard, our understanding of the previously simplified model

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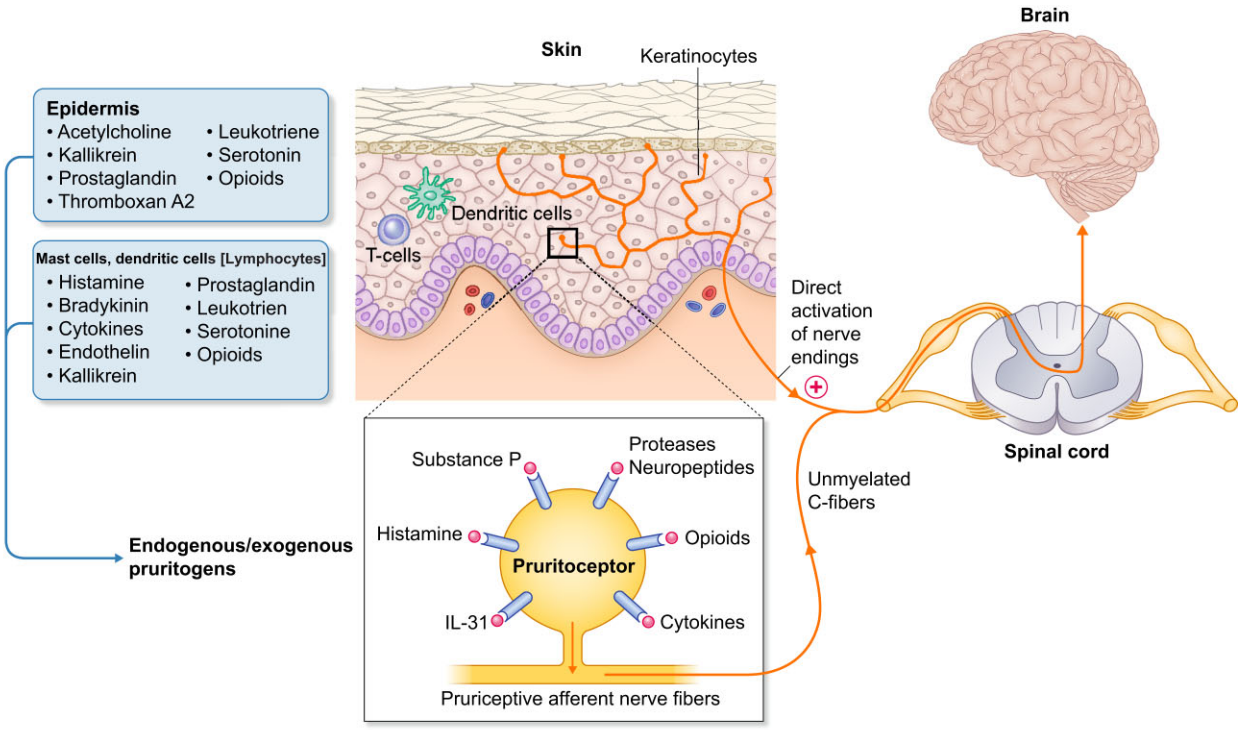

FIGURE 1. Overview of the connections and signalling pathways in itch.

of the pathophysiology has become much more complex [2, 12]. This article aims to summarize the current knowledge on the pathophysiology of pruritus from different perspectives. Figure 2 demonstrates involved factors in CKDaP.

THE SKIN

Chronic renal failure and dialysis cause multiple changes in the skin that most commonly include de- or dyspigmentation, ecchymosis, xerosis and hair and nail abnormalities [13–15].

Skin dryness is a particularly common dermatologic condition in end-stage renal disease (ESRD) [16, 17]. It is characterized by the atrophy of secretory glands and a thickened basement zone resulting in an elevated pH and decreased hydration of the stratum corneum. Of note, generally the barrier function is still intact [18–20]. Additionally, microangiopathy is one of the characteristic findings in chronic kidney disease (CKD) [21, 22]. It was first described in the skin in 1980 as thickening of the basement membrane, endothelial activation and chronic inflammatory cell infiltrates in cutaneous capillaries [23]. Today microangiopathy in CKD is perceived as a spectrum of structural remodelling of small vessels (diameter $<$100–300 μm) and multifactorial endothelial dysfunction caused by hypertension, metabolic [24–27], endocrine {e.g. in the calcium phosphate balance [28, 29] and parathyroid hormone (PTH) [30]} and immune alterations in a uremic environment [21, 22]. These lead to hypoxia, oxidative stress, apoptosis, a decrease in endothelial progenitor cells and disturbed angiogenesis [21]. In turn, those factors cause primarily capillary rarefication and, in later stages, lead to fibrosis. Some of those alterations (especially microangiopathy) improve after renal transplantation, linking those changes causally to a uremic state [23, 31]. While clinical observations show that many patients with pronounced xerosis do not suffer from pruritus, it has nevertheless been reported that pruritus can be improved by moisturizing and rehydrating the skin [16]. Therefore a possible causal relationship with the development of CKDaP has also been suggested [16, 19]. Thus skin alterations that may contribute to the intensity of CKDaP probably do not represent the triggering cause of itch [11].

METABOLIC CHANGES

There are several observations that problems of the skin and the prevalence of pruritus decrease after kidney transplantation [32, 33]. This indicates that suboptimal renal replacement in relation to the dialysis dose as well as other renal tasks (e.g. hormonal regulation and mineral bone balance) may lead or promote CKDaP. Unidentified or unmeasurable metabolites have also long been held responsible for the development of CKDaP [4, 34]. In a randomized controlled trial, the use of high-permeability (or 'high cut-off') haemodialysis filters versus conventional haemodialysis demonstrated decreased levels of PTH, β2-microglobulin and intensity of pruritus [34]. This hypothesis is supported by the description of positive correlations between dialysis dose/adequacy and pruritus intensity [35–37]. On the other hand, some observational studies did not show significant associations between the occurrence and characteristics of itch and dialysis dose measured by Kt/V [38, 39]. Thus, the detoxification function of the kidney probably contributes to the changes that eventually lead to the development of itch, but it is probably not the only determining factor.

Furthermore, CKD is often associated with hyperphosphataemia, hypocalcaemia and decreased calcitriol, causing secondary hyperparathyroidism. Previous studies have demonstrated associations of pruritus with typical parameters of chronic kidney disease–mineral and bone disorders (CKD-

Table 1. Summary of the main mechanisms discussed in CKD-associated pruritus

Localization of itch-related factors	Hypothesized involved pruritogenic alterations and factors in CKD		
Skin	Skin atrophy	Xerosis	
		Microangiopathy	
	Increased mast cell density and activity	Proinflammatory cytokines, (putative) pruritogens	
Systemic alterations	Metabolic changes	Suboptimal renal replacement	Dialysis dose (Kt/V)
			Inflammatory response to dialysis filters
		MBD	Increased calcium deposition
			Dysbalance of calcium, phosphate, PTH levels
		Anemia	Lower iron serum levels and hemoglobin levels (possibly via increased hepcidin)
	Inflammation	Th1/Th2 lymphocyte dysregulation	
		Proinflammatory cytokines	CRP, IL-2, IL-4, IL-13 and IL-31
Nerves and central nervous system	Neuropathy	Increased susceptibility	
	Dysregulation of the endogenous opioid system Genetic variants of opioid receptors	μ-opioid overexpression and κ-opioid downregulation	
Psyche	Depression Impaired mental health		

MBD) (like calcium, phosphate, PTH and, to a lesser degree, magnesium) [38, 41–43]. One possible explanation is that an increasing calcium–phosphorus product leads to more dermal calcium deposition [44], which in turn would be favoured by elevated PTH levels. Another support for this explanatory approach was provided by reports that parathyroidectomy could cure pruritus [45–47]. However, these associations have not been reproduced in all studies [38, 48]. Furthermore, zinc deficiency has also been suggested to contribute to uremic pruritus via activation of the histamine pathway, but a recent case–control study found no correlation between zinc levels and pruritus [40].

Some recent hypothesis-forming observations describe a possible role of acidosis in itch development. For example, single experimental studies have observed that itch can be triggered or intensified by exposure to protons (e.g. during CKD-associated acidosis) at acid-sensitive ion channel 3 (ASIC3) [49, 50] and transient receptor potential channels subfamily V (TRPV) members (TRPV 1 [51] and TRPV 3 [52]). Therefore, optimal management of CKD-MBD parameters and adequate dialysis are likely to be important factors in CKDaP.

Iron deficiency (and anaemia) has also been implicated in the development of pruritus associated with renal insufficiency. In iron deficiency states, there is upregulation of interleukin-6 (IL-6) and induction of hepcidin that resembles chronic inflammation [53]. Lower iron serum levels and haemoglobin levels are observed in some studies of patients with CKDaP [54, 55].

Further, there is evidence that possibly the dialysis membrane itself may have an influence on pruritus. For example, it has been observed that patients dialysed with a polyarylethersulfone membrane suffer more CKDaP than those dialysed with a polysulfone membrane [38].

INFLAMMATION

The interdependence in the pathophysiology of inflammation between the immune system and the nervous system is substantial. An imbalance in the interactions between the cutaneous immune system and the nervous system contributes to inflammation and itch sensation. CKD is thought to initiate and maintain a state of systemic microinflammation, which subsequently also contributes to the development of pruritus.

This hypothesis is also based on the observation that many immunosuppressive therapies, e.g. ultraviolet light or tacrolimus, influence the prevalence and intensity of pruritus [10, 56, 57]. Interestingly, a lower prevalence of pruritus was observed in patients with glomerulopathies [38]. One explanation could be that these patients are more often treated with immunosuppressive therapies that suppress inflammation and thus also pruritus.

Historically, histamine is certainly the best characterized mediator of pruritus and pruritogen. The release of histamine from mast cells in the dermis causes pruritic urticaria characterized by itching, rash and swelling. In this context, the number of mast cells correlates with the severity of itch [58] and ultraviolet light therapy leads to a reduction in mast cell numbers and an improvement of pruritus in CKD patients [59, 60]. Interestingly, an increased number of mast cells and mast cell activity in the dermis is found in patients with CKD [54, 61, 62]. However, in CKDaP, there is no association of serum histamine levels and uremic pruritus [63]. Furthermore, oral antihistamines are not effective in the treatment of CKDaP. However, mast cells are known to release many (putative) pruritogens [e.g. tumor necrosis factor (TNF)-α and IL-2] and proteases (e.g. tryptases and chymases) in addition to histamine.

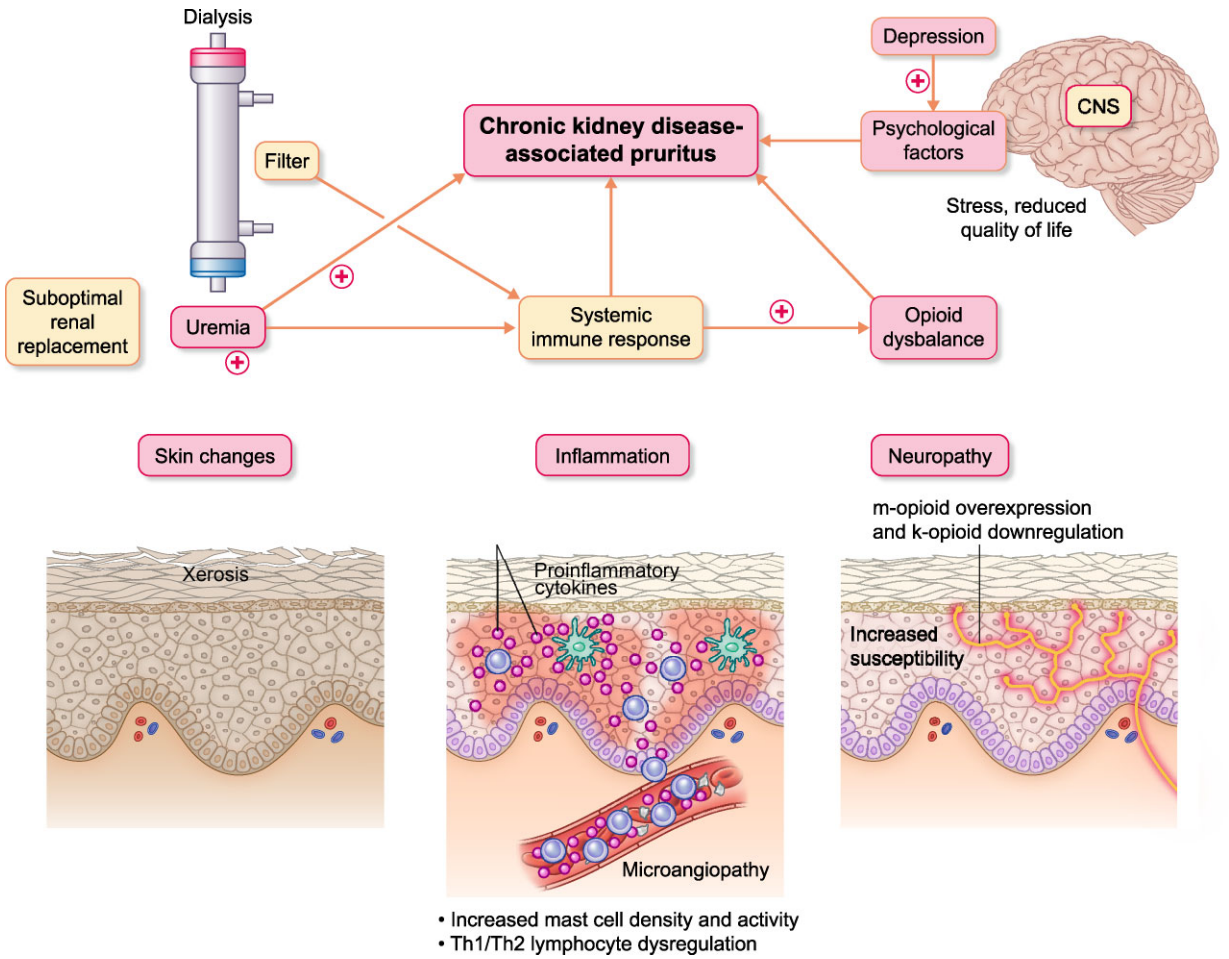

FIGURE 2. Overview of factors involved in CKD-associated pruritus.

Mentioned substances may also contribute to the development of CKDaP. Increased serum tryptase levels have been demonstrated in haemodialysis patients compared with the general population [64, 65]. In addition, serotonin levels are also elevated in CKDaP patients [66]. Fittingly, ondansetron (a 5-HT3 receptor inhibitor) has been described to improve pruritus [2].

In turn, messengers secreted by mast cells cause the release of neuropeptides in the sensory nerves of the skin to activate other immune cells and nonneuronal cells in turn [2]. Thus tachykinins such as substance P may activate transcription factors in immune cells that increase transcription and translation of proinflammatory cytokines (e.g. IL-2). Consistent with the hypothesis, intradermally injected IL-2 elicits itch [67].

This multitude of small molecules interacts with neuronal receptors and possibly promotes itch.

In addition to mast cell activity, other dysregulations of the immune system as well as inflammation likely play an important role in the pathogenesis of CKDaP, as CKD is characterized by a microinflammatory state due to postsynthetic modifications of proteins, oxidative stress and dialysis-associated factors. In particular, impaired T helper (Th) lymphocyte differentiation and an increased proportion of Th1/Th2 lymphocytes [measured by interferon (IFN)-γ secretion] have been reported in CKD patients [68]. Accordingly, increased Th1 cells, higher C-reactive protein (CRP) and increased IL-6, IL-2 and IFN-γ—suggesting Th1 overactivity—can be detected in CKDaP patients, further emphasizing the important role of inflammation in the development and expression of pruritus [56, 68, 69]. Consistent with the observation of dysregulation of TH balance, serum levels of various classical inflammatory parameters such as CRP, IL-6 and IL-31 are elevated in haemodialysis patients with pruritus [37, 68, 70, 71].

Calcineurin is a protein phosphatase that induces IL-2 expression in T cells, matching the hypothesis; calcineurin inhibitors treatment with tacrolimus ointment significantly reduces the severity of CKDaP in chronic dialysis patients and, in particular, reduces Th1 cytokines [72–74]. Of note, these patients also have a higher all-cause mortality rate than patients without pruritus, linking chronic inflammation to CKDaP and poor outcome [70]. The major cytokines involved in pruritus and nociception include IL-2, IL-4, IL-13, and IL-31 [2]. IL-31 may play an especially important role in the pathophysiology of CKDaP [71]. Blocking antibodies to IL-31 or its receptor rapidly reduces itch in humans [2, 75, 76]. Therefore IL-31 is the cytokine probably most directly involved in mediating pruritus.

THE NERVES

Another possible factor in the pathogenesis of CKDaP is neuropathy, occurring both peripherally and centrally in CKD patients [11, 77, 78]. Dialysis patients show an altered

neurophysiological response [79]. Further, peripheral cutaneous nerve endings rarify in uraemia [80]; however, they also sprout irregularly into the epidermis, possibly leading to easier excitability [81].

In this context, the degree of paraesthesia with respect to pain correlates with the severity of itch [78]. Moreover, there are associations between central nervous system (CNS) damage and itch [82, 83]. Consistent with these observations, it has been shown *ex juvantibus* that the drugs gabapentin and pregabalin, which are effective in neuropathic pain, have potent antipruritic effects in CKDaP [84–87]. Further, itch was reported to be reduced via inhibition of substance P release by topical capsaicin [88, 89]. Thus, neuropathic changes appear to be at least partially responsible for the distressing CKDaP.

Furthermore, there is increasing evidence that dysregulation of the endogenous opioid system may play an important role in the pathogenesis of uremic pruritus (as summarized in [2, 3, 6, 10, 12]). This hypothesis is based on the observation that pruritus can be triggered by opioid agonists [3]. Three main receptor types with their corresponding ligands mainly describe the opioid system: μ-opioid receptor (MOR) with endorphins, κ-opioid receptor (KOR) with dynorphins and δ-opioid receptor (DOR) with enkephalins [1]. Historically, the opioid receptor system has been considered primarily in relation to the CNS and pain. However, all of the opioid receptors and ligands mentioned above can also be detected in peripheral nerve fibers in the skin [1, 90, 91]. It is important to understand that the endogenous ligands are not specific to one receptor but always cross-bind to other receptors as well. Some of the ligands may act as agonists at one type of receptor and show antagonistic activity at others.

Currently the KOR system is understood as suppressing itch and the MOR system as stimulating itch [1]. In particular, overstimulation of the central MOR by endogenous opioids has been proposed as a mechanism in CKDaP. While no statistical correlation between opioid levels and severity of pruritus in dialysis patients has been shown [92], clinical trials of MOR antagonists (e.g. naloxone and naltrexone) showed improvement of pruritus in uraemia [93–96]. However, in a placebo-controlled, double-blind crossover study in uremic patients with persistent, treatment-resistant pruritus, naltrexone did not improve pruritus [97].

On the other hand, an association between KORs and the intensity of itch has been shown in CKDaP patients [98]. A κ-opioid agonist (nalfurafine) has been used—with limited effects—in the treatment of patients with uremic pruritus [99, 100]. Recently this hypothesis was supported by a randomized controlled clinical trial showing the effectiveness of difelikefalin, a new κ-opioid agonist, which showed a significant reduction in itch intensity and improved itch-related quality of life in dialysis patients, providing further support for the opioid hypothesis [101].

Furthermore, there is increasing evidence that inflammation is also involved in the modulation of the opioid system and thereby potentially itch as well. The starting point of the hypothesis was the observation that opiates have a stronger analgesic effect in inflamed tissue [102]. The discovery that opioid receptors and nerve terminals on sensory nerves are upregulated during inflammation prompted the search for endogenous ligands in inflamed tissue. Here, opioid peptides were also found in granulocytes, monocytes/macrophages and lymphocytes [103–108] as summarized by Stein *et al.* [102].

Nevertheless, it is important to keep in mind that differences exist between the effects of opiate receptor agonists/antagonists depending on the state of inflammation [102]. Therefore similar effects are expected in the context of pruritus as well. This further complicates the understanding of the pathophysiological mechanisms.

Currently, regarding pain, regulatory mechanisms are believed to exist between inflammation and pain perception [109, 110]. Interestingly, IL-6 and TNF-α [111] produce opioid-mediated analgesia in inflamed tissue. Depending on the stage and type of inflammation, these effects are mediated by different opioid peptides [112–114].

However, in noninflamed tissue, cytokines such as IL-1α, IL-1β, IL-6 and TNF-α have been found to induce hyperalgesia [115]. Several chemokines have also been described to induce pain or reduce the analgesic effect of other agents [116, 117]. In addition, anti-inflammatory effects of opiate receptor agonists/antagonists have been demonstrated. Possible underlying mechanisms include the decreased release of proinflammatory neuropeptides or cytokines and decreased expression of adhesion molecules [118–120]. These findings may be contributing in part to the beneficial effects of peripheral opioid receptor agonists and antagonist.

Another aspect to potentially consider in the future regarding opioid ligands in pruritus treatment is the importance of genetics. Here there is evidence that genetic variants of opioid receptors potentially account for differences in susceptibility to pruritus or therapeutic effects [121–123]

THE PSYCHE

In addition to specific nerve damage, associations between inflammation, mental health and itching in dialysis patients can be described [5, 124]. The causality is obviously initially in the direction of reduced quality of life due to the distressing symptom of itch. However, depressive symptoms may be a predictor of the risk of severe pruritus in haemodialysis patients, suggesting an inverse influence as well [7].

SUMMARY

The exact molecular pathophysiology of uremic pruritus remains unclear. In the absence of convincing experimental models to study CKDaP, a large number of clinical studies have generated various explanatory approaches. Thus the model of pathophysiology has become complex and includes several levels of mutual interactions in the skin, nerves, inflammatory processes, opioid system and CNS, as well as the psyche. In recent decades, based on these observations, numerous treatment approaches have been developed to alleviate CKDaP. Encouragingly, efficacy has been demonstrated for some of the newer therapeutic approaches, underscoring the validity of the models described. However, as with other forms of pruritus, probably there will be no single therapeutic target that will allow CKDaP to be completely controlled.

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CONFLICT OF INTEREST STATEMENT

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