Acute renal failure. I. Relative importance of proximal vs. distal tubular injury*

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Bonventre, J. V., M. Brezis, N. Siegel, S. Rosen, D. Portilla, and M. Venkatachalam. Acute renal failure. I. Relative importance of proximal vs. distal tubular injury. In: Acute renal failure forum, edited by W. Lieberthal and S. K. Nigam. Am. J. Physiol. 275 (Renal Physiol. 44): F623–F632, 1998.—For more than 15 years, there has been an ongoing debate regarding the nephron segment(s) most severely injured in acute renal failure (ARF) induced by an ischemic or toxic insult. Although some investigators have argued that the proximal tubule (and particularly the S3 segment) is the major target of injury in ARF, others have held the view that damage to the distal nephron [particularly the medullary thick ascending limb (MTAL) segment] plays a more important role in this disease. In this discussion, the first of three on different aspects of ARF that have been hotly debated, we have invited several experts to discuss their opinions on this issue. The goals of this first discussion (and the subsequent two articles in this forum) are to establish areas of consensus in each area of controversy and also to identify unanswered questions that represent important areas for future research.

isolated perfused kidney; acute tubular necrosis; single injury experimental model

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THE LAST SEGMENT of the proximal tubule (the S3 segment) and the medullary thick ascending limb (MTAL) are both located in the outer medulla of the kidney. This region of the kidney is marginally oxygenated under normal circumstances and suffers the most severe and persistent hypoxia after an ischemic insult, because the return of blood flow to this region is delayed (10). Although both of these segments of the nephron are metabolically quite active with high transport activity, the metabolic characteristics of the two segments differ substantially. One striking difference between these two segments is their capacity to generate energy (ATP) by glycolysis. Proximal tubules have little capacity for glycolysis, as evidenced by their failure to produce lactate either under control conditions or in the presence of blockade of oxidative phosphorylation with antimycin A (2). By contrast, lactate production by the MTAL increases more than three orders of magnitude in response to antimycin (2). Consistent with their superior glycolytic capacity, glycolytic enzymes are more abundant in the MTAL and other distal nephron segments than in the proximal tubule (61). Thus, the MTAL has a greater capacity than the S3 segment to generate ATP by glycolysis when oxidative metabolism is impaired in the setting of poor outer medullary blood flow after ischemia-reperfusion injury.

* First in a series of invited articles on controversies related to acute renal failure.
In experimental models of unilateral or bilateral renal ischemia, induced either by transient, complete cessation of renal blood flow (62, 63) or partial reduction of blood flow (24, 63, 65), cell injury and necrosis has been uniformly shown to be more severe in proximal than distal tubules. Also, Venkatachalam and his colleagues (21, 62) have reported that the S3 segment of the proximal tubule is more susceptible than the S1 or S2 segments to ischemic injury in vivo. Similarly, Hanley (29) demonstrated that when rabbit nephron segments were isolated from kidneys subjected to 60 min of ischemia, although both proximal and distal segments had impaired transport ability, only the S3 segment of the proximal tubule had damage sufficient to leak inulin. However, it should be pointed out that not all studies agree that the S3 segment is the part of the proximal tubule most severely injured following oxygen deprivation. Ruegg and Mandel (52) have reported that tubules isolated from the S3 segment have higher glycolytic capacity than isolated S1 and S2 segments and are less susceptible than the proximal convoluted segments when subjected to anoxic and hypoxic injury in vitro. The greater susceptibility of the S3 segment than the S1 and S2 segments following ischemia-reperfusion injury in vivo is therefore most likely primarily related to the hemodynamic factors that result in persistent impaired perfusion of the outer stripe of medulla (60).

Although injury to the MTAL segment is not a prominent feature of ischemic models in vivo, we and other investigators have shown that the cells of the MTAL demonstrate a very well-developed response to ischemia that is characterized by an alteration in the expression of many genes (53). Ischemia increases the expression of a number of immediate early genes that encode transcription factors (5, 63) and cytokines (54) while downregulating other genes (for example, the genes encoding Tamm-Horsfall protein and epidermal growth factor) (48, 53). The reasons for the localization of these genetic responses to ischemia to the cells of the MTAL segment and the implications of these responses, if any, for injury or repair of the kidney must remain speculative at the present time. However, one possibility is that this response is adaptive and results in decreased susceptibility of this segment to injury. It is also possible that increased expression of some genes within the MTAL encode the production of paracrine growth factors that may contribute to the regenerative response in the cells of the adjacent S3 segment that survive the injury, dedifferentiate, and enter the cell cycle (53, 63). It is also possible that some of the genetic responses of the MTAL to injury are "maladaptive." For example, the generation of cytokine products of the J E and KC genes expressed by MTAL cells after ischemic injury (54) may contribute to the inflammatory response associated with acute renal failure (ARF) that is characterized by infiltration of the kidney by polymorphonuclear leukocytes and monocytes, which contribute to tubular injury and dysfunction following ischemic injury (18, 34, 60).

If the damage in experimental models of ischemic injury in vivo occurs primarily in the S3 segments of the proximal tubule, how do we explain the predominant injury to the MTAL segment that occurs in the isolated perfused kidney (IPK) (1, 12)? Furthermore, is this pattern of injury relevant to the pathogenesis of ARF in vivo? It is important to emphasize that the localization of injury to the MTAL segment is observed only in the IPK when the perfusate is free of erythrocytes. Under these conditions, the outer medulla is severely hypoxic because of the poor oxygen-carrying capacity of the red blood cell-free perfusate. However, other features of ischemia present following a reduction in renal blood flow in vivo, including acidosis, substrate depletion, and accumulation of metabolic waste products, are absent in the IPK. Under these conditions, the proximal nephron may be less susceptible than the MTAL to hypoxic injury because of a more favorable balance between oxygen delivery and demand. It is important to recognize, however, that the selective damage to the MTAL does not occur in the isolated kidney when red blood cells are added to the perfusate (22, 23, 37). In addition, when the isolated kidney perfused in the presence of red blood cells is subjected to ischemia (37) or hypoxia (22, 23), the pattern of injury is comparable to that seen following ischemia in vivo, i.e. widespread proximal tubule injury with sparing of the MTAL segment.

At the heart of this debate, of course, is the question: What segments of the nephron are most severely injured in human ARF? Interestingly, different investigators have interpreted the same literature in different ways. In one review, Brezis and Epstein (8) state, "Both old and recent clinicopathological studies have confirmed the predominance of distal tubular and outer medullary injury in human ARF." In referring to the classic studies of structure-function relationships in human acute tubular necrosis (ATN) performed by Oliver et al. (42, 43), Brezis and Rosen (10) state, "the original descriptions of lower nephron nephropsis in patients who died of ARF emphasized the presence of focal necrosis along distal nephrons." In referring to the same report, however, Kreisberg and Venkatachalam (35) state, "In the more common ischemic type of ATN, necrosis is patchy. Short lengths of tubules are affected, the straight segments of the proximal tubules being the most vulnerable."

In ARF in the human transplanted kidney, tubular necrosis occurs primarily in the S3 segment in a pattern practically identical to that seen in experimental rat renal isografts (44). Olsen and Hansen (45) found that the number of missing medullary tubule epithelial cells, marking sites of cell desquamation, was significantly increased in both MTAL and S3 segments in renal biopsies taken from patients with ischemic ARF.

In conclusion, ischemia-reperfusion models in vivo and in erythrocyte-perfused isolated kidneys result in damage primarily to the S3 segment. These models mimic the pattern of injury seen in the human allograft with ARF. The relative contribution of proximal versus
The distal tubule has distinct responses to injury that are different from those of the PT. First, hypoxic injury to the MTAL in the erythrocyte-free IPK is remarkably protected by inhibition of tubular transport (13–15). This is in contrast to the PT, which is not protected by inhibition of transport (15). Second, the cells of the MTAL respond to ischemic injury by altered expression of many genes (53, 63). Third, hypoxia rapidly induces signals of apoptosis in the distal tubule, but not in the PT (3, 33).

Extensive and selective injury to the MTAL, originally recognized in the isolated perfused rat kidney, has been repeatedly reproduced in a variety of ARF models in vivo based on a combination of insults (salt depletion, angiotensin II infusion, radiographic administration, inhibition of prostaglandin and/or nitric oxide synthesis, and exposure to cyclosporin, amphotericin, or chronic hypercalcemia). These data have been recently reviewed (10, 20) and strongly suggest that MTAL injury is not an artifact of the IPK model, as suggested by Bonventre (above), but a remarkable in vivo indicator of medullary hypoxia in synergistic renal insults which compromise the homeostatic mechanisms governing medullary oxygen balance. These multiple-insult models (10, 20) appear to recapitulate the common type of ARF resulting from synergistic toxic and ischemic insults, whereas the experimental ischemia-reflow model would appear to resemble those forms of ARF in humans that result from ischemic injury alone (e.g., ARF following transplantation or aortic surgery).

In humans, necrosis along the distal tubule (and not along the PTs) is present significantly more often in ARF than in controls (57). Glycosuria or renal tubular acidosis, each an expected consequence of PT damage, is rarely seen in clinical ARF. By contrast, medullary injury in humans with ARF is suggested by the presence of nucleated cells in the vasa rectae, by a consistent loss of urinary concentrating ability, by the urinary granular casts rich in Tamm-Horsfall protein (which is released specifically by thick ascending limbs), and by morphological observations indicating damage along Henle’s loop and in S3 segments (45). Hidden in the medulla, and usually not sampled in kidney biopsies, these lesions are more difficult to document but are perhaps more specific for ARF in humans than are the PT changes. As reviewed elsewhere (10), medullary hypoxia is a price the mammalian kidney pays for efficient urinary concentration (8, 10). Medullary oxygen balance is regulated by multiple paracrine homeostatic mechanisms (such as prostaglandins, adenosine, nitric oxide, and tubuloglomerular feedback). Interference with these mechanisms predisposes the kidney to focal hypoxic injury at sites of strategic importance for renal function. The zones most vulnerable to hypoxic injury are in the outer medulla and in the medullary rays, where they may involve both proximal and distal nephrons in ARF.

In conclusion, the PT, because of its high permeability to water, high fluidity, and low metabolic reserve,
readily and nonspecifically displays plastic changes prominent in "single insult" models of ARF. The distal tubule responds to work in hypoxia by rapid cell fragmentation associated with selective induction of growth response genes and signals of apoptosis. Synergy between hypoxic and toxic insults, as seen in clinical ARF, lead to predominant outer medullary damage with gradients of intrarenal oxygenation determining the distribution of injury for both proximal and distal tubular cells.

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M. Brezis

**IT HAS BEEN TEMPTING** to postulate that injury to a particular nephron segment, either the S3 segment of the proximal tubule or the MTAL segment of the distal tubule, is more important or relevant than the other in the pathogenesis of ARF. In my opinion, these arguments have generated considerable heat but little light. In the final analysis, the issue is moot as regards the pathogenesis of ARF in humans. The predominant sites of tubular injury in humans cannot be determined because routine renal biopsies cannot be justified, whereas noninvasive techniques to assess and compare injury in different nephron segments are not available. What is of greater importance to our understanding of the cell biology of renal injury is the recognition of the differences in the response of these nephron segments to acute injury.

The proximal tubule is dependent on oxidative phosphorylation for energy production. As a result, depletion of ATP has been demonstrated to be a critical component of injury to this nephron segment both in vivo and in cell culture. Inhibiting ATP depletion or augmenting ATP repletion will diminish the extent of injury or accelerate the process of repair of these cells (56). Energy depletion in the segment is associated with the characteristic structural changes, which includes sloughing of the brush border, exfoliation of live and injured cells, increased intratubular pressure, and backleak of tubular fluid. The molecular alterations that underlie these structural changes are dramatic. Dissociation of the actin cytoskeleton leads to migration of integral membrane proteins such as Na-K-ATPase from their polarized domain (38, 39), loss of adhesion molecules and tight junction proteins resulting in diminished cell-cell attachment (4), and disruption of integrins which uproot cells from the basement membrane (25). Therefore, in the proximal tubule, the consequences of energy depletion are the dissolution of cellular structure and function mediated by the modification of critical proteins in all cellular domains, apical, lateral, and basal. Thus, the proximal nephron will be particularly sensitive to disruption of blood flow, which reduces ATP below a threshold, or to toxins, which in turn disrupt oxidative metabolism and ATP production.

The MTAL demonstrates a relatively unique susceptibility to hypoxia because of a critical balance between oxygen supply and demand related to the workload in this segment (10). Although perturbations in ATP metabolism can modulate injury to the S3 segment in vivo, hypoxic damage to the MTAL in the IPK can be ameliorated by increasing oxygen delivery (e.g., by adding red blood cells to the perfusate) (22, 23, 37) or by diminishing the work load demanded (e.g., with furosemide or ouabain) (10). The characteristic lesion in the MTAL such as mitochondrial swelling and nuclear pyknosis can be modulated by changes in the perfusion of the medulla and alterations in glomerular filtration and transport activity (10). Thus, these medullary nephron segments that dwell on the brink of injury will be affected by alterations both in oxygen delivery and energy demand.

What we have learned from detailed and intense studies of the response of these nephron segments to acute injury is not which one is more severely injured. Rather, we have developed an appreciation of the critical biological importance of the interrelationship between metabolic processes and the susceptibility of renal epithelial cells in different nephron segments to injury. Important questions that remain to be answered by future research include: 1) the mechanisms by which injury in one site may lead to molecular alterations in another, e.g., the extent to which injury in the S3 segment induces gene expression in the MTAL segment (53), and 2) whether production of growth factors by the distal nephron influences recovery in the proximal tubule (28, 46). Our understanding of these phenomena will result from the melding of metabolic and molecular studies of the response to injury of both segments of the nephron.

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N. Siegel
IN ANY ARGUMENT about the proximal and distal nephron, there are certain statements about which I believe all can agree: 1) Ischemic and toxic ARF in humans is associated with limited histological evidence of injury; clinically (and paradoxically) this circumstance is referred to as acute tubular necrosis (ATN). The implication is that renal hemodynamics no longer permit glomerular filtration to continue in a successful manner, although there is sufficient blood flow to maintain the histological integrity of most of the renal parenchyma. In contrast to human ARF, there is extensive destruction of the renal parenchyma in experimental models of ARF, initiating with S3 injury and, as the time of vascular obstruction increases, involving S1 and S2 segments as well. The distal nephron is generally unaffected unless the obstruction is prolonged. 3) ARF in humans following renal transplantation is a modified example of ischemia-reflow, in which metabolic processes are reduced by diminishing temperature and/or the time of warm ischemia. Indeed, both clinical and experimental studies show that hypothermia confers remarkable protection; thus, the limited histological findings in this situation are more in the continuum of usual ATN rather than typical ischemia-reflow.

Therefore, it is quite apparent that global ischemia and its manifest injury cannot be responsible for clinical ATN in which histological changes are relatively unimpressive. Yet the renal transplant is an example of global ischemia that produces limited histological change in the face of complete organ failure. How can this paradox be explained? If global ischemia can be modified so that flow alterations are minimized and relatively limited destructive changes occur, then the region that would be most affected would be the one most hypoxic to begin with: the medulla. Thus, the modified ischemia-reflow in the transplant kidney is the environment in which usual ATN supervenes, i.e., glomerular filtration occurs in the setting of medullary hypoxia with its injurious consequence to the MTAL. Indeed, the studies of Heyman et al. indicate that distal nephron injury does occur in ischemia-reflow apparently as a response to augmentation of glomerular filtration in the face of medullary hypoxia.

Until recently, no animal model has been developed that mimics the situation of limited parenchymal change and renal failure in humans. Nephrotoxins in high doses produce ARF, but obvious proximal tubular necrosis occurs as well. On the other hand, when multiple insults are used, for example, when pharmacological doses of nephrotoxic drugs are administered in combination, acute renal failure can be produced where morphological injury is limited to the distal nephron (10). In these situations, the degree of damage closely correlates with the severity of renal failure (10). Finally, we cannot exclude the possibility that there is significant tubular injury in human ARF in areas such as the outer medulla that are often inadequately sampled at the right time by a renal biopsy. Reports of individual cases indicate that this is correct. Additionally, our studies have indicated that distal nephron injury may be readily reversible (9), but the physiological consequence of such injury is less immediately repairable.

In any discussion of the proximal and distal nephron, it must be made clear that in human material and indeed in whole organ animal studies, little attention has thus far been paid to the distal nephron. On the other hand, anatomists led by Dr. Kriz's group have elegantly described the histology of the kidney, defining the complicated nature of the renal medulla, and these descriptions have been the basis for understanding the complex and perilous oxygenation of both the medulla and medullary rays of the cortex (7, 10, 50). Multiple studies illustrate the vulnerability of the medulla to both acute and chronic injury from well-known nephrotoxins (10, 32, 31, 51). The construct of the microenvironment both from a comparative anatomical and structural viewpoint cannot be ignored. The outer medulla in the rat has an obvious outer stripe in which S3 is the dominant tubular component; in the human, the outer stripe is far more limited and irregular. The studies of Ruegg and Mandel clearly illustrate the danger of generalizing from isolated tubules to the intact organ; i.e., in vivo, of all the proximal tubular segments, S3 is the most vulnerable to ischemia-reflow, whereas, in vitro, it is the most resistant to hypoxia (52). In the final analysis, ATN cannot be explained simply by dysfunction of either the proximal or distal nephron segment; it is the whole organ that fails adequately to serve the needs of the body.
segments to ischemic or toxic injury, and I agree with these comments. However, another aspect that has not been discussed, and which may also contribute to differences in the metabolic responses to ischemic injury between proximal and distal nephron segments, relates to the role that fatty acid oxidation enzymes may play during ischemia. Recent studies demonstrate that these enzymes (acyl CoA oxidase and cytochrome P4A1), predominantly localized in the kidney cortex, are transcriptionally modulated by a proximal tubular transcription factor named peroxisome proliferator receptor activated-\(\alpha\) (PPAR-\(\alpha\)). This transcription factor is exclusively present in the nuclear fraction of the S3 segment (6, 59). During ischemia, profound downregulation of these enzymes occurs (26, 27) and could account for the excessive accumulation of toxic metabolites including long-chain acylcarnitines and long-chain acyl CoA, which may contribute to cell damage in this nephron segment (47). Therefore, in addition to regulation of transcription factors present in the distal tubule, metabolic control of this proximal tubule transcription factor may account for the structural alterations observed during ischemia in the proximal tubule.

Regarding the debate as to the tubular segment most severely injured in ARF, I believe that it is premature to assign a hierarchy to either the proximal or the distal tubule as the primary site of injury. Clearly, both segments display unique functional and metabolic characteristics. Thus, it should not be surprising that they may display different susceptibility and responses to injury. Future studies are necessary to elucidate differences in the response of proximal and distal tubules to the same injury and to establish whether injury to one nephron segment alters the response of another to injury.

D. Portilla

I DO NOT BELIEVE that it is possible yet to assign primacy to any one nephron segment in the pathogenesis of ARF. The kidney and its vascular supply are complex by nature’s design to allow precision in fluid and electrolyte homeostasis. This complexity, which involves interaction between various components within the kidney, makes it difficult to study function or dysfunction in one nephron segment in isolation from the other nephron segments. This applies particularly to the kidney affected by the bewildering and multifarious array of insults that lead to ARF in humans. Our attempts to develop a simple “unified theory” to explain “everything” in ARF have not enhanced our understanding of the pathogenesis of ARF but have, in my opinion, represented a vexing source of confusion instead.

One roadblock to a rational understanding of “ischemic acute tubular necrosis” is interspecies variation in the renal vascular response to transient arterial occlusion in the popular clamp model. Rats typically show persistent vasoconstriction and poor reflow of blood after the clamp is released. The vascular defect is more severe in the deep cortex and medulla. This may lead to continuing piecemeal necrosis of tubules many hours to days after reflow is established. More interestingly, as pointed out by all of the primary discussants, persistent hypoxia of glycolytically competent deep cortical and medullary nephron segments may lead to alterations of gene expression and hypoxia-driven but energy-dependent apoptosis. Incremental necrosis of proximal tubules and medullary defects attributable to persistent ischemia are fully correctable by measures that prevent persistent vascular dysfunction. Most other interventions, including growth factors, morphogens, and peptides, which accelerate recovery following the renal artery clamp model of ischemia in the rat are also associated with beneficial vascular effects that may help improve renal blood flow during the critical hours following the release of the arterial clamp.

However, persistent ischemia by vasoconstriction or poor reflow is not a feature of ARF that follows renal arterial occlusion in dogs. Thus, many of the agents shown to be beneficial in the rat may have little or no effect in ARF in dogs or other species that do not exhibit persistent postischemic vascular dysfunction. This may explain why atrial natriuretic peptide, which ameliorates ischemic ARF dramatically in rats, is without therapeutic effect in humans with ARF. The negative results from this recent clinical trial certainly underscores the need for us to study interspecies variations in the light of lessons that have been learned in the past.

There appears to be universal agreement that medullary hypoxia is an important factor in human ARF. However, it is not at all certain that medullary hypoxia plays the dominant role or that damage/necrosis of medullary/distal nephron segments overrides in importance the injury and/or dysfunction to other tubule segments or vascular compartments in humans. It has been suggested that abnormal tubuloglomerular feedback mechanisms dependent on medullary pathology may reflexively lead to decreased glomerular filtration rate and blood flow. However, even if this hypothesis were to be accepted as fact, assigning primacy to this mechanism would ignore the major contribution of other factors such as tubular necrosis and obstruction.

Reductionist approaches are useful in studying the renal pathology of ARF at the cellular level in specific tubular or vascular structures. However, as suggested by Dr. Siegel (above), integrated renal function requires that mechanisms at the cellular, tubular, and vascular levels in various regions of the kidney be interactive. Therefore, a holistic view of pathology and pathophysiology that takes into account all specific and regional cellular, tubular, and vascular mechanisms will be needed, if we are to arrive at an integrated understanding of renal dysfunction at the organ level. This demands that we correctly interpret and take into account the many lessons we have learned in the past and use this information as background to view the existing new body of knowledge on the molecular and cellular biological aspects of cell and tissue injury and repair. Additionally, there is a pressing need to conduct ARF
EDITORIAL COMMENTS

The experts chosen to participate in this discussion have highly individual and, in some instances, disparate opinions on the relative importance of proximal versus distal tubular injury in the pathogenesis of ARF. However, there are important areas of consensus that are worth emphasizing. Most investigators agree that the tubular segments situated within the outer medulla of the kidney (the S3 and MTAL) are likely to suffer the most severe injury after an ischemic or toxic insult due to the persistent reduction in blood flow to this region of the kidney. However, many experts also feel that available evidence does not provide any clear-cut answer as to which of these is most severely injured in humans with ARF and that continuing debate is useful until the issue can be resolved by appropriate and definitive clinical studies. Emphasis should rather be placed on developing future research goals that will elucidate the mechanisms involved in the pathogenesis of ARF in humans.

Clearly, the factors that determine the severity of injury to both proximal and distal tubules are complex and multifactorial. Drs. Bonventre, Brezis, and Venkatachalam all point out (above) the need to develop animal models of ARF that are more representative of the process of ATN in humans than those currently available. Available experimental models that emphasize multiple rather than single nephrotoxic insults and those that take into account interspecies variations may more accurately represent the events that occur following ARF in humans. For the record, however, it seems reasonable to assume that both proximal and distal cell dysfunction occurs and that morphological changes in various tubule segments, while indicative of injury, may not accurately reflect mechanistic dysfunction in other tubular segments.

Also, many of the discussants emphasize the need for research that investigates the role of alterations in gene expression in the MTAL in the pathogenesis of ARF and the potential interactions between acutely injured S3 and MTAL segments that lie adjacent to one another within the outer medulla. One of the intriguing questions raised by the discussants is whether the alterations in gene expression that occur in the cells of the MTAL modulate the susceptibility of this segment to injury or result in the production of paracrine factors (such as growth factors) that influence the regenerative response in the adjacent proximal tubule. Another important question for future investigation is whether some of the genetic responses of the MTAL to injury contribute to the tubular injury by inciting the inflammatory response associated with ARF. All of these questions represent exciting areas for future investigation at a molecular and cell biological level. Many are not easily examined in animal models and will require the use of cell culture models for ARF.

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REFERENCES


M. Venkatachalam

Studies in larger animals in which responses to injury may be more like that of human kidneys. Nothing less will suffice, if we are to make further inroads to prevent and heal tubular dysfunction, injury, and death in human ARF.


