

Optimizing Long-Term Outcomes with Kidney Anti-rejection Therapies



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Acute and Chronic Rejection

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The background is a surrealist painting by Salvador Dalí, 'The Persistence of Memory'. It depicts a desolate, rocky landscape under a pale, hazy sky. In the foreground, several pocket watches are melting and distorting. One watch is draped over a twisted, branch-like structure. Another is on a small table with a bowl of olives. A third is draped over a reclining figure. The overall mood is one of timelessness and decay.

Absent Tolerance or Twins:

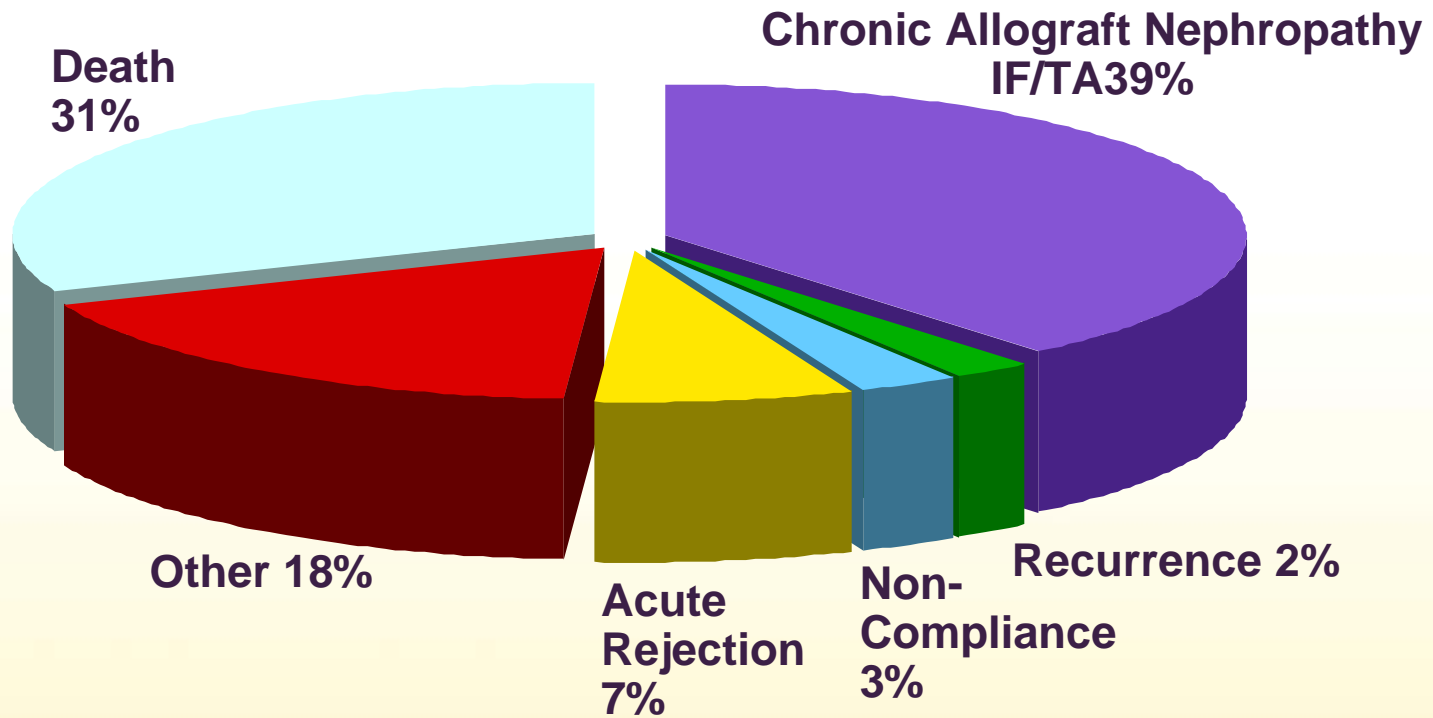
All T Transplants Reject.....

What matters to recipients is
how fast.....



Prevalence of Allograft Failure/Rejection

Causes of Renal Graft Loss After First Year (130,000 transplants - 16,000 failures)



Chronic Allograft Nephropathy

...the persistent inexorable decline in transplant renal function with time...



Antigen Dependent

Acute Rejection

Re-Transplants

HLA antibodies

Non-HLA antibodies

Antigen Independent

Ischemia/Reperfusion

Nephrons: age, gender, size

Nephrotoxic Drugs

Hypertension

Hyperlipidemia

CMV/other infections

Hyperfiltration?

Clinical Manifestations of Acute Renal Allograft Rejection



- **Local**
 - *Pain and swelling over graft, redness*
- **Systemic**
 - *Fever and Chills*
 - *Lethargy*
 - *Decreased urine output*
 - *Edema and SOB*
 - *Hypertension*
- **Metabolic**
 - *Increased serum creatinine, BUN, potassium*
 - *Acidosis*
 - *Proteinuria*

Kidney Transplant Outcomes

One year Acute Rejection Rates (%)



Agents

No Ab

Induction Ab

Aza+Pred

80

50-60

CsA+Pred

50-60

FK+Pred

45

MMF+Pred

53

CsA+Aza+Pred

50

45

CsA+MMF+Pred

40

10-20

FK+MMF+Pred

35

10-20



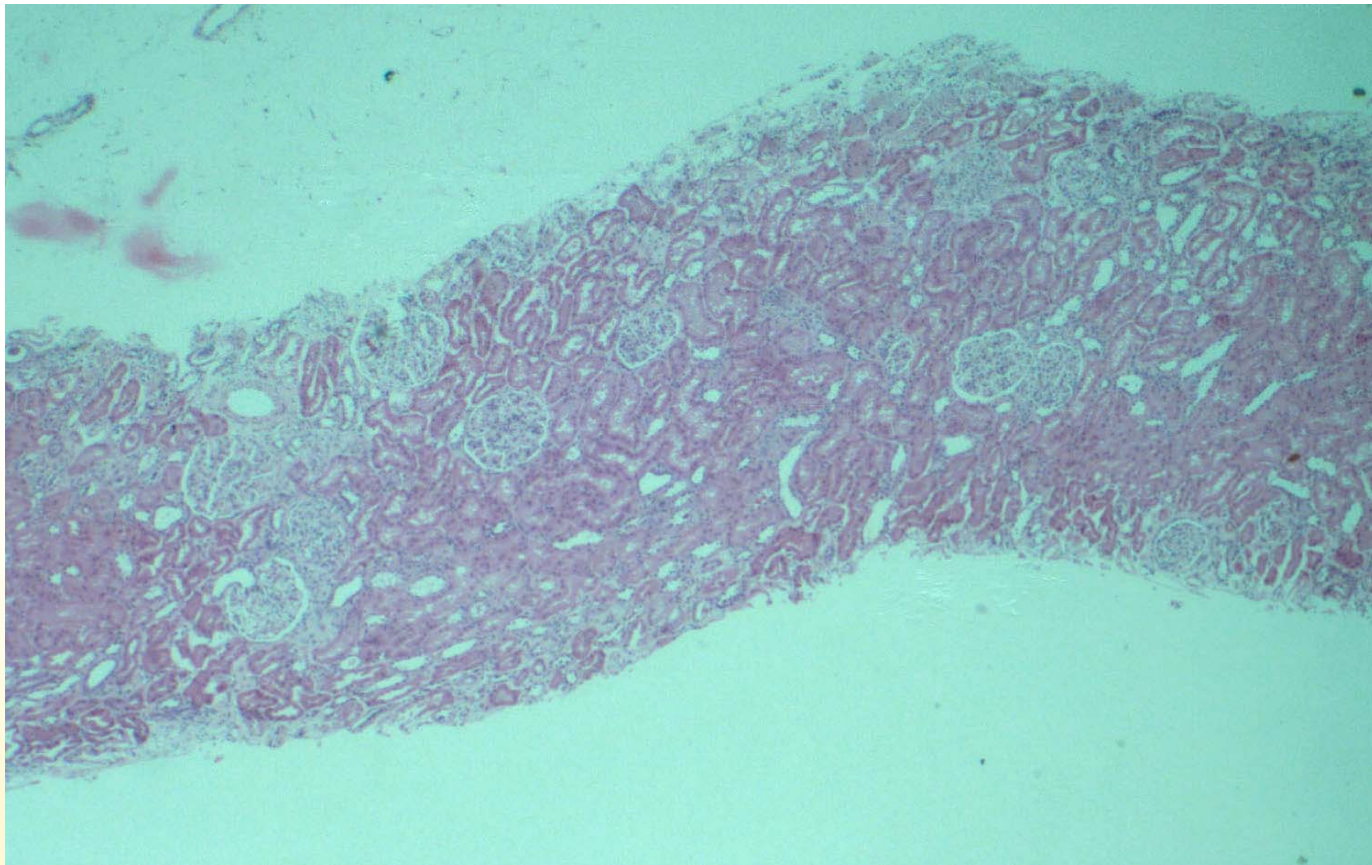
Causes of Failure/Rejection

Types of Renal Allograft Rejection

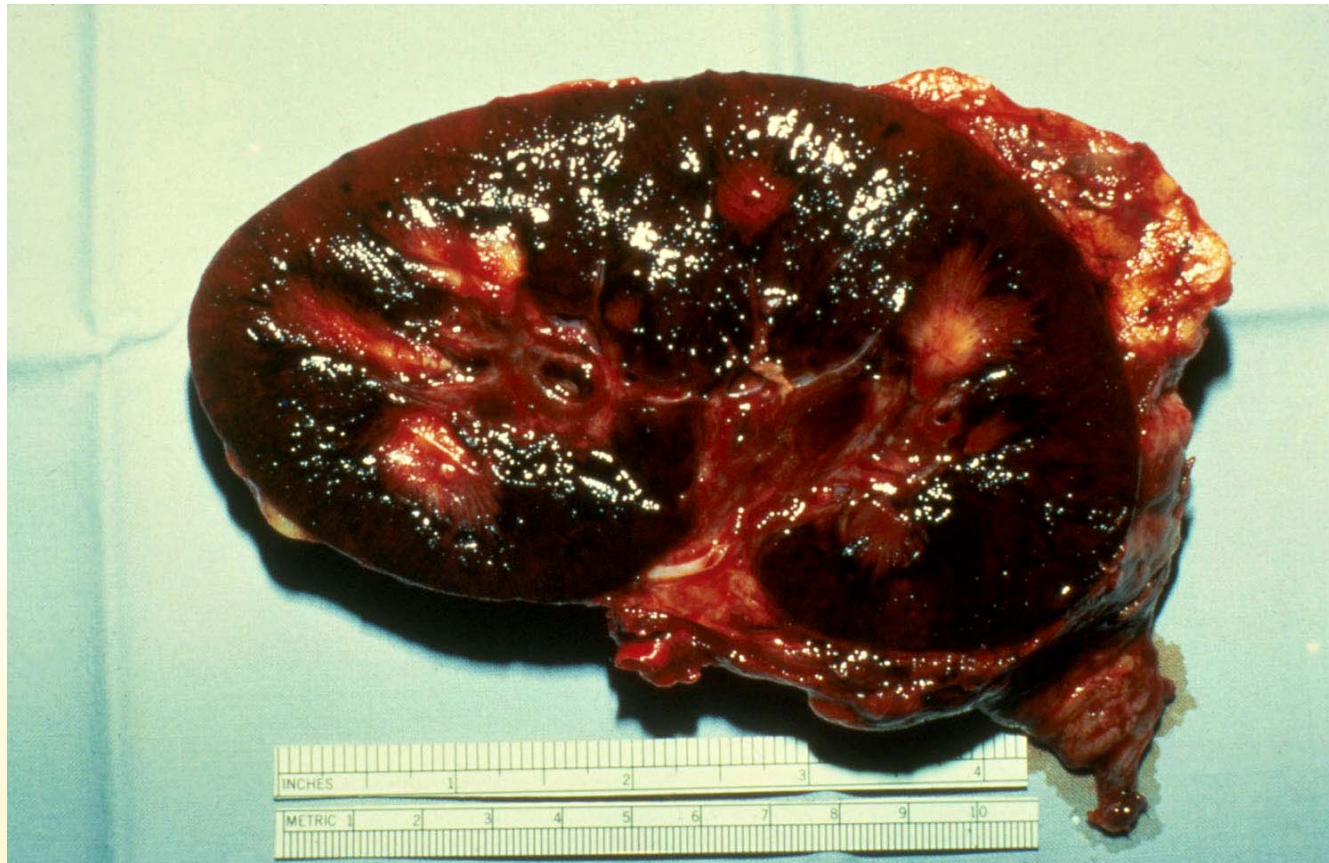


	<u>Hyperacute</u>	<u>Acute</u>	<u>Chronic</u>
Time after transplant	Minutes to Hours	Days to Years	Months to Years
Mediating Factors	Preformed anti-HLA or ABO antibodies: Class I or II	Cellular and humoral Immunity	Antigen dependent Antigen independent
Sequelae	Intravascular Coagulation	Tissue Destruction Tubular injury	Obliterative Graft Fibrosis
Prevention/Therapy	ABO typing and lymphocyte crossmatching	Immunosuppression Induction therapy Maintenance therapy	→ Prevent AcR Control Secondary Risk Factors

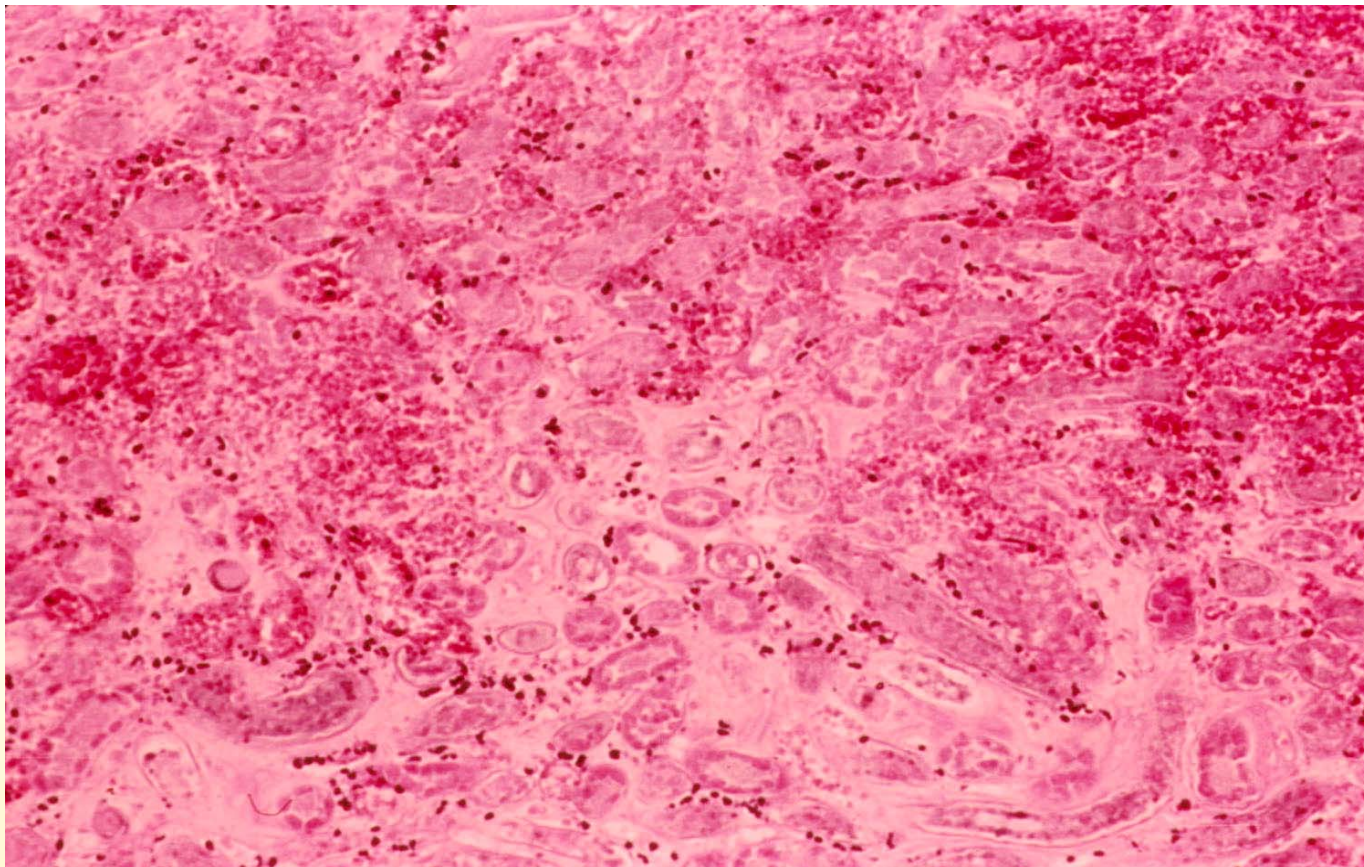
Normal Kidney



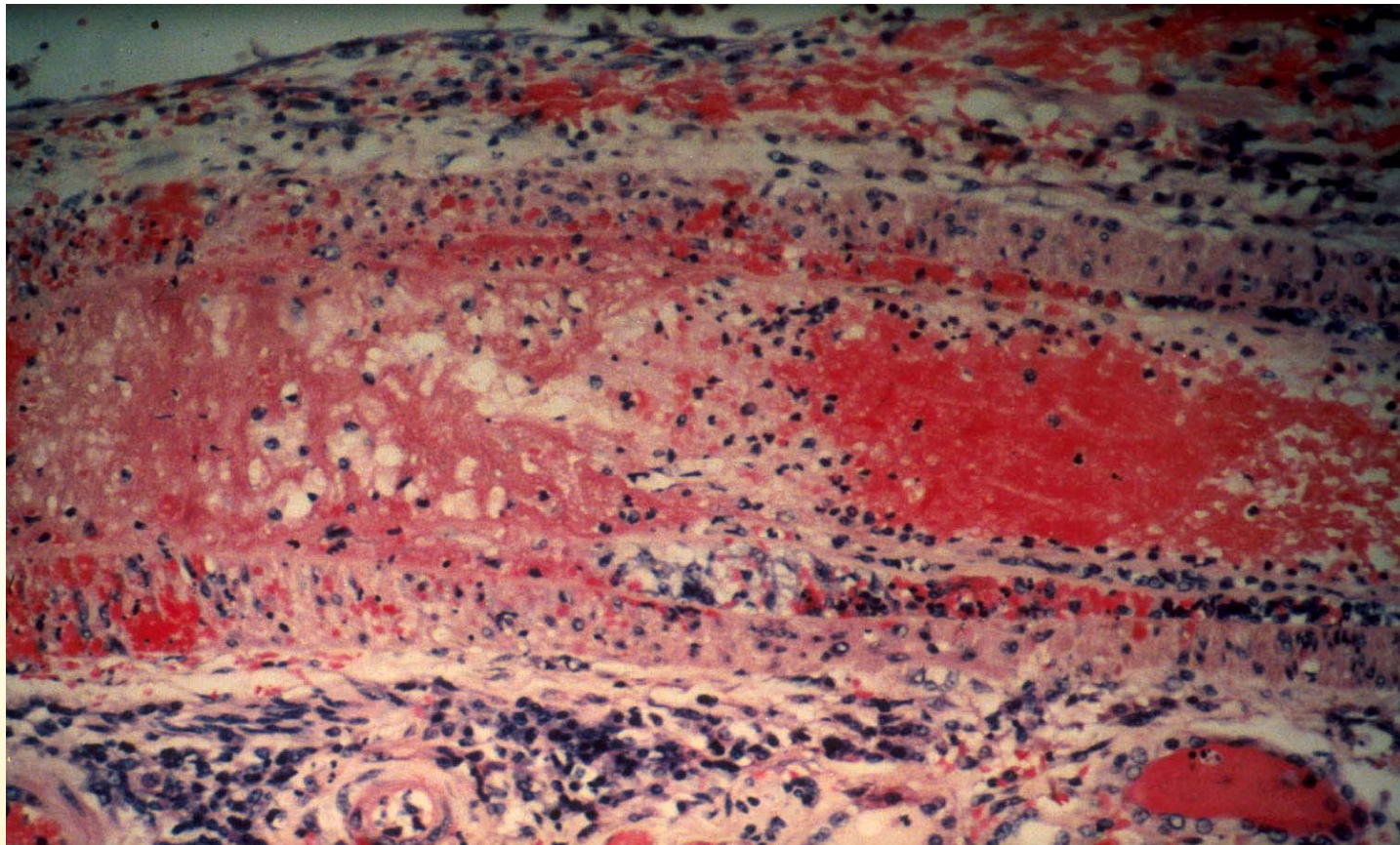
Hyperacute Rejection



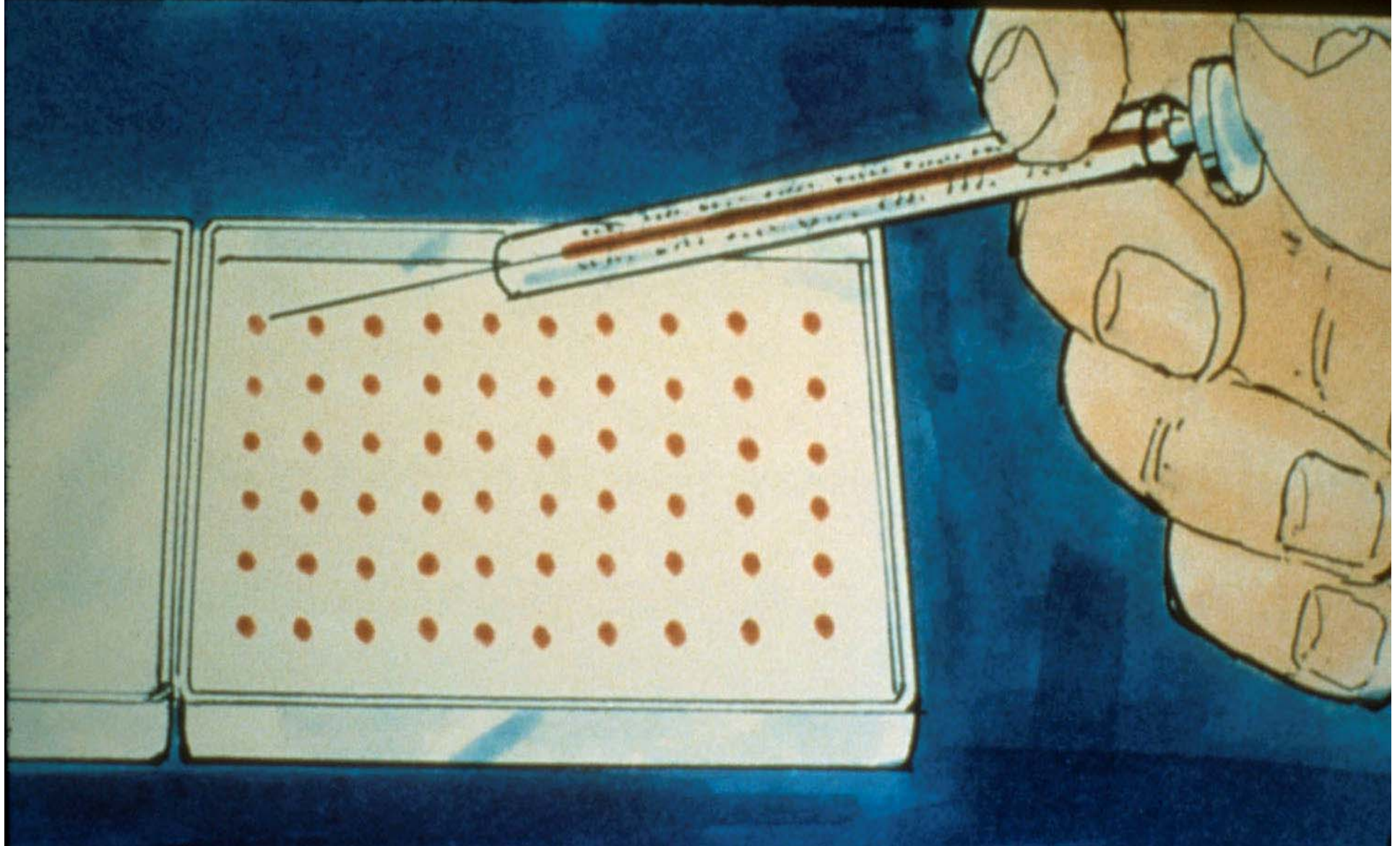
Hyperacute Rejection: hemorrhagic necrosis



Hyperacute Rejection: platelet thrombi

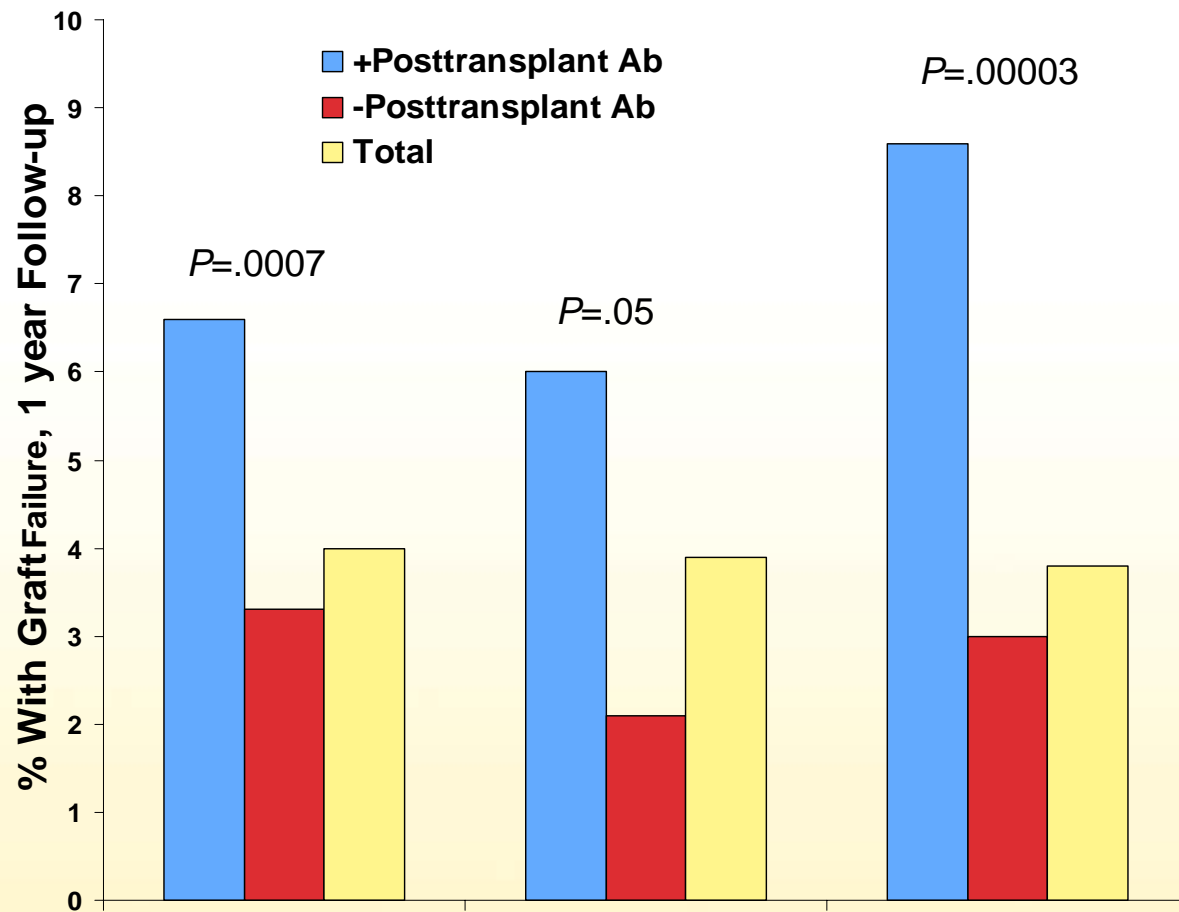


CROSSMATCH

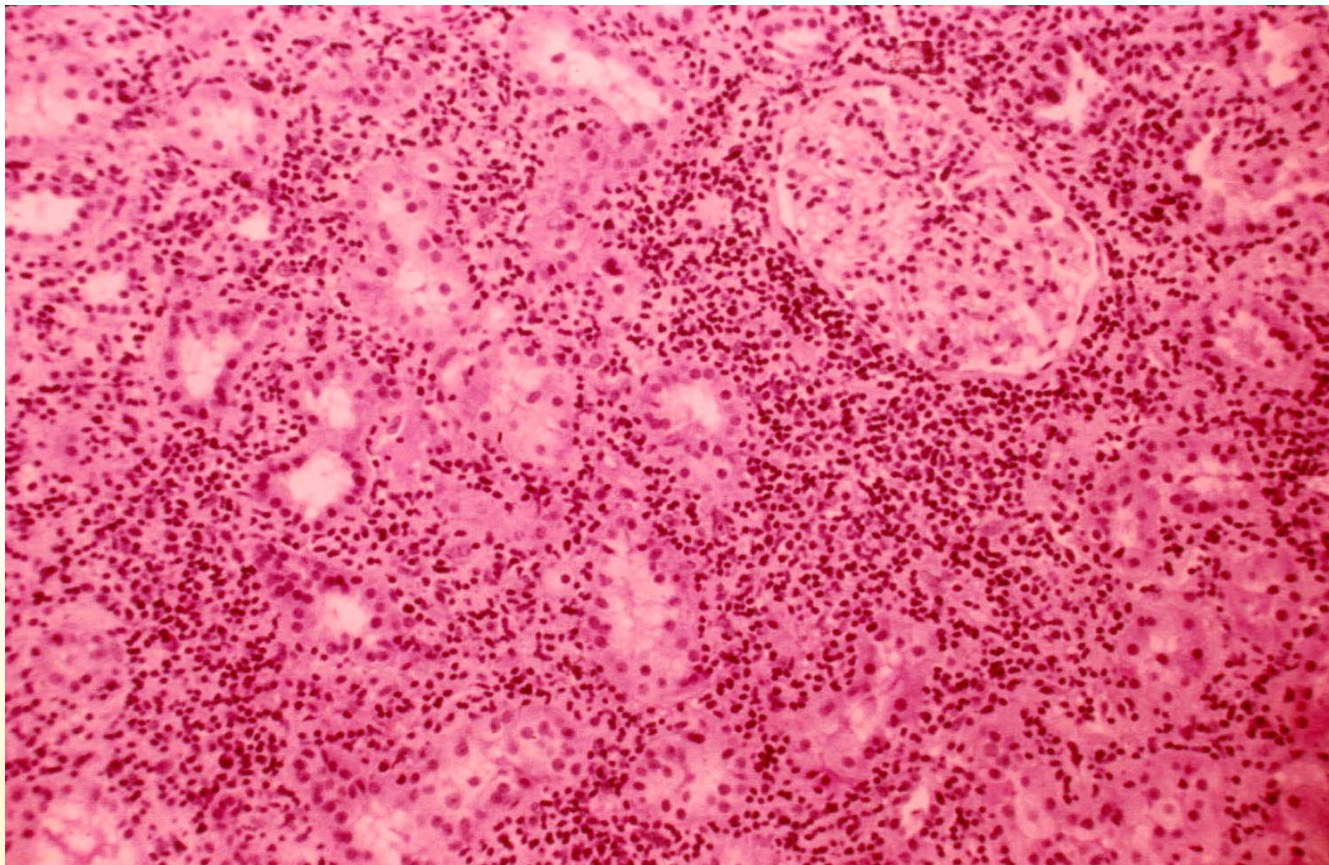


HLA Antibodies Predict Kidney Graft Failure

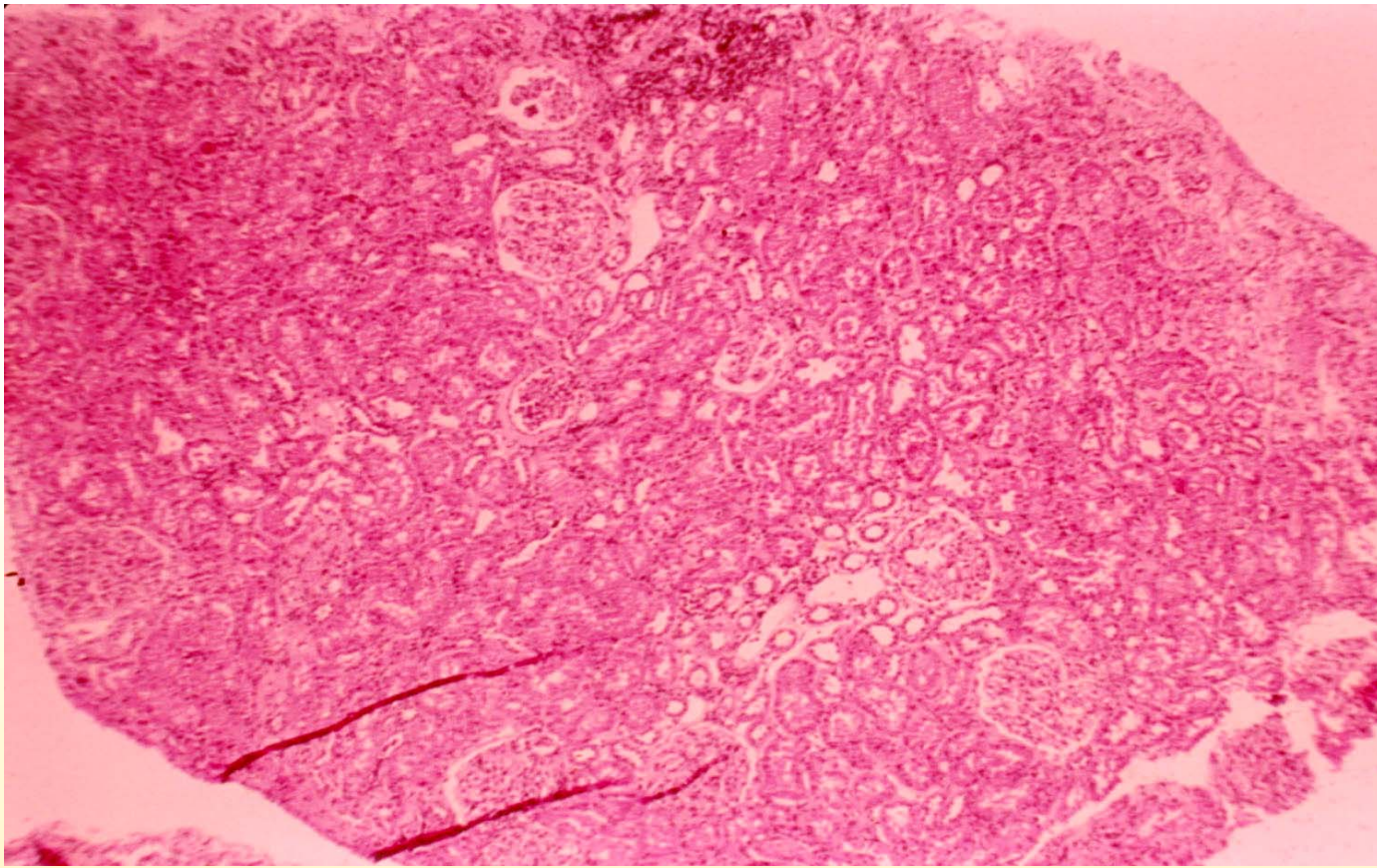
2278 patients in 23 centers



Acute Cellular Rejection



Resolved Acute Rejection: Post Steroids

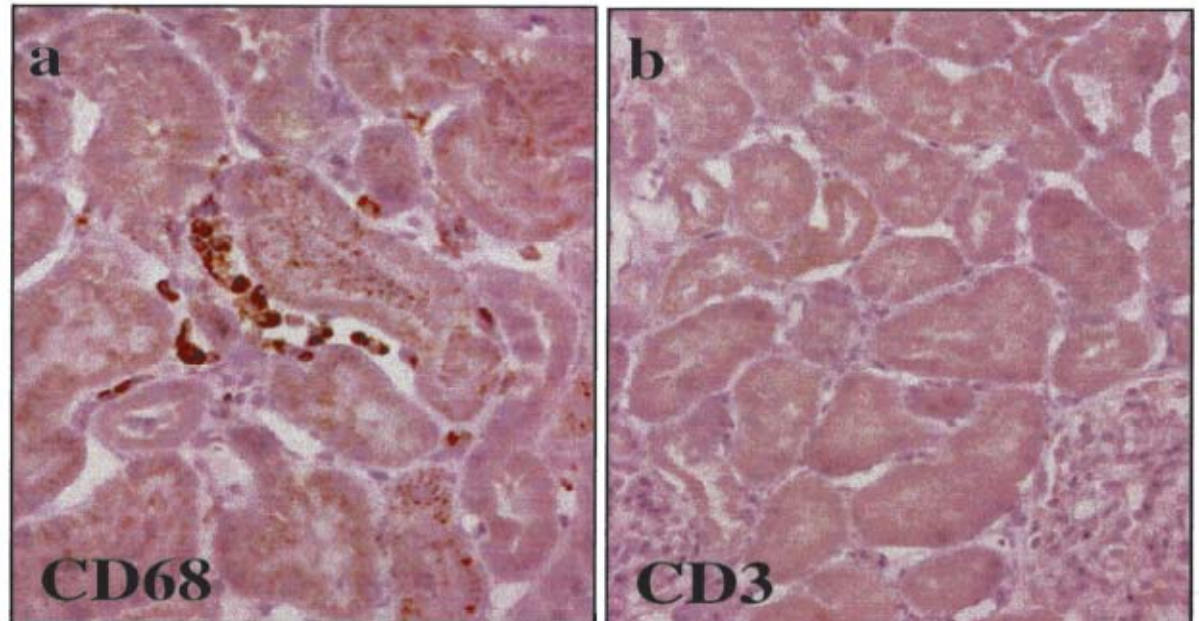


T cell Depletion Alone Does Not Produce Tolerance

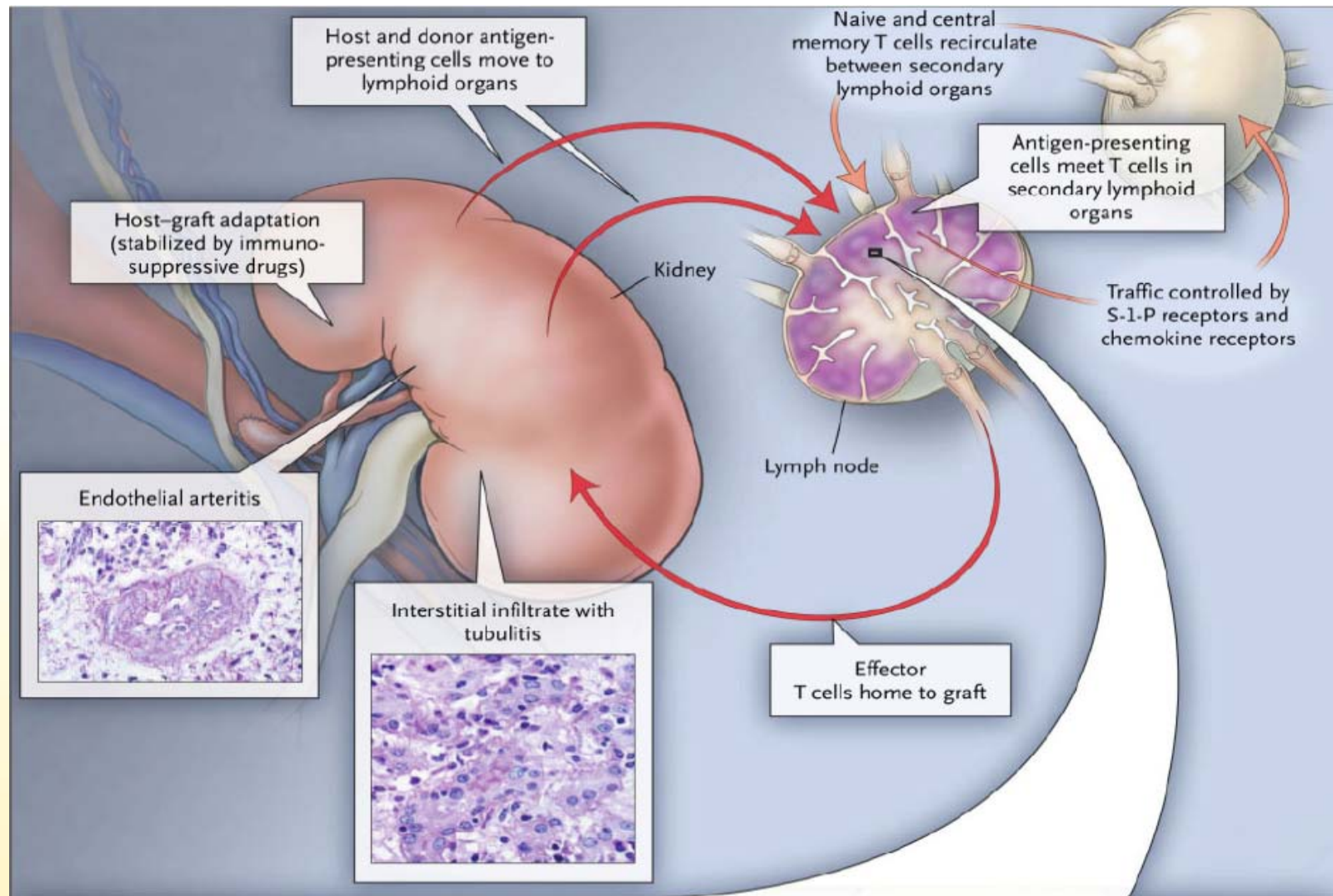


- Seven unsensitized LD recipients: No maintenance therapy
- C-1-H .3mg/kg plus iv MP 250-500mg- 3 doses pretransplant
- All seven with clinical rejection (\uparrow SCr) day 14-28 (4/6 Banff I-II)
- CD3,4,or 8 Pos T cells absent in periphery during these AcR
- Diminished expression of T cell transcripts during AcR

Return of monocytes
predate return of
lymphocytes between
weeks 2-3



The Process of Rejection – T Cell Trafficking



BANFF Criteria: Revised 2005



1. Normal
2. Antibody Mediated Rejection-DSA identified
 1. I. ATN-like; C4d+ minimal inflammation
 2. II. Capillary margination and/or thrombosis, C4d+
 3. III. Arterial C4d+
 4. Chronic active antibody mediated rejection C4d+
3. Borderline changes-suspicious for acute T cell mediated rejection
4. T cell Mediated Rejection
 - Acute (i, t, v)
 - Ia inflammation >25% parenchyma (i2 or i3); moderate tubulitis t2
 - Ib inflammation >25% parenchyma (i2 or i3); severe tubulitis t3
 - IIa cases with intimal arteritis (v1)
 - IIb cases with severe intimal arteritis (v2)
 - III transmural arteritis; fibrinoid changes; necrosis smooth muscle
 - Chronic rejection (cv, cg)
 - arteriopathy-intimal fibrosis with mononuclear glomerulopathy-double contours GBM

BANFF Criteria: Revised 2005



5. Interstitial Fibrosis and Tubular Atrophy (TAIF) without evidence of specific etiology

- *Grade I: mild TAIF < 25% of cortical area*
- *Grade II: moderate TAIF 26-50% of cortical area*
- *Grade III: TAIF >50% of cortical area*
- *May include non-specific vascular and glomerular sclerosis, graded by TAIF*

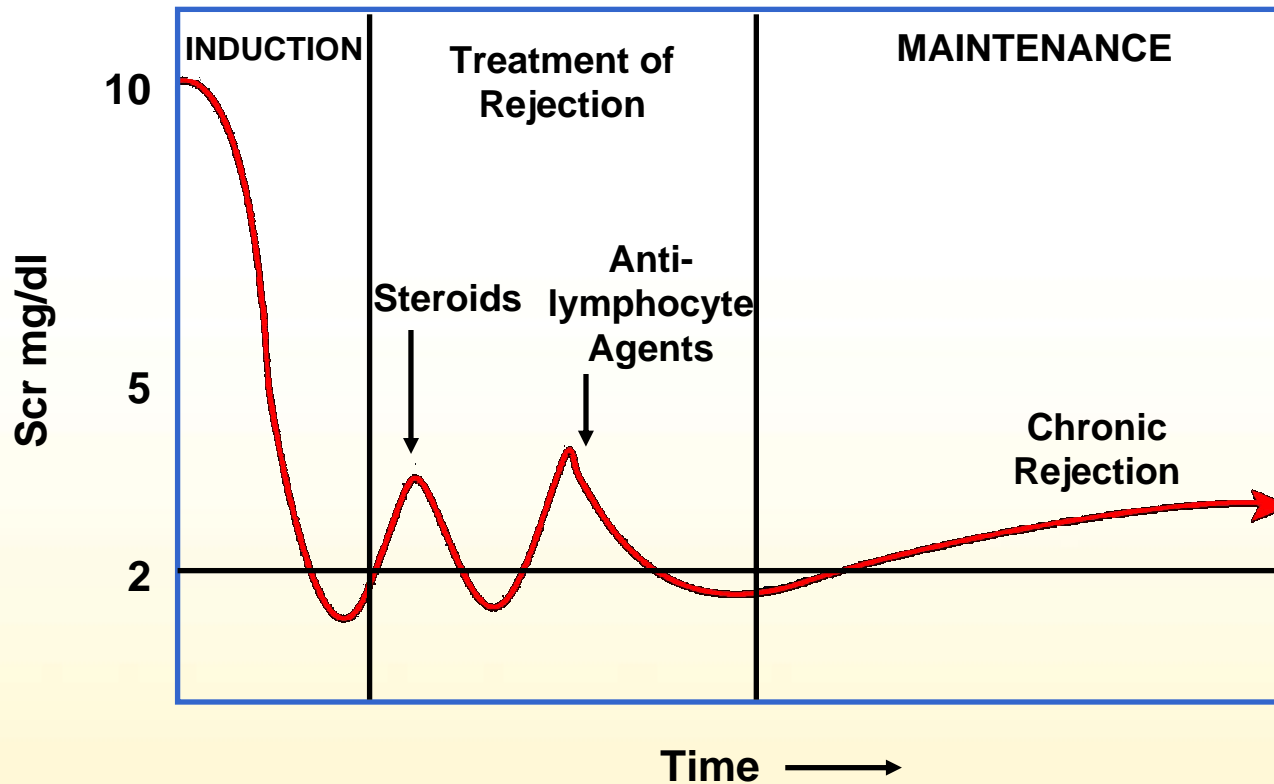
6. Other changes not rejection, acute or chronic

- *drug toxicity: CNI drugs*
- *recurrent disease*
- *viral infection: polyoma, cmv etc.*
- *bacterial infection*
- *severe hypertension*

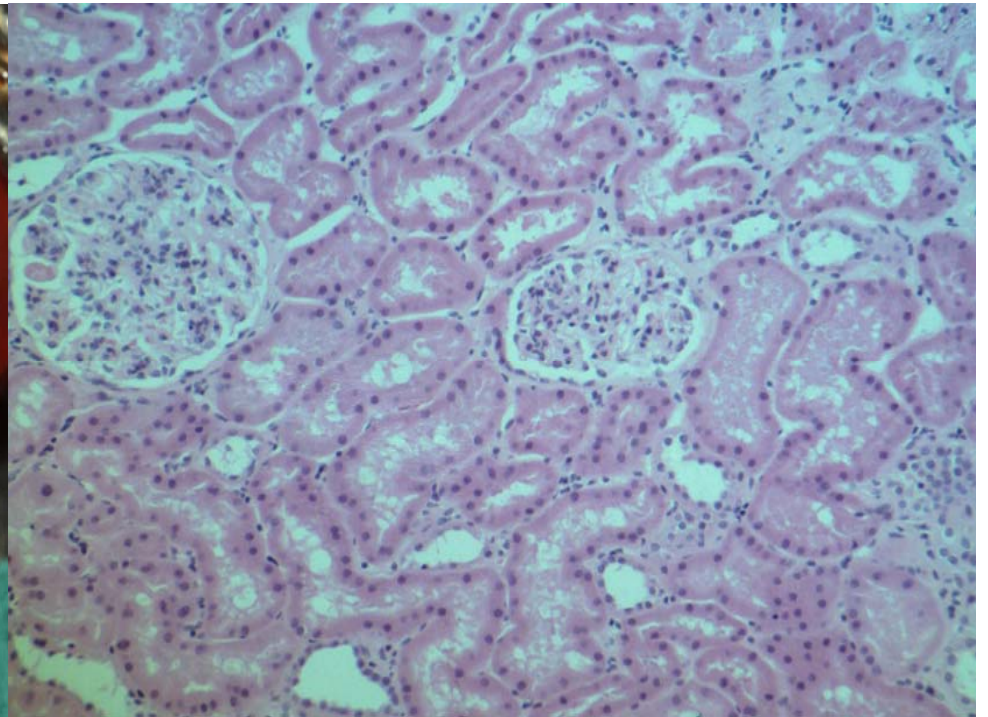
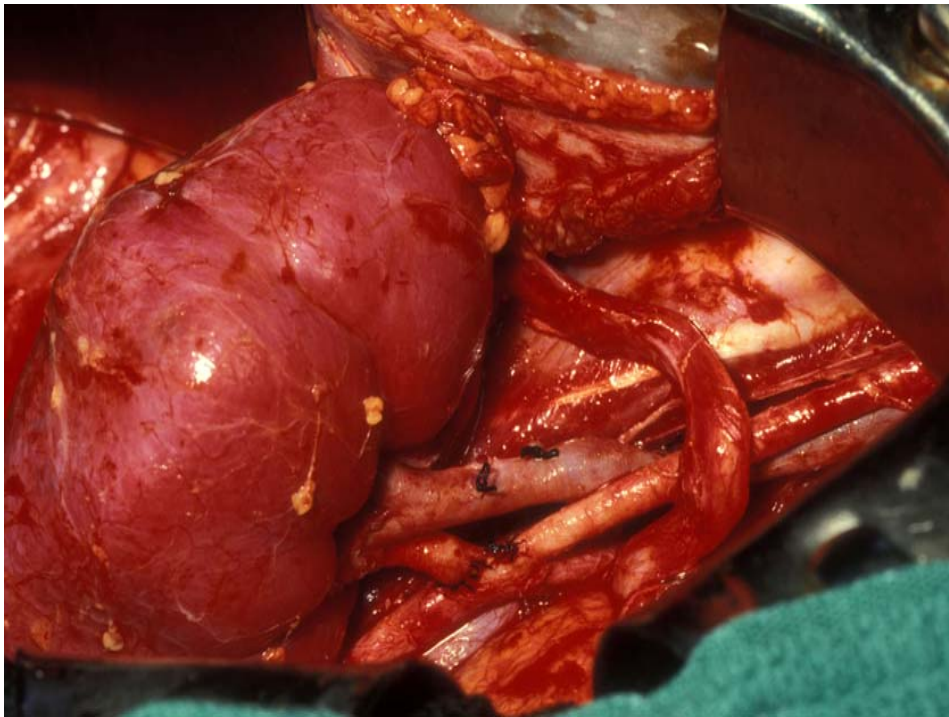


Time Course of Failure/Rejection

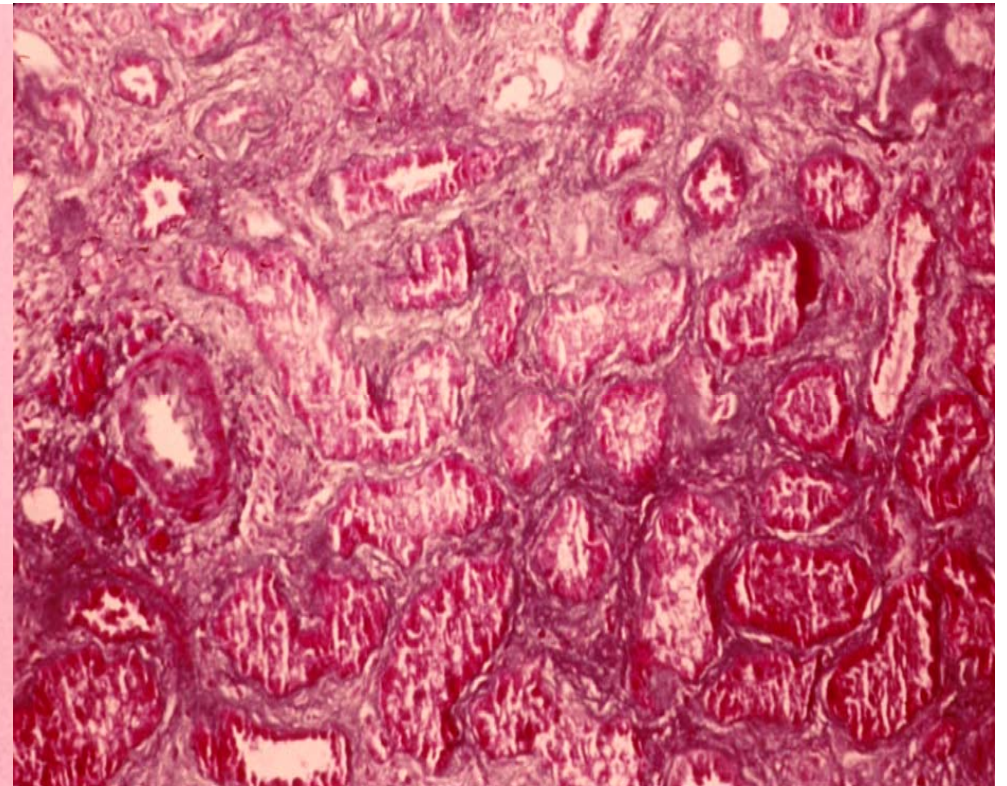
The Fate of Renal Allografts -Immunosuppression



Transplant Kidney: Day 0

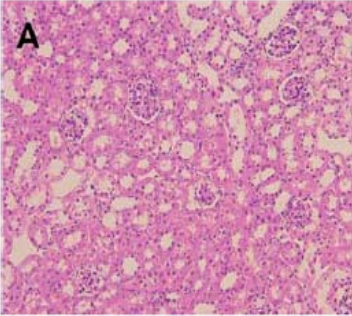
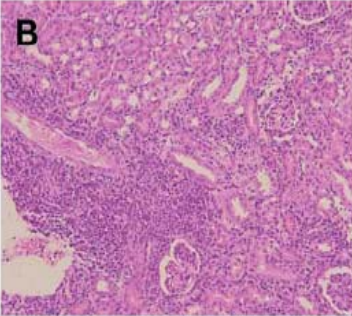
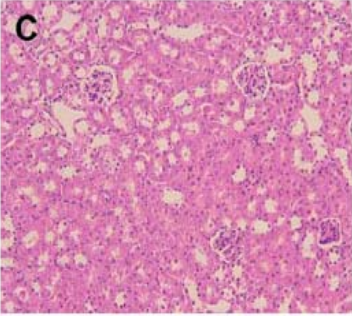
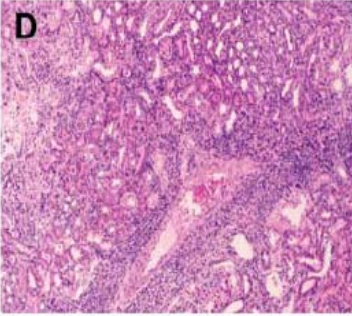
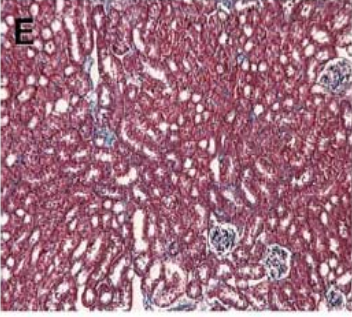
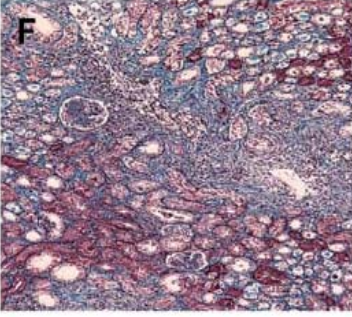


Transplant Kidney: Chronic Allograft Nephropathy



The Progression of Alloimmune Injury



	Isografts	Allografts C57BL and Balb/c	
Week 2			Acute inflammation with edema, vasculitis, and tubulitis
Week 4			Progressive acute inflammation with vasculitis and tubulitis
Week 6			Extensive fibrosis, tubular atrophy, chronic inflammatory cell infiltrates, arteriosclerosis, and glomerulosclerosis

Chronic Immune Injury of Renal Allografts



T-Cell Mediated (Cellular) Rejection

Targets

interstitium
tubular epithelium
arterial intima

Results

fibrosis
atrophy, mesenchymal transition
fibrous intimal thickening

B-Cell Mediated (Humoral) Rejection

Targets

capillary endothelium
(peri-tubular)
glomeruli

Results

complement activation
C4d and PMN margination
double contours

Summary



- Acute and chronic rejection are the consequences of different HLA antigens on the donor and recipient.
 - *the incidence of acute rejection episodes has diminished.*
 - *the incidence of chronic rejection may be increasing.*
- The changes that occur in kidney grafts over time are due to both antigen dependent and antigen independent mechanisms.
- Histologic assessment of kidney grafts is the most accurate way to diagnose acute and/or chronic rejection, and to rule out other causes of renal dysfunction.
- Most rejection episodes are due to both cellular and humoral immune activation; detection of donor specific antibody before or after the transplant correlate with diminished graft outcome.