

# **RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE**

**RICHARD N FINE MD  
PROFESSOR OF PEDIATRICS  
STONY BROOK MEDICINE**

# **RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE**

- **IN 1598 GASPARE TAGLIOCOZZI, AN ITALIAN PHYSICIAN/SURGEON ,WAS ASKED TO REPLACE A NOBLEMAN’S SYPHILITIC NOSE WITH THAT OF A PEASANT. HE DISCARDED THE IDEA OF USING THE FLESH OF ANOTHER WITH THE STATEMENT THAT “ THE SINGULAR CHARACTER OF THE INDIVIDUAL ENTIRELY DISSUADES US FROM ATTEMPTING THIS WORK ON ANOTHER PERSON”**

# **RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE**

- **THIS SINGULAR CHARACTER OF THE INDIVIDUAL WHICH WAS IDENTIFIED AS THE SMALL LYMPHOID CELL BY JAMES MURPHY IN 1912 AS THE PRIMARY CELL INVOLVED IN TISSUE REJECTION STILL DISSUADES US FROM THE ABILITY TO AFFECT LONG-TERM ALLOGRAFT SURVIVAL IN PEDIATRIC SOLID ORGAN TRANSPLANT RECIPIENTS**

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **THE ABILITY TO PRODUCE IMMUNOLOGIC UNRESPONSIVENESS – IMMUNOLOGIC TOLERANCE – WAS FIRST DEMONSTRATED EXPERIMENTALLY BY BILLINGHAM, BRENT & MEDAWAR WHEN THEY SHOWED THAT INNOCULATION OF FETAL MICE OR CHICK EMBRYOS WITH DONOR TISSUE RESULTED IN PERMANENT ACCEPTANCE OF DONOR SKIN ALLOGRAFTS AFTER BIRTH OR HATCHING. THIRD PARTY ALLOGRAFTS WERE REJECTED.**

**NATURE 172:603,  
1953**

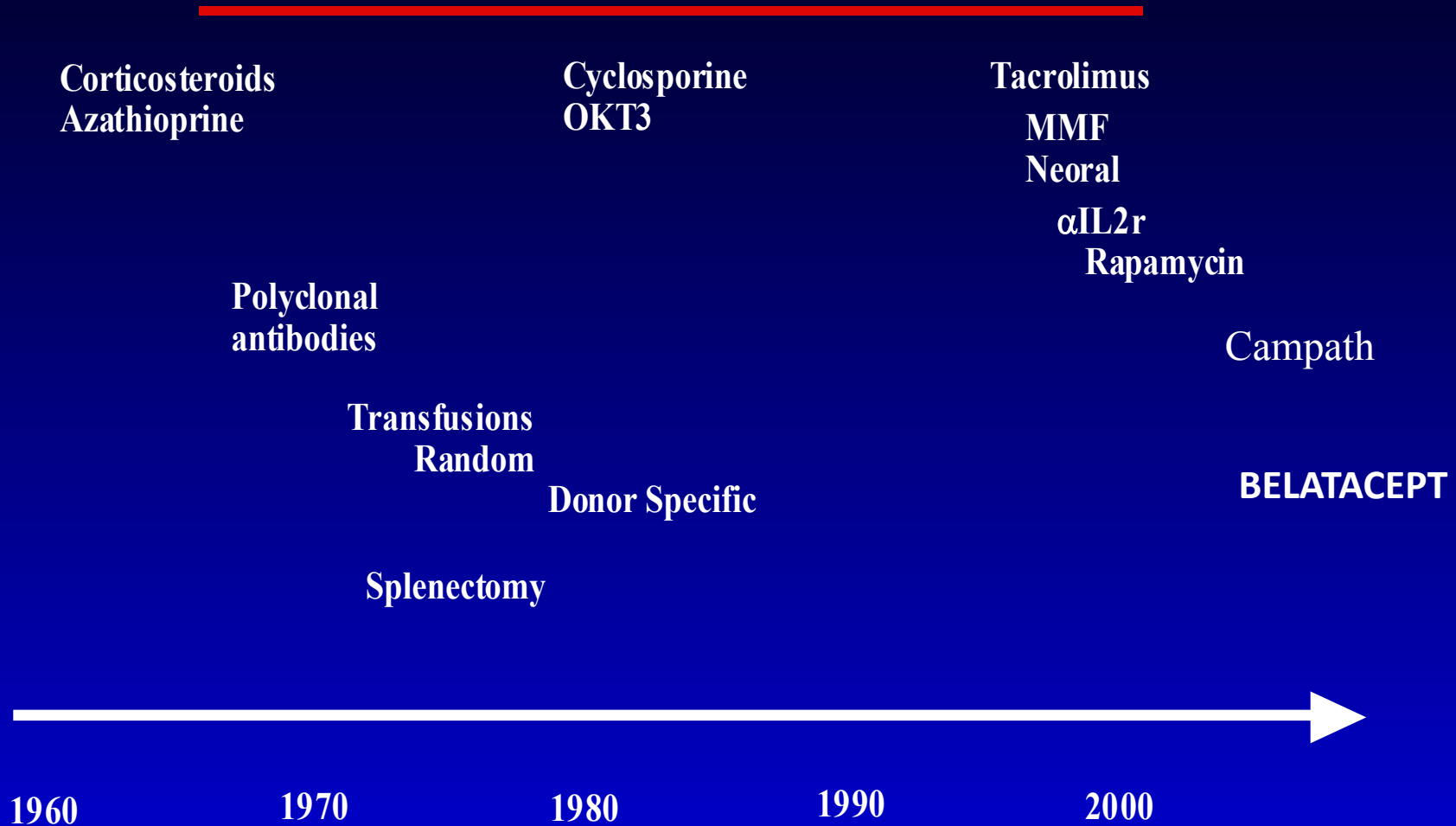
# **RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE**

- **FOR MORE THAN 60 YEARS SINCE THE FIRST SUCCESSFUL TRANSPLANT BETWEEN IDENTICAL TWINS (ISOGRAFT) IN 1954 BY MURRAY AND COLLEAGUES IN BOSTON INTENSE INVESTIGATION HAS BEEN DIRECTED TOWARD DEVELOPING THE METHODOLOGY TO PRODUCE CLINICAL TOLERANCE IN HUMAN SOLID ORGAN TRANSPLANTATION**

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- IN THE ABSENCE OF THE ABILITY TO ACHIEVE IMMUNOLOGIC TOLERANCE, CLINICAL SOLID ORGAN TRANSPLANTATION HAS PROGRESSED DURING THE PAST > 60 YEARS BY SUPPRESSING THE IMMUNE SYSTEM WITH A MYRIAD OF IMMUNOSUPPRESSIVE AGENTS

# Changes in transplant immunosuppression



# **RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE**

- **WHAT WAS THE IMMUNOSUPPRESSIVE REGIMEN INITIALLY UTILIZED IN OUR PEDIATRIC RENAL TRANSPLANT POPULATION?**

**FINE ET AL J PEDIATR 76:347, 1970**



# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **PREDNISONE**: 75mg/m<sup>2</sup> DAILY (MAXIMUM 100mg/day) FOR 2 - 6 WEEKS IN LRD AND 2 – 3 MONTHS IN DD RECIPIENTS WITH TAPERING TO 7.5 – 15mg DAILY @ 1 YEAR
- **AZATHIOPRINE** (IMURAN) 2 – 3 mg/kg/day WITH SERUM CREATININE <2.0mg/dl AND ↓ TO 0.5 – 1.5mg/kg/day WITH REDUCED GRAFT FUNCTION

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **TREATMENT OF REJECTION :**
  - **PREDNISON**: 200 – 300mg/day  
AND REDUCED BY 25 – 50mg/day  
UNTIL MAINTENANCE DOSE OF  
25 – 75mg/day WAS REACHED





**BANNERS**  
LAMINATION & MOUNTING

1230

Printing D

PASSPORT  
PHOTOS

SHOP LA



**Kidney Transplant – 1967**

**Splenectomy – 1978**

**Partial left Orchiectomy due to trauma – 1990's**

**Basil/Squamous cell carcinoma (left neck) 2003**

**Melanoma (upper left arm) – 2006**

**Squamous cell in-situ (right chest) – 2006**

**Escherichia Coli bacteremia – 2006**

**Squamous cell/pre/part Aurical Partoid 7-2010**

**Radiation therapy due to Squamous cell carcinoma Aurical Partoid Oct/Dec-2010**

**Radiation therapy due to Squamous cell carcinoma Left thumb Dec 2012**

**Radiation therapy on Right hand above wrist Dec 2012**

**Osteomyelitis L3-L4 – July/August 2014**

**Radiation therapy due to Squamous cell on Right Finger March-April 2015**

**Keratosis' and squamous cell skin issues continuing**

**PREDNISON 5MG TABLETS 1 per day**

**RAPAMUNE 1MG TABLETS .5 per day**

**OMEGA-3 Salmon Oil 1 gm capsule (a.m. and p.m.)**

**ATORVASTATIN 20 MG TABLET generic for LIPITOR 1 per day (taken at bedtime)**

**LEVOTHYROXINE 50 MCG tablet 1 tablet per day**

**ENALAPRIL MALEATE GENERIC FOR VASOTEC 20 MG TABLET 1 Tablet daily**

**SODIUM BICARB 650 mg one tablet twice a day**

**CEPHALEXIN GENERIC FOR KEFLEX 500 MG CAPSULE as needed**

**VITAMIN D 1000 UNIT TAB**

**Sometimes VITAMIN C**

# **RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE**

- **WHAT WERE THE PREVAILING OPINIONS REGARDING THE THERAPUETIC USE OF RENAL TRANSPLANTATION TO PROLONG THE LIVES OF CHILDREN WITH END-STAGE RENAL DISEASE IN THE 1960'S AND EARLY 1970'S?**



# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **CONRAD M RILEY MD (J PEDIATR 65:797,1964)**  
COMMENTING ON THE EXPERIENCE @ THE  
UNIVERSITY OF COLORADO PROFFERED THAT: “IF  
ALL GOES WELL IN THE LONG RUN , THE KIDNEY  
MAY BE HOUSED IN A HEALTHY DWARF”; “ALL THE  
DISCOMFORT FACTORS MAKE THE PICTURE  
SOUND VERY BLEAK”; “FROM THE POINT OF VIEW  
OF THE CHILD OR EVEN ADOLESCENT THESE  
NEGATIVE FACTORS COULD WELL OUTWEIGH A  
SMALL EXTENSION OF LIFE”

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- JOHN B REINHART (**J PEDIATR 77:505, 1970**) FROM PITTSBURGH CHILDREN'S HOSPITAL INDICATED THAT "WHEN THE COST TO THE CHILD IN TERMS OF PHYSICAL AND EMOTIONAL DISCOMFORT IS CONSIDERED, I SERIOUSLY DOUBT THE VALUE OF CHRONIC DIALYSIS OR RENAL TRANSPLANTATION FOR THESE PATIENTS"; "GOD GRANT US SERENITY TO ACCEPT THE THINGS WE CANNOT CHANGE, THE COURAGE TO CHANGE THE THINGS WE CAN, AND THE WISDOM TO KNOW THE DIFFERENCE" THE DOCTOR'S DILEMMA

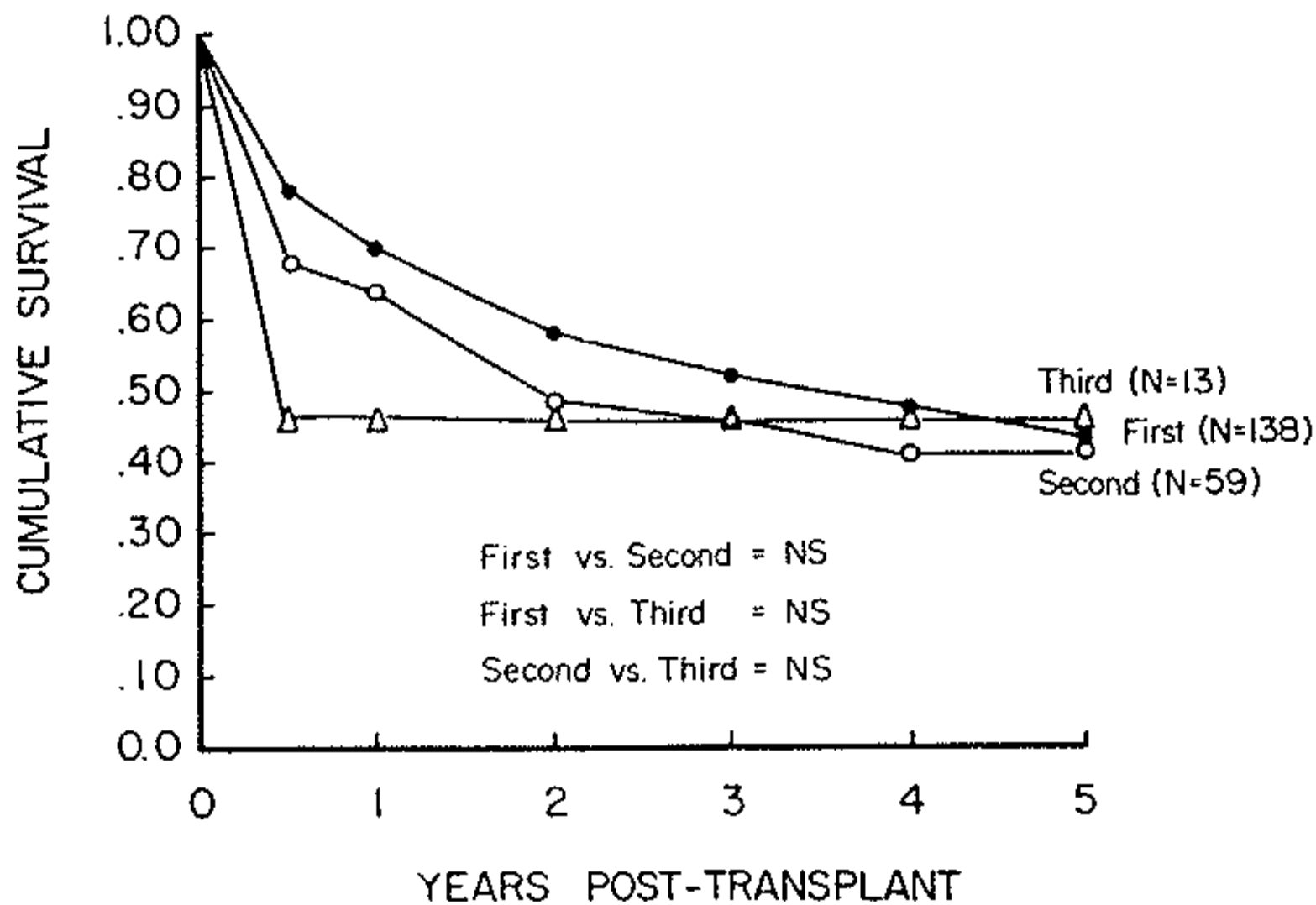
# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- IN RESPONSE TO DR REINHART, BARBARA KORSCH AND I COUNTERED IN THE ACCOMPANYING EDITORIAL COMMENT WITH A QUOTE FROM HAMLET: “DISEASES DESPERATE GROWN, BY DESPERATE APPLIANCE ARE RELIEV’D OR NOT AT ALL”

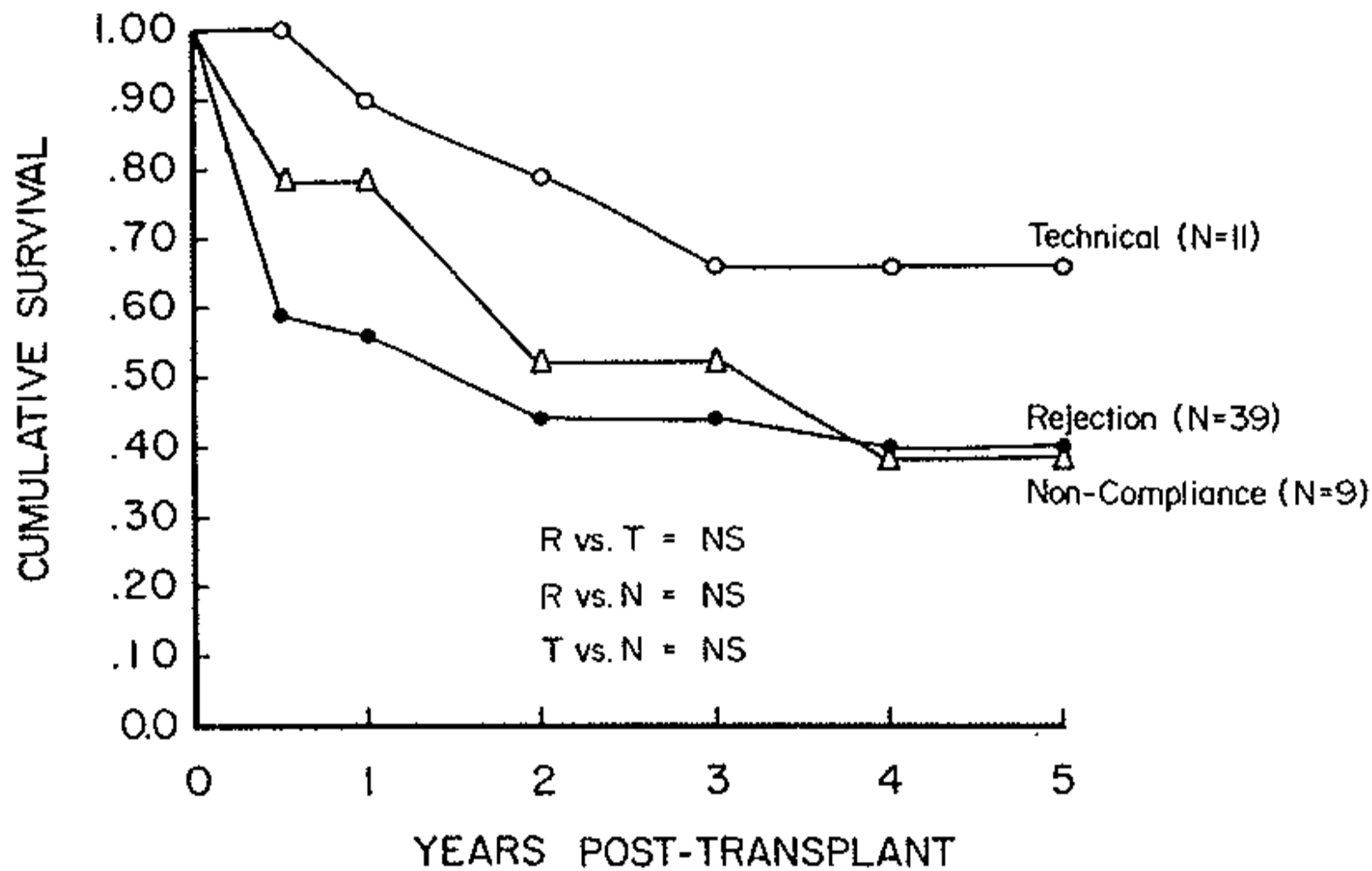
# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- WHAT WERE THE INITIAL 5 YEAR GRAFT SURVIVAL RATES FOR PEDIATRIC RECIPIENTS TRANSPLANTED BETWEEN 1967 AND 1978 UTILIZING ONLY AZATHIOPRINE AND CORTICOSTEROIDS AS THE PRIMARY (ATG INTRODUCED IN 1976) IMMUNOSUPPRESSIVE AGENTS?

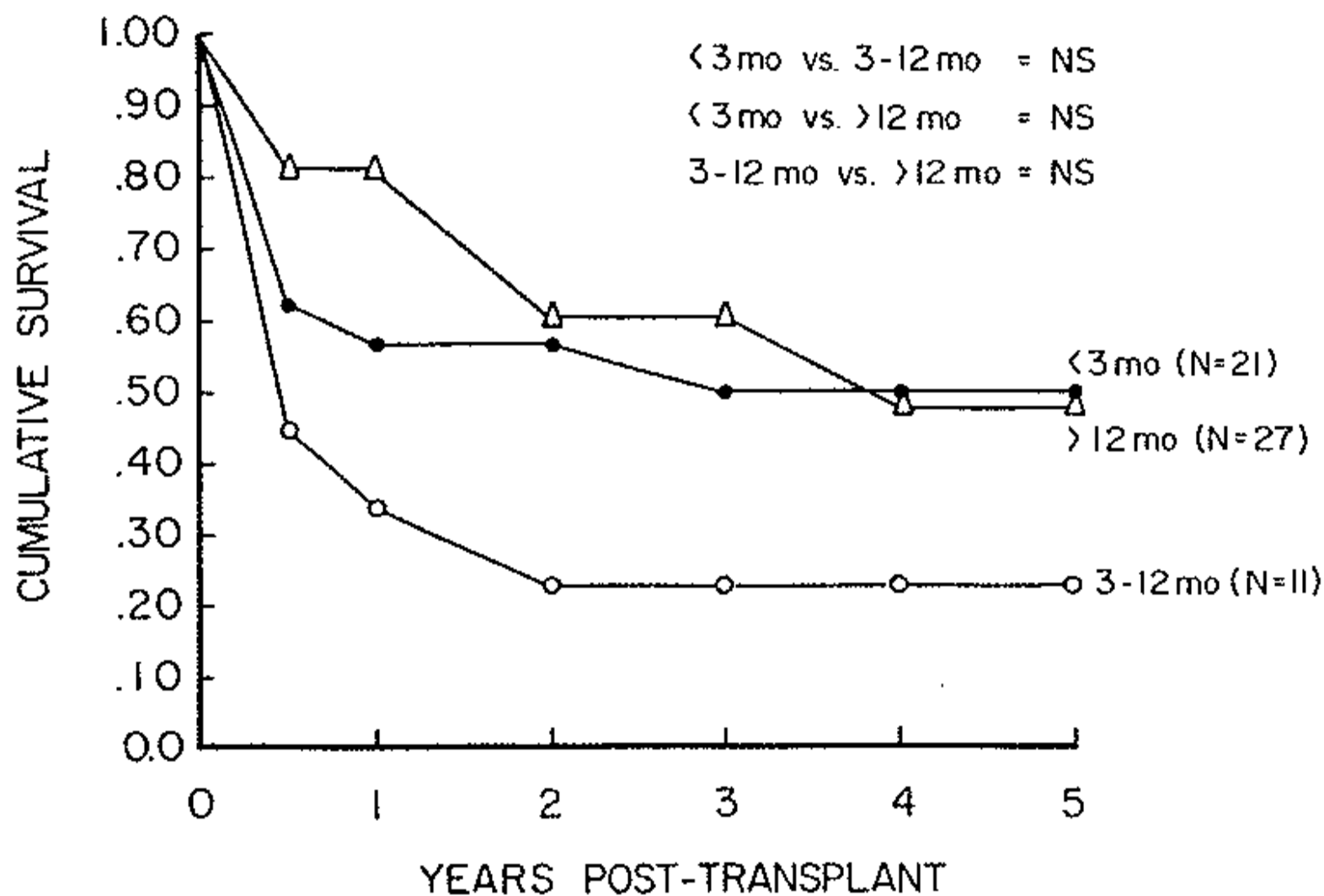
FINE ET AL J PEDIATR 95:244,1979



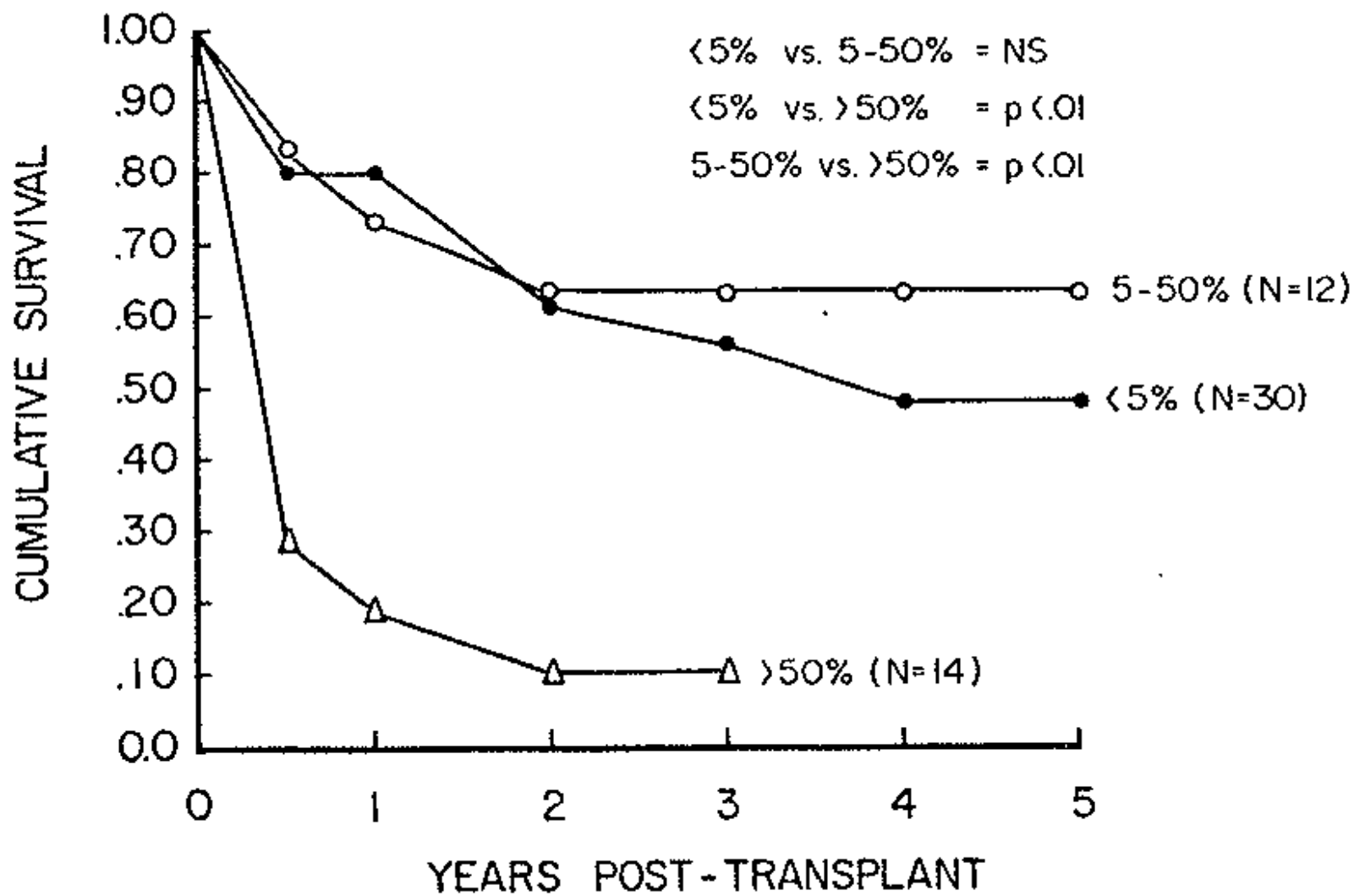
**Fig. 1.** Actuarial cadaver allograft survival (February, 1968 to October, 1978).



**Fig. 2.** Survival of second allograft related to etiology of initial allograft failure.



**Fig. 3.** Survival of second allograft related to duration of initial allograft survival.



**Fig. 4.** Presensitization of second allograft.



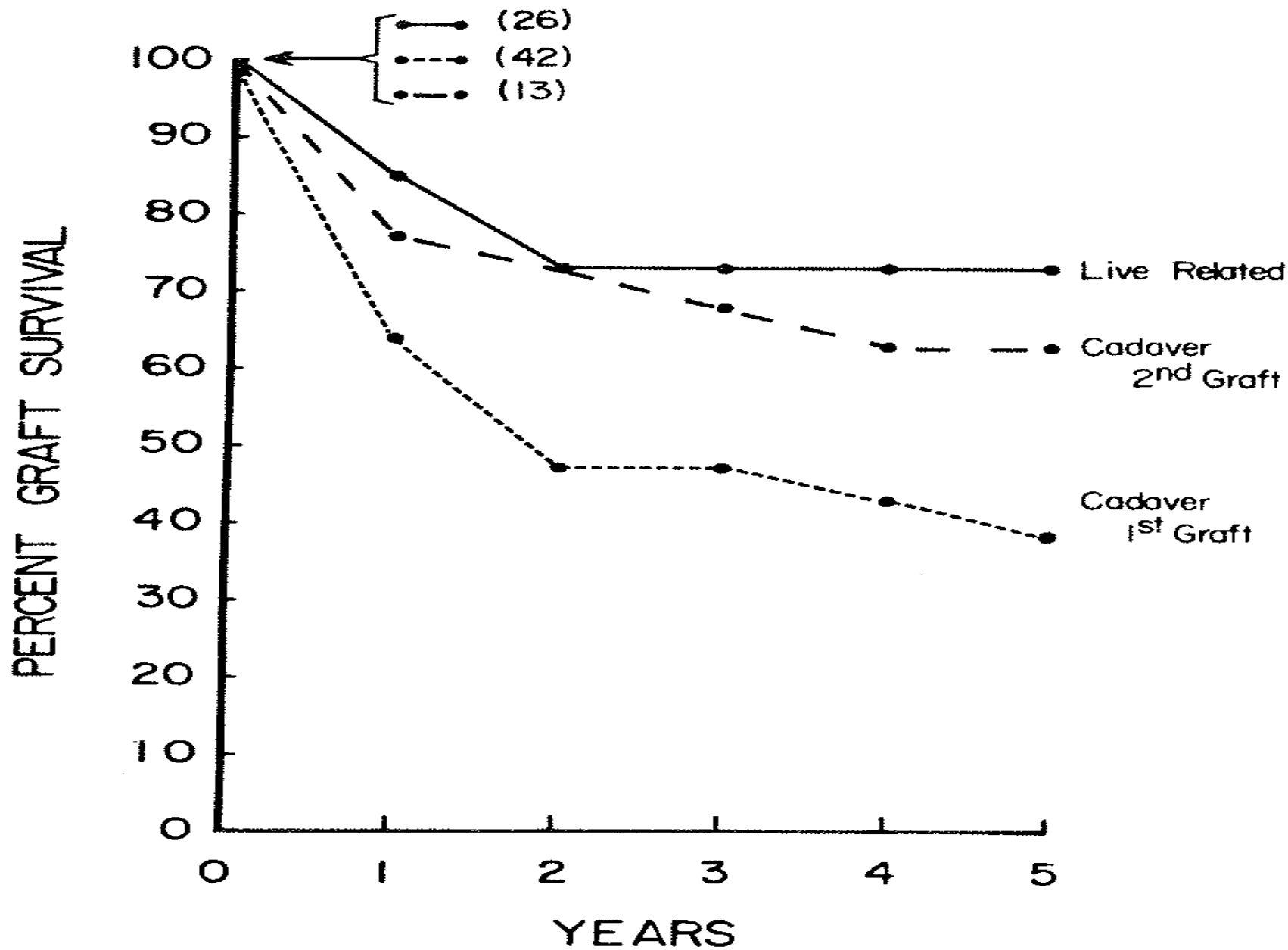


FIG. 2. Actual graft survival (years).

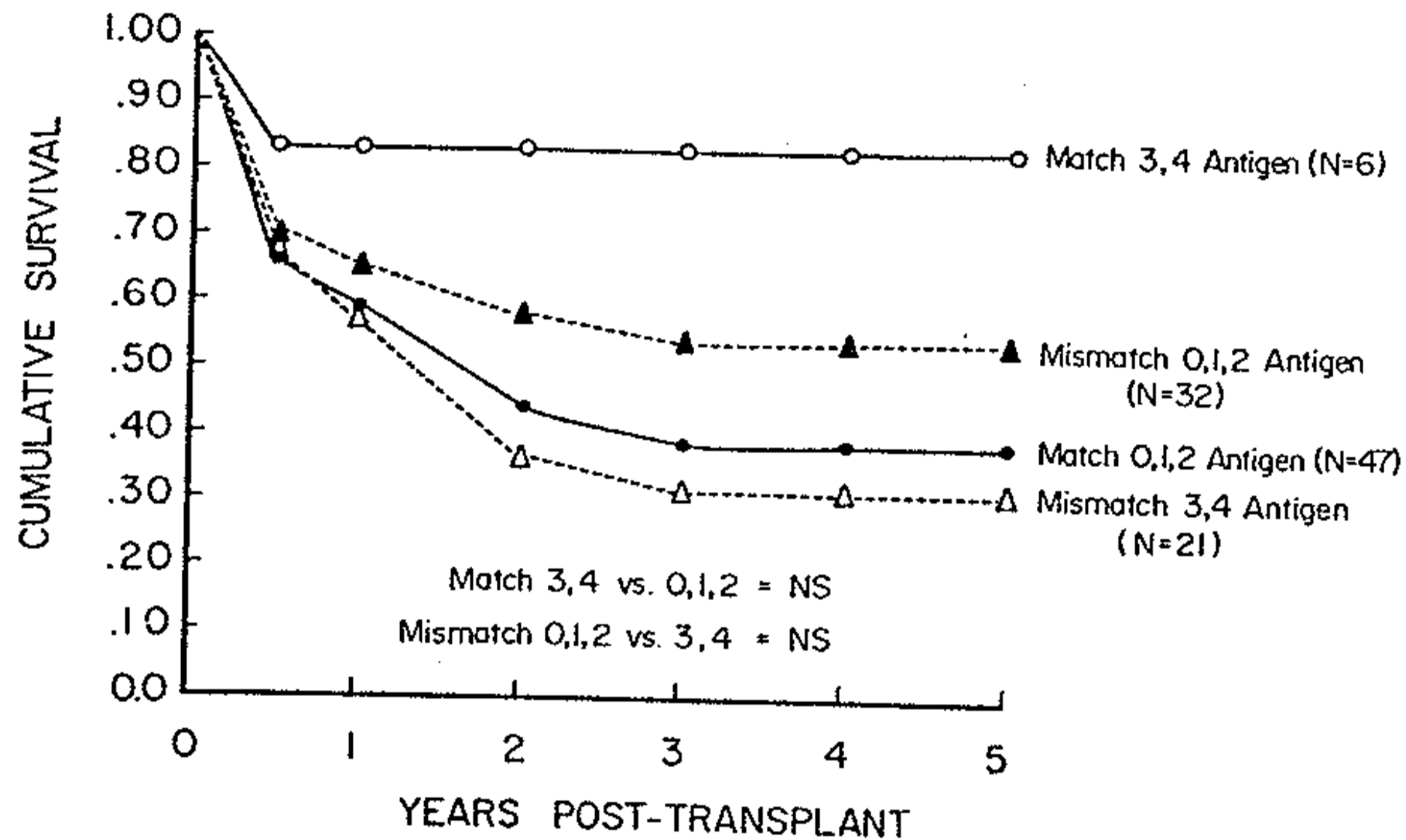
# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

Cohort Group	GRAFT SURVIVAL RATES					
	LIVING DONOR			DECEASED DONOR		
	1yr	3yr	5yr	1yr	3yr	5yr
1987-1991	90.3	82.4	76.3	76.4	65.3	56.9
1992-1996	92.1	87.0	81.6	87.0	77.9	70.9
1997-2001	95.4	91.4	86.3	93.1	84.5	78.3
2002-2006	96.3	92.0	86.4	94.4	84.1	79.2
2007-2013	96.4	93.4	--	95.8	90.4	--

**DD APPROXIMATING LD SURVIVAL AT 1, 3 YEARS FOR THE  
MOST RECENT COHORT**

# **RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE**

- **WHAT WAS THE IMPACT OF HLA-ANTIGEN HISTOCOMPATIBILITY MATCHING ON GRAFT OUTCOME IN THE LATE 1960'S AND EARLY 1970'S?**



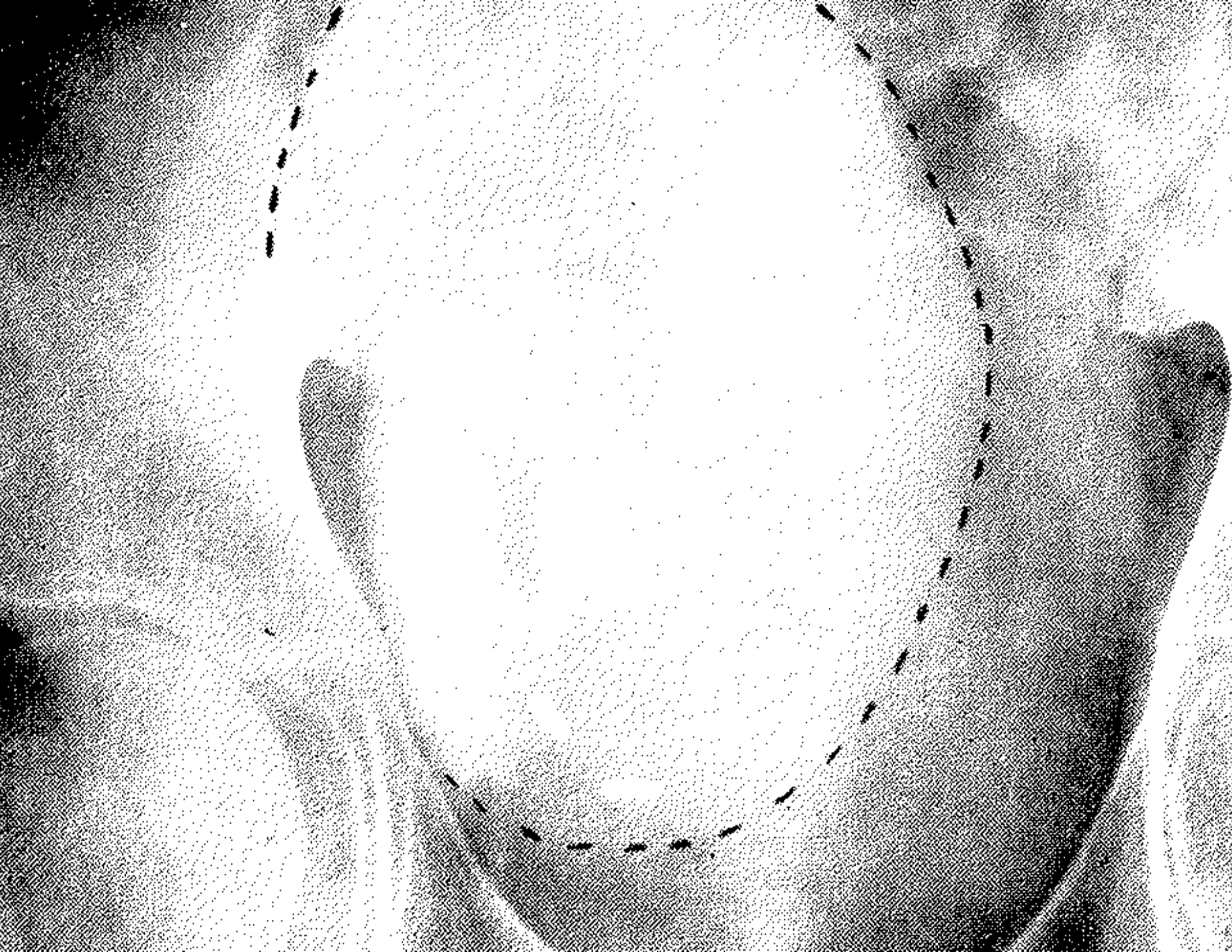
**Fig. 5.** HLA A&B antigen histocompatibility.

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- SHOULD YOU USE PEDIATRIC DD KIDNEYS FOR PEDIATRIC RECIPIENTS?
- 4 RECIPIENTS AGED 12 – 17 YEARS RECEIVED A SINGLE KIDNEY FROM DONORS AGED 2 – 5 YEARS OF AGE (ONLY 2 PREVIOUS REPORTS @ THAT TIME USING PEDIATRIC DD FOR PRIMARILY ADULT RECIPIENTS)
- ONE GRAFT LOST @ 2 MONTHS CONSEQUENT TO ACUTE REJECTION AND 3 WERE FUNCTIONING @ 7 - 9 MONTHS

**FINE ET AL JAMA 210:477,1969**



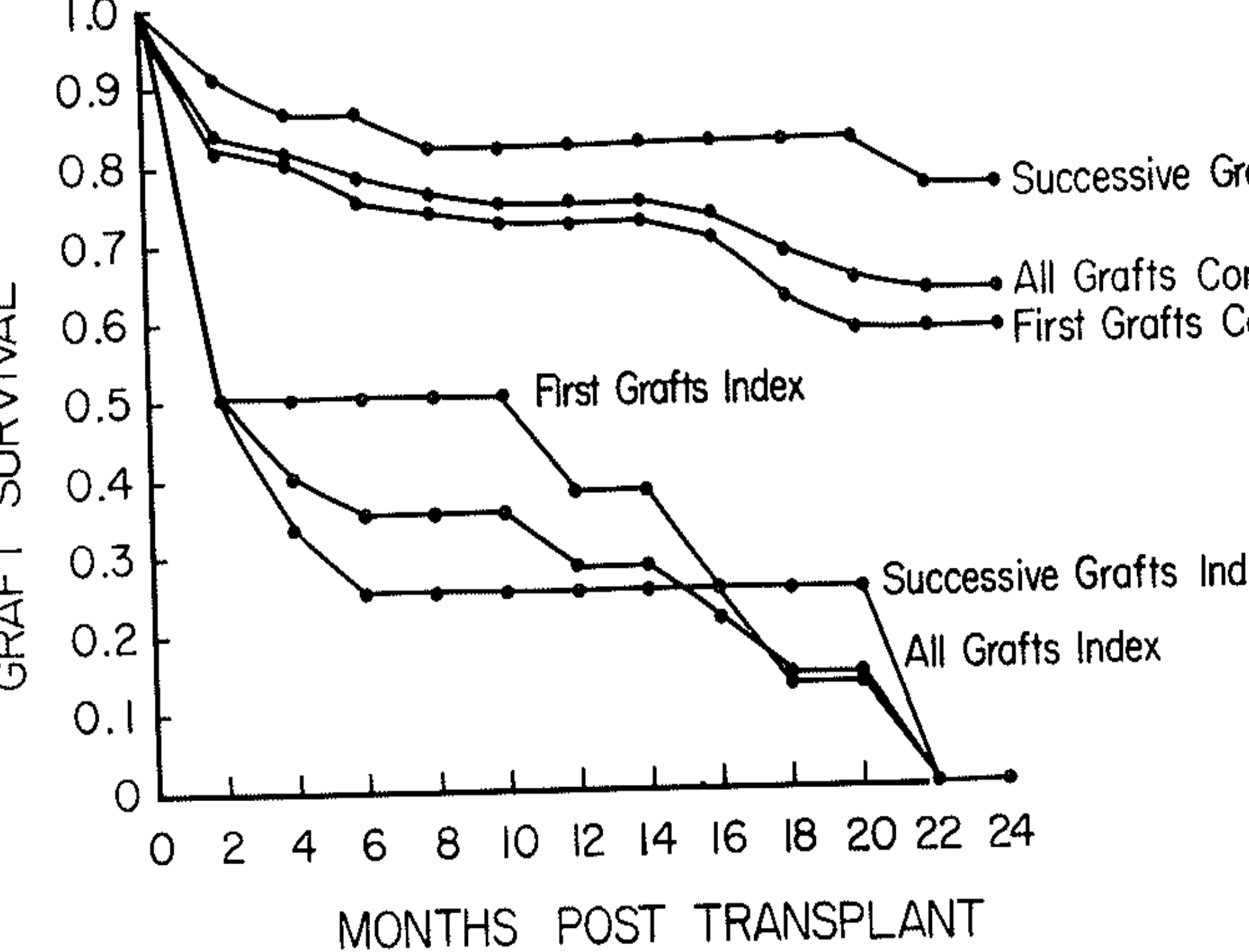


# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- SEIZURES DISORDERS WERE FREQUENT IN PEDIATRIC RENAL ALLOGRAFT RECIPIENTS – 11/75 (15%) DD RECIPIENTS ('68 – '75)
- PHENOBARBITAL AND DIPHENYLHYDANTOIN INDUCED LIVER ENZYMES THAT ACCELERATED THE METABOLISM OF CORTICOSTEROIDS
- ALLOGRAFT SURVIVAL RATES OF RECIPIENTS RECEIVING ANTICONVULSANTS WAS SIGNIFICANTLY REDUCED

WASSNER ET AL J PEDIATR: 88,134, 1976





# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **CLINICAL MANIFESTATIONS OF REJECTION:**
  - **ACUTE:**
    - ❖ MILD: ↑ BUN/CREATININE; PROTEINURIA
    - ❖ MODERATE: FEVER, ANOREXIA, HYPERTENSION AND GRAFT TENDERNESS
    - ❖ SEVERE: REINSTITUTION OF HEMODIALYSIS
  - **CHRONIC:**
    - ❖ ↑ SERUM CREATININE >2.0mg/dl @ >12 MONTHS POST-TRANSPLANT
    - ❖ PROTEINURIA >2.0 gm/24 HOURS

# **RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE**

- **WHAT WERE THE SIGNIFICANT UNANTICIPATED COMPLICATIONS ENCOUNTERED DURING OUR INITIAL EXPERIENCE WITH RENAL TRANSPLANTATION IN CHILDREN?**

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **CYTOMEGALOVIRUS INFECTION**
  - 21 RECIPIENTS BETWEEN 2/67 AND 11/69
  - CMV CULTURED FROM URINE OF 8 AND BLOOD OF 2
  - CLINICAL MANIFESTATIONS WERE PRIMARY CRYPTOGENIC FEVER, ANICTERIC HEPATITIS AND TRANSPLANT LUNG
  - ASSOCIATED WITH ACUTE REJECTION ESPECIALLY WHEN IMMUNOSUPPRESSION ↓

FINE ET AL AMER J DIS CHILD 120:197, 1970

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **HEPATIC DYSFUNCTION**

- 63 RECIPIENTS BETWEEN 2/67 AND 9/71
- 9/63(14%) MANIFESTED HEPATIC DYSFUNCTION (ELEVATED BILIRUBIN AND LIVER ENZYMES)
- 8/9 ATTRIBUTED TO AZATHIOPRINE TOXICITY AND CMV IN 1/9
- 7/8 REMITTED WITH ADJUSTMENT IN THE AZATHIOPRINE DOSAGE AND 1/9 ATTRIBUTED TO CMV REMITTED SPONTANEOUSLY

MALEKZADEH ET AL J PEDIATR 81:279, 1972

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **HYPERTENSION (5 GROUPS DELINEATED):**
  - 77 RECIPIENTS BETWEEN 2/67 AND 11/72
  - GROUP 1: IMMEDIATE POST-TRANSPLANT (<3 MONTHS) ATTRIBUTABLE TO HIGH DOSE CORTICOSTEROIDS AND/OR SALT AND WATER RETENTION
  - GROUP 2 : ASSOCIATED WITH ACUTE REJECTION
  - GROUP 3 : ASSOCIATED WITH CHRONIC REJECTION

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- GROUP 4: ASSOCIATED WITH RENAL ARTERY STENOSIS (RAS)
- GROUP 5: HYPERTENSION THAT DEVELOPS AFTER THE FIRST POST-TX MONTH AND PERSISTED FOR >6 MONTHS WITHOUT EVIDENCE OF DECREASED GRAFT FUNCTION

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- PLASMA RENIN ACTIVITY INCREASED IN 4 GROUP 4 PATIENTS AND 3 GROUP 5 PATIENTS
- ANGIOGRAPHY REVEALED RAS IN 4 GROUP 4 PATIENTS AND AN INTRARENAL LESION IN ALL GROUP 5 PATIENTS
- SURGICAL CORRECTION WAS SUCCESSFUL IN 2/4 GROUP 4 PATIENTS (2 GRAFTS WERE LOST) AND ANTIHYPERTENSIVE TREATMENT WAS SUCCESSFUL IN THE 3 GROUP 5 PATIENTS

MALEKSADEH ET AL J PEDIATR 86:370, 1975



# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **RECOMMENDATION**: RENAL ANGIOGRAPHY SHOULD BE PERFORMED AND PRA DETERMINATIONS OBTAINED IN ANY PEDIATRIC ALLOGRAFT RECIPIENT WHO EITHER DEVELOPS DE NOVO HYPERTENSION AFTER THE FIRST POST-Tx MONTH OR HAS PERSISTENT HYPERTENSION FOR > 6MONTHS POST-Tx

**MALEKZADAH ET AL J PEDIATR 86:370,1975**

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **ASEPTIC NECROSIS**

- 171 RECIPIENTS BETWEEN 2/67 AND 8/77
- 11/171(6%) DEVELOPED ASEPTIC NECROSIS
- PAIN PRECEDED X-RAY CONFIRMATION BY AS LONG AS 7 MONTHS
- INITIAL SYMPTOMS OCCURRED FROM 2 MONTHS TO 4 YEARS POST-TRANSPLANT
- 3/5 WITH DESTRUCTION OF THE FEMORAL HEAD REQUIRED HIP REPLACEMENT
- THERE WAS NO ASSOCIATION WITH TOTAL STEROID DOSE DURING FIRST POST-TRANSPLANT YEAR

UITTENBOGAART ET AL AM J DIS CHILD 132:765, 1978

# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

- **NON-COMPLIANCE(ADHERENCE)(NC)**
  - 14 (12 FEMALE/2 MALE AND 13 ADOLESCENTS) OF 80 (17.5%) WELL DOCUMENTED PATIENTS TRANSPLANTED OVER A 10 YEAR PERIOD HAD NC CONFIRMED BY THE PSYCHOSOCIAL STAFF WHICH WAS SUGGESTED BY ↓ CUSHINGOID FACIES, WEIGHT LOSS AND ↓ RENAL FUNCTION
  - 8/14 LOST THEIR GRAFTS AND 6/14 HAD PERMANENT REDUCTION IN GRAFT FUNCTION
  - NO CLEAR EXPLANATION ACCOUNTED FOR ALL INSTANCES OF NC; BUT FAMILY DYSEQUILIBRIUM AND FATHERLESS HOUSEHOLDS WERE FREQUENT

**KORSCH ET AL PEDIATRICS 1978**

# **RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE**

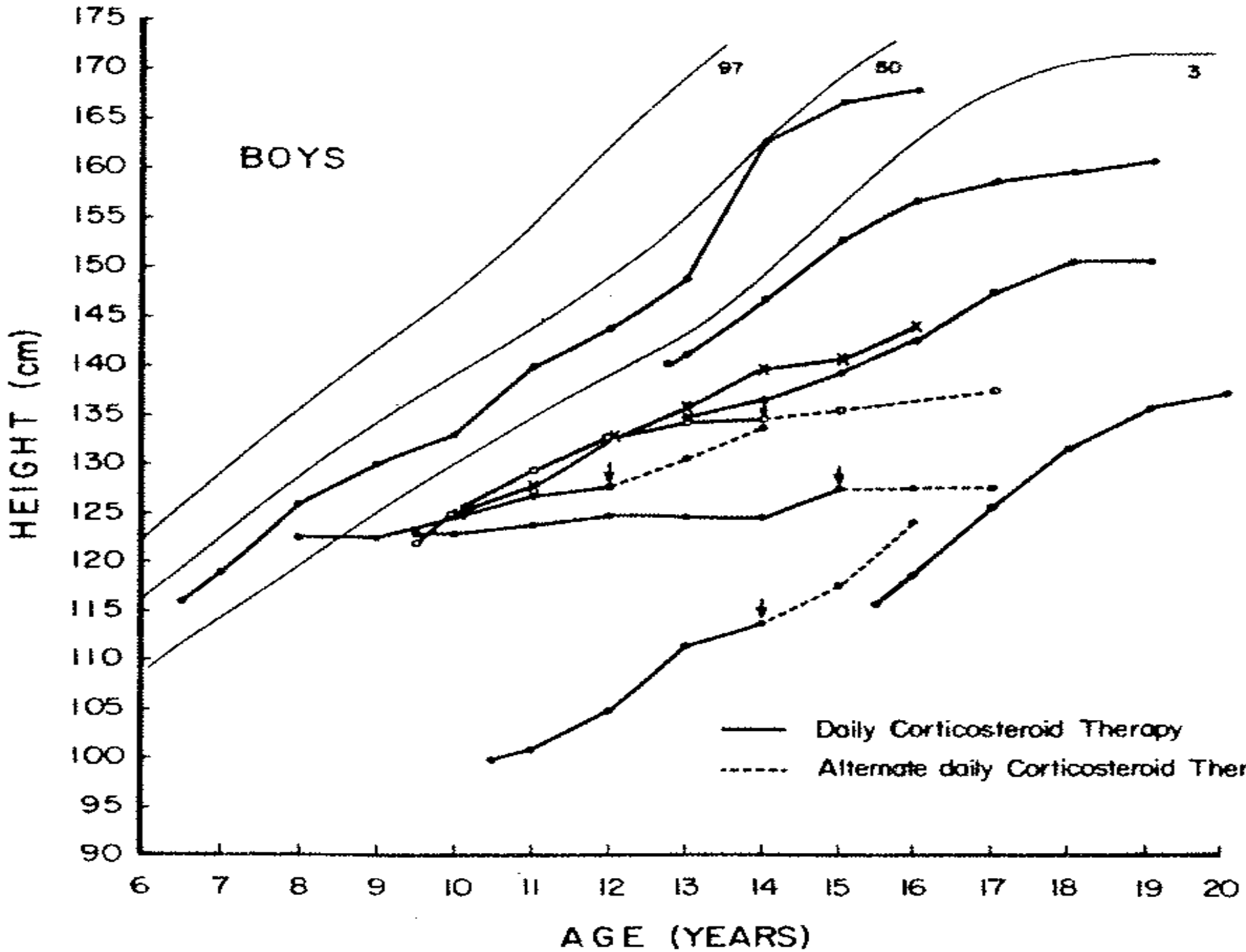
- **WHAT WAS THE MORTALITY RATE FOR THE 69 PEDIATRIC RECIPIENTS DURING THE INITIAL 5 YEAR PERIOD (1967-1972) OF THE PEDIATRIC PROGRAM @ CHLA?**
  - **15/69 DIED (22%): 9(13%) FROM COMPLICATIONS POST-TRANSPLANT (6 RELATED TO INFECTIONS) AND 6 FOLLOWING RETURN TO DIALYSIS**
    - ❖ **CMV (2), GRAM NEGATIVE SEPSIS (2), CANDIDA (1) AND PNEUMOCYSTIS (1)**

**FINE ET AL PEDIATRICS 61:641,1978**

# **RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE**

- **WHAT WAS THE INITIAL EXPERIENCE WITH GROWTH IN CHILDREN FOLLOWING RENAL TRANSPLANTATION?**
  - **26 CHILDREN SURVIVED 1 – 4 YEARS POST-Tx**
  - **NO “CATCH-UP GROWTH”**
  - **6/14 WITH BONE AGE < 12 YEARS AND ONLY 1/12 WITH A BONE AGE >12 YEARS @ Tx HAD “NORMAL GROWTH”**
  - **GRAFT FUNCTION WAS “EXCELLENT” IN 25/26 AND PREDNISONE DOSE WAS VARIABLE**

**GRUSHKIN AND FINE AM J DIS CHILD 125:514, 1973**















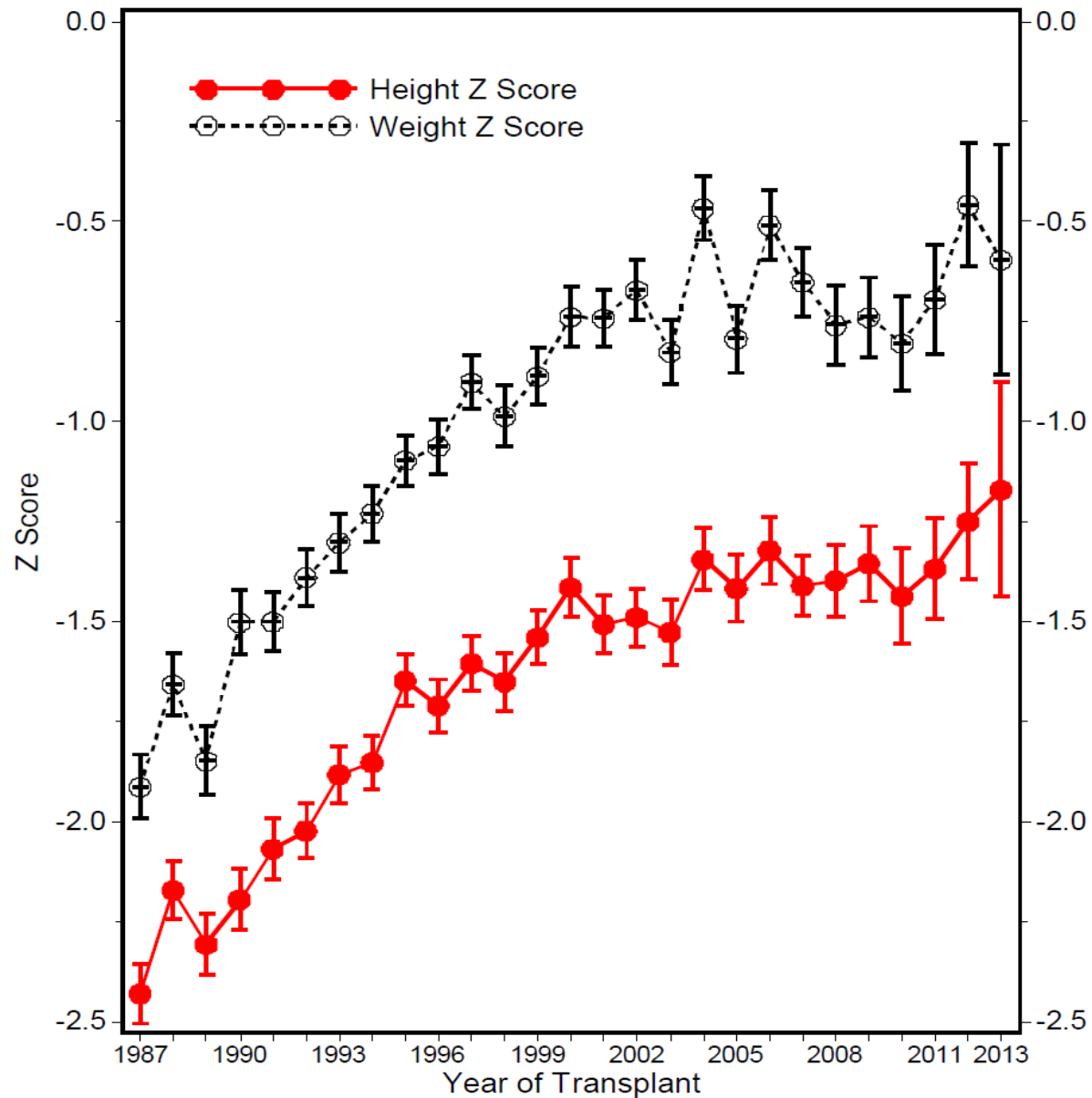








# MEAN HEIGHT SCORES AT TRANSPLANT





# RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

<b>ERA</b>	<b>FINAL HEIGHT FINAL HEIGHT Z SCORE</b>
<b>1987-1991</b>	<b>-1.93</b>
<b>1992-1996</b>	<b>-1.51</b>
<b>1997-2001</b>	<b>-1.05</b>
<b>2002-2010</b>	<b>-0.94</b>





