RENAL TRANSPLANTATION IN CHILDREN: AN HISTORICAL PERSPECTIVE

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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 EXPERIMENTIALLY 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

MURRAY ET AL SURGICAL FORUM 442, 1995
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

- **Corticosteroids**
- **Azathioprine**
- **Polyclonal antibodies**
- **Transfusions**
  - Random
  - Donor Specific
- **Splenectomy**

- **Cyclosporine**
- **OKT3**

- **Tacrolimus**
  - MMF
  - Neoral
  - αIL2r
  - Rapamycin

- **Campath**
- **BELATACEPT**
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/m² 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
• TREATMENT OF REJECTION:
  - **Prednisone**: 200 – 300mg/day and reduced by 25 – 50mg/day until maintenance dose of 25 – 75mg/day was reached
Kidney Transplant – 1967
Spleenectomy – 1978
Partial left Orichiectomy 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
PREDNISONE 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)
LEVOTHYROIDINE 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 THERAPEUTIC 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
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

<table>
<thead>
<tr>
<th>Cohort Group</th>
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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 HISTOCOMPATABILITY 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
RENNAL 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
– 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 GAFTs were lost) and antihypertensive treatment was successful in the 3 group 5 patients.

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

![Graph showing mean height scores at transplant with error bars](image)
# Renal Transplantation in Children: An Historical Perspective

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NAPRTCS 2010