To my father and my mother,

who helped me to become a doctor

To Professor M. Polito and Mr. C.J. Rudge,

my teachers of Surgery

To my wife,

who always assisted me in my career

To Maria Letizia, Gianluca and Pierluigi,

for their future
THE RELATIONSHIP BETWEEN INFECTION AND REJECTION IN RENAL TRANSPLANT PATIENTS

Ph. D. Degree

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ABSTRACT

Despite the advances in clinical transplantation, infections remain a major problem: the importance of infections in the renal transplant patients may extend beyond the direct effect of the infection on graft function and on patient morbidity, but it has already been observed that there could exist an immunostimulatory effect of the infection itself, thus triggering or potentiating the rejection process.

In the first instance we reviewed retrospectively a group of 160 kidney transplant patients, aiming to observe if an infectious process is able to affect graft function and patient survival. Then we looked particularly at urinary tract infections and correlated them with the symptoms presented by the patients and eventually with impairment of renal function. Furthermore we looked at all the rejection episodes, their relationship with timing and localization of the infectious process and the infectious organisms responsible for them.

From the analysis of our patients population, we can draw that factors important for the development of infections in the post-transplant course are: type of pre-transplant dialysis, native kidneys disease, some predisposing conditions, some complications, type of immunosuppression, matching, cold ischemia time, type of ureteric anastomosis. Factors important for graft survival are mainly native kidney disease and type of immunosuppression. Factors important for patient survival are
mainly the type of pre-transplant dialysis and the native kidney disease. Looking at all the rejection episodes in our patient population I could observe that 19.72% of them were preceeded by an infection, with acute vascular rejection accounting for most of them.

We then analyzed cellular infiltration by monoclonal antibodies labelling in 36 renal allograft biopsies taken before, at predetermined times after transplantation and during rejection episodes; the aim of the study was to see whether increased levels of infiltration could be detected following transplantation and to observe whether there are differences in cellular infiltration in biopsies taken from patients whose rejection episodes were preceeded or not by infection. From the analysis of our data we can observe that there is a steady increase of the mean area of cellular infiltrate when considering respectively peri-transplant biopsies, stable renal function biopsies, acute rejection not preceeded by infection and acute rejection preceeded by infection.

Finally we wanted to use an experimental model of renal transplantation in 16 rat, to study the effect of infection on the expression of renal antigens. No microscopic abnormality was found in normal control kidneys; the differences in microscopic abnormality in grafts without infection and after infection were evident. In rat kidney graft with infection, as assessed by monoclonal antibodies, there was an higher degree of infiltration of monocytes, T cells and Class II antigens with respect to grafts without infection.
INDEX

INFECTIONS IN RENAL TRANSPLANT RECIPIENTS:
INTRODUCTION Page 7

TIMETABLE OF INFECTIONS IN RENAL TRANSPLANT PATIENTS Page 11

URINARY TRACT INFECTIONS AFTER RENAL TRANSPLANTATION: OUTCOME AND EFFECT
ON GRAFT FUNCTION Page 15
Introduction Page 15
Virulence factors Page 16
Host factors Page 21
Immunology of urinary tract infections Page 22
Urinary abnormalities predisposing to infections Page 24
Urinary tract infections in renal transplant recipients Page 25
Organisms causing UTIs in renal transplant recipients Page 27
Predisposing conditions to UTIs in renal transplant recipients Page 30
Signs and symptoms of UTIs Page 35
Bacteremia Page 39
Prevention of UTIs in renal transplant recipients Page 39

MANAGEMENT OF UTI Page 42
Non specific therapy Page 42
Principles of anti-microbial therapy Page 43
Serum, tissue and urine concentration of antimicrobial agents Page 43
Response to therapy Page 44
Recommended therapy Page 47

IMMUNOLOGICAL BACKGROUND:

THE IMMUNE RESPONSE Page 50
The induction phase of the immune response Page 57
The effector phase of the immune response Page 70
* Cytotoxic T lymphocytes Page 70
* Natural killer cells Page 76
* Macrophages Page 77
* The role of B cells and antibodies Page 79
* Antibody-dependent cellular cytotoxicity (ADCC) Page 84
* Complement Page 85
* Immune-complexes Page 89

MECHANISMS OF REJECTION Page 90
- Types of rejection Page 95
* Hyperacute rejection Page 95
* Acute rejection Page 96
* Chronic rejection Page 100

REGULATION OF IMMUNE RESPONSES Page 104

INFECTION AND REJECTION IN RENAL TRANSPLANT PATIENTS Page 107
- Immunomodulation by bacterial infections Page 109
- Immunomodulation by viral infections Page 112
* Increase in MHC antigens display in cells infected with viruses Page 114
INFECTIONS IN RENAL TRANSPLANT RECIPIENTS:

INTRODUCTION

During the past two decades, remarkable strides have been made in the field of renal transplantation.

This remarkable clinical achievement has been accomplished by the attainment of considerable progress in the areas that determine the outcome for a patient receiving a transplant:

1. Optimal tissue typing and matching of donor organ to potential recipient, thus minimizing the incidence and extent of the rejection process;

2. Careful procurement and preservation of the donor organ and proper preparation of the recipient;

3. Impeccable surgical technique, resulting in a minimum of tissue injury, secure vascular and ureteral anastomoses, and the prevention of fluid collections;

4. More precise management of the immunosuppressive regimes; on the one hand, effectively preventing allograft rejection and, on the other, minimizing the global depression of the host defences against infection, the major side effect of the immunosuppressive agents currently available;
5 - Prompt diagnosis and specific therapy of those infections that do occur (1).

The net result has been better control of rejection and better prevention and treatment of infection, the two major barriers to successful organ transplantation (2, 3). These two are closely related: any intervention that decreases the incidence of infection will permit the safe employment of more intensive immunosuppression and thus better management of rejection; and any intervention that decreases the intensity and extent of rejection, thus permitting lesser amount of immunosuppressive therapy, will be associated with a lower rate of infection.

Rejection and infection may therefore be regarded as two sides of the same problem (1).

Many are the reasons for the occurrence of infections in transplant patients:

1 - The chronic requirement for immunosuppression to prevent allograft rejection not only increases the incidence and severity of acute infections, but also results in chronic, progressive disease from microbic agents unlikely to have such effects in immunologically intact individuals. Examples of this are the effects of chronic infections with such Cytomegalovirus (CMV), Epstein-Barr virus
(EBV), Hepatitis B, and Papillomavirus. The combination of chronically impaired host defences and infection with these agents can lead to progressive eye, liver and skin disease, and even cancer at a rate and in a form virtually unknown in the normal host.

2 - The potential sources of infection for the transplant patients are many, including endogenous organisms, the allograft itself, the enviroment, and patients' food and water.

3 - The prevention of infection is a primary aim in this patient group, as every episode of clinical infection requiring treatment, carries the potential for lethal consequences. In particular, the prevention of opportunistic infections of nosocomial origin and the prevention of infections due to technical error are of greatest importance.

4 - The prompt recognition and aggressive therapy of those infections that do occur is a critical factor in successful treatment of this patient population.

This may be a particularly difficult problem in patients whose inflammatory response may be greatly suppressed by the antiinflammatory effects of the immunosuppressive therapy being administered. This suppressed inflammatory response often blunts the signs and symptoms of infection, with difficulty to interpret the
significance of what, in a normal host, might be an innocuous skin lesion or radiographic finding (1).
TIMETABLE OF INFECTIONS IN THE RENAL TRANSPLANT PATIENTS

Different types of infections occur at different points in the post-transplant period. For example, although Cytomegalovirus is the most important single cause of clinical infectious disease syndromes in the period 1-4 months post-transplant, it rarely has clinical effects in the first 20 days. It is useful therefore to divide the post-transplant period into three phases when evaluating the patient for possible infections (1, 2, 4).

1 - Infections in the first month post-transplant:

The infectious disease problems in this time period are of three types:

a) infections that were present in the allograft recipient prior to transplant and which continues post-transplant, perhaps exacerbated by post-transplant immunosuppression; the prime concerns here are hepatitis (both B and C), latent bacterial infections, tuberculosis;

b) infections transmitted with a contaminated allograft, with allograft infections either being acquired from the donor (usually) or in the procurement and preservation process prior to the transplant operation;
c) the common bacterial infections of the surgical wound, lungs, intravenous lines, and bladder catheters found in non-immunosuppressed patients undergoing comparable types of surgery.

It is important to emphasize that infections from opportunistic agents, such as Aspergillus sp., Legionella sp., Nocardia asteroides etc., are not commonly observed in the first month post-transplant. The lack of such infections under normal circumstances at a time when the daily dosage of immunosuppressive therapy is at its highest underlines an important point: the duration of immunosuppression is a more important determinant of the net state of immunosuppression than the particular dose of drug being administered over a few days.

2 - Infections 1-6 months post-transplant:

Two groups of infections are the major problems in this time period: infections due to a variety of viruses, particularly the Herpes group viruses, and most particularly CMV; and infections due to a variety of opportunistic pathogens, such as Pneumocystis carinii, Fungi and Listeria.
The duration of immunosuppression is now sufficient so that conventional bacterial infections are no longer the major problem, with viral infections constituting the major hazard.

In addition, some viruses are themselves immunosuppressing, and it is the group of transplant patients with viral infections that is at major risk of opportunistic infections.

3 - Infections in the late period, more than 6 months post-transplants:

The infectious disease problems of patients with functioning renal allografts (and thus receiving continuous immunosuppressive therapy) in the late period may be divided into three general categories:

a) those with chronic viral infections acquired earlier, and with progressive disease due to the interaction of the chronic viral infection with a chronically immuno-suppressed state (for example progressive chorioretinitis due to CMV, progressive liver disease due to Hepatitis B or C virus, and hepatocellular carcinoma and B-cell lymphoproliferative disease associated with Hepatitis B and Epstein-Barr virus, respectively);

b) patients free of chronic viral infections, with good renal function, who are receiving minimal immunosuppressive therapy, and whose infectious disease problems are similar to
those in the general community, such as viral upper respiratory tract, influenza, etc.

c) patients with chronic allograft rejection who have received too much acute and chronic immunosuppression, who have chronic infection with the immunomodulating viruses, and who are at the greatest risk of life-threatening opportunistic infections (Fig.1).

Fig. 1 - Time table for the occurrence of infection in renal transplant patients (1)
Despite the advances in clinical transplantation, infection remains a major problem; more than 80% of renal transplant patients suffer at least one episode of infection in the first year post-transplant (1,5) and infection remains the leading cause of death (6).

Urinary tract infections (UTIs) are the most common form of bacterial infection in transplant recipients; they may be associated with severe morbidity in terms of sepsis, and have been implicated as a possible cause of transplant rejection.

Introduction

Significant bacteriuria describes the number of bacteria in voided urine that exceed the numbers usually due to contamination from the anterior urethra (i.e. > $10^5$ CFU bacteria/ml), at which level infection must be seriously considered whether asymptomatic or symptomatic (7).

Relapse of bacteriuria caused by the same infecting organism that was present before therapy was started is due to persistence of the organism in the urinary tract. Reinfection is caused by a different organism from the original infecting one. Occasionally reinfection may
occur with the same microorganism, which may have persisted in the vagina or faeces and this can be mistaken for a relapse. The organisms causing UTI gain access via ascending, hematogenous, or lymphatic routes. The commonest causative organisms are uropathogenic E. coli especially serogroups 01, 02, 04, 06, 07, 75, (8). Certain strains of E. coli are selected from faecal flora by the presence of virulence factors that enhance colonization and invasion of the urinary tract and the capacity to produce disease (9).

**Virulence factors**

Recognised virulence factors include: Increased adherence to uroepithelial cells thus avoiding the washing action of urine, this being the first necessary step in colonization of host mucosa prior to invasion (10). Adhesion is mediated by hemagglutinin: Mannose Resistant Hemagglutinins (MRHA) and Mannose Sensitive Hemagglutinin (MSHA), both are mediated by fimbriae (9) whose expression is regulated by phase variation. Fimbriae mediating MRHA can be either P fimbriae or type 1 fimbriae.

The ability of the bacteria to mediate MRHA and express P fimbriae or to adhere to epithelial cells is influenced by prior exposure to subinhibitory concentrations of a variety of antimicrobial agents,
decreased by ampicillin, sulfonamides, trimethoprim and tetracycline, enhanced by nalidixic acid (11). Cotrimoxazole at a concentration below MIC reduces synthesis, expression and adherence of type 1 fimbriae.

P fimbriae are important in the pathogenesis of UTI primarily because they mediate Gal-Gal specific bacterial adherence to the epithelial cells within the human urinary tract, thereby permitting bacterial colonization and stimulating inflammation. In compromised hosts the requirements for P fimbriae in initiating serious UTI is decreased suggesting that P fimbriae are necessary for E. coli to overcome certain components of the normal host defences system.

Type 1 fimbriae are common among E. coli strains from all clinical categories of UTI and among faecal strains also. The adherence of type 1 fimbriated strains to host cells in the urinary tract may promote the development of cystitis, and stimulation of polymorphonuclear leukocytes may promote bacterial killing. However, binding to Tamm-Horsfall protein (THP) may allow the host to eliminate them from the urinary tract before they can initiate colonization or infection.

Several bacterial properties (including P fimbriae, type 1 fimbriae, each with different serologic and binding specificities), hemolysis, aerobactin, the K1 capsule and serum resistance are fairly well established
as virulence factors expressed simultaneously in causing E. coli acute symptomatic urinary infections.

This conclusion is based on epidemiological observation that these properties are over represented among isolates from patients with UTI in general or with more severe forms of UTI. The currently recognized virulence factors account for only a fraction of the total virulence of the wild-type strains (Table 1).

<table>
<thead>
<tr>
<th>E. coli isolated from</th>
<th>Adherence to uroepithelium</th>
<th>MRHA</th>
<th>P-fimbriae</th>
<th>Type 1 fimbriae</th>
<th>Hemolysins</th>
<th>K1 capsule</th>
<th>Serum resistance</th>
<th>Aerobactin production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyelonephritis or bacteremia</td>
<td>70-100</td>
<td>50-80</td>
<td>70</td>
<td>60</td>
<td>49</td>
<td>32</td>
<td>61</td>
<td>73</td>
</tr>
<tr>
<td>Cystitis</td>
<td>55</td>
<td>17-52</td>
<td>36</td>
<td>71</td>
<td>40</td>
<td>14</td>
<td>63</td>
<td>49</td>
</tr>
<tr>
<td>Asymptomatic bacteriuria</td>
<td>30</td>
<td>11-19</td>
<td>24</td>
<td>58</td>
<td>20</td>
<td>22</td>
<td>25</td>
<td>38</td>
</tr>
<tr>
<td>Faecal strains</td>
<td>23</td>
<td>2-29</td>
<td>19</td>
<td>60</td>
<td>12</td>
<td>23</td>
<td>52</td>
<td>41</td>
</tr>
<tr>
<td>Immunosuppressed with pyelonephritis</td>
<td>-</td>
<td>-</td>
<td>45</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urine strains</td>
<td>64</td>
<td>38</td>
<td>22</td>
<td>48</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Modified from Johnson, 12)
The binding of E. coli to epithelial cell receptors containing globoseries glycolipid accounts for the attachment of most strains causing kidney infections. The globoseries glycolipid receptors are distributed throughout the urinary tract, particularly in the kidney. Urinary mucus or slime is rich in mannose residues, and hence E. coli possessing mannose-sensitive adhesins adhere avidly to urinary slime (13). Adherent bacteria not only persist within the urinary tract but have growth advantages and enhanced toxicity due to restricted diffusion of products secreted by eukaryotic cells (14).

Phase variation is the alteration by the urinary pathogen of its surface expression or presentation of adhesins so as to ensure its survival (15). E. coli ceases to express type 1 fimbriae on reaching the renal parenchyma since these increase their susceptibility to neutrophil phagocytosis, while neutrophils lack receptors for P fimbriae which block phagocytosis. A similar aspect of adherence in the pathogenesis of UTI is mediated by fimbriae of Proteus mirabilis, Klebsiella spp., Staphylococcus saprophyticus (better adherence to uroepithelium than S. aureus, S. epidermidis). The significance of adherence has been emphasised by inhibition of experimental ascending E. coli UTI by the use of epithelial cell surface receptor analogues.
In "complicated" UTI, including those following bladder instrumentation, virulence factors and uropathogens are not necessary (12).

Histochemical studies revealed that bacterial adherence was increased by the removal of a surface mucopolysaccharide, the glycosaminoglycan, which seems to be responsible for the natural resistance to adherence (16), preventing small inocula of bacteria from adherence, leaving the bacteria suspended in urine and removed by voiding.

Other bacterial characteristics which may be important in the tendency to upper tract infection are as follows:

1. Mobile bacteria can ascend in the ureter against the flow of urine.

2. Endotoxin of Gram negative bacilli has been shown to decrease ureteric peristalsis, but contributes to renal parenchymal inflammatory response by phagocytic cell activation (9).

3. Urease production, e.g. by Proteus, may be related to the ability to cause pyelonephritis (17).

4. The greater the number of organisms reaching the kidneys, the more the chance of producing infection.
5. Renal cortex is infected by 10,000 times the number of organisms needed to infect the medulla (18), due to the high concentration of ammonia, which may inactivate complement (19) and to the poor chemotaxis of polymorphonuclear leukocytes (PNL) into an area of high osmolality, low pH and low blood flow (20).

Host Factors

Susceptibility to infection is also affected by host factors such as receptor density. In women and children with recurrent UTI, an increased avidity of bacterial attachment has been found to vaginal periurethral and uroepithelial cells (21).

Generally normal urinary tract mucosa other than urethra is resistant to bacterial colonization and has several defence mechanisms that eliminate both pathogenic and non-pathogenic bacteria, including mechanical flushing.

Anaerobic bacteria and other fastidious organisms of urethral flora usually do not multiply in the urine. Extremes of osmolality, high urea concentration, and low pH levels are inhibitory to the growth of some of the bacteria that cause UTI (22), but less inhibitory in urine from pregnant
women and diabetics (23). Furthermore, urine has been shown to inhibit the migrating, adhering and killing functions of neutrophils (24).

In women, urethral, periurethral and introital colonization by Enterobacteriaceae almost invariably precedes episodes of significant bacteriuria, especially in those with recurrent UTI. These patients may have a biologic predisposition to infection due to defective local perineal and vaginal mechanisms.

Kunin et al (25) stated that all women who do not have a structural or neurologic problem in the voiding mechanism are approximately at the same risk of having a first UTI, but once established, each infection sets the stage for the next episode, since infection itself may lead to colonization unless periurethral colonization is eradicated by therapy. Antimicrobial therapy per se may alter periurethral flora in favour of colonization with enteric organisms.

**Immunology of Urinary Tract Infections**

**Humoral Immunity:**

During acute pyelonephritis, there is a systemic antibody response. Antibodies against the O-Antigen and occasionally the K-Antigen of the infecting bacteria, and also antibodies to type 1 and P fimbriae were described (26). IgM antibodies dominate in first upper UTI but not in
subsequent episodes. High levels of IgG antibodies to lipid A correlate with the severity of renal infection and progression of renal parenchyma destruction (27). IgG and secretory IgA antibodies can be detected in urine even in renal transplant recipients on immunosuppressive therapy (28).

By contrast, lower urinary infection is usually associated with a reduced or nondetectable serologic response reflecting the superficial nature of the infection, particularly the absence of antipili antibodies (29). However, local coating of bacteria with antibodies within the kidney (and prostate) has formed the basis of modern localisation techniques. Antibodies may limit the damage of infection within the kidney or prevent colonization preceding recurrence, but may not protect against bladder infection.

Cell mediated immunity did not prove to play a major role against UTI (30).

During pyelonephritis, the inflammatory response not only limits bacterial spread and persistence within the kidney but may also cause tissue damage and renal scarring.

There is the possibility of autoimmunity causing the progression of the lesion in "chronic pyelonephritis" to persistent bacterial antigens. These are increased serum antibody titres against THP in acute
pyelonephritis (31); this protein is formed in the tubular region and is excreted in the urine, and may act as autoantibody in the renal parenchyma. Cross-reactivity between the THP and Gram negative bacteria has been reported by Fasth et al (32), raising the possibility of antibody induced by Gram negative bacilli injuring the renal cells even after elimination of the bacteria. Antibodies to this protein were seen in patients with vesico-ureteric reflux even in the absence of bacteria.

**Urinary abnormalities predisposing to infections**

The following urinary abnormalities can predispose the onset of UTIS in the general population:

**I** Obstruction, resulting in stasis with increasing susceptibility to infection

* Extrarenal obstruction: congenital anomalies of ureter or urethra, calculi, extrinsic ureteral compression; prostatic hypertrophy
* Intrarenal obstruction: nephrocalcinosis, uric acid nephropathy, analgesic nephropathy, polycystic disease, hypokalemic nephropathy, sickle cell disease or trait.

**II** Vesicoureteral Reflux: congenital abnormality, bladder overdistetion, infection especially in children or idiopathic.

IV instrumentation of the urinary tract.

Urinary tract infections in renal transplant recipients

In addition to the urinary abnormalities predisposing to infection in the general population, the high incidence of UTIs in renal transplant recipients is due to many factors: the normal immune response is compromised by immunosuppressive therapy; there can exist bladder dysfunction due to lack of use or primary urological disease; infection may be introduced by post-operative urinary catheters, by the native kidney or the donor kidney; even the ischemia time has been suggested to be important in establishing a renal tissue infection (33).

The incidence of UTIs in transplant recipients has been reported to vary from 35 to 88% (33-35); approximately 60% of bacteremias observed in transplant patients originate from the urinary tract (36, 37).

The timing of infection after renal transplantation is important (1); the overall incidence of UTIs declines rapidly after the first three months of transplantation (3, 34, 38), and most UTIs occurring in the late post-
transplant period (i.e. after six months) are asymptomatic, do not affect graft and patient survival and can be managed by a conventional course of antibiotics (1, 37-39). In contrast, UTIs occurring during the first three months are frequently symptomatic and may be associated with overt pyelonephritis, bacteremia, a high rate of relapse when treated with a conventional course of antibiotics, and therefore affect both graft and patient survival (40).

The explanation for these different effects of UTIs occurring at various stages in the post-transplant period can lie in the anatomical site of infection (1); it has already been observed that, in non-immunosuppressed patients, kidney infections are characterized by tissue invasion and a propensity to relapse, while bladder infections are a superficial process, that is easily eradicated and rarely associated with bacteremia (41-44).

There is little doubt that in some patients after transplantation the infection is confined to the bladder, especially where a functioning ureteric valve is preserved or constructed, but it is likely that UTIs in the early post-transplant period can manifest a higher likelihood of developing a renal tissue lesion, at a time closely following bladder catheterization, kidney trauma, and the highest doses of immunosuppressive therapy (33, 34). On the other hand, a renal lesion, with chronic pyelophritis, can be
manifested in patients with recurrent urinary tract infections, (i.e. those developing six months or later post-transplant), in patients with vesico-renal reflux (45).

The importance of UTIs in the renal transplant population may extend beyond the direct effect of the infection on graft function, as it must be considered that there could exist an immunostimulatory effect of the infection itself, thus triggering or potentiating the rejection process.

Thus, the importance of UTI for the renal transplant recipients lies in two areas (1, 46):

1) the direct morbidity and mortality from the infection itself, and
2) the possible immunostimulatory effect, which may affect graft function by initiating allograft rejection.

Organisms causing UTIs in renal transplant recipients

The infecting organisms show a preponderance of Escherichia coli in community acquired uncomplicated UTI, while hospital acquired and recurrent infections have increased frequency of Proteus, Pseudomonas, Klebsiella, Enterobacter spp., Enterococci and rarely anaerobes; Enterococci, P. aeruginosa and Candida mostly occur in catheter-associated infections.
In renal transplant patients, the microrganisms most frequently isolated both from acute or recurrent UTIs are gram-negative rods (Table 2) (33). The high incidence of Escherichia Coli as the most frequent etiologic agent for UTIs has been confirmed by other authors (7, 35); the poly-antibiotic resistant organisms, such as Klebsiella-Enterobacter, Proteus and Pseudomonas, are also common; among gram-positive bacteria, Streptococcus faecalis or other strains show a high incidence (7).

The importance of the ascending route in post-transplant UTIs has been pointed out as well. In 65% of UTIs due to Escherichia Coli, an organism of the same serotype had been previously isolated from faeces, while in the Pseudomonas aeruginosa infections an organism of the same serotype and phage type has been isolated from faeces or a high vaginal swab (33). Infections due to other gram-negative bacilli and gram-positive cocci have often derived from an abscess in the area of the transplant, particularly when surgical complications such as ureteric necrosis are more common (33).

Culture negative UTI could be associated with Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum, Mycobacterium spp., Haemophilus influenzae, Campylobacter spp., Legionella pneumophila, Salmonella spp., Shigella spp., and Gardnerella
vaginalis and DF coryneform bacteria. C. trachomatis is a common cause of urethral syndrome and cystouretheritis in young adult women and is also associated with chronic prostatitis (47).

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>PRIMARY</th>
<th>RECURRENT</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCH. COLI</td>
<td>35%</td>
<td>28%</td>
<td>30%</td>
</tr>
<tr>
<td>PROTEUS MIRABILIS</td>
<td>12%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>PROTEUS SPP.</td>
<td>6%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>KLEBSIELLA AEROGENES</td>
<td>12%</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>PS. AERUGINOSA</td>
<td>6%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>STREPT. FAECALIS</td>
<td>17%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>STAPH. AUREUS</td>
<td>12%</td>
<td>2%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Urinary shedding of CMV and HSV type 2 viruses occurs. Hemorrhagic cystitis is caused mainly by viruses including varicella HSV type 2 and adenovirus type 11 and 21 (47).
Predisposing conditions to UTIs in renal transplant recipients

Among the predisposing conditions for the development of UTIs in renal transplant patients are:

a) the renal disease that precipitated patients' renal failure; the highest incidence of post-transplant UTIs is among patients with either chronic pyelonephritis (and associated bladder abnormalities), or polycystic kidneys as cause of end stage renal failure (Table 3) (7, 48-52);

**TABLE 3 - DISEASES CAUSING RENAL FAILURE AND ASSOCIATED URINARY TRACT INFECTION** (adapted from Ramsey (7))

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>% OF INFECTED PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic glomerulonephritis</td>
<td>43</td>
</tr>
<tr>
<td>Arteriolar nephrosclerosis</td>
<td>80</td>
</tr>
<tr>
<td>Congenital hypoplasia</td>
<td>33</td>
</tr>
<tr>
<td>Chronic proliferative G.N.</td>
<td>60</td>
</tr>
<tr>
<td>Chronic pyelonephritis</td>
<td>100</td>
</tr>
<tr>
<td>Polycystic kidneys</td>
<td>100</td>
</tr>
<tr>
<td>Other</td>
<td>44</td>
</tr>
</tbody>
</table>
b) **sex**, as women have a higher incidence of infection than male patients (Table 4) (7, 53);

| TABLE 4 - UTIs IN RENAL TRANSPLANT PATIENTS
<table>
<thead>
<tr>
<th>(adapted from Hamshere (53))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALE</strong></td>
</tr>
<tr>
<td>N. PATIENTS</td>
</tr>
<tr>
<td>First infection</td>
</tr>
<tr>
<td>Recurrence</td>
</tr>
</tbody>
</table>

c) **age**, as 75% of patients older than 40 years develop infection, compared to 41.5% in those younger (7); it has been observed that the mean age of those patients who remain free from infection is 33.6 years, those in whom a non-persistent infection develops have a mean age of 35 years, but those who had a persistent infection have a mean age of 45.4 years (7);

d) **the immunosuppression**: it has been demonstrated that the incidence of UTI in Cyclosporine A (CyA)-immunosuppressed patients is at least comparable with that in the azathioprine-treated patients in the first 4 months after transplantation, but may be less in the later period,
more than 4 months post-transplant (54); complications due to UTIs in the era when patients were immunosuppressed with azathioprine-prednisolone were often severe, but seem to be few and non-fatal in Cyclosporine A-treated patients (55).

An explanation for the better outcome of the CyA group in the later courses may be the more selective effect of this drug on certain T-cell subpopulations, which may outweight other side effects (33); on the other hand, leucopenia induced by azathioprine and the usually higher doses of prednisolone used with azathioprine may be considered (56). The more severe infections with azathioprine may be historically associated with the high doses of steroids.

It has been observed that after six months, the infectious complications become much less frequent, and it is likely that this improved prognosis after six months is correlated with the lower dosage of steroids. The large dosage of steroids associated with treatment of rejections do, however, increase the percent of persistent infections (7);

e) the incidence of episodes of rejection, with the need for further immunosuppression; in the modern immunosuppressive regimes, the major goal is to decrease the dosage of corticosteroids, used in clinical transplantation, both for maintenance immunosuppression and for
treatment of acute rejection episodes (57-77); in addition, a major effort has been directed towards finding alternative means of treating and preventing rejection that would be more specific (less globally immunosuppressive) and even more steroid sparing (1); such efforts include polyclonal antilymphocyte sera and globulins (78-80), monoclonal antibodies specific for particular lymphocytes (81-89), or total lymph node irradiation (90-93);

f) surgical complications: surgeons performing renal transplantations must have a meticulous attention to surgical technique, focusing on gentle handling of the vessels, the kidney itself, ureter and bladder; in most transplant centres, ureteroneocystostomy is the procedure of choice, because of its simplicity and low incidence of complications (94-96).

It has been observed that the incidence of UTIs is higher in patients with urological complications rather than other surgical complications (vascular or wound complications) (7).

The urological complications can be divided in:

- ureteric obstruction: incidence 1 - 9.7% (94, 97, 98); it can be subsequent to extrinsic (periureteric fibrosis or collection, ureteric compression by the kidney or spermatic cord) or intrinsic (fibrosis, kinking, torsion, stones, infection, tumor, blood clots) obstruction; this
complication can occur even up to several years following transplantation (97, 98);

- ureteric fistula: incidence 0.5 - 10% (99-101); it appears that vascular insufficiency is the most important factor in the development of the ureteric fistula, by means of partial devascularization of the ureter at the time of the donor nephrectomy, and may be aggravated by rejection, leading to ureteric ischemia and subsequent necrosis (94); this complication has also been found to have a higher incidence in the diabetic patient (102);

- vesical fistula: incidence 0.6 - 4.4% (95, 99-101); it may develop at the site of the anterior cystostomy closure or at the ureteral hiatus; to prevent this complication a three-layer watertight closure has been recommended (94); an increased incidence of vesical fistulas has been described following retransplantation, due to the formation of scars (103);

- calyceal fistula: incidence 1.3 - 2.2% (95, 99); they are related to segmental renal ischemia as a result of ligation or thrombosis of an accessory renal artery (104);

- the period of post-operative catheterization: it has been observed that if the catheter is removed on or before the second post-operative day, and the patient does not require further insertion, the infection rate is 5.6% within the next 2 or 3 weeks; if the catheter is not removed until the
third post-operative day or later, and there is no need for further recatheterization, the infection rate is 17.2%; if the patient requires recatheterization, the infection rate is up to 79% (7).

**Signs and symptoms of UTIs**

UTIs can be classified in symptomatic or asymptomatic, that is without signs and symptoms of infection.

A further subdivision of UTIs is in acute or persistent infections; a persistent or recurrent UTI is defined as one that continued (but is not necessarily continuous) throughout a three months period (8).

In addition, UTIs can be confined to the lower tract (urethra or bladder) or may extend to the kidney (upper tract).

Fever, frequency, dysuria and abdominal or flank pain are the classic symptoms but may not be prominent especially at extremes of age. Recurrent or persistent UTI can be asymptomatic especially in presence of an indwelling catheter, where bacteriuria occurs without lower urinary symptoms but fever and flank pain are common.

Alterations in renal function occur in pyelonephritis which may produce a concentration defect perhaps due to increased production of prostaglandins which is reversible by early antimicrobial therapy and
prostaglandin inhibitors. Renal insufficiency can result from progressive destruction of the kidney particularly in the presence of obstruction.

Screening for asymptomatic bacteriuria with pyuria helps to prevent the increased morbidity and mortality of untreated infections in vulnerable groups like pregnant women, elderly and renal Tx recipients (105, 106).

It has already been observed that UTIs occurring during the first three months after transplantation are more likely to be symptomatic, and to extend to the upper tract, with the subsequent development of pyelonephritis and bacteremia.

Myerowitz (36) reported that 60% of the bacteraemic episodes observed in renal transplant recipients, arose from infections in and around the transplanted kidney and ureter (ureteral leakage, ureteral obstruction, infected perinephric hematoma).

Rubin (34) developed a test, the antibody-coated bacteria (ACB) assay, that could correlate with the diagnosis of the site of infection; this assay is based upon the observation that infection of the kidney excites an immunological response that results in specific antibody coating the infecting organisms, while bladder infection is restricted to the superficial mucosa and excites minimal antibody response, resulting in a negative ABC assay. In his study (34), he observed that 34% of patients developed infection in the first 3 months after transplantation, with 88% of them
having positive ABC test; in contrast, 6% of patients developed UTI more than 3 months post-transplantation, all with negative ABC assay.

In the series reported by Ramsey (7), the majority of UTIs in 65 patients followed up for a mean period of 14.7 months were asymptomatic; pyuria, defined as more than 50 White Blood Cells per High Power Field (HPF), was present only in 42% of cases. Pearson (107) reported an incidence of asymptomatic bacteriuria of 30-40%, when considering 959 patients followed up for up to 13 years.

Pyelonephritis after renal transplantation may be associated with fever, chills, allograft tenderness and deteriorating renal function; initial renal scans usually show decreased renal function (in uptake and excretion parameters); these signs and symptoms closely mimic the clinical presentation of acute allograft rejection that occurs in the first 2-3 weeks after transplantation (107, 108). If pyelonephritis occurs early in the post-transplant period, it is difficult to make a differential diagnosis with acute rejection; after 3 months a rejection episode in the allograft is more insidious and the symptoms involved do not mimic those of pyelonephritis.

It has been observed that, when the etiology of the original renal failure is pyelonephritis, the incidence of pyelonephritis in the transplanted kidney is high, up to 52% (107); in the study by Gillum (108), the overall
incidence of pyelonephritis as the etiology of graft failure was observed to be 10%; and Hrincko (109) observed that 40% of patients with transplant pyelonephritis died, many of these having urological complications. When the etiology of renal failure is diabetes or polycystic renal disease, or when there is a history of genitourinary tract abnormalities, the incidence of pyelonephritis is low (107). It is likely that pyelonephritis developing early in the post-transplant period can lead to graft loss, while those developing later are less likely to affect graft and patient survival (54, 55).

Couvelier (38) and Hamshere (52) observed that UTIs developing 3 months or later after renal transplantation failed to affect graft and patient survival in a follow-up of 9 years; it has been observed that the incidence of late UTIs is between 43% (38) and 61% (52), with 29% of those patients having recurrent infections (38); renal function at 5 years was virtually identical in patients with or without UTI (110). Morbidity was low, as only 32% of the episodes were symptomatic, but in some patients UTIs could lead to severe complications, such as septicaemia, for example in patients with diabetes or azathioprine-induced leukopenia. These observations suggest that close and prolonged attention is required in the monitoring of urinary infection.
**Bacteraemia**

Myerowitz (36) reported that 58% of all the bacteraemic episodes occurred in the first 3 months after transplantation, and 91% occurred in the first year; 34% of patients with bacteraemia died, and 45% of them had preceding renal failure; among the patients who survived, 43% underwent nephrectomy or died within 2 months.

**Prevention of UTIs in renal transplant recipients**

The first step in the prevention of infections in graft recipients is the selection of the donor: clearly all potential living donors should have been free of any infection, particularly systemic, that could have involved the kidney, and all potential cadaveric donors with documented systemic sepsis are unacceptable (46). It is possible that even prolonged catheterization of the graft donor prior to transplantation is one way of transporting bacteria into the transplant.

The second step in preventing post-operative infections is the careful surveillance of the perfusate media. Spees (111) and Weber (112) reported that kidneys whose perfusate culture revealed to be contaminated can develop arterial disruption or aneurysm; on the other hand, Majeski (113) observed that bacterial contamination of perfusate solutions were relatively insignificant to the fate of the renal allografts and
the development of infections, provided that a prompt and specific antibiotic therapy is instituted.

Furthermore, it is mandatory to look at pre-existing infections in the allograft recipient. In the first years of transplantation many surgeons performed bilateral nephrectomy prior or at the time of transplantation in patients with native kidney disease that could affect the renal allograft; this could be the case of patients with chronically infected kidneys (47, 48, 114); currently, it is believed that strict criteria for nephrectomy should exist, and therefore nephrectomy is not recommended as part of the routine pretransplant preparation of the patients on chronic hemodialysis. The high morbidity, prolonged and expensive hospitalization, and the loss of the erythropoietin system suggest that, when clinically safe, kidneys should be left in place (48); furthermore, patients who must be maintained on hemodialysis for long periods have more complications when they are anephric (48).

Currently, the indications are limited in cases of drug-resistant hypertension, infection or reflux with hydroureteronephrosis, massive polycystic organs, persistent hematuria and some case of primary rapidly progressive nephritis of immunological origin, that preclude safe homotransplantation (49-51).
Since it appears that the development of UTIs after renal transplantation may result from trauma to the kidney by handling, ischemia, rejection (115), surgery, immunosuppression and the introduction of bacteria via the urinary catheter (1, 34, 35, 116), any effort should be taken in the prevention and management of all these conditions.

In animal models, the combination of bacteria inoculated into the bladder and trauma to the kidney will result in pyelonephritis, whereas bladder infection without renal trauma results only in a transient cystitis (114).

The type of surgery performed is also important; Mathew (117) reported that the incidence of ureterovesical reflux in patients who have had ureterovesical anastomosis performed can be up to 24%, and that such reflux was associated with late graft failure, not because of rejection but because of mesangiocapillary glomerulopathy. The pathogenesis of this lesion appears to be a combination of reflux nephropathy and UTI in the immunosuppressed host. Thus, the construction of an antirefluxing ureterovesical anastomosis seems to be important.
MANAGEMENT OF UTI

Generally, symptomatic UTI requires only one positive culture giving >10^5 CFU/ml, while asymptomatic bacteriuria requires 2 or more positive cultures (118, 119).

Non Specific Therapy

Hydration:

Forcing fluids produces rapid dilution of the bacteria and removal of infected urine by frequent bladder emptying, which in the presence of minimal residual volume may offset the logarithmic growth of Gram negative bacilli. The rapid reduction of bacterial counts is mostly reversed when hydration is stopped. Medullary hypertonicity tends to inhibit leukocytic migration into the renal medulla, and the high concentration of ammonia tends to inactivate complement (19). These may be reversed by abolition of medullary hypertonicity. In addition, a reduction of bacteria counts in the urine by hydration would enhance the effect of factors otherwise overwhelmed by large numbers of bacteria such as bladder mucosal defences or the effect of relatively low concentrations of antimicrobial drugs.
But hydration may have the disadvantage of increasing vesicoureteral reflux and may cause acute urinary retention in the partially obstructed bladder. Large urine output results in dilution of antibacterial substances normally present in the urine as well as lower urinary concentrations of antimicrobial agents. Water diuresis also decreases urinary acidification, which enhances the antimicrobial agents.

In renal transplant there might be a minimal concentration or acidification defect due to anoxic challenge to the transplanted kidney affecting urine concentration, action of antibiotics such as nitrofurantion or the relative bacterial counts in urine. In those patients acidification of urine as a complementary method to treat UTI is not applicable as it may challenge the borderline renal function and tip patients into systemic acidosis.

Principles of Antimicrobial therapy

To choose the least toxic, most effective drugs, to use bactericidal drugs in those with relapsing UTI and renal transplants.

Serum, Tissue and Urine Concentration of anti-microbial Agents

A poor correlation exists between response of bacteriuria and blood levels of antimicrobial agents (120). The dosage of oral antimicrobial
agents used for UTI do not achieve serum levels above the MIC for most urinary pathogens. Disappearance of bacteriuria is more correlated with the sensitivity of the microorganism to the concentrations of the drug achieved in urine. But blood levels of the drug may be critical in patients with bacteremia and may be important in the cure of patients with renal parenchymal infection, transplanted kidney and for those who relapse.

In patients with renal insufficiency, dosage modifications are necessary for agents that are excreted mainly by the kidneys. In renal failure, the kidney may not be able to concentrate an antimicrobial agent in the urine and difficulty in eradicating bacteriuria may occur. This could be an important factor in failure of therapy for UTI with aminoglycosides. In addition, high concentrations of magnesium and calcium as well as low pH level can raise the MIC of aminoglycosides for Gram negative bacilli to levels above those achievable in the urine of patients with renal failure (121). In general, penicillins and cephalosporins attain adequate urine concentrations despite severely impaired renal function and are the agents of choice in renal insufficiency (34), and probably also in renal transplant.

Response to Therapy

The objective of therapy is to eliminate bacteria from the urinary tract. Therefore, the results of therapy can only be determined by follow-
up urine cultures. There are four patterns of response: cure, persistence, relapse and reinfection (122).

Quantitative bacterial counts in urine should decrease within 48 hours after initiation of the antimicrobial agent to which the organism is sensitive in vitro. Measuring bacteriuria at 48h is, however, likely to be inaccurate because of the presence of antimicrobials at high concentration. If counts do not decrease within this time, the therapy being given will almost be unsuccessful and should be changed by that time, as the organism is resistant. To measure cure, negative urine cultures are required at two weeks after its cessation.

Persistence of the infecting organism can have two forms, either persistence of significant bacteria after 48 hours of therapy or persistence of the infecting organism in low numbers in urine after 48 hours. This necessitates investigations to exclude obstruction, intrarenal or perinephric abscesses, by ultrasound, CT scan and perhaps an intravenous pyelography. Significant bacteriuria usually persists only if urinary levels of the drug are below the MIC; this happens when the infecting strain is resistant to urinary levels usually attained or because the levels are inordinately low; these events can occur from not taking the drug, for insufficient dosage, for poor intestinal absorption or poor renal excretion as in renal insufficiency. Persistance in low titres in urine may mean
persistence in the urinary tract or contamination from urethra or vagina. Anyhow, bacteria may persist within urinary tract especially if urologically abnormal or in a transplanted kidney without excretion of significant numbers of organism in the urine. Sites of persistence include the renal parenchyma, calculi, and prostate.

Prompt relapse of significant bacteriuria usually follows persistence of the organism in the urinary tract. Relapse usually occurs within 1-2 weeks after cessation of chemotherapy and is often associated with renal infection, structural abnormalities of the urinary tract or chronic bacterial prostatitis. Generally relapse indicates the persistence of the microorganism in urinary tract during therapy. Persistence is common in polycystic renal disease, and if present may require treatment by long course of lipid-soluble antibiotics (e.g. cotrimoxazole) or surgical aspiration with drainage (123).

Sometimes reinfection by the original organism after more than a month of stopping of treatment can occur if bacteria migrate from a reservoir such as intestine, vagina or the external urethra. Reinfection can occur after initial sterilisation of urine or during administration of chemotherapy or at anytime thereafter, by a different bacteria species, different serotype or even the same serotype.
Test of Cure: Although symptoms may disappear within a few days of starting suitable antibiotic therapy, the infection may persist asymptomatically when the treatment is stopped. Urine samples for tests of cure are collected:

(1) Between 3 & 5 day after stopping antibiotics
(2) between 4 & 6 week after stopping antibiotics

When the original infecting organism is not re-isolated from either (1) or (2) the patient is regarded as bacteriologically cured (124).

Recommended Therapy

25-35% of strains of E. coli are now resistant to oral sulphonamides, ampicillin or amoxycillin (125). Accordingly oral antimicrobial agents advocated for Gram negative bacillis UTI include: trimethoprim, trimethoprim-sulfamethoxazole, cephalaxin, amoxycillin-clavulanic acid and the new quinolones norfloxacin and ciprofloxacin.

In community-acquired acute pyelonephritis with Gram negative bacilli empiric therapy includes: aminoglycosides (e. g. gentamicin 3-5mg/kg/day), aztreonam (3-6g/d), ureido-penicillins (mezlocillin, azlocillin or pireracillin 1-8g/d), the ampicillin- sulbactam combination or the ticarcillin-clavulanic acid combination and third-generation cephalosporins
(e. g. cefotaxime, ceftriaxone). Ceftazidime has a substantial anti-pseudomononal activity.

In hospital acquired Gram negative infection particularly when seriously ill, the antibiotic selection should not leave any hiatus in the spectrum of activity and should anticipate the possibility of resistant microorganisms, here the recommended combination are: ceftazidime (3-6g/day), ticarcillin-clavulanic acid, aztreonam, or imipenem 2g/d plus aminoglycosides.

We have to bear in mind that renal transplant patients may have some degree of renal impairment whether minimal or frankly apparent, and should be carefully considered when prescribing drugs or antibiotics. Cephalosporins can precipitate coagulopathy in renal insufficiency such as cefazolin, cefamandole, cefoperazone and ceftriaxone, and therefore there is needs of vitamin K supplement for correction of coagulopathy. Cephalin can cause vestibular and renal toxicity and cephalothin may be toxic to the kidneys.

Aminoglycosides nephrotoxicity, ototoxicity and neuromuscular blockade is well known. In high doses ampicillin may be nephrotoxic, while other penicillins may cause nervous system toxicity; aminoglycoside inactivation or coagulopathy platelet inhibition occurs particularly with carbenicillin and ticarcillin.
Cotrimoxazole has the potential of causing a false increase in serum creatinine, nephrotoxicity and hypoglycemia. Cephalothin, nalidixic acid and nitrofurantoin should be avoided (126). Prophylactic trimethoprim-sulphamethoxazole (TMP-SMZ) was proven to decrease the incidence of UTI by fourfold (127-131). It has been reported that two double-strength TMP-SMZ tablets (320/1,600 mg) daily significantly:

1) Reduced hospital days with fever
2) Resulted in fewer bacterial infections following the removal of the bladder catheter
3) Reduced the incidence of infection following discharge from the hospital after transplantation.

Furthermore, fewer UTIs once the catheter was removed, fewer bacteremic episodes, and fewer infection due to gastro-enteric organisms enterococci and S. aureus were observed in treated group. There are appreciable differences in colonization of TMP-SMZ-resistant organism, such as Candida, Pneumocystis, Nocardia and Listeria-related infections (132).

Recently, in the view of the propensity of TMP-SMZ to induce renal dysfunction or exacerbate Cyclosporine nephrotoxicity (130, 131), ampicilline or cephalxin have been used, and they provide an efficacious, safe and inexpensive alternative for UTIs prophilaxis (129).
IMMUNOLOGICAL BACKGROUND: THE IMMUNE RESPONSE

The most important question arising from the study of infections in renal transplant patients in the way is which they can affect graft function; in fact, the high correlation of infectious complications with rejection suggests that there could be a pathogenetic relationship between the two; that is, the infectious process is not only a consequence of the greater amount of immunosuppressive therapy used for the treatment of rejection episodes, but it can trigger or potentiate the rejection process by means of an immunostimulatory effect.

In this process, the expression of Major Histocompatibility Complex (MHC) antigens is involved.

The MHC is a highly polymorphic region of the genome containing a number of genes whose products play important roles, either as regulatory or as effector molecules, in the immune system. Of these, perhaps the most important are those genes coding for antigens, expressed on the surface of cells, known as histocompatibility antigens (133).

Analogous genes have been identified in every mammalian species and it is clear that the MHC is of paramount importance in determining
the fate of a transplant performed between genetically different members of the same species (an allograft).

MHC is a complex gene region located on the short arm of the mouse chromosome 17 (H-2) or of the human chromosome 6 (HLA, human leucocytes antigen) (134, 135). (Fig. 2)

It encodes two structurally distinct Classes of cell surface molecules, called Class I and II, and also Class III, which encodes the C2, C4 and Bf (properdin factor B) complement components (136-139) and also the tumour necrosis factor TNF-α and TNF-β and the heat shock protein Hsp 70; the HLA Class III molecules are soluble and do not act as transplantation antigens, nor do they present antigen to cells.

Fig. 2 - The HLA Complex.
Although the MHC was originally identified by its role in self non-
self discrimination and transplant rejection, it is now recognized that
proteins encoded in this region are involved in many aspects of
immunological recognition (140).

The MHC proteins are of different genetic types as determined by
their structure and functions.

The Class I antigens consist of two polypeptides; the larger peptide
(heavy or alfa chain) is a Mr 40.000-45.000 transmembrane glycoprotein,
is encoded by the MHC on chromosome 6, and is non-covalently
associated with the polypeptide Beta 2-microglobulin (Mr 12.000), which
is encoded outside the MHC, by a gene on chromosome 15. The entire
molecule is anchored in the cell membrane by the alfa-chain, which
contains 338 amino acid residues and can be divided into 3 regions: an
extracellular hydrophilic region (residues 1-281), a transmembrane
hydrophobic region (residues 282-306), and an intracellular hydrophilic
region (residues 307-338). The extracellular region is divided into 3
domains termed alfa-1, alfa-2 and alfa-3; it has been demonstrated that
the vast majority of HLA antigenic determinants reside in the alfa-1 or
alfa-2 domains (139) (Fig. 3).
The Class I molecules are expressed on virtually all nucleated cells and normally function as restriction elements for cytotoxic T lymphocytes and as target antigens of alloreactive T-cells (Table 5).
There are three Classes I HLA molecules, HLA-A, -B, and -C, with single genes for each (138).

Each locus product in a given individual bears a unique so-called private antigen and additional public antigens that are shared more widely among the population (139).

<table>
<thead>
<tr>
<th>TABLE 5 - COMPARISON OF CLASS I AND II HLA</th>
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<tr>
<td>Properties</td>
</tr>
<tr>
<td>ANTIGENS</td>
</tr>
<tr>
<td>INCLUDED</td>
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<tr>
<td>Tissue distribution</td>
</tr>
<tr>
<td>Functions</td>
</tr>
</tbody>
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The recognition of the Class I glycoprotein is apparently mediated through the T8 glycoproteins of cytotoxic T-lymphocytes (CD8) and the T-cell receptor complex (139).

Class II antigens consist of two noncovalently associated polypeptides, an alfa chain of Mr 30.000-35.000 and a beta chain of Mr
27,000-30,000. Like the Class I heavy chain, the alfa and beta chains each consists of 3 regions: an extracellular hydrophilic region, a transmembrane hydrophobic region, and an intracellular hydrophilic region: the last 2 of these anchor the chains in the cell membrane (Fig. 4).

![Diagram of HLA-DR molecule](image)

Fig. 4 - Schematic representation of an HLA-DR molecule.
The Class II glycoproteins have a limited cellular distribution and are found chiefly on immunocompetent cells, such as antigen-presenting cells (macrophages and dendritic cells), B lymphocytes and, in humans, activated T-cells; in addition, cells that do not normally express Class II molecules (such as resting T cells, endothelial cells and thyroid cells) can be induced to express them (139). The role of endothelial cells is of particular importance in clinical transplantation, since they are the first allogeneic cells encountered by the recipient's immune system.

The function of Class II molecules is to present processed antigenic peptide fragments to CD4 (generally helper) T lymphocytes during the initiation of the immune response. Just as CD8 T lymphocytes recognize peptide fragments only in the context of a Class I molecule, CD4 T lymphocytes recognize peptide fragments only in the context of Class II molecules (HLA restriction) (140-146).

There are three Class II molecules, HLA-DP, -DA, and -DR, generally recognized on cell surfaces, termed subregions of the D region (Class II) (139).

Since HLA molecules are the major target for allore cognition, the up-regulation of these molecules may be of importance both for the recognition of the transplant and as a target for destruction.
The rejection process can be conceptualized as a series of four related processes. These processes are: T cell triggering and commitment; clonal expansion and differentiation within the immune system; recruitment and organization of the immune response, including changes in gene expression in the graft; and injury and destruction of donor parenchimal and endothelial cells. The key molecules involved in these processes can be classified as the specific recognition system (T cell receptor), MHC Class I and II products, and immunoglobulins; cytokines and their receptors; and the cell adhesion molecules.

The induction phase of the immune response

In light of these informations, what may one propose that a T lymphocyte sees on a molecular level when it encounters a transplant? (147, 148). Knowledge of the molecular structure of the MHC molecules allows one to deduce the subtle changes of amino acids in certain positions in the molecules which determine the phenotypes and/or peptide binding specificities.

The mechanism whereby the foreign HLA molecule actually sensitises the host is not clear, but may occur in at least two ways. First, there are cells within all tissues which are probably of the monocyte/macrophage lineage, termed dendritic cells (149). These cells
are very potent antigen presenting cells and so as a "passenger leucocyte" within the transplant, they could readily present foreign HLA and peptide to the host's T cells.

Dendritic cells express both Class I and II HLA molecules, and both may be important in the initiation of the immune response. These cells are resident within the transplanted organ.

The host's cells circulate within the transplant, encounter dendritic cells and become activated, or the passenger leucocytes may end up in the spleen or lymph nodes and present antigen there (150-153).

Furthermore, there are cell types other than leucocytes which are capable of presenting antigen, including mesangial cells (154), vascular endothelial cells (155) and tubular epithelial cells within the kidney (156).

It may also be relevant that allografts may secrete soluble HLA molecules (157, 158) which can be presented by Class II molecules of the host, thereby leading to T cell activation (159).

While Class II HLA molecules are likely to be the major stimulus for the initiation of transplant rejection, the Class I HLA molecules are also likely to have a role. Furthermore, rejection occurs frequently between HLA identical siblings (not identical twin) renal allografts (160), presumably caused by recognition of the so-called minor histocompatibility antigens.
These antigens are not well characterized at the molecular level, but antibodies to non-HLA antigens on monocytes and endothelial cells are strongly associated with rejection of HLA identical renal transplant, and the antibodies can be eluted from the rejecting grafts (161, 162).

A certain type of molecules may be immunogenic without the apparent participation of T lymphocytes; such molecules (T-independent antigens) appear to be able to directly trigger B-lymphocytes; bacterial polysaccharides and some polymerized proteins are thymus-independent antigens, that is the immunologic response consists largely or exclusively in production of IgM Class antibodies, and little or no immunologic memory is engendered. Recently it has been observed that many of these antigens, if not all, do require some degree of T cell help, and it may be more accurate to consider them as T-efficient rather than T-independent antigens (151).

Most antigens are T-dependent, that is effective antibody responses to most antigens depend on Th-B cells cooperation.

Major Histocompatibility Complex - restricted recognition of foreign antigens form the basis for grouping T-cells into two general subsets:

1 - cytotoxic T-cells (Tc, T8), that recognize antigen in association with Class I MHC products;
2 - helper T-cells (Th, T4), that recognize antigen in association with Class II MHC products (163-166) (Fig. 5).

The activation of T cells requires the presentation to the TCR (T cell receptor) of antigen peptide fragments bound to MHC molecules on the surface of antigen presenting cells (APCs).

This interaction is highly specific with only a very small proportion of T cells bearing a TCR that will be able to react with, and so be activated by a given MHC antigen complex. However, in association with this specific MHC-TCR interaction, a number of non-specific accessory cell-to-cell interactions occur which are necessary if normal T cell activation is to ensue; many of these accessory interactions are thought to have a primarily adhesive function and can play a role in signal transduction. For example, CD4 (CD = cluster of differentiation) and CD8, belonging to the Ig (Immunoglobulin) superfamily, appear to function as adhesion molecules stabilising TCR-MHC binding and as co-receptors in signal transduction (167).

Antigen independent interactions between adhesion molecules on the T cell surface and on B cells, APCs, endothelium, target cells and other T cells have been shown to be essential for normal T cell activation. The first of these involves the integrin LFA-1 on the T cell surface, and the Ig superfamily members, ICAM-1 and -2. Typically ICAM-1 is thought of
as being expressed on the APC or target cell, but it may also be on other lymphocytes and so the T cell can provide both the ligand and the receptor for this interaction.

LFA-1/ICAM-1 bonding is attracting increasing attention, not least as a potential target for therapeutic strategies in transplantation.

Fig. 5 - CD4 T cells (left) recognize processed antigen in the context of Class II molecules through the T cell receptor and recognize an epitope on the monopolymorphic region of the Class II molecules through CD4. In contrast, CD8 T cells (right) recognize processed antigen in the context of Class I molecules through their T cell receptor and an epitope on the monopolymorphic region of the Class I molecules through CD8.

Another adhesion molecule interaction known to contribute to cell activation is that between two members of the Ig superfamily, CD2 on the
T cell surface and LFA-3 on the APC or target cell; this interaction is the basis of the ability of T cells to form rosettes with sheep red blood cells (LFA-3+).

For T cells to be normally activated, either by APCs or target cells, the interaction of at least these three sets of complementary molecules is required: first, TCR, MHC with its antigenic peptide and either CD4 or CD8; second, LFA-1 and ICAM-1; and third, CD2 and LFA-3 (Fig. 6).

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Fig. 6 - Diagramatic representation of the major adhesion molecule interactions involved in T cell activation and killing.
Each amplifies the other and each may mediate signal transduction as well as adhesion.

APCs not only present antigen to lymphocytes, but release a soluble factor, Interleukin-1 (IL-1), which facilitates the response of these cells.

In the induction of cell-mediated immunity, T-cells, via T cell receptor, recognize simultaneously an epitope (or antigenic determinant or hapten) of the foreign antigen, and a determinant in the polymorphic domain of the MHC products expressed on the surface of the APCs (114). The T-cell antigen receptor is a glycoprotein of about 80,000 daltons, composed of alfa and beta subunits, each of about 40,000 D (168-171).

The molecule is noncovalently associated on the cell surface with CD3, a complex of at least 5 polypeptides that may participate in mediating activation signals; it is found on all mature T lymphocytes and a fraction of thymocytes (172, 173).

CD3 is functionally important because it is required for the expression of the T-cell receptor (TCR) on the cell surface. T-cells, in fact, can be activated directly by antibodies specific for the CD3 complex (174).
The protein appears to be closely associated with the T-cell receptor in a CD3-T-cell-receptor complex (175, 176).

A critical event in the initiation of the immune response in the activation of T-cells by IL-1, produced by APCs; it also promotes the secretion of optimum amounts of Interleukin-2 (IL-2) and induces the expression of IL-2 receptors on the T-cell surface (177-180) (Fig. 7).

The induction of antibody-mediated responses varies with the type of antigen.

There is no doubt that antibodies mediate hyperacute rejection; they may be directed against Class I or Class II HLA antigens or ABO blood group antigens on the vascular endothelium. Antibodies directed against a non-HLA monocyte endothelial antigen may play a major role in the rejection of HLA identical transplant.

Antibody production requires both the activation of B lymphocytes and their differentiation into antibody-producing plasma cells.

The T-independent antigens may be presented directly to those B cells which recognize the antigen, i.e. have specific receptors for it, that is antibody molecules, and the interaction stimulates the events leading to antibody production (181).
Fig. 7 - Grand scheme of adoptive immune system.
While the Th cell is being activated, relevant B cells have also been engaging immunogen through their antigen receptors, which are membrane-bound forms of the antibodies they will later secrete. Antigen binding is followed by endocytosis of the antigen-receptor complex, which appears to furnish an activating signal; however, this is insufficient for full activation of B cells, which require additional signals from Th cell-lymphokines, that are B cell growth factor (BCGF) and B cell differentiation factor (BCDF).

Because B cells can also function as APCs, they process endocytosed antigen and transport immunogenic epitopes complexed with Class II molecules to their surface. These complexes then activate T cells or induce the formation of memory T cells (139, 182).

The Th cells are the principal orchestrators of the immune response, because they are needed for the activation of the major effector cells in the response (cytotoxic T cells and antibody-producing B cells).

The activated Th cells trigger the Tc cells (cell-mediated responses), whose major function is the killing of cells that express foreign or non-self antigens, and B cells, which differentiate into antibody-producing plasma cells.
Tc cells, like Th cells, also require activating signals; one is provided by interaction of the T cell antigen receptors with a complex of a foreign epitope and Class I MHC on the target cells; the second signal is furnished by IL-2 produced by the activated Th cell. The activated Tc cells then release cytotoxins that kill the target cell (139, 177).

Certain other adhesion molecules contribute to cell activation. It has been suggested that CD28 induces expression of IL-2 and other cytokines and it is now thought that stimulation of this CD28 pathway may represent a distinct and critical process that must be triggered for TCR induced activation to occur.

Thus normal T cell activation may require the involvement of many molecules; this suggests either a surprising degree of redundancy in the process or a very complex system.

The most likely explanation is that different combinations of stimuli lead to different T cell responses with different consequences in terms of surface molecule expression and cytokine secretion (167).

In recent years, understanding of the role of the endothelial cells in the inflammatory process has broadened considerably; endothelial cells actively orchestrate the inflammatory process via control over:

1) local blood flow, via vasodilators and vasoconstrictors secreted by the endothelial cell and acting on adjacent smooth muscle;
2) fluid extravasation, due at least partially to histamine induced contraction;

3) leucocyte adhesion;

4) leucocyte trafficking to the local site of inflammation;

5) leucocyte activation.

The initiating event in endothelial activation is a signal or injury as a result of contact with a noxious agent (e.g. bacterial product) or a factor from a marrow derived cell in the interstitium or a signal from a damaged parenchymal cell.

The endothelial cell interacts with leucocytes through human endothelial adhesion molecules; immediate (5-30 minutes) and early (2-6 hours) events in the cascade of endothelial cell activation predominantly attract neutrophils, while the delayed events (6-48 hours) involve lymphocytes and monocytes.

P-selectin is probably the first adhesion molecule to attract leucocytes, causing neutrophils bearing CD15 to adhere rapidly and avidly at the site of inflammation (183).

Subsequently, there is an enhanced endothelial cell synthesis and surface expression of platelet activation factor (PAF), that upregulates synthesis of neutrophil adhesion molecules belonging to CD18 family (184), which enhances expression of ICAM-1 and ICAM-2. Induced
expression of ICAM-1 can be activated by cytokine mediators of inflammation, such as IL-1, INF-γ and TNF with level increasing 3-5 fold (185); both IL-1 and TNF cause the endothelial cell to synthesise and secrete IL-8, that stimulates neutrophil movement.

After 4-6 hours, an inflammatory infiltrate often changes in character from neutrophil predominant to being a mixture of neutrophils and monocytes, change that correlates with changes in endothelial cell adhesion molecule expression; in particular, vascular cell adhesion molecule 1 (VCAM-1) synthesis is induced in endothelial cells in response to IL-1 and TNF (186), whose lymphocyte ligand is VLA-4 (187).

Thus endothelial cell can regulate the nature and timing of leucocytes that cross the endothelial barrier to sites of inflammation, ensuring activated leucocytes to concentrate at the site of inflammation.

Given the key roles that adhesion molecules play in immune responses, inflammation and tissue responses to injury, it is natural that their role in organ transplantation is attracting increasing interest; because regulated changes in adhesion molecules are obligatory for inflammatory process, adhesion events are candidates for immunosuppressive strategies.

Investigators have recently shown that ICAM-1 expression is increased in transplant rejections (188, 189); this is not surprising, given
the known inducibility of ICAM-1 by INF-γ and other cytokines, which are
produced in abundance during rejection.

In renal allografts, it has been shown that increased expression is
most marked on endothelium, on infiltrating mononuclear leucocytes and
on proximal tubular epithelium, which does not show detectable staining
in normal kidney (188-190). In biopsies from patients with cardiac
allograft rejection, ICAM-1 expression was upregulated on both capillary
and post-capillary venule endothelium (191).

Therefore, the general rule may be that the cells in each organ that
are most susceptible to injury are those induced by cytokines to express
MHC and adhesion molecules.

The effector phase of the immune response

1) Cytotoxic T lymphocytes

The phenomenon of rejection continues to be the single largest
impediment to success in the field of transplantation; there is no doubt
that T lymphocytes play a central role in the rejection of a renal
transplant. The athymic nude mouse will not reject a skin allografts and B
rats and mice (thymectomised, lethally irradiated and reconstituted with
syngeneic B lymphocytes) will not reject skin or renal allografts (192);
both CD4+ and CD8+ T cells will transfer rejection of skin transplant in mice (193).

The acute rejection of a renal transplant consists of a sensitisation phase, where the host detects the presence of the foreign tissue, and an effector phase where the immune system responds to and destroys the transplanted organ (194).

When resting T lymphocytes are exposed to alloantigens, they undergo a series of changes termed activation; a sequence of events takes place, which includes signal transduction, gene activation, protein synthesis, changes in morphology, cellular proliferation and maturation to a new state of activity (195).

As already explained, specific activation of T lymphocytes is initiated by binding of surface expressed antigen and MHC molecules to the T cell antigen receptor; the presence of costimulation provided by bone marrow derived cells is a prerequisite for full T cell activation, that can exist because of activation of T cell adhesion molecules, i.e. clusters of differentiation of monoclonal antibodies (CD) among leucocyte differentiation antigens.

All mature T cells will express either CD4 or CD8. CD4 physically associates with the T cell receptor and Class II MHC and antigen and thereby restricts the reactivity of CD4+ T cells to Class II reactivity. CD8
on the other hand physically associates with the T cell receptor and Class I MHC and antigen and thereby restricts the reactivity of CD8+ T cells to Class I (196-205). Both CD4 and CD8 are therefore adhesion molecules. Their role, however, seems to be very complex, since their cytoplasmic domains are linked to a T cell specific protein kinase, that causes phosphorylation (205). Phosphorylation of T cell structures is an important part of T cell physiology, acting on IL-2 receptor (CD25), the transferrin receptor (CD71), CD3, Class I HLA, and the leucocyte common antigen (CD45).

There are many other structures which probably play an important role: CD5, CD6 and CD7 are all capable of activating T cells (206-215).

Lymphocyte function associated antigen 1 (LFA-1,CD11a/18) mediates adhesion and activation of the T cell, with a ligand termed intercellular adhesion molecule (ICAM-1, ICAM-2) (216).

CD23 (IgE receptor) and CD26 (217, 218) are also able to activate T cells, as well as adhesion molecules (Fig. 8).

After an alloantigen encounters the T cell antigen receptor, the second signal is delivered and the signals are transduced to the nucleus, then a wide variety of genes are activated.

From this stage on, the T cell coordinates the rejection process via a cascade of cytokines.
Fig. 8 - Receptor-ligand pairs involved in T cell-target interactions.

The T cell expresses a receptor for IL-1 to which the monokine IL-1 binds (219). IL-2 is necessary for T cell growth and maturation and also leads to maturation of B cells (220). IL-5 also induces B cells to mature (221). IL-3 stimulates haematopoietic cells from every lineage (222).

IL-4 induces expression of HLA Class II molecules on B cells, synergises with Ig-specific antibodies in the stimulation of resting B cells, induces specific switching to IgG and IgE, and stimulates pre-B cells and thymocyte growth. IL-7 supports the growth of pre-B cells and thymocytes and activates mature peripheral T cells (223).
Tumor necrosis factor α and β are released in response to various stimuli including endotoxin, and produce widespread changes in cellular metabolism and cachexia (224). IL-6 also known as β2- Interferon, promotes the proliferation and differentiation of B cells and binding to its receptor on T cells lead to a candidate second signal (225). IL-8 activates neutrophils (226). IL-9 supports the growth of certain T helper cells but apparently not cytotoxic T cells, and along with IL-10 supports the growth of mast cells (227). IL-10 enhances Class II HLA expression on B cells. IL-11 stimulates B cell development and synergises with IL-3. IL-12 synergises with IL-2 to induce cytotoxic T cells (228). γ-interferon upregulates HLA Class II expression and leads to activation of macrophages. Monokines such as platelet derived growth factor and transforming growth factor B may lead to fibroplasia within the allograft (229). Procoagulant activity may also be present (230).

Messenger RNA has been detected for a variety of cytokines in renal allografts undergoing rejection.

Local synthesis of TNF-β, γ-interferon, IL-2 and IL-6 have been reported; IL-2 and its soluble receptor appear in the blood and urine of patients undergoing rejection (231).

The means by which cytotoxic T cells lyse their targets have been thought to be granules, that they develop as they mature; the granules
contain a pore forming protein termed perforin and six serine esterases
termed granzymes; perforin is capable of lysing cells.

The target cell is recognized by the interaction of T cell receptor and MHC peptide; several of the accessory molecules lead to adhesion and they may form a closed space into which the lytic components of the granules are released.

![Diagram](image)

**Fig. 9 - Cytokine signalling in the immune response.**
Sensitized T cells expressing the Th/i subset phenotype mediate the so-called delayed-type hypersensitivity reactions. (Fig. 9).

2 - Natural Killer cells

It has already been observed that during rejection episodes the large granular lymphocytes (LGL) population is among the first cells to appear (209). LGL, derived from bone marrow with phenotypic characteristic associated partially with T lymphocytes and also with monocytes and myeloid cells (232, 233), contain natural Killer (NK) cells, which destroy certain tumor and virally infected target cells in absence of known prior immunization (234, 235).

All NK cells express CD56 and CD16, but lack expression of the CD3/TCR.

Unlike most CTL, NK cells recognize and kill both autologous (self) and allogeneic tumors without requiring recognition of MHC antigens on the target cells. This MHC- unrestricted citotoxicity is not confined to NK cells, and a small subset of T lymphocytes can also mediate this function.

The most important role of NK cells is probably in defense against viral infections; because NK cells do not require prior exposure to the antigen to respond, they may provide the initial antiviral defense during
the latent period before development of antibodies and antigen-specific CTL.

It is possible that NK cells have a role in the maturation and regulation of CTL and/or other immunocompetent cells (236). NK cells have immunoregulatory activity, expressed by the ability to produce interferon in response to stimulation with adjuvants, viruses, mitogens and other agents (209, 237).

In addition, it has recently been demonstrated that NK cells can be activated by certain cytokines to increase their cytotoxic activity and proliferate; for example, after a few hours of exposure to IL-2 in tissue culture, NK cells acquire the capacity to kill essentially all tumor cell types without damaging most normal tissues. This phenomenon is called lymphokine-activated killer (LAK) activity (238).

In addition to increasing cytotoxic activity, IL-2 acts as a growth factor and directly induces the proliferation of NK cells; the cytotoxic activity of NK cells can also be increased by alpha interferon and, to a lesser extent, by gamma interferon (229).

3 - Macrophages

The role of mononuclear phagocytes in the process of allograft rejection is not well understood; several factors, such as fibronectin, T-cell-
derived lymphokines, increased vascular permeability, are responsible for localization of macrophages in areas of inflammatory injury, including allograft sites (209). It is difficult to establish whether macrophages are only active effectors of allograft destruction or are involved even in an accessory role, such as amplification of the alloimmune T-cell response.

Monocytes and macrophages can serve as APCs for T lymphocytes, since they express both Class I and Class II MHC glycoproteins, and are able to present antigen to CD8 and CD4 T lymphocytes. Activated lymphocytes, in turn, secrete factors that affect monocyte and macrophage function and differentiation.

The role of macrophages in inducing acute inflammation and in amplifying allograft reactivity could well be related to IL-1 production, that stimulates T-helper cells to produce IL-2, which in turn leads to expansion and amplification of activated cytotoxic T-cell clones and other T-cell-dependent immune responses (209).

In addition, IL-1 stimulates B-cell proliferation and suppressor T-cell activities as well as NK activity and fibroblast proliferation, the latter contributing to the chronic inflammatory process seen in chronic allograft rejection (239).
4 - The role of B cells and antibodies

The antibody response to allogeneic histocompatibility antigens is T dependent, thus T cells play a pivotal role in both cellular and humoral immune response; since the non-specific response includes macrophages, natural killer cells, lymphokine activated killer cells, K cells and so on, it is evident also that lymphokines elaborated by many cells during the allogeneic response play an amplyfing role by recruiting cells, including B cells.

B cells constitute one of the major arms of the immune system (235-245).

Their main function is to produce antibodies to many antigens, in general deleterious to the organism. Antibodies are divided into nine immunoglobulin isotypes (IgM, IgD, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgE), each of which has several advantages.

It has to be stressed that almost all of the humoral response against allogeneic cells is confined to IgM and IgG isotypes, at least in the circulation, and most are directed to cell surface antigens coded by Major Histocompatibility Complex (MHC) Class I and Class II loci.

The development of B cell lineage can be divided into two main phases: a first antigen independent step (from pre-B cells to mature B
lymphocytes) and a second antigen dependent step (mature B lymphocytes to antibody secreting cells or plasmacytes).

B cells, that encounter appropriate antigens for their surface immunoglobulin receptors and that receive T help, undergo major changes leading to either long-lived memory cells or their differentiation into antibody secreting plasma cells. Antigens that cross-link surface Ig molecules, induce B cells to enter in the cell cycle, increase in size and start DNA synthesis for cell division. Antigens are internalized and can be reexpressed in association with MHC Class II molecules at the cell surface and then recognized by T cells via their T cell receptor.

Thus B cells, like macrophages, antigen presenting cells and other Class II positive cells, can present antigen to T cells and stimulate production of T cell secreted factors that induce differentiation and proliferation of B cell themselves. B cell maturation leads either to mature plasma cells that produce large amounts of antibody molecules or to long-lived memory B cells. Several interleukin are involved in the regulation of B cell maturation. IL-4 was shown to be involved mainly in the early activation of resting B cells. IL-5 was found to be responsible for the proliferation of activated B cells. IL-6 is an important factor in the final differentiation of activated B cells into high rate Ig secreting cells. IL-2 and
INF-g also show differentiation activity and induce Ig secretion in B cells (246).

In addition to their surface antibody, B cells express a large number of other cell surface receptors to regulate their complex responses.

The mature B cells express receptors for complement fragments (C3d and C3b), IgG antibodies, interferons and IL-4, which is a major B stimulating factor produced by activated T cells. Upon their activation, B cells express additional receptors that can modulate their growth and differentiation.

Recognition is the function of variable regions of immunoglobulins and effective action is the function of constant regions, by interacting with other molecules or cells (246).

Immunoglobulins have two sites, one of which recognises and reacts with a foreign molecule (antigen) and one of which activates one or more of the host defence mechanisms.

The structure of the heavy chains determines the location and type of host response to be recruited, while the structure of the light and heavy chains confer antigen specificity on the system (196).

Following rejection of tissue grafts differing at the MHC, antibodies appear in the serum of the recipient which are able of detecting MHC products on the surface of many donor cells.
This antibody response is generally rapid and strong, consisting of both an early IgM and then a late IgG phase. Other histocompatibility antigens can also induce antibody responses.

This property of the MHC has made tissue typing in allogeneic population possible.

The mechanisms involved in the destruction of grafted tissues by humoral antibodies involve a wide variety of effector agents, including complement, granulocytes, mononuclear cells, platelets and vasoactive substances.

It has been found, for example, that xenografts of primarily vascularized organs can be routinely destroyed in acute fashion by preformed, "naturally occurring" antibodies or by antibodies formed in response to the foreign tissue itself, whereas skin grafts, that possess no MHC antigens that are foreign to their new hosts, fail to provoke detectable humoral responses, and their rejection appears to be largely mediated by immunologically specific mononuclear cells (240). There are even instances in which antibodies specifically reactive with graft antigens have been shown to be responsible for prolongation rather than curtailment of the survival of allografts (241-243).

Much of the difficulty posed by the action of humoral antibody can be avoided through the use of screening procedures that identify those
individuals whose sera contain antibodies that would be expected to cause graft damage; the immediate and principal effects on organ grafts are invariably found to be alterations in the structure and function of small vessels within the graft (240, 244), and this is particular clear in the case of preformed major blood group antibodies or anti-HLA antibodies.

In the usual circumstances in which transplantation is carried out, the problem of rejection is thought to be created largely by cellular responses of the graft recipient, and suppression of T-cell functions is accompanied by the suppression of humoral antibody formation as well, either because of direct effects on B-cells or because helper activity is greatly diminished (240).

Antibodies generated in response to foreign antigens can manifest other actions:

- promote phagocytosis and subsequent digestion of microorganisms by acting as cytophilic antibodies or opsonins;

- when combining with the surface of microorganisms may prevent their attachment to susceptible cells or susceptible mucosal surfaces;

- when specific for microbial toxins, neutralize the effect of these materials;
- by combining with microbes and antigens and activating the complement sequence, induce inflammatory response and bring fresh phagocytes and serum antibodies to the site of infection;

- when combining with surface antigens, may activate the complement sequence and cause cell lysis; host cells bearing new antigens on their surface as a result, for example, of virus infection, are lysed in the same way;

- when combining with the surface of microorganisms, agglutinate them, reducing the number of separate infectious units and making them more readily phagocytosed (182).

5 - Antibody dependent cellular cytotoxicity

Antibody dependent cell cytotoxicity (ADCC) has traditionally been attributed to killer cells, macrophages and NK cells, which bind to antibody coated target cells through Fc receptor on the effector cells.

The population of K cells mediating ADCC is phenotypically indistinguishable from the NK population; in addition to sharing common membrane antigen phenotypes, both NK and K cells have IgGFc receptors capable of affixing cytophilic antibody.

The apparent phenotypic similarity between K and NK cells suggest the same cell might mediate both cytotoxic activity.
In human transplant recipients, specific donor directed ADCC has been associated with acute rejection in some studies (245, 247, 249), but in other studies ADCC has been infrequently detected during rejection (250). Several reports have demonstrated the presence of anti-donor ADCC in recipients with functioning transplant, and consequently suggested that it does not represent a relevant effector mechanism of rejection.

On the basis of available information, ADCC would appear to represent a highly sensitive, ancillary effector mechanism that may have an important role in delayed or chronic rejection in immunosuppressed host, and/or perhaps in genetic recipient/donor combination that tend to preferentially elicit alloantibody responses (246, 251).

6 - Complement

Antibodies were discovered between 1880 and 1890, but it was revealed soon after that the ability of antibody to inactivate foreign material depends upon the collaboration of another factor, the complement.

Complement consists of a series of proteins, many of which are proteinases. This system of enzymes non-specifically complements the
immunologically specific effect of the antibodies by the opsonization and lysis of red cells (in experimental systems) and bacteria.

The complement system performs three vital functions:

- cell activation
- cytolysis
- opsonization: rendering cells vulnerable to phagocytosis by the adherence of opsonins, for example, that is complement components (252).

The proteins of the complement system form two interrelated enzyme cascades, termed the classical and alternative pathways, providing two routes to the cleavage of C3, the central event in the complement system (Fig. 10).

The enzyme cascades are generated by the activation of precursors which are fixed in turn to biological membranes.

Because each enzyme can activate many enzyme precursor molecules, each step is amplified, the whole system forming an amplifying cascade associated to membranes or immune complexes.

The first component (C1) consists of three principal subfractions, C1q, C1r and C1s, and is activated in the classical complement pathway, after C1q combines with immunoglobulin in immune complexes (antibodies bound to antigens). The activated first component is an
enzyme system, and acts on the next component to form a larger number of molecule of the second component's enzyme. This in turn activates larger amounts of the next component, and so on, producing a cascade reaction. The later complement components have various biological activities, including inflammation and cell destruction.

Fig. 10 - Classical and alternative pathways in complement activation.
A convertase can also be generated independently of antigen-antibody reactions and C142 formation. It can be generated by certain substances such as microbial polysaccharides and endotoxins, IgA antibodies in an immune complex, or as a result of activation of the properdin system (182).

C3b is recognized by receptors on many various cell types, including macrophages and B cells and the binding of C3b to antibody coated bacteria is an essential step for the phagocytosis of these agents by macrophages bearing receptor for C3b. On the other hand, C3b is critical for the engagement of the terminal components of complement (C5, C9) to form the membrane attack complex which causes cellular lysis; the C5b-C9 is responsible for the complement lesion in membranes.

In addition to the role of the complement system in opsonisation and as a lytic material, several of the complement fragments (C3a, C5a) formed during activation are potent mediators of inflammation. C3a binds to receptors on mast cells and basophils and induces the release of histamine and mediators of anaphylaxis. C5a is also a chemotactic attractant for neutrophils and monocytes (246)
7 - Immune-complexes

Another way by which immunological tissue damage can be produced is the immune complex-mediated tissue damage, that occurs when soluble antigens combine with soluble antibodies. This form of tissue damage is not confined to the surface of cells, and can occur locally in a particular tissue or systematically via the circulation.

Its inflammatory effect follows the activation of complement and phagocytic cells by immunoglobulins of classes IgG, IgA or IgM.

The combination of antibodies with microbial toxins and other pathogen-derived factors has an important physiological role in neutralizing their effects and antibodies are also of critical importance in transporting antigen to germinal centres in lymphoid tissues, to stimulate the recruitment and proliferation of B lymphocytes.
MECHANISMS OF REJECTION

Allografts are susceptible to destruction by both immunologically specific cellular and humoral mechanisms, and also by various non-specific inflammatory mechanisms (199, 253).

Factors that may explain differences in the sensitivity of various types of solid allografts to rejection include lymphatic drainage, access of the host circulation to the graft by ingrowing host capillaries or direct anastomoses between recipient and donor blood vessels, and the extent to which recipient alloreactive cells come into contact with donor alloantigen presenting cell populations that express Major Histocompatibility Complex antigens, including tissue macrophages, dendritic cells, endothelial cells, and passenger leukocytes in the graft (209); there is now convincing evidence to suggest that dendritic cells within the allograft are a major immunologic stimulus for elicitation of the rejection process (254-256).

The changes which occur in transplant rejection have been described under 3 main headings: cellular, vascular and glomerular. It is appreciated that, from the point of view of aetiology and pathogenesis, this may be an artificial division. For example, in the case of cellular rejection, host cells damage the endothelial cells of the interbular
capillaries of the graft allowing cells to escape into the interstitial tissues. By the time a human kidney graft is removed or biopsied, these changes have usually progressed, so that the picture is one of cellular infiltration of the oedematous interstitial tissues; for this reason, this type of change is described under cellular rejection although, clearly, damage to vessels is responsible for the characteristic appearances.

In vascular rejection there is swelling and frequently deposition of fibrin within the vessel lumen or wall and later, intimal changes occur which severely restrict the lumina of the vessels involved. Sometimes the fibrin deposition may be associated with cellular infiltration, resulting in an arteritis. Generally, the earliest changes of rejection tend to be associated with cellular infiltration and the later ones with vascular damage, but the two may coincide or overlap.

In fact, it has been attempted to unify the cellular and vascular types of rejection by suggesting that both were due to the activity of characteristic mononuclear cells.

In cellular rejection, these cells damaged the endothelium of the intertubular capillaries, whilst in vascular rejection they disrupted the endothelium of the preglomerular vessels.
It is now evident that whilst the cellular type of rejection represents cell-mediated immunity, the various forms of vascular rejection are related to humoral immune mechanisms.

Porter (257) described 4 main types of transplant rejection:

**Type 1:** Acute and immediate rejection, due to some form of presensitization, or major blood group incompatibility. This may occur almost immediately and is characterized by a sludging of red cells and the formation of thrombi within the glomerular capillaries. This is frequently called hyperacute rejection.

**Type 2:** Acute and early rejection, which usually occurs between the second and the tenth day. This form of rejection is characterized by cellular infiltration, particularly in relation to the peritubular capillaries.

**Type 3:** Acute and later rejection, from the eleventh day onwards. This is essentially a vascular form of rejection, which is due to a deposition of immunoglobulins and complement on arterial, arteriolar, and glomerular capillary walls. Platelets and fibrin may be found lining these vessels.

**Type 4:** Insidious and late rejection related to the subendothelial formation of deposits of IgM and complement in the glomerular capillary wall.
Type 1 of Porter's classification has been described as immediate or hyperacute rejection; it is due to the presence in the recipient of preformed circulating antibodies which become fixed to the graft immediately the blood of the recipient begins to circulate through it. This form of rejection does not often pose a problem for the pathologist. The transplant surgeon frequently recognizes its occurrence before the operation is completed.

Type 2, 3 and 4 of Porter's classification correspond approximately with cellular, vascular and glomerular changes which are usually used to describe the alterations occurring in rejection. Although cellular rejection occurs characteristically in the early stages of the life of a transplant, varying degrees of rejection may be found throughout the life of any transplant. Vascular rejection may occur as an early manifestation of rejection, or as a late phenomenon in a transplant which has functioned for many years. In the more acute form of vascular rejection, the changes consist of the deposition of fibrin in the walls and lumina of arteries and arterioles, sometimes associated with inflammatory changes. In the more chronic form of vascular rejection, there is intimal proliferation which produces narrowing of the vessels concerned. Although the more acute form is usually seen early in the life of the graft, it may be found at any time. Similarly, the intimal proliferative changes are more characteristic of
a transplant which has survived for some years, but they may also be found within weeks or months.
**Types of rejection**

1. **Hyperacute rejection**

   It occurs rapidly, often within minutes of establishing blood flow, and is characterized by heavy platelet deposition, endothelial damage in both large and small vessels, prominent polymorphonuclear leukocyte infiltrate, relatively poor lymphocyte infiltrate (258, 259). Antibodies have been shown to be deposited within the rejected kidneys, and this type of rejection is generally thought to be due to preformed humoral antibodies directed against donor alloantigens (209, 260). It is often apparent to the surgeon who performs the transplant when, after an initial period of normal tone and colour, the kidney becomes soft and cyanotic. If urine formation has commenced, this then ceases abruptly. The morphological appearances of this hyperacute form of rejection are dependent upon the time which lapses between the establishment of the blood supply and taking of the biopsy.

   If the homograft is left in situ, further changes will take place. Thrombosis of arterioles and glomerular capillaries occurs with necrosis of their walls, accompanied by interstitial edema and hemorrhage, and tubular necrosis. Within a few days, the histological picture is one of patchy cortical necrosis leading to complete infarction.
Immediate or hyperacute rejection is usually seen where there is a major ABO blood group incompatibility between donor and recipient, or when the recipient has been presensitized.

2 - Acute rejection

Acute rejection can be of cellular or vascular type.

When rejection occurs early in the course of the renal transplant, it is usually manifested histologically by focal infiltrates of mononuclear cells. These cells consist of small lymphocytes, plasma cells, and larger cells, many of which have a round or indented vesicular nucleus with 1 or more nucleoli, and abundant basophilic cytoplasm; these large mononuclear cells have been called activated T lymphocytes.

The infiltrating cells tend to be perivascular and periglomerular in their distribution.

The close proximity of the large mononuclear cells to the endotelium of the intertubular capillaries has been observed. It is believed that these cells damage the endothelial cells of the capillaries allowing the escape of red cells and plasma into the interstitial tissues (261, 262) (Fig. 11).

Progressive damage with disruption of the walls of the peritubular capillaries follows, allowing more fluid and cells to accumulate in the
interstitial tissues in the areas previously occupied by the intertubular capillaries. This leads to an inadequate tubular perfusion, with resultant tubular necrosis and oliguria. The very early stages of cellular rejection are
not often seen in the human allograft, because a biopsy may not be taken until the changes have progressed sufficiently to cause clinical evidence of rejection. As cellular rejection develops, varying degrees of separation of the tubules by cells and fluid occur, and there may be interstitial haemorrhages. Usually the cellular infiltrate is focal in nature, but may sometimes appear diffuse. The maximum concentration of cells is usually around small blood vessels. These arterioles and small intertubular arteries frequently show swelling and eosinophilia of the muscle layer and are lined by swollen endothelial cells, which often project into the lumen.

If cellular rejection is treated adequately the cellular infiltrates and interstitial oedema disappear. Tubular epithelium regenerates and it is common, in biopsies taken during rejection, to see varying number of mitotic figures in the tubules.

It is not uncommon to see minor abnormalities involving small arteries and arterioles in rejection occurring early in the post-transplant period. These changes occur mainly in vessels which are in the area of the graft affected by the cellular infiltration, but may also be seen in areas where this is absent. The muscle fibres of the media are swollen, poorly defined, and often exhibit a patchy eosinophilia. A conspicuous vacuolation of the muscle fibres may often be present. The endothelial cells instead of forming a flat lining are swollen, rounded, and rather prominent. Since
vessels away from the areas of cellular infiltration may be affected, it is possible that some of the changes are merely a reflection of non specific ischaemic damage. The principal histopathological changes seen during vascular rejection are:

1) Fibrin deposition in arterial and arteriolar walls, sometimes associated with inflammatory changes.

2) Intimal changes producing varying degrees of narrowing of the lumina of involved vessels.

These 2 pathological manifestations of rejection may also be interpreted as acute and chronic respectively, both with regard to the nature of the change and with reference to the element of time.

Acute allograft rejection is the most common cause of allograft loss in transplantation; it continues to be seen with all types of immunosuppression and can even occur in HLA identical donor recipient pairs (209). It has been observed that acute rejection occurs far more commonly in the initial 6 weeks after allografting, and decreases in both incidence and severity after this time (263).

However, the great majority of acute rejection episodes occur within the first 90 days post-transplant.

The higher is the degree of vascular injury and the presence of antibody-producing cells in the graft, the poorest is prognosis for survival
of the allograft (262, 264, 265). Cellular infiltration within the interstitium of graft can often be rapidly and completely reversed by immunosuppressive agents, especially the steroids, whereas vascular damage is more resistant to reversal by immunosuppressive drugs (209).

3 - Chronic rejection

Whilst it is evident that acute rejection is obvious to the clinician, the same cannot be said of chronic rejection. This is a slow and insidious process and may occur in a well-established, and apparently well-tolerated, transplant. Frequently the only clinical manifestation of chronic rejection is a slowly progressive deterioration in renal function.

Porter et al. (257) described changes in the glomeruli in 46 patients who were biopsied at a time when there was no clinical evidence of rejection. In 24 of these cases the glomeruli showed capillary basement membrane thickening which was obvious in 4-micron sections. In the 22 cases which appeared normal on light microscopy, all showed fusion of the epithelial foot processes on electron microscopy, and in over 60 per cent there was small deposits between basement membranes and endothelial cells.

In most of the 24 cases which were optically abnormal, the P.A.S.-positive basement membrane thickening was patchy, and associated with deposits of P.A.S.-positive material in the mesangium. Less frequently, the
basement membrane thickening was generalized, producing appearances resembling membranous glomerulonephritis. These changes were associated with local areas of hypercellularity in 21 per cent of the cases, and in 37 per cent adhesions were present between the tuft and glomerular capsule. Electron microscopy showed that in all 24 cases there was fusion of the epithelial pedicles and subendothelial deposits of amorphous material of varying density and compactness. Hypertrophy of both epithelial and endothelial cells was frequently present, and often the mesangial cells showed hyperplasia.

Biopsies from 24 of 46 patients taken in the absence of clinical rejection had glomerular abnormalities obvious on light microscopy, whilst in the remainder the glomeruli appeared normal; many of the 24 patients with obvious glomerular pathology had low creatinine clearances and proteinuria. There is much evidence to suggest that, whilst these cases did not show overt clinical signs of rejection, they probably represented a showly progressive or insidious form of this complication. Certainly a progressive decrease in the creatinine clearance or an increase in the degree of proteinuria would be regarded by many nephrologists as indicating a low grade or chronic form of rejection.

The characteristic glomerular pathology of chronic rejection is often described as a transplant glomerulopathy, and is usually seen in
transplants which survive for several years. There is an irregular thickening of the glomerular capillary walls due to subendothelial deposits and circumferential mesangial interposition. There may be areas of endocapillary proliferation, but often the mesangial changes consist of an expansion of the cytoplasm and matrix rather than an increase in the number of cells.

The obliterative arterial lesion lead to glomerular ischaemia, and in the involved glomeruli the basement membrane is thickened and wrinkled. The affected capillary loops may appear collapsed, and this change plus the expansion of the mesangium produces obliteration of the glomerular capillary lumina.

Chronic rejection has particular morphologic characteristics, different ranking of immunologic mediators, and probably also non immunologic mechanisms for continuing deterioration of renal allograft function in an inexorable course (266, 267) (Fig. 12).

From laboratory studies, it has been suggested that antibody-dependent cell-mediated cytotoxicity (ADCC) may be important in chronic rejection (251, 268).
Fig. 12 - Cellular and molecular cascades in chronic rejection.
REGULATION OF IMMUNE RESPONSES

Most important in the regulation of the immune responses are interferons (INFs), cellular proteins which have a range of effects on cells, including the induction of an antiviral state in cells (269).

Three different types are recognized, denoted as alpha, beta and gamma (270). INF-alfa and beta are produced by cell in response to virus infections (271); INF-gamma is a lymphokine produced by T-cells in response to proliferative signals (270).

It has been clear for some times that INFs are able to induce the expression of MHC antigens (272); INF alfa and beta induce only Class I antigens, whilst INF gamma induces both Class I and (on certain cell types only) Class II antigens.

It has already been observed that in cells infected with certain viruses there can be a decrease in MHC antigen display; this could occur either as a decrease in constitutive (mainly Class I antigen) expression or as inhibition of INF-induced expression (especially important for Class II and in tissue with low level of Class I antigens) (269).

A major level of regulation occurs at the transcriptional stage; for both classes of genes, cis-acting DNA elements (promotors and enhancers)
and trans-acting factors (that bind to these elements) have been identified (273).

The regulation of MHC gene transcription and subsequent processing to produce differential expression in different tissues and increased expression in response to INFs is complex, and a number of genes that regulate the expression of MHC have been identified (274, 275).

Factors other than INFs are probably involved in the regulation of MHC antigen expression, although it is not always possible to be sure that other factors may not be functioning via the induction of INFs (269).

For example, tumour necrosis factor (TNF-alfa) and lymphotoxin (closely related to TNF-alpha and usually referred to as TNF-beta) may directly induce MHC antigens (276, 278).

The different INFs interact, INF alfa and beta inhibiting Class I induction by INF-gamma (276, 279, 280); also, prostaglandins and corticosteroids may act antagonistically (281, 282).

INFs can modulate the function of cytotoxic T lymphocytes, via the expression of Class I MHC antigens (283-285).

An essential step in the induction of an immune response to an antigen is the activation of T helper cells, via presentation by APCs which
display Class II antigens, and therefore any modulation of Class II antigen expression may influence immune responses (286).

Macrophages can be induced to express Class II antigens by INF-gamma (287, 288) and Interleukin-2 was found to induce Class II antigen expression as well (289). From different studies, it is concluded that the ability of cells to present antigen to helper (CD4+) T cells is directly proportional to the density of Class II MHC antigens on their surface (289-292).

INF-gamma augments Class II expression and hence the ability of cells to present antigen to T cells (293-297).

INF-gamma may also play a role in the further amplification of an immune response by augmenting Class II MHC expression on other Class II-negative cells (196).
During the 1960s, more than 50% of transplanted patients were dying of infection, with fungal and other opportunistic infections accounting for as many of these deaths as conventional bacterial infections (298).

The importance of infections in the renal transplant patients may extend beyond the direct effect of the infection on graft function, but it has already been observed that there could exist an immunostimulatory effect of the infection itself, thus triggering or potentiating the rejection process.

As early as 1970, Simmons et al. (299) considered infection as a possible trigger for rejection; in fact, they observed that episodes of infection often do not follow treatment for rejection, but can precede and accompany the elevation of serum creatinine on which the diagnosis of rejection usually depends.

Byrd et al. (300) found that Streptococcus faecalis urinary tract infections (UTIs) seemed to be associated with renal allograft rejection, possibly mediated by group A bacterial antigens, which cross-reacted with human HLA antigens; they also reported hyperacute rejection in
transplant recipients with group A Streptococcal bacteremia, presumably transmitted by the donor kidney (301), and hyperacute rejection after peritonitis caused by Streptococcus faecalis (302).

Recently, it has been observed urinary IL-6 production in response to a gram-negative bacterial urinary tract infection in humans, responsible for a more acute output of IgA from mucosal surface, as well as for the systemic responses leading to fever and the acute-phase reaction (303).
1 - **Immunomodulation by bacterial infections**

Endotoxins and lipopolysaccharide (LPS) have been shown to regulate the expression of Ia or MHC Class II genes, the influence being variably positive (304, 305) or negative (306, 308).

LPS possesses a wide spectrum of biologic activities affecting the immune system: it is mitogenic for B lymphocytes (309, 310), a powerful adjuvant (311), and highly immunogenic, eliciting specific as well as polyclonal antibody responses (312, 313).

Administration of LPS to mice causes INF and IL-1 to appear in their blood stream (314), prostaglandin-E release from human monocytes (315) and TNF production (316). In murine spleen cultures LPS has been shown to exert three effects (278, 317);
- first, LPS induces DNA synthesis in most bone marrow-derived B lymphocytes (309, 318, 319);
- second, high concentrations of LPS increase background immune responses to a wide variety of determinants, and the maturation of antibody forming cells is independent of added antigen and has been termed the polyclonal response (309, 320, 321);
- third, low concentrations of LPS stimulate immune responses to antigenic determinants presented in non-immunogenic forms (317).
Mitogenic responses to LPS require the interaction of lipid A with the surface of most B lymphocytes (317, 321, 322); in contrast, the induction of immune responses to LPS results from the interaction of antigenic determinants in the polysaccharide region with immunoglobulin receptors on B lymphocytes (207, 323, 324).

The ability to respond well to LPS is dominant, as shown by the response of F1 hybrid mice of low responder and high responder strains (317).

In case of inhibition of Ia antigen expression, it has been suggested that LPS inhibits gamma-interferon (INF) regulation of macrophage Ia antigen expression by stimulating macrophage prostaglandin-E2 production, and consequently enhancing intracellular cAMP levels, outlining the inhibitory pathway involved in the regulation of macrophage Ia antigen expression, and explaining, in part, the reported immunosuppressive effects of LPS (306).

Macrophages play a central role in the modulation of the immune response. Injection of live bacteria (e.g. Listeria monocytogenes) cause an increase not only in the number of macrophages, but also in the percentage of Ia bearing macrophages (20 to 60 % Ia+ cells), and this event is a T-cell dependent event mediated by the action of lymphokines
a lymphokine responsible for Ia induction in vitro has been identified as gamma-interferon (328-330).

The ability of macrophages to present antigens to T lymphocytes has been shown to be directly related to the level of Ia expression by the macrophage population (331-333).

Ziegler et al. (304) concluded that both LPS- and Lysteria monocytogenes-induced macrophage populations stimulate the proliferation of antigen-specific T cells more effectively than normal macrophages in LPS-responder mice.

Furthermore, Steinman et al. (325) and Steeg et al. (334) reported that culture supernatants of Trypanosoma cruzi-activated spleen cells enhanced macrophage Ia antigen expression in vitro; but, it was demonstrated (307) that Escherichia coli endotoxin and Saccharomyces cervisiae zymosan A can inhibit T-cell activation by interfering with antigen presentation, reducing the proportion of Ia bearing cells in the macrophage population, and that this reduction correlates with a depression in antigen-induced T-cell activation.

Different cell lines derived from non-marrow derived cells respond in vitro with increased MHC product expression, with an increase in Class I or Class II mRNA, indicating that transcription is probably a major site of control via the "de novo" synthesis of a transacting activator protein.
it has already been established that INFs induce mainly increased MHC product expression, and only gamma-interferon can induce "de novo" Class II antigen expression (340, 341).

Jayawardena et al. (342) found an enhanced expression of H-2K and H-2D antigens on reticulocytes infected with *Plasmodium yoelii*, and that it correlated closely with the ability of these strains to control the infection.

It has recently been observed that CD4+ and CD8+ T lymphocytes both contribute to acquired immunity to blood-stage *Plasmodium Chabaudii AS* (343).

2 - Immunomodulation by viral infections

Another question studied by different authors is whether Cytomegalovirus (CMV) infection can induce allograft dysfunction, and if so, how. Some investigators found no correlation between these two events (344, 345), whereas others reported a striking correlation (346, 347).

Fryd et al. (348) reported a 20% decrease in one-year graft survival in patients with CMV infection compared with those without infection.
Richardson et al. (349) indicated that CMV infection can result in acute allograft dysfunction, that is associated with distinctive glomerular abnormalities. This lesion consists of endothelial cell injury, accumulation of mononuclear cells and deposition of IgM, C3 and fibrin in the glomerulus, suggesting the possibility of an immune complex-mediated lesion. Both immunoglobulins and CMV antigens were demonstrable in the mesangium by immunofluorescence. In murine CMV infection, viral replication occurs in the mesangium and a mesangiopathic glomerulonephritis results (350, 351).

Endothelial involvement in human CMV disease has been documented as well, with classical CMV-associated morphologic derangements (cytomegaly, nuclear and cytoplasmic inclusions) (352-354).

Baldwin et al. (355) found that transplant patients, who develop primary CMV infections, produce elevated levels of circulating IgM and IgM-immune complex-like material; but as reported by Johny et al. (356), there is no correlation between the occurrence of these antibodies and reversible or irreversible rejection episodes.
Increase in MHC antigens display in cells infected with viruses

Von Willebrand et al. (357) observed that 86% of cases with proved CMV disease were associated with a cytological diagnosis and/or clinical episode of rejection, while the frequency of rejections in transplant recipients without proved CMV disease was only 17%.

Their results suggest that the display of Class II antigens on the graft, presumably mediated by gamma-interferon or other virally induced lymphokines, is the reason for graft rejection in the context of CMV disease. On the other hand, there may be situations where viral infection of cells may directly induce the expression of MHC antigens without the intervention of INFs (358).

Fleyer et al. (359) found that fibroblasts infected with Moloney murine leukemia virus (M-Mu-Lv) exhibited up to 10-fold increase in cell surface expression of the Class I MHC antigens. M-Mu Lv appears to exert its effect at the genomic level, because mRNA specific for Class I antigens, as well as Beta-2-microglobulin, show a fourfold increase. The same authors, on the other hand, found that Moloney sarcoma virus (MSV) shows no increase in MHC antigen expression or Class I mRNA synthesis. Quantitative differences in Class I antigen expression on virus-infected cells were also found to influence the susceptibility of infected cells to lysis by H-2 restricted, virus specific cytotoxic T lymphocytes.
Measles viruses induce Class I and II antigens on astrocytes (360).

Infection with Simian immunodeficiency virus (SIV) or Human immunodeficiency virus (HIV-1) induces Class II MHC antigens on T cell tumour lines in vitro (361), and the infected cells do appear not to secrete INF or any other factor able to induce Class II antigens.

After intrathymic inoculation, the Radiation leukemia virus (Rad LV) also induces an increase in the expression of H-2D on the thymocytes of resistant strains, whereas leukemic cells in susceptible strains do not express Class I antigens (330); the mechanisms responsible for these modulations are still not clear.

b - Decrease in MHC antigens display in cells infected with viruses

Decrease in MHC expression in cells infected with viruses benefits survival of the virus itself: decreased "visibility" of the virus results in reduced immunogenicity and in reduced effector cell recognition (362).

Class I:

Decreases in Class I antigen expression in infected cells have been described for cells infected by Vesicular stomatitis virus (VSV) (363), Herpes simples virus type 1 (HSV-1) and type 2 (HSV-2) (364),
Adenoviruses (365, 366), Hepatitis-B virus (HBV) (367, 368), Rous sarcoma virus (RSV) (369), Moloney sarcoma virus (MSV) (320), and Kirsten MSV (Ki-MSV) (362, 370).

The mechanisms of action are apparently diverse, affecting gene transcription, the post-transcriptional processing or the induction of INF-inducible genes (362). The consequences of reduced Class I antigen expression are expected to include reduced susceptibility to T-cell lysis.

High Class I expression can be restored, for example, in Adenovirus-transformed cells, with alpha or beta-INF (371) or gamma-INF (372, 373), leading to the loss of tumorigenicity of the cells.

Rosenthal (253) observed that transformation of primary rat cell cultures by the oncogenic Adenovirus 12 (Ad-12) results in suppression of the transplantation antigens (MHC Class I), thus enabling the transformed cells to escape the immune detection by Class I-restricted cytotoxic lymphocytes and efficiently form tumours in vivo; in contrast, transformation of the same cell with the non-oncogenic Adenovirus 5 (Ad-5) does not suppress the transplantation antigens and consequently they elicit an effective MHC-restricted immune response (374).

This difference in oncogenicity has been associated with the early region (E1A) of Ad5 and Ad12, which, early in infection and in
transformed cells, produces two major transcripts, 125 and 135, coding for nuclear phosphoproteins of 220 and 266 aminoacid residues (330); thus, E1A gene products can apparently influence Class I gene expression both positively and negatively, by mechanisms that are not fully understood, but appear to involve cellular transcription factors. In contrast, the non-oncogenic Ad5 interferes with Class I expression at a post-transcriptional level, by producing a glycoprotein, designated E19, which binds to nascent Class I molecules in the endoplasmic reticulum and prevents their transport to the membrane (330).

**Class II:**

Induction of Class II antigen expression in mouse fibroblasts by INF is inhibited by infection with Ki-MSV (375).

However, there is little information on whether viruses able to reduce Class I expression can also reduce Class II expression (370).

c - **Other mechanisms of immunomodulation**

London et al. (376) showed that antibodies directed against Hepatitis B virus surface antigen (anti-HBsAg) were clearly associated with early kidney-graft rejection, perhaps related to an early recognition of HLA antigens (while the presence of HBsAg did not affect graft
survival); it was subsequently observed that Y-linked histocompatibility antigens (H-Y antigen) influenced the host response to both HBsAg and HLA antigens (377). Collard (378) and Yarchoan (379) observed that Influenza virus stimulated in vitro T cell-dependent specific antibody production by human lymphocytes; these findings were confirmed by Lamb et al. (380), who found that the virus-specific antibodies production to Influenza A virus induced antigen-specific and HLA restricted induction of helper activity mediated by cloned human T lymphocytes.

Manus (366) observed that Retroviruses have a pronounced effect on proximal tubule cells, affecting the alterations not only in morphology and antigen expression, but also in cellular mechanisms that appear to be necessary for progression to a full malignant phenotype.

Some authors (382-384) observed that Epstein-Barr virus (EBV) may be responsible for a B-cell lymphoproliferative syndrome; Schooley et al. (385) observed that all primary or reactivated Herpes virus infections occurring in the first three months after transplantation in recipients of cadaveric grafts were accompanied by a persistent inversion of OKT4 to OKT8 lymphocytes; these patients are more likely to show glomerular lesions and not episodes of rejection, that would be accompanied by an increase of OKT4/OKT8 ratio (80, 386, 387).
The pathogenesis of glomerulopathy is unclear, but it could also be possible that it is a special form of graft rejection that is somehow promoted by viral infection.
Two distinctive features of Class I and Class II antigens in renal allografts are that they have different distribution in the kidney and can be induced in different ways (266) (Table 6).

Class I antigens are present constitutively on essentially all cell types of the renal parenchima, but are located intracellularly in the tubular cells and less densely on dendritic cells than are Class II antigens (388, 389). In contrast, Class II antigens are densely represented on dendritic cells, but are absent from large vessel endothelium, glomerular epithelial cells in Bowman's capsule and tubular epithelial cells when there is no ongoing immune activity. Other important renal sites of Class II antigens include the mesangial cells that are bone-marrow derived, and the endothelium of glomerular capillaries, efferent arterioles, interlobular cortical and medullary capillaries, and vasa recta (388-391).

The interstitial dendritic cells, which are a special portion of the bone-marrow-derived "passenger leukocytes" and richly endowed with Class II HLA antigens, are the most potent source of recipient sensitization. The Class of HLA antigens, their location and their density...
### Table 6 - HLA-ANTIGENS IN THE KIDNEY

<table>
<thead>
<tr>
<th></th>
<th>Vascular Endothelium</th>
<th>Glomerulus</th>
<th>Tubules*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endothelium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>Artery</td>
<td>Capillary</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Endothelium</td>
<td>Mesangium</td>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>++</td>
<td>++</td>
<td>0/+</td>
</tr>
<tr>
<td>(HLA-A, -B, -C)</td>
<td>++</td>
<td>++</td>
<td>0+</td>
</tr>
<tr>
<td>Class II</td>
<td>0/+ $^\uparrow$</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>(HLA-DR)</td>
<td></td>
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</tbody>
</table>

* The location of Class I and class II antigens may be on the cell membrane as well as intracellular, depending on whether an immunofluorescence or immunoperoxidase technique was used.

A inducible most notably in rejection.

From Braum W.E., 1989 (266)
may all influence the type of rejection that occurs. For example, the dense presence of Class II antigens on interstitial dendritic cells would be expected to elicit predominantly Th lymphocyte infiltrates in the interstitium (385, 392).

<table>
<thead>
<tr>
<th>Increased</th>
<th>Decreased</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic control</td>
<td>Chloramphenicol</td>
<td>Lypopolysaccharides</td>
</tr>
<tr>
<td>G2 phase of cell cycle</td>
<td>Glucorticoids</td>
<td>Viral infection</td>
</tr>
<tr>
<td>Cell differentiation stages</td>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Interferon (IFN alfa, beta, gamma)</td>
<td>Prostaglandine</td>
<td></td>
</tr>
<tr>
<td>Tumor necrosis factor</td>
<td>Ultraviolet light</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Immune complexes</td>
<td></td>
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<tr>
<td>Calcitriol</td>
<td>Fc receptors binding</td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>alfa-Fetoprotein</td>
<td></td>
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<tr>
<td>Mitogens</td>
<td>Certain neoplasms</td>
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<tr>
<td>Microbial antigens</td>
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<tr>
<td>Adjuvants (beryllium)</td>
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<tr>
<td>Activated T cells</td>
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<tr>
<td>Allograft rejection</td>
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<tr>
<td>GVH I disease</td>
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<td></td>
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<tr>
<td>Autoimmune states</td>
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</tbody>
</table>

(adapted from Braun (266))
In contrast, if Class I are the incompatible ones, then predominantly Tc lymphocytes would appear at the more broadly distributed sites of Class I antigens in the kidney (385, 393).

Incompatibilities for both Class I and Class II would elicit both Tc and Th cellular infiltrates (394).

Factors that enhance HLA expression or increase the number of cells having dense HLA antigen expression, increase the immunogenicity of that tissue and provoke a more vigorous host response (395) (table 7).

The most dramatic changes in expression of HLA antigens relate to Class II molecules (389, 396). The role of Class II antigen expression in provoking rejection is supported by the fact that Cyclosporine, either directly or through the inhibition of IL-2, inhibits the production of gamma-interferon and thereby Class II antigen expression, an effect that may be an additional support to its immunosuppressive action (385).

It has been demonstrated that increased levels of Class II antigens may be detected after transplantation (388). During episodes of allograft rejection, some authors observed that there is a marked increase of MHC Class II expression in the proximal tubular epithelium of the kidney and vascular endothelial cells (397-401); on the other hand, other authors observed not even an absolute correlation between increased levels of
Class II antigens on renal tubules and clinical rejection, but a more significant association between the degree of cellular infiltration and increased Class II expression (385). Since the expression of HLA-DR on the plasma membrane of antigen-presenting cells is usually necessary for stimulation, the increased membrane expression on HLA-A, B, C makes the cells more vulnerable to specific cytotoxic effector mechanisms. In vitro studies have demonstrated that cells on which Class II antigens have been induced are able to function as antigen-presenting cells (402-403). Renal tubular cells expressing Class II antigens may, therefore, act as antigen presenting cells and be an important stimulus of the rejection process (404).

It has been suggested that increased HLA antigen expression on parenchimal cells of the graft during rejection episodes contributes to the pathogenesis of the rejection response, either by increasing immunostimulation or by making the cells more vulnerable to cell-mediated lysis (389).

Bishop et al. (405, 406) suggested that increased HLA expression by graft tubular cells is unlikely to play a role in the induction of the rejection response, but may play an important role in the effector phase of the immune response, by ensuring that only specific cytotoxic effector cells mediate cytotoxicity and that non-specific cytotoxic effector cells that are
attracted to the site do not lyse parenchymal cells on the graft; the specificity of effector mechanisms is enhanced by interferon-gamma induction of HLA antigens.
INFECTION IN RENAL TRANSPLANT PATIENTS: IMPACT ON GRAFT FUNCTION AND PATIENT SURVIVAL

We have encountered, in our clinical practice, a number of apparent rejection episodes in recipients of renal allotransplants which were accompanied by episodes of rather mild local or systemic infection; in some case the infection appeared to precede, rather than follow, the renal functional deterioration. The correlation of infections complications with rejection suggests that there is a pathogenetic relationship between the two which is not solely the result of excessive dose of immunosuppression. The immunosuppressed patient is highly susceptible to infection. However, the coincidence of infection and rejection has not been extensively considered as a possible trigger for rejection; generally, has been assumed that the rejecting kidney is treated with such large doses of immunosuppressive drugs that severe infection follows.

The occurrence of nonlethal infections associated with mild reversible deteriorations in renal function has been a striking and consistent finding in renal transplantation; however, often the infections do not follow treatment for rejection; they precede and accompany the elevations of serum creatinine levels on which the diagnosis of rejection usually depends.
The functional loss as well as the infections themselves may be either mild or severe. The milder episodes may respond to short courses of antirejection therapy and may well respond merely to the subsidence of the infection. On the other hand, other infections may precede rejection episodes which are difficult to control. In practice therefore sudden deterioration of renal function should suggest an occult infection and even mild infections should prompt a search for renal functional deterioration.

No simple explanations for the concurrence of infection and rejection are at hand, but a number of possibilities should be considered.
UNANSWERED QUESTIONS

There are some questions that need to be answered, in order to elucidate if there is a mechanism by which infectious agents can affect human allograft function, i.e. how can the infectious process upset the immunological balance that has been established between the donor organ and the host:

1 - to which extent can an infectious process affect graft function and patient survival?

2 - since it has already been observed that an episode of infection can trigger allograft rejection, it would be important to establish which cells inside the graft can be altered during an infectious process, and whether this implies the induction or re-expression of MHC Class I and Class II antigens.

3 - The infectious agent could act on renal parenchymal cells, affecting their morphology and antigen expression, or the induction of HLA antigen.

4 - The graft function could be affected by antibodies formed during the infection itself and deposited in the glomerular capillary wall or in the mesangium, leading eventually to an immune-complex lesion.
PERSONAL EXPERIENCE

To our knowledge, this is the first comprehensive review of the effects of infections complications on graft and patient survival and the relationship between infection and rejection in clinical renal transplantation.

In the first part of our clinical study we reviewed retrospectively a group of transplant patients, aiming to observe if an infectious process is able to affect graft function and patient survival.

Then we looked particularly at urinary tract infections and correlated them with the symptoms presented by the patients and eventually with impairment of renal function.

Furthermore, we looked at all the rejection episodes, their relationship with timing and localization of the infectious process and the infecting organisms responsible for them.

Materials and methods

We considered 160 patients, aged between 15 and 73 years (mean age 43), transplanted between 1985 and 1990 at the Renal and Transplant Unit of the Institute of Urology and Nephrology, University
The patients underwent transplantation in a stable and well dialysed state. All the transplants were performed using end-to-side vascular anastomoses to external iliac vessels and the ureteral anastomosis direct to the bladder; in patients with an abnormal lower urinary tract (e.g. ileal conduit, augmentation cystoplasty, etc.) the ureteral anastomosis was performed to the segment of bowel. An ureteral double J stent was inserted and it was removed 3 months after transplantation. A bladder catheter was kept in place for three days.

At the time of transplantation, the patients were given i.v. antibiotics that were continued in the post-operative period as required.

Post-operatively, the patients were placed on standard therapy (Cyclosporine A and low dose oral prednisolone); the CyA dosage is adjusted so as to maintain CyA levels at 115 - 250 ng/ml in the first nine weeks post-transplant, and thereafter between 60 - 115 ng/ml.

Patients who received a previous transplant, highly sensitized patients or those who showed CyA nephrotoxicity were placed on triple therapy, adding azathioprine.

Antilymphocyte globuline (ALG) was given to all patients who had at any time a panel reactivity of > 80% or who were not functioning on the day after transplantation.

All the patients were followed up regularly after discharge from the hospital on an outpatient basis.

- predisposing conditions to post-transplant infections
- complications
- blood group
- immunosuppression
- immediate graft function

b) as far as concerning the graft

- source (cadaver vs. living donor)
- donor age
- number of antigens matched
- cold ischemia time (all the kidneys were perfused in citrate solution)
- infection of the donor / culture of the perfusate

c) as far as concerning the type of surgery

- type of ureteric anastomosis

(all of the transplant were performed using end-to-side vascular anastomoses to external iliac vessels, while, in patients with an abnormal lower urinary tract, different ureteric anastomoses were performed).

d) type of infection

All the collected data were analyzed with BMDP-77 (Biomedical Computer Programs P-series) installing on IBM-4381 Computer; the obtained data were correlated with the number and type of infections developed in the first year after the transplant, with the graft function and with patient survival.

The statistical elaboration of all the data has been made by package BMD-P and by the test "Z Fischer" for proportions; the results of the test were considered to be significant when the values of Z are ≥ 1.96, that corresponds to values of p ≤ 0.05 (i.e. significant with a 5% of probability of error).
The computer analysis was used to determine the prevalence ratio of infections in each group of patients, that is the incidence of the infections in relation to the number of patients, and to observe the percentage of 1-year graft and patient survival.

**Results**

The type of infections that occurred in the first year after the transplant in our patients population have the following localization:

<table>
<thead>
<tr>
<th>Localization</th>
<th>Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>urine</td>
<td>193</td>
</tr>
<tr>
<td>lung</td>
<td>24</td>
</tr>
<tr>
<td>systemic viral infections</td>
<td>19</td>
</tr>
<tr>
<td>peritoneum</td>
<td>12</td>
</tr>
<tr>
<td>upper respiratory tract</td>
<td>10</td>
</tr>
<tr>
<td>blood (bacteraemia)</td>
<td>8</td>
</tr>
<tr>
<td>wound</td>
<td>6</td>
</tr>
<tr>
<td>kidney</td>
<td>4</td>
</tr>
<tr>
<td>cerebral</td>
<td>1</td>
</tr>
<tr>
<td>pelvic abscess</td>
<td>1</td>
</tr>
</tbody>
</table>
Most of the infections occurred in the first 6 months after the transplant; after that period, we could observe only the presence of recurrent urinary tract infections. (Tab. 8 e 9).

<table>
<thead>
<tr>
<th>Table 8 - Site and onset time of infections in our patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Urine</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Systemic viral</td>
</tr>
<tr>
<td>Peritoneum</td>
</tr>
<tr>
<td>Upper resp. tract</td>
</tr>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>Wound</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Cerebral</td>
</tr>
<tr>
<td>Pelvic abscess</td>
</tr>
</tbody>
</table>
Table 9 - Site and onset time of infections in our patient population

<table>
<thead>
<tr>
<th>Site</th>
<th>1 month</th>
<th>2 month</th>
<th>3 month</th>
<th>4 month</th>
<th>5 month</th>
<th>6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>16</td>
<td>14</td>
<td>6</td>
<td>2</td>
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<tr>
<td>E. coli</td>
<td>28</td>
<td>20</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>7</td>
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<tr>
<td>Strept. faecalis</td>
<td>22</td>
<td>15</td>
<td>8</td>
<td>2</td>
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<td></td>
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<tr>
<td>Proteus</td>
<td>5</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Candida</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nocardia</td>
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</tr>
<tr>
<td>Strept. Pu</td>
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</tr>
<tr>
<td>Aspergillus</td>
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</tr>
<tr>
<td>Pseudomonas</td>
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<td>Legionella</td>
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<td>P. aeruginos</td>
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<td>Pneumocystis</td>
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</tr>
<tr>
<td>Unknown *</td>
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<tr>
<td>Systemic viral</td>
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<td>HSV</td>
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<td>CMV</td>
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<td>3</td>
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<td>Peritoneum</td>
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<tr>
<td>Candida</td>
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<tr>
<td>Upper resp. tract</td>
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</tr>
<tr>
<td>Viral</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>1</td>
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</tr>
<tr>
<td>Blood</td>
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</tr>
<tr>
<td>Strept. faecalis</td>
<td>2</td>
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<td>E. coli</td>
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<tr>
<td>Wound</td>
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<tr>
<td>Staph. aureus</td>
<td>4</td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>Pseudomonas</td>
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<tr>
<td>Kidney</td>
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<tr>
<td>Pseudomonas</td>
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<td>E. coli</td>
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<tr>
<td>Pseudomonas</td>
<td></td>
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</tr>
</tbody>
</table>

* Cases clinically suspected but bacteriologically unproven
UTIs are the most common form of post-transplant infections; they represent 69.42% of all the infections considered in the first year post-transplant; in particular they represented 65.62% of infections in the first month post-transplant and 67.96% of infections in the first three months post-transplant. The most commonly isolated organism was Escherichia coli (35.75%), and then Streptococcus faecalis (24.35%), Pseudomonas spp. (19.68%), Klebsiella spp. (8.29%).

If we look now particularly at each group of patients and at the types of infections that occurred, we can make the following observations:

1 - age: patients aged between 15 and 20 years present the highest incidence of infections (prevalence ratio 2.23), 88.89% of which are urinary tract infections. If we look carefully at this group of patients, we can observe that 7 of them (77.8%) had reflux nephropathy as cause of E.S.R.F. (end stage renal failure), and all of them manifested urologic complications in the post-transplant period; 1 patient (11.1%) had a ureteric anastomosis performed to an augmented bladder; in this group of patients, in fact, UTIs account for most of infections (88.89%); 3 of these patients were not on dialysis.

Patients aged between 41 and 50 years have the lower incidence of infections; by the careful analysis of this group of patients we can observe that only 2 patients were not on dialysis; reflux nephropathy as cause of
E.S.R.F. was present in 4 of them (11.1%) and diabetes in 3 patients (8.33%), while most of the patients underwent to dialysis for glomerulonephritis (36.1%).

27 of these patients (75%) did not have any of the considered predisposing conditions subsequently discussed, and 24 of them (66.6%) did not have complications in the post-transplant course; urologic complications were observed only in 3 patients (8.33%).

Considering the overall incidence of infections with respect to age, we can observe that age is not important in determining the prevalence ratio of total infections; however, serious infectious complications, such as lung infections and septicaemia, are more frequent in older patients.

2 - recipient's sex: it is not important in determining the incidence of post-transplant infections.

3 - type of pre-transplant dialysis: 48 of our patients (30%) were on C.A.P.D. (Continuous Ambulatory Peritoneal Dialysis), 84 (52.5%) were on H.D. (Hemodialysis); 14 patients (8.75%) received mixed forms of dialysis (they started on C.A.P.D. and then turned to H.D. or viceversa); 14 patients (8.75%) received a kidney transplant when not yet on dialysis.
Table 10 analyzes the relationship between the type of pre-transplant dialysis and the incidence of post-transplant infections; pre-dialysis patients have a significant lower incidence of infections ($z = 1.28$, significant at 5%); UTIs are present in patient on each type of dialysis, with no significant difference; patients not yet on dialysis do not experience infections other than UTIs; patients on CAPD are at lower risk of developing septicaemia in comparison to patients on HD ($z=4.58$, significant at 1%).

The graft survival is not affected by the type of pre-transplant dialysis, while pre-dialysis patients survive significantly longer with respect to patients on CAPD ($z=4.50$), HD ($z=7.57$), HD+CAPD ($z=5.86$).

**TAB. 10 - RELATIONSHIP BETWEEN TYPE OF PRE-TRANSPLANT DIALYSIS AND INCIDENCE OF POST-TRANSPLANT INFECTIONS**

<table>
<thead>
<tr>
<th>TYPE OF DIALYSIS</th>
<th>NºPTS.</th>
<th>NºINFECT.</th>
<th>PREVALENCE RATIO</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PAT. SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPD</td>
<td>48</td>
<td>101</td>
<td>2.11</td>
<td>76.74%</td>
<td>90.69%</td>
</tr>
<tr>
<td>HD</td>
<td>84</td>
<td>141</td>
<td>1.68</td>
<td>86.04%</td>
<td>94.18%</td>
</tr>
<tr>
<td>HD+CAPD</td>
<td>14</td>
<td>19</td>
<td>1.35</td>
<td>81.94%</td>
<td>95%</td>
</tr>
<tr>
<td>PREDIALYSIS</td>
<td>14</td>
<td>18</td>
<td>1.28</td>
<td>92.35%</td>
<td>100%</td>
</tr>
</tbody>
</table>
4- native kidneys disease: in table 11, a correlation between native kidneys disease and the incidence of post-transplant infections can be observed; the patients were divided in 9 groups, according to the kidneys
disease leading to end stage renal failure (E.S.R.F.); most of our patients (28%) had E.S.R.F. due to reflux nephropathy, followed by glomerulonephritis (23%), polycystic kidneys (12.5%), and hypertensive nephropathy (11.8%); the lowest incidence of post-transplant infections is among patients with glomerulonephritis as cause of E.S.R.F. (prevalence ratio 1.23); in our experience diabetic patient have the highest prevalence ratio of infectious complications; in particular, UTIs accounted for 41.38% of all infections (compared for example to 78.73% in patients with reflux nephropathy and to 65.95% in patients with glomerulonephritis as cause of E.S.R.F.), while lung infections accounted for 27.59%, septicaemia for 13.80%, and systemic viral infections for 10.35% of the recorded infections; these values are higher than those observed in transplanted patients with different native kidneys diseases.

Patients with reflux nephropathy or renal calculi as cause of E.S.R.F. follow diabetic patients as far as infectious complications are concerned, with UTIs accounting for most of them (incidence 78.73% and 75.0% respectively), and they suffer from serious infectious complications as well, such as lung, bacteraemic and renal infections.

Interesting is to observe that patients with glomerulonephritis as cause of E.S.R.F. do not experience bacteraemic episodes in the post-
transplant course, and have the lowest incidence of systemic and lung infections.

The lowest graft (50%) and patient (80%) survival is among diabetic patients (6.8% of our patients population); these data differ in a statistically significant way (z=2.15 and 2.20 respectively) when compared to survival rates of patients with other native kidneys diseases.

5 - pre-transplant predisposing conditions: patients with recurrent UTIs or peritonitis in the pre-transplant period, or with urinary diversion or augmented bladder for an abnormal lower urinary tract, or patients who received a previous transplant are more prone to infectious complications in the post-transplant period than patients without these types of predisposing conditions (table 12).

In our experience, we have recorded a 2.47 prevalence ratio of infections in patients with an abnormal lower urinary tract, with UTIs accounting for 81.25% of all the infections, followed by septicaemia (9.38%) and lung infections (6.25%). Patients with recurrent UTIs the pre-transplant period have a 84.62% incidence of UTIs following transplantation; however these patients seem to less prone to septicaemia (incidence 2.20%) and lung infections (1.10%) than patients with an abnormal urinary tract. Patients with recurrent peritonitis in the
pretransplant period have a 2.15 prevalence ratio of infections complications, with peritoneal infections accounting of an high proportion of them (26.67%).

**TAB. 12 - RELATIONSHIP BETWEEN PRE-TRANSPLANT PREDISPOSING CONDITIONS AND INCIDENCE OF POST-TRANSPLANT INFECTIONS**

<table>
<thead>
<tr>
<th>PREDISPOSING CONDITIONS</th>
<th>Nº PTS</th>
<th>Nº INFECT.</th>
<th>PREVALENCE RATIO</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PAT. SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent UTIs</td>
<td>35</td>
<td>91</td>
<td>2.60</td>
<td>85.71%</td>
<td>100%</td>
</tr>
<tr>
<td>Previous Tx</td>
<td>17</td>
<td>31</td>
<td>1.83</td>
<td>77.77%</td>
<td>100%</td>
</tr>
<tr>
<td>Urinary diversion/augmented bladder</td>
<td>13</td>
<td>32</td>
<td>2.47</td>
<td>84.61%</td>
<td>100%</td>
</tr>
<tr>
<td>Recurrent peritonitis</td>
<td>14</td>
<td>30</td>
<td>2.15</td>
<td>68.75%</td>
<td>81.25%</td>
</tr>
<tr>
<td>Total</td>
<td>79</td>
<td>184</td>
<td>2.33</td>
<td>79.21%</td>
<td>95.32%</td>
</tr>
<tr>
<td>None</td>
<td>81</td>
<td>95</td>
<td>1.18</td>
<td>86.02%</td>
<td>97.84%</td>
</tr>
</tbody>
</table>

Patients with a previous transplant do not seem to be more prone to infections than patients who did not receive a kidney transplant;
however, this evidence can be partly explained by the fact that the 1 year graft survival is low (77.77%); these patients have the highest incidence of severe infectious complications, such as lung (29.04%) and systemic infections (22.59%), and septicaemia (9.68%), while UTIs account for 25.81%.

The overall prevalence ratio of infectious complications in patients with the above-considered predisposing conditions is 2.33, compared to 1.18 in patients without them. Even the 1-year graft survival seem to be affected by the above-mentioned predisposing conditions, since it is 79.52% compared to 83.52% in patients without them.

6 - complications: in table 13 we analyze the relationship between post-transplant complications (that we divided in urologic, lymphatic and vascular complications) and the incidence of post-transplant infections; the highest rate of infections is among patients with urologic complications (such as ureteric obstruction or fistula) (prevalence ratio 2.28), followed by patients with lymphatic complications (obstructing or non-obstructing lymphocele) (prevalence ratio 1.74), while patients with vascular complications do not seem to be prone to post-transplant infections (prevalence ratio 0.4); the lower incidence of infections in patients with vascular complications is statistically significant (z=2.09); but this finding
can be related to the fact that vascular complications lead to early graft failure with the need of nephrectomy.

**TAB. 13 - RELATIONSHIP BETWEEN POST-TRANSPLANT COMPLICATIONS AND INCIDENCE OF POST-TRANSPLANT INFECTIONS**

<table>
<thead>
<tr>
<th>COMPLICATIONS</th>
<th>N° PTS</th>
<th>N° INFECT.</th>
<th>PREVALENCE RATIO</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PATIENT SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>10</td>
<td>4</td>
<td>0.40</td>
<td>61.53%</td>
<td>100%</td>
</tr>
<tr>
<td>Urologic</td>
<td>39</td>
<td>89</td>
<td>2.28</td>
<td>85.71%</td>
<td>97.61%</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>23</td>
<td>40</td>
<td>1.74</td>
<td>90.30%</td>
<td>91.95%</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>133</td>
<td>1.84</td>
<td>79.52%</td>
<td>92.34%</td>
</tr>
<tr>
<td>None</td>
<td>88</td>
<td>146</td>
<td>1.65</td>
<td>83.52%</td>
<td>97.67%</td>
</tr>
</tbody>
</table>

Patients with urologic complications experience the highest incidence of post-transplant UTIs (prevalence ratio 1.89) and septicaemia (prevalence ratio 0.17), with statistically significant differences with the other groups of patients.
Looking at graft and patient survival rates, we can observe that urologic and lymphatic complications, in particular, do not seem to affect 1-year graft and patient survivals.

7 - **blood group:** blood group is not important in determining post-transplant infectious complications.

8 - **immunosuppression:** then we looked at the relationship between the type of immunosuppression and the incidence of post-transplant infections (table 14).

<table>
<thead>
<tr>
<th>IMMUNOSUPPRESSION</th>
<th>N° PTS</th>
<th>N° INFECT.</th>
<th>PREVALENCE RATIO</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PAT. SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CyA+ predn.</td>
<td>67</td>
<td>103</td>
<td>1.54</td>
<td>86.67%</td>
<td>94.52%</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>93</td>
<td>176</td>
<td>1.90</td>
<td>80.0%</td>
<td>98.94%</td>
</tr>
<tr>
<td>ATG/ALG</td>
<td>41</td>
<td>62</td>
<td>1.51</td>
<td>71.42%</td>
<td>97.14%</td>
</tr>
</tbody>
</table>
67 of our patients are on standard therapy (Cyclosporine A and prednisone) and 93 are on triple therapy (Cyclosporine A, prednisone and azathioprine); among the 93 patients on triple therapy, we have to consider 41 patients who received antithymocyte/antilymphocyte globulin (ATG/ALG) because of patient sensitization or rejection, and then were converted to triple therapy.

Patients on triple therapy seem to have more infectious complications than patients on standard therapy, but the difference is not significant (z=1.64, not significant at 5%).

Even patients who received ATG/ALG do not experience higher infection rates, the z being 1.50, that is not significant at 5%.

Considering each type of infections, it appears that patients who received ATG/ALG are more prone to lung infections (z=2.46), while there is no difference in the incidence of other types of infections.

There is not statistically significant difference in 1-year graft and patient survival between patients on standard and triple therapy; patients who received ATG/ALG and thereafter triple therapy have a lower graft survival in comparison to patients on standard therapy (z=2.11) (probably because it is used in patients who experience episodes of acute vascular rejection and therefore have more chances to loose their kidney transplant
because of it) while the patient survival is not affected by the type of immunosuppression.

9 - **graft function**: a further correlation we have done aiming to find a relationship between early graft function and the incidence of post-transplant infections (table 15).

In 65 patients (40.62%) there was no post-transplant immediate graft function; the prevalence ratio of infections in this group of patients is 2.10; 88% of patients with delayed graft function who required dialysis after transplantation had a rejection episode in the first three months. In 95 patients (59.38%) there was immediate graft function and the prevalence ratio of infections in this group of patients is 1.24, difference that is statistically significant ($z = 4.32$).

If we look carefully at all the infections observed in patients without early function, we can see that all the types of infections have an higher incidence in this group of patients, except pyelonephritis.

The difference in 1-year graft survival between patients with and without immediate graft function is statistically significant, while it doesn't seem to affect patient survival.
TAB. 15 - RELATIONSHIP BETWEEN GRAFT FUNCTION AND INCIDENCE OF POST-TRANSPLANT INFECTIONS

<table>
<thead>
<tr>
<th>IMMEDIATE FUNCTION</th>
<th>N° PTS</th>
<th>N° INFECT.</th>
<th>PREVALENCE RATIO</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PATIENT SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>65</td>
<td>139</td>
<td>2.10</td>
<td>77.77%</td>
<td>97.91%</td>
</tr>
<tr>
<td>YES</td>
<td>95</td>
<td>140</td>
<td>1.24</td>
<td>85.41%</td>
<td>93.65%</td>
</tr>
</tbody>
</table>

10 - cold ischemia time (tab. 16): among cadaver kidneys, those with cold ischemia time less than 30 hours, have a lower incidence of post-transplant infectious complications than those with longer cold ischemia time (that is more than 30 hours) (z=2.57); in particular, we can observe that when the cold ischemia time is less than 30 hours, the prevalence ratio of septicaemia is 0.05, when it is more than 30 hours it is 0.12; when the cold ischemia time is less than 30 hours the prevalence ratio of lung infection is 0.03, while when it is more than 30 hours, lung infections have a prevalence ratio of 0.33; the difference are statistically significant (z>1.96).

We have furthermore observed that the incidence of immediate graft function is lower in patients who received a kidney with a longer cold ischemia time, with the subsequent increased risk of early rejection.
Trying to explain why patients who received a kidney from a living donor have a high incidence of infections complication, we analyzed this group of patients and observed that 87% of infections are UTIs; most of the patients had reflux nephropathy as cause of E.S.R.F. with recurrent UTIs in the pre-transplant period; 60% of them had urologic complications in the post-operative course.

**TAB. 16 - RELATIONSHIP BETWEEN COLD INCHEMIA TIME AND INCIDENCE OF POST-TRANSPLANT INFECTIONS**

<table>
<thead>
<tr>
<th>COLD ISCHEMIA TIME</th>
<th>N° PTS</th>
<th>N° INFECT.</th>
<th>PREVALENCE RATIO</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PAT. SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-130 mins</td>
<td>46</td>
<td>101</td>
<td>2.20</td>
<td>85.10%</td>
<td>97.87%</td>
</tr>
<tr>
<td>Live donors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 - 20 hrs</td>
<td>12</td>
<td>14</td>
<td>1.17</td>
<td>81.81%</td>
<td>83.33%</td>
</tr>
<tr>
<td>21 - 30 hrs</td>
<td>50</td>
<td>62</td>
<td>1.24</td>
<td>83.01%</td>
<td>98.11%</td>
</tr>
<tr>
<td>31 - 40 hrs</td>
<td>17</td>
<td>45</td>
<td>2.65</td>
<td>94.11%</td>
<td>100%</td>
</tr>
<tr>
<td>41 - 49 hrs</td>
<td>25</td>
<td>42</td>
<td>1.68</td>
<td>80.76%</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 50 hrs</td>
<td>10</td>
<td>15</td>
<td>1.50</td>
<td>62.50%</td>
<td>90.0%</td>
</tr>
</tbody>
</table>
So we can conclude that patients receiving a kidney from a living donor are not more prone to infections.

Old kidneys have a lower survival rate, while patient survival is not affected by the cold ischemia time.
**TAB. 17 - RELATIONSHIP BETWEEN DONOR INFECTIONS AND INCIDENCE OF POST-TRANSPLANT INFECTIONS**

<table>
<thead>
<tr>
<th>DONOR INFECT</th>
<th>N° PTS</th>
<th>N° INF.</th>
<th>LOCALIZATION</th>
<th>TYPE OF INFECTIONS</th>
<th>TOT N° INFECT</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PATIENT SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV positive</td>
<td>16</td>
<td>25</td>
<td>urine 16</td>
<td>2 CVM</td>
<td>12</td>
<td>CVM</td>
<td>93.75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>systemic 8</td>
<td>7 CVM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>septicaemia 1</td>
<td>1 HSV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>kidney 1</td>
<td>Staph. aureus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>lung 4</td>
<td>CVM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 CVM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 Legionel.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 Psittac.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest infection</td>
<td>3</td>
<td>4</td>
<td>septicaemia 2</td>
<td>Staph. aur. E. coli</td>
<td>/</td>
<td>33.33%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>urine 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococc. meningitis</td>
<td>3</td>
<td>6</td>
<td>urine 3</td>
<td>2 E. coli</td>
<td>/</td>
<td>33.33%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>systemic 1</td>
<td>1 Sta. aur. HSV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>wound 1</td>
<td>Staph. aur.</td>
<td>/</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>peritoneum 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfusate E. coli</td>
<td>1</td>
<td>1</td>
<td>pyelonephrit. 1</td>
<td>E. coli</td>
<td>66.66%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Perfusate S. aureus</td>
<td>2</td>
<td>2</td>
<td>pyelonephrit. 2</td>
<td>Staph. aur.</td>
<td>66.66%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>160</td>
<td>279</td>
<td></td>
<td>279</td>
<td>82.62%</td>
<td>95.92%</td>
<td></td>
</tr>
</tbody>
</table>
11 - infection of the donor and/or culture of the perfusate (tab. 17):

Patients receiving a kidney from a donor with positive antibodies titres against Cytomegalovirus developed viral infection in the post-transplant course in a high percentage of cases, but the graft and patient survivals are not affected. In our experience, CMV infection did not develop in recipients of kidneys whose donors did not have positive antibodies titres against Cytomegalovirus. Kidneys harvested from donors with chest infections or pneumococcal meningitis have a very low survival, significantly lower when compared to the mean survival in our patient population (z=2.14). Most interesting is to observe that the 3 patients whose perfusate media grew bacteria, developed pyelonephritis early in the post-transplant course; all of these patients developed early vascular rejection following pyelonephritis, and 1 kidney was lost because of this.

12 - graft source: cadaver donor recipients are not more prone to infections than living donor recipients, as already discussed in a previous chapter (tab. 18).

13 - donor age does not predispose the recipient to infections (tab. 19).
TAB. 18 - RELATIONSHIP BETWEEN GRAFT SOURCE AND INCIDENCE OF POST-TRANSPLANT INFECTIONS

<table>
<thead>
<tr>
<th>GRAFT SOURCE</th>
<th>N° PTS</th>
<th>N° INFECT.</th>
<th>PREVALENCE RATIO</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PATIENT SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.D.</td>
<td>114</td>
<td>178</td>
<td>1.57</td>
<td>81.57%</td>
<td>95.61%</td>
</tr>
<tr>
<td>L.D.</td>
<td>46</td>
<td>101</td>
<td>2.20</td>
<td>85.10%</td>
<td>97.87%</td>
</tr>
</tbody>
</table>

TAB. 19 - RELATIONSHIP BETWEEN DONOR AGE AND INCIDENCE OF POST-TRANSPLANT INFECTIONS

<table>
<thead>
<tr>
<th>DONOR AGE</th>
<th>N° PTS</th>
<th>N° INFECT.</th>
<th>PREVALENCE RATIO</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PATIENT SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-10</td>
<td>6</td>
<td>11</td>
<td>1.84</td>
<td>76.66%</td>
<td>100%</td>
</tr>
<tr>
<td>11-20</td>
<td>15</td>
<td>31</td>
<td>2.07</td>
<td>85.71%</td>
<td>100%</td>
</tr>
<tr>
<td>21-30</td>
<td>38</td>
<td>52</td>
<td>1.37</td>
<td>87.50%</td>
<td>97.5%</td>
</tr>
<tr>
<td>31-40</td>
<td>32</td>
<td>58</td>
<td>1.82</td>
<td>86.66%</td>
<td>100%</td>
</tr>
<tr>
<td>41-50</td>
<td>35</td>
<td>62</td>
<td>1.78</td>
<td>80.55%</td>
<td>100%</td>
</tr>
<tr>
<td>51-60</td>
<td>20</td>
<td>37</td>
<td>1.85</td>
<td>80.95%</td>
<td>90.47%</td>
</tr>
<tr>
<td>over 60</td>
<td>14</td>
<td>29</td>
<td>2.08</td>
<td>81.42%</td>
<td>92.85%</td>
</tr>
</tbody>
</table>
14 - **ureteric anastomosis**: patients with an abnormal lower urinary tract have a higher incidence of post-transplant UTIs (tab. 20).

147 of our patients had a normal lower urinary tract, and therefore a ureteric anastomosis direct to the bladder was performed; 13 of our patients, on the other hand, had an abnormal lower urinary tract (due for example to bladder estrophy, posterior urethral valves, neurologic bladder voiding dysfunctions, etc.) and they had previous surgery for the correction of the anomalies, consisting in urinary diversion (ileal loop) or bladder augmentation.

We can observe that, in patients with an abnormal lower urinary tract, the overall incidence of post-transplant infectious complications is higher than in patients with normal bladder function, although the difference is not significant ($z=1.16$, not significant at 5% level).

The higher incidence of post-transplant infections in patients with an abnormal lower urinary tract is mainly due to the higher incidence of UTIs ($z=2.52$); patients with a kidney draining into an ileal loop experience more episodes of septicaemia and lung infections than patients in other groups.
TAB. 20 - RELATIONSHIP BETWEEN TYPE OF URETRIC ANASTOMOSIS AND INCIDENCE OF POST-TRANSPLANT INFECTIONS

<table>
<thead>
<tr>
<th>URETERIC ANASTOM.</th>
<th>Nº PT S</th>
<th>Nº INF.</th>
<th>PREV. RATIO</th>
<th>LOCALIZATION</th>
<th>%</th>
<th>PREV. RATIO</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PATIENT SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>To ileal loop</td>
<td>6</td>
<td>17</td>
<td>2.84</td>
<td>Urine</td>
<td>12</td>
<td>70.59</td>
<td>2.0</td>
<td>83.33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>septicemia</td>
<td>3</td>
<td>17.65</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lung</td>
<td>2</td>
<td>11.77</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To augmented bladder</td>
<td>7</td>
<td>15</td>
<td>2.14</td>
<td>urine</td>
<td>14</td>
<td>93.33</td>
<td>2.0</td>
<td>91.66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>upp.res.tra.</td>
<td>1</td>
<td>6.66</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Direct to bladder</td>
<td>14</td>
<td>247</td>
<td>1.69</td>
<td>Urine</td>
<td>168</td>
<td>68.02</td>
<td>1.15</td>
<td>82.99%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lung</td>
<td>22</td>
<td>8.91</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>systemic</td>
<td>19</td>
<td>7.70</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>peritoneum</td>
<td>12</td>
<td>4.86</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>upp.resp.tr.</td>
<td>9</td>
<td>3.65</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>wound</td>
<td>6</td>
<td>2.43</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>septicemia</td>
<td>5</td>
<td>2.03</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>kidney</td>
<td>4</td>
<td>1.62</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cerebral</td>
<td>1</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pelvic absc.</td>
<td>1</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
</tbody>
</table>

Looking at 1-year graft and patient survival, there is not a significant difference between the three groups.
15 - **HLA matching** in table 21 we can observe the relationship between HLA matching and incidence of post-transplant infections; the matching for each locus antigen (A, B, and DR respectively) is considered.

Considering the matching for the A locus, the differences in the incidence of infections when 0, 1 and 2 antigens respectively are matched is not statistically significant.

Considering the matching for the B locus, there is no difference in the overall incidence of infections when 0, 1 and 2 antigens are matched respectively; but interesting is to observe that patients with 2 antigens matched do not experience lung and systemic viral infections.

Considering the matching for DR-antigens, there is not a statistically significant difference in the overall incidence of infections when 0, 1 and 2 antigens are matched respectively.

Therefore, in the overall it appears that there is not a correlation between matching and infection. Looking at each type of infection, however, our data show that patients with 0 DR-antigens matched experience a significantly higher incidence of systemic viral infections ($z=5.05$).

If we consider afterward the overall number of antigens matched, we can observe that in patients with no antigen matched (A:0, B:0, DR:0), the prevalence ratio of infectious complications is 1.69, while in patients
with 3 antigens matched (e.g. A:1, B:1, DR:1, or A:0, B:1, DR:2, etc.) the prevalence ratio is 1.37, and in patients with 6 antigens matched (A:2, B:2, DR:2) the prevalence ratio is 1.50; however, these differences are not statistically significant.

Looking in particular at each type of infection, from our data we can observe the following significant aspects: 1) the prevalence ratio of lung infection is 0.15 in patients with 6 antigens mismatched, while in patients with 3 antigens matched (A:1, B:1, DR:1) it is 0.11, the difference being statistically significant ($z=2.19$), and in patients with no mismatches there is no incidence of lung infections; 2) septicaemia shows an incidence of 0.10 when no antigen is matched, while it doesn't appear when 3 and 6 antigens respectively are matched; 3) systemic viral infections show a prevalence ratio of 0.08 in patients with no antigen matched and 0.06 in patients with 3 antigens matched, the difference being significant ($z=3.53$), while they are absent in patients with 6 antigens matched.

Our experience is therefore in accordance with that of other authors who found a beneficial effect of HLA matching on graft survival (407-417).
### TAB. 21 - RELATIONSHIP BETWEEN HLA MATCHING AND INCIDENCE OF POST-TRANSPLANT INFECTIONS

<table>
<thead>
<tr>
<th>HLA Ag</th>
<th>Nº MATCHES</th>
<th>Nº PTS.</th>
<th>GRAFT SOURCE</th>
<th>Nº INFECT.</th>
<th>PREV. RATIO</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PATIENT SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>70</td>
<td>C.D. 62, L.D. 8</td>
<td>118</td>
<td>1.69</td>
<td>76.81%</td>
<td>98.55%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>77</td>
<td>C.D. 47, L.D. 30</td>
<td>141</td>
<td>1.99</td>
<td>87.17%</td>
<td>94.87%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>13</td>
<td>C.D. 5, L.D. 8</td>
<td>20</td>
<td>1.54</td>
<td>92.30%</td>
<td>92.30%</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>88</td>
<td>C.D. 73, L.D. 15</td>
<td>160</td>
<td>1.82</td>
<td>8045%</td>
<td>96.55%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>60</td>
<td>C.D. 34, L.D. 26</td>
<td>107</td>
<td>1.79</td>
<td>86.88%</td>
<td>96.80%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12</td>
<td>C.D. 7, L.D. 5</td>
<td>12</td>
<td>1.00</td>
<td>83.33%</td>
<td>91.66%</td>
</tr>
<tr>
<td>DR</td>
<td>0</td>
<td>97</td>
<td>C.D. 67, L.D. 30</td>
<td>170</td>
<td>1.76</td>
<td>78.12%</td>
<td>98.95%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>50</td>
<td>C.D. 36, L.D. 14</td>
<td>88</td>
<td>1.76</td>
<td>88.0%</td>
<td>94.0%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>13</td>
<td>C.D. 11, L.D. 2</td>
<td>21</td>
<td>1.62</td>
<td>100%</td>
<td>91.66%</td>
</tr>
</tbody>
</table>
Then we looked in particular at all the episodes of UTIs observed in our patients population (table 22), and we correlated them with the timing after the transplant.

Most of UTIs occur in the first three months after the transplant (90.22%), while at 6 months the incidence of UTIs is 1.04%; 34 of our patients (21.24%) had recurrent UTIs in the post-transplant course; recurrent UTIs, otherwise, are the only type of infectious complications observed after 6 months in our patient population.

**TAB.22 - POST-TRANSPLANT UTIs AND SYMPTOMS**

<table>
<thead>
<tr>
<th>%</th>
<th>50</th>
<th>40</th>
<th>30</th>
<th>20</th>
<th>10</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>month</td>
<td>2nd month</td>
<td>3rd month</td>
<td>4th month</td>
<td>5th month</td>
<td>6th month</td>
</tr>
</tbody>
</table>

Timing after transplant
If we look at the symptoms presented by the patients while having a UTI (tab. 23), we can observe that in the first three months there is an higher incidence of pyrexia and/or increase of creatinine, while, later on, most of UTIs are asymptomatic or provoke dysuria, but they do not seem to affect graft function or patient performance.

SUMMARY OF SIGNIFICANT RESULTS

From the analysis of our patients population, we can draw some conclusions:

1 - Factors important for the development of infections in the post-transplant course:

a) type of dialysis: pre-dialysis patients have a lower incidence of infectious complications;

b) native kidneys disease: reflux nephropathy and diabetes are the most important conditions for the development of infections;

c) predisposing conditions: patients with recurrent UTIs or peritonitis in the pre-transplant period, or with urinary diversion or augmented bladder for an abnormal lower urinary tract, or patients who received a previous transplant are more prone to infectious complications in the post-transplant period;
## TAB. 23 - POST-TRANSPLANT UTIs AND SYMPTOMS

<table>
<thead>
<tr>
<th>TIMING</th>
<th>N° INFECT.</th>
<th>%</th>
<th>SYMPTOMS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st month</td>
<td>84</td>
<td>43.30</td>
<td>dysuria 29</td>
<td>34.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pyrexia 23</td>
<td>27.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fever, creat. incr. 17</td>
<td>20.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>asymptomatic 14</td>
<td>16.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(urin. divers. 11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>haematuria 1</td>
<td>1.20</td>
</tr>
<tr>
<td>2nd month</td>
<td>61</td>
<td>31.45</td>
<td>pyrexia 24</td>
<td>39.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dysuria 16</td>
<td>26.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>asymptomatic 15</td>
<td>24.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(urin. divers. 11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fever, creat. incr. 6</td>
<td>9.84</td>
</tr>
<tr>
<td>3rd month</td>
<td>30</td>
<td>15.47</td>
<td>asymptomatic 14</td>
<td>46.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dysuria 11</td>
<td>36.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pyrexia 4</td>
<td>13.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fever, creat. incr. 1</td>
<td>3.34</td>
</tr>
<tr>
<td>4th month</td>
<td>9</td>
<td>4.64</td>
<td>asymptomatic 6</td>
<td>66.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dysuria 2</td>
<td>22.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pyrexia 1</td>
<td>11.12</td>
</tr>
<tr>
<td>5th month</td>
<td>8</td>
<td>4.13</td>
<td>asymptomatic 5</td>
<td>62.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dysuria 2</td>
<td>25.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pyrexia 1</td>
<td>12.50</td>
</tr>
<tr>
<td>6th month</td>
<td>2</td>
<td>1.04</td>
<td>asymptomatic 1</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dysuria 1</td>
<td>50.0</td>
</tr>
<tr>
<td>Recurrent</td>
<td>34 patients</td>
<td>/</td>
<td>asymptomatic,</td>
<td>/</td>
</tr>
<tr>
<td>UTIs</td>
<td></td>
<td></td>
<td>sometimes dysuria</td>
<td></td>
</tr>
</tbody>
</table>
d) **complications**: patients with urologic complications have the highest incidence of post-transplant UTIs and septicaemia;

e) **immunosuppression**: patients who received ATG/ALG do not seem to be over-immunosuppressed, but they have higher incidence of lung infections;

f) **matching**: severe infectious complications are less frequent in patients with a better matching;

g) **cold ischemia time**: the longer is the cold ischemia time, the higher is the incidence of serious post-transplant infectious complications;

h) **ureteric anastomosis**: patients with an abnormal lower urinary tract have an higher incidence of post-transplant UTIs.

2 - Factors important for graft survival:

a) **native kidneys disease**: diabetes accounts for the lowest graft survival rate;

b) **immunosuppression**: patients who received ATG/ALG have a lower graft survival; and this is probably due to the fact that they have more episodes of vascular rejection;
3 - Factors important for patient survival:

a) **type of dialysis**: pre-dialysis patients have a longer survival;

b) **native kidneys disease**: diabetic patients have the lowest survival rates.
RELATIONSHIP BETWEEN INFECTION AND REJECTION
IN OUR PATIENTS POPULATION

The possibility of graft rejection has confronted the clinicians since the beginning of clinical renal transplantation, and various means have been used to prevent the host's immune system from mounting a defense against foreign tissue antigens.

It is useful to remember that allograft rejection and infection are closely related: any intervention that decreases the incidence of infection will permit the safer employment of more intensive immunosuppressive therapy and thus better management of rejection; any intervention that decreases the intensity and extent of rejection, thus permitting lesser amounts of immunosuppressive therapy, will be associated with a lower rate of infection; and we have already observed in clinical practice that infection can trigger allograft rejection.

In tables 24 e 25 I analyze all the rejection episodes in our patients population; most of the acute rejection episodes (83.02%) occur in the first three months after the transplant; their incidence declines in the following months (table 25); after six months, the renal function progressively deteriorate due to chronic rejection (11.75% chronic cellular
rejection and 3.41% chronic vascular rejection); but we could observe 1 episode of acute cellular rejection 8 months after the transplant, and 2 episodes of acute vascular rejection respectively at 10 and 12 months.

Observing the 1-year graft and patient survival, we can see that the earlier is the rejection (especially vascular rejection), the lower are the survival rates; the graft and patient survival is low even in late chronic vascular rejection (50% and 80% respectively); cellular rejection, both acute or chronic, compromizes to a lesser extent the survival rates than vascular rejection.

**TAB. 24 - REJECTION EPISODES IN OUR PATIENT POPULATION**

<table>
<thead>
<tr>
<th>TIMING</th>
<th>TYPE OF REJECTION</th>
<th>N° OF PATIENTS</th>
<th>N° OF CASES</th>
<th>%</th>
<th>1-YEAR GRAFT SURV.</th>
<th>1-YEAR PATIENT SURV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st month</td>
<td>vascular</td>
<td>32</td>
<td>52</td>
<td>35.38</td>
<td>65.62%</td>
<td>96.87%</td>
</tr>
<tr>
<td></td>
<td>cellular</td>
<td>31</td>
<td>43</td>
<td>29.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd month</td>
<td>vascular</td>
<td>8</td>
<td>10</td>
<td>6.81</td>
<td>75.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>cellular</td>
<td>9</td>
<td>14</td>
<td>9.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd month</td>
<td>vascular</td>
<td>2</td>
<td>2</td>
<td>1.37</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>cellular</td>
<td>1</td>
<td>1</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th month</td>
<td>chronic</td>
<td>1</td>
<td>1</td>
<td>0.69</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>cellular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5th month</td>
<td>cellular</td>
<td>2</td>
<td>2</td>
<td>1.37</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>6th month</td>
<td>chron. cell.</td>
<td>.17</td>
<td>17</td>
<td>11.57</td>
<td>83.33%</td>
<td>100.0%</td>
</tr>
<tr>
<td>or more</td>
<td>chron. vasc.</td>
<td>5</td>
<td>5</td>
<td>3.41</td>
<td>50.0%</td>
<td>80.0%</td>
</tr>
</tbody>
</table>
In table 26 I looked at all the rejection episodes in our patients population; I could observe 147 episodes of rejection, of which 108 (73.46%) were not preceded by infection, while 39 (19.72%) were preceded by an infection, with acute vascular rejection accounting for most of them (64.10%); even chronic cellular rejection was preceded by an infectious episode (17.94%).

The observed rejection episodes followed an infection in a period 1 to 7 days.
In Table 27, I looked at all the types of infections that can lead to rejection; patients with pyelonephritis experience a rejection episode in 100% of cases, followed by peritoneal, systemic and urinary tract infections; patients with lung, blood or wound infections never manifest rejection episodes associated with the infection itself.

In Table 28, I looked at the relationship between infection and rejection with respect to timing and localization of the infectious process and the infecting organisms associated in some way with a rejection episode.

In the first month post-transplant, I could observe 28 episodes of infections followed by rejection; in particular, 13 UTIs (caused by E. coli,
Ps. aeruginosa and Strept. faecalis) triggered 10 episodes of acute vascular rejection and 3 episodes of acute cellular rejection; among this group of patients, there were 4 graft losses, while the patient survival was not affected.

**TAB 27 - INFECTION AND REJECTION IN OUR PATIENT POPULATION - II**

<table>
<thead>
<tr>
<th>TYPE OF INFECTION</th>
<th>N° FOLLOWED BY REJECTION</th>
<th>% FOLLOWED BY REJECTION</th>
<th>% NOT FOLLOWED BY REJECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>194</td>
<td>24 acute vasc. 13</td>
<td>12.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>acute cell. 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>chronic cell. 7</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Systemic</td>
<td>19</td>
<td>6 acute vasc. 6</td>
<td>31.57</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>12</td>
<td>4 acute vasc. 3</td>
<td>33.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>acute cell. 1</td>
<td></td>
</tr>
<tr>
<td>Upp.resp.tract</td>
<td>10</td>
<td>1 acute cell. 1</td>
<td>10.0</td>
</tr>
<tr>
<td>Septicaemia</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wound</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kidney</td>
<td>4</td>
<td>4 acute vasc. 3</td>
<td>100.0</td>
</tr>
</tbody>
</table>
## TAB. 28 - RELATIONSHIP BETWEEN INFECTION AND REJECTION IN OUR PATIENTS POPULATION

<table>
<thead>
<tr>
<th>TIMING AFTER Tx</th>
<th>TYPE OF INFECTION</th>
<th>INFECTING ORGANISM</th>
<th>TYPE OF INFECTION</th>
<th>1-YEAR GRAFT SURVIVAL</th>
<th>1-YEAR PATIENT SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>1st month</td>
<td>Urine</td>
<td>E. coli 4</td>
<td>ac. vas. rej 3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudomonas 4</td>
<td>ac. vas. rej 3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strept. faecalis 5</td>
<td>ac. vas. rej 4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ac. cell. rej 1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic</td>
<td>HSV 4</td>
<td>ac. vas. rej 4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CMV 2</td>
<td>ac. vas. rej 2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Upp. resp. tract</td>
<td>Viral 1</td>
<td>ac. cell. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>E. coli 2</td>
<td>ac. vas. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudomonas 1</td>
<td>ac. vas. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Staph. aureus 1</td>
<td>ac. vas. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peritoneum</td>
<td>Staph. aureus 3</td>
<td>ac. vas. rej 2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E. coli 1</td>
<td>ac. cell. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ac. vas. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3rd month</td>
<td>Urine</td>
<td>Strept. faecalis 1</td>
<td>ac. cell. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4th month</td>
<td>recurrent UTIs</td>
<td>Gram-neg. rods 1</td>
<td>chr.. cell. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5th month</td>
<td>recurrent UTIs</td>
<td>Staph. aureus 1</td>
<td>chr.. cell. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8th month</td>
<td>recurrent UTIs</td>
<td>E. coli 1</td>
<td>ac. cell. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nephrectomy 30 months after Tx</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10th month</td>
<td>recurrent UTIs</td>
<td>Gram-neg. rods 1</td>
<td>chr.. cell. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strept. faecalis 1</td>
<td>ac. vas. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11th month</td>
<td>recurrent UTIs</td>
<td>Gram-neg. rods 1</td>
<td>chr.. cell. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strept. faecalis 1</td>
<td>ac. vas. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>12th month</td>
<td>recurrent UTIs</td>
<td>Gram-neg. rods 3</td>
<td>chr.. cell. rej 3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>more than 12 months</td>
<td>recurrent UTIs</td>
<td>Gram-neg. rods 3</td>
<td>chr.. cell. rej 1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Systemic viral infections (4 Herpes simples virus and 2 Cytomegalovirus) were always associated with acute vascular rejection, with 2 graft losses.

The overall number of UTIs in the first month post-transplant is represented by 84 episodes of infection; rejection is associated with UTIs in the 15.49% of cases, that is a considerably high percentage, especially if we consider the graft losses followed by early rejection.

After 1 case of viral upper respiratory tract infections I observed an episode of acute cellular rejection, with no affection of graft and patient survival.

In the first month post-transplant we could observe 4 episodes of pyelonephritis (2 E. coli, 1 Ps. aeruginosa, 1 Staph. aureus) associated with acute vascular rejection in 3 cases and acute cellular rejection in 1 case.

Finally, there were 4 episodes of peritonitis (3 Staph. aureus and 1 E. coli) associated with acute vascular rejection in 3 cases (with graft and patient loss in 1 case) and acute cellular rejection in 1 case.

In the second month post-transplant, I did not observe any relationship between infection and rejection.
In the third month, I observed 1 case of *Strept. faecalis* UTI associated with acute vascular rejection, without affecting graft and patient survival.

In the fourth month, I observed chronic cellular rejection in a patient with recurrent gram-negative rods UTIs, leading to graft loss 1 year post-transplant. After 5 months, the only infections associated in some way with rejection are UTIs, especially recurrent UTIs that seem to trigger or potentiate chronic rejection; but in 3 cases, after 8, 10 and 12 months post-transplant, I observed in 1 patient acute rejection (cellular vascular and vascular respectively) in patients with UTIs due to E. coli (after 8 months) and Strep. faecalis (after 10 and 12 months); all of these acute episodes of rejection led to graft loss.

Most data support the idea that the immunosuppressed patient is highly susceptible to infection and that the most common cause of death is a lethal infection associated with rejection; however, the frequent coincidence of infection and rejection has not always been considered as a possible trigger for rejection; it has generally been assumed that the rejecting kidney is treated with such large doses of immunosuppressive drugs that severe infection follows.
In our experience we have observed that in some cases infection is responsible for rejection of renal allografts.

What I believe to be interesting in our series is:

1) that 36.11% of the rejection episodes are preceded by infection;

2) that 31.57% of systemic viral infection and 100% of kidney infection are followed by rejection;

3) that also urinary tract infection, peritonitis, and upper respiratory tract infections can be followed by rejection;

4) that rejection can occur even late in the post-transplant period, up to more than 12 months;

5) that chronic rejection can occur beside acute rejection;

6) that a variety of bacteria and viruses can trigger the rejection process.
ANALYSIS OF CELLULAR INFILTRATION ASSESSED BY MONOCLONAL ANTIBODIES LABELLING IN RENAL ALLOGRAFT BIOPSIES.

The hallmark of acute renal allograft rejection is generally accepted as injury to both endothelial and parenchymal cells, leading to impaired renal function.

It has been shown that renal allograft biopsies performed in patients with rejecting allografts are invariably characterized by an interstitial infiltrate; however, the histologic picture of acute interstitial rejection is not always easy to differentiate from other diseases accompanied by an interstitial infiltrate.

Analysis of leukocyte infiltration of the kidney after transplantation may provide insight into the effector cell populations responsible for graft rejection.

Early studies demonstrated massive cellular infiltration in rejecting grafts with leukocyte identification based upon histologic characteristics (418-420). The advent of monoclonal antibodies to specific cell surface antigens (421, 422) has allowed more accurate recognition of the mononuclear cell infiltrate and its various subgroups.
We have evaluated the cellular infiltrate in serial renal biopsies taken before, and at predetermined times after transplantation, in patients receiving Cyclosporine and prednisolone.

The aims of the study was to see whether increased levels of infiltration could be detected following transplantation, and, if so, to determine their relationship with rejection episodes; in particular, to observe whether there are differences in cellular infiltration in biopsies taken from patients whose rejection episodes were preceded or not by episodes of infection.

MATERIALS AND METHODS

We have considered 36 patients transplanted at the Renal and Transplant Unit of the Institute of Urology and Nephrology, University College and Middlesex School of Medicine of London.

Preanastomosis wedge biopsies were obtained from kidneys after donor nephrectomy and preservation but before graft insertion. Harvested kidneys were perfused with hypertonic citrate solution, with the cold ischemia time ranging from 1 to 48 hours. Post transplantation percutaneous needle core biopsies were routinely obtained at approximately 7 days after transplantation, and at other times as clinically
indicated; in particular, of course, needle core biopsies were taken during episodes of rejection.

Immunoperoxidase staining (CD45RB, CD21, CD43, MAC 387, HLA-DR, CD35, IgA, IgM, Igk Igλ) has been performed on allograft biopsies taken in patients during rejection episodes and in those with stable renal function as well. Stable renal function has been defined as variability of plasma creatinine level of less than 15% 10 days before and after biopsy; mean plasma creatinine level at the time of biopsy was 160 ± 60 Mmd/L.

The original histologic diagnoses, made with knowledge of clinical data, were coded from the pathologic files as acute vascular rejection, acute cellular rejection, chronic vascular rejection, chronic cellular rejection.

Evaluation of the clinical status has been performed examining the patients for the following five predetermined clinical criteria, in accordance to Fuggle et al. (388):

1. Graft tenderness or swelling
2. Pyrexia (in absence of infection)
3. Olyguria (in absence of ureteric obstruction) or decreasing urine output of approximately 10%/day on the two preceding days
4. Rising creatinine of approximately 10%/day on the two preceding days, or dialysis
5. Response to course of i.v. methylprednisolone.

A minimum of three positive criteria were required for the clinical diagnosis of rejection.

Among the 36 patients evaluated, we could observe 44 episodes of rejection; of these, 13 were episodes of acute cellular rejection, and 31 were episodes of acute vascular rejection.

Among the 13 episodes of acute cellular rejection, 6 were related to infection; in particular in 3 cases an Escherichia Coli UTI preceded the rejection episode, in 2 cases a Streptococcus faecalis UTI and in 1 case a viral upper respiratory tract infection preceded the rejection episode, while in 7 cases there was no relationship between infection and rejection.

The 31 episodes of acute vascular rejection were related to infection in 15 cases; in particular in 8 cases rejection was preceded by UTI (due respectively to Pseudomonas in 4 cases, Streptococcus faecalis in 3 cases and E. coli in 1 case), in 4 cases it was preceded by an Herpes Simplex viral infection, in 1 case by a Cytomegalovirus infection and in 2 cases rejection was preceded by Staphilococcus aureus peritonitis.

The tissue sections were routinely stained with haematoxylin-eosine and in addition stained with monoclonal antibodies according to
the immunoperoxidase method with the Labelled Streptavidin - Biotin (LSAB) staining technique.

The reagents were harvested from Universal DAKO LSAB kit, Peroxidase K 680 (Dako Corporation, Carpinteria, CA, U.S.A.), and consisted of the following antibodies:

1) CD 45 RB (DAKO CD45RB, PD7/26), Monoclonal Mouse anti-Human Leucocyte Common Antigen; this antigen, consisting of four isoforms of CD45, is found on B cells, subset of T cells, monocytes, macrophages and granulocytes (dilution 1:100).

2) CD21 (DAKO CD21, 1F8), Monoclonal Mouse anti-Human B-cell; this antigen is expressed on B-cells, and, even more strongly, on dendritic reticulum cells; it functions as a receptor for C3d component of complement and also for Epstein-Barr virus (dilution 1:10).

3) CD43 (DAKO CD43), Monoclonal Mouse anti-Human T-cell; this antigen is found on leucocytes, including T-cells and granulocytes; it is involved in activation of T-cells, B-cells, NK cells and monocytes (dilution 1:50).

4) Monoclonal Mouse anti-Human Myeloid/Histiocyte Antigen (DAKO - MAC 387); this antigen labels the cytoplasm of many cells of the monocyte/macrophage series, in particular granulocytes, blood monocytes and tissue histiocytes (dilution 1:50).
5) Monoclonal Mouse anti-Human HLA-DR (DAKO HLA-DR); HLA-DR antigen is expressed on B cells, monocytes, macrophages, Langherans cells, dendritic cells and human endothelium (dilution 1:10).

6) CD35 (DAKO C3bR), Monoclonal Mouse anti-Human C3b-Receptor; this antigen, also known as complement receptor for C3b, is widely distributed on various cell types, including B cells, monocytes, granulocytes, some NK cells and follicular dendritic cells; the functions of CD35 are processing of immune complexes and promotion of binding and phagocytosis of C3b-coated cells (dilution 1:50).

7) Monoclonal Mouse anti-Human IgA (DAKO-IgA): it reacts with the heavy chain (alpha-chain) of both IgA subclasses (IgA1 and IgA2), labelling plasma cells and their precursor including B cell immunoblasts (dilution 1:20).

8) Monoclonal Mouse anti-Human IgM (DAKO-IgM): it reacts with the heavy chain present in all types of human IgM and is useful in the detection of B cells (dilution 1:50).

9) Monoclonal Mouse anti-Human Kappa light chains (DAKO-Kappa): it reacts with IgG and therefore labels B cells (dilution 1:50).

10) Monoclonal Mouse anti-Human Lambda light chains (DAKO-Lambda): it can be used for detecting surface immunoglobulin on B cells (dilution 1:25).
The LSAB staining technique has been performed as follow:

1. Tissue sections have been deparaffinized in four changes of xylene for 20 minutes, then immersed in absolute ethanol for 10 minutes and in 95° ethanol for 5 minutes.

2. To inhibit endogenous peroxidase activity, the slides are immersed in 0.3% \( \text{H}_2\text{O}_2 \) in absolute methanol for 30 minutes at room temperature.

3. Rehydration is then achieved through graded alcohols to water.

When a proteolytic digestion is required, the slides should be immersed in the trypsin bath and incubated for 30 minutes at 37° C; then they are rinsed under gently running cold tap water for 5 minutes. The trypsin solution is prepared by dissolving 0.1 gr trypsin in 100 mls prewarmed distilled water containing 0.1% calcium chloride; the pH is adjusted to 7.8 with 0.1 N sodium hydroxide.

4. The slides are placed in a TBS (Tris Buffered Saline) bath for 5 minutes.

TBS, 0.05 M, pH 7.6, is prepared by dissolving 6.1 g of Tris (triohydroxymethyl amino methane) base in 50 mls. distilled water, then adding 37 mls. of 1N-hydrochloric acid, and diluting to a total volume of 1 liter with distilled water; the pH should be 7.6 ± 0.2 at 25°.
5. Normal goat serum is applied and incubated for 20 minutes at room temperature

6. The serum is then tapped off and the excess is wiped away.

7. After all these processes, the diluted monoclonal mouse primary antibody is applied to incubate overnight at 4°C. Antibodies dilutions are made in TBS 0.05 M, pH 7.6.

8. The slides are washed in a buffer bath for 15 minutes with three changes, then

9. The biotinylated anti-mouse immunoglobulin is applied and incubated for 30 minutes at room temperature, and then washed in a buffer bath for 15 minutes with three changes.

10. The peroxidase-conjugated streptavidin is applied, incubated for 30 minutes at room temperature and washed in a buffer bath for 15 minutes with three changes.

11. The slides are then immersed in the substrate solution to give coloured end products for 4 minutes at room temperature and then washed in running tap water for 5 minutes.

The substrate solution is prepared after dissolving 5 gr. of 3 - 3' diaminobenzidine tethrahydrochloride in 125 mls of 0.05 M TBS, pH 7.6; it is stored aliquoted at -20°C and immediately before use 3 mls of
All specimens were examined by one investigator who had prior knowledge of the clinical and pathological diagnosis. This has been thought by someone to cause problems as far as objectiveness of the evaluation is concerned.

The different tested variables were grouped with a computer to give mean values and standard deviations. Statistical analysis was performed by using the Mann-Whitney U test.
filtered stock solution are diluted in 240 mls of TBS and then 10 mls of 0.3% hydrogen peroxide is added.

12. The slides are counterstained in Mayer's Haematoxilyn for 2 minutes and rinsed briefly in tap water; then they are dehydrated and a coverslip is applied.

13. Negative controls are performed substituting the primary monoclonal antibodies with non immune mouse ascites.

Phometric analysis of tissue sections

The monoclonal antibodies labelled cellular infiltrate within each serial section was assessed by point counting using a square grid in the eyepiece of a Leitz microscope, with each high-power field (400 X) corresponding to an area of approximately 0,178 mm².

Fifteen fields of renal parenchyma were counted in each case; infiltrating cells were expressed as the number of positive cells per square millimeter and results, expressed as the mean ± 1SD, are expressed as percentage area of the tissue section infiltrated by cells.

Results

The mean number of infiltrating cells in patients with stable renal function was approximately half the number of cells seen in biopsies
These data proved to be statistically significant, with a $p < 0.01$. 
performed during rejection. There was no relationship between the time at which the biopsy was performed and the number of infiltrating cells.

Satisfactory immunoperoxidase staining was achieved with all monoclonal antibodies.

The patterns of the monoclonal antibodies positivity in correlation with histologic and clinical diagnosis are summarized in table 29.

In pre-transplant control biopsy specimens the mean area of cellular infiltration was $4.98 \pm 3.34\%$; after transplantation, in biopsy taken from kidneys with stable renal function the mean area of cellular infiltration was $23.38 \pm 11.34\%$; in biopsy showing acute rejection not related to infection from the clinical point of view, the mean area of cellular infiltration was $44.52 \pm 8.46\%$, while in biopsy taken from kidneys during episodes of rejection following infection the mean area of cellular infiltration $52.46 \pm 9.36\%$. Analysis of cellular infiltrate in a few biopsies taken during infection not associated with rejection showed a mean area of cellular infiltration of $11.09 \pm 5.35\%$.

From the analysis of table 30 we can observe that there is a steady increase of the mean area of cellular infiltrate when considering respectively peri-transplant biopsies, stable renal function biopsies, acute rejection not preceded by infection and acute rejection preceded by infection; this means that infiltration by inflammatory cells, such as
biopsies, while an important cellular infiltrate is present in kidneys with stable function; it nearly doubles when an episode of acute rejection is present.

From our data it is evident that cellular infiltrate is greater when infection is involved in the rejection episodes. Similarly, an increased staining with monoclonal antibodies against IgA (staining of tubular epithelium) and IgM (staining of interstitium, with intratubular and intravascular deposits) with respect to peritransplant biopsies has been detected on the glomerular endothelium, mesangium and intertubular structures (capillaries and interstitial dendritic cells).

It has been observed that three patterns of Class II expression exist in the post-transplant biopsies (388):

a) generalized increase in Class II antigen expression: the renal tubules and the endothelium of large vessels were also strongly stained, in association with a marked infiltration by mononuclear cells;

These data proved to be statistically significant, with a $p < 0.01$. 

$^{1}$
Table 29 - Comparison of histologic and clinical diagnoses with coded categories of monoclonal staining pattern

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Histologic diagnosis</th>
<th>CD 45RB</th>
<th>CD 21</th>
<th>CD 43</th>
<th>MAC 387</th>
<th>HLA-DR</th>
<th>CD 35</th>
<th>Ig A</th>
<th>Ig M</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rejection</td>
<td>Peritransplant biopsy</td>
<td>7.3 ± 5.1 %</td>
<td>2.1 ± 1.5 %</td>
<td>1.6 ± 0.2 %</td>
<td>11.8 ± 0.8 %</td>
<td>normal</td>
<td>2.1 ± 1.3 %</td>
<td>0.9 ± 0.8 %</td>
<td>1.0 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Stable renal function</td>
<td>42.7 ± 27.3 %</td>
<td>12.1 ± 7.0 %</td>
<td>9.4 ± 0.6 %</td>
<td>38.5 ± 15.9 %</td>
<td>normal or focal induction</td>
<td>14.2 ± 6.9 %</td>
<td>6.1 ± 2.9 %</td>
<td>10.5 ± 5.5</td>
</tr>
<tr>
<td>Rejection not preceded by infection</td>
<td>Acute rejection</td>
<td>73.6 ± 15 %</td>
<td>21.3 ± 6.9 %</td>
<td>26.8 ± 2.6 %</td>
<td>68.5 ± 7.7 %</td>
<td>generalized induction</td>
<td>32.4 ± 10.8 %</td>
<td>12.1 ± 3.3 %</td>
<td>16.3 ± 2.7</td>
</tr>
<tr>
<td>Rejection preceded by infection</td>
<td>Acute rejection</td>
<td>86.9 ± 18.3 %</td>
<td>27.5 ± 8.8 %</td>
<td>32.5 ± 5.3 %</td>
<td>75.8 ± 8.7 %</td>
<td>generalized induction</td>
<td>39.6 ± 6.7 %</td>
<td>15.5 ± 5.3 %</td>
<td>20.1 ± 6.9</td>
</tr>
</tbody>
</table>
Table 30 - Phenotypic composition of the cellular infiltrate

1 - Peritransplant biopsy
2 - Stable renal function
3 - Rejection not preceded by infection
4 - Rejection preceded by infection
b) focal increase in Class II antigen expression, that was frequently perivascular or associated with a mononuclear infiltrate, with focal involvement of distal tubules and large vessels endothelium;

c) no increase in Class II antigen expression, where a cellular infiltrate that contained an HLA Class II positive component was often present, but there was no increased Class II staining of renal tubules.

It has been observed (388) that the degree of cellular infiltration in the examined biopsy specimens is related to the level of HLA-DR expression, i.e. normal, focal induction or generalized induction.

We have then reported the phenotypic composition of the cellular infiltrate on a graphic (tab. 30).

To explain the very low levels of infiltration in peritransplant biopsies it has been suggested that the vast majority of interstitial leukocyte in renal allografts are host derived; the composition of the infiltrate has been shown to be relatively constant and appears to be independent of several factors, such as timing after transplantation, graft status or function, immunosuppression (423).

The analysis of renal biopsies has demonstrated that marked leukocyte infiltration occurs also in well functioning grafts; the severity of this infiltrate is less than in acute rejection, but it has been shown that the proportion of different cell subpopulation is similar to rejecting grafts.
patients with stable function has not been shown to imply a bad prognosis for graft survival, it has been suggested that it could represent a very attenuated form of cellular rejection (424).

The sparse cellular infiltration seen in peritransplant control biopsies was invariably diffusely distributed throughout the interstitium after transplantation; focal infiltration (perivascular, periglomerular, or both) was also seen.

In rejecting graft there is a marked increase of interstitial cellular infiltrate; the degree of cellular infiltrate is much higher in kidneys whose rejection is preceded by infection; the highest proportion of cellular components of the infiltrate is emphasized by the monoclonal antibodies CD45 (leucocyte common antigen) and MAC 387 (monocyte / macrophage series).

The presence of significant leukocyte infiltration in well functioning renal allografts is subject to speculation. A similar occurrence has been reported in the rat renal allograft model, in which passive enhancement with donor-specific alloantibody effectively suppress rejection (425, 426), despite the accumulation of large numbers of mononuclear cells in the graft.

While this infiltrate may represent a low-grade host response against the graft, the infiltrate need not to be associated with graft rejection if the
cells. It is interesting to observe that in "long-term" biopsies, obtained several years after transplantation, the magnitude of the total leukocyte infiltrate was not different from control biopsies, but the T lymphocyte component (both CD4+ and CD8+ cells) remained elevated.

It has already been observed a significant association between the degree of cellular infiltration and increased Class II expression (423); the infiltrate in biopsies with increased Class II expression was significantly greater. A similar association was seen with T lymphocyte infiltration, which is in accordance with T lymphocyte involvement in Class II antigen induction in vivo.

In vitro studies have demonstrated that cells on which Class II antigens have been induced are able to function as antigen-presenting cells (402); increased tubular Class II expression would provide additional targets and may render the graft more vulnerable to destruction by effector mechanisms, leading to further damage to the renal parenchyma.

No relationship has been observed between the number of interstitial infiltrating cells and the degree of interstitial fibrosis at the time of biopsy (424).
SUMMARY OF SIGNIFICANT RESULTS

The staining with the monoclonal antibodies used in this study is proportionally greater when considering respectively peritransplant biopsies, biopsies taken from patients with stable renal function, biopsies taken from kidneys with rejection not preceded by infection and biopsies taken from kidneys with rejection preceded by infections.

Therefore, the degree of cellular infection is much higher in kidneys whose rejection is preceded by infection; similarly staining kidneys with IgA and IgM antibodies is increased in rejecting kidneys.

The analysis of human renal biopsies employed in this study has demonstrated that marked leukocyte infiltration occurs not only during acute rejection, but also in well-functioning grafts.

The very low levels of infiltration in day 0 control biopsies indicate that the vast majority of interstitial leukocytes in renal allografts are host-derivated. The allograft infiltrate varies in magnitude with time and graft status.
Infections of the urinary tract have been studied extensively in experimental animals since Kass first introduced the concept of quantitative bacteriological examination of the urine (427).

Because of the limitations of human studies, experimental studies in the rat, rabbit and dog have been used to investigate the host response to urinary tract infection. A variety of procedures have been used to induce renal infection in animals, most of which involve either ureteric obstruction or trauma to the kidney. Although induction of infection is almost certainly due to the dual effects of local trauma and bacterial lodgement, the clinical and bacteriologic course of the disease parallels many aspects of the disease in man (428). The models have many advantages, not the least being that the pathologic changes including scarring, lymphocytic infiltrate, colloid casts and interstitial fibrosis, features which lack specificity in human disease, are associated directly with an infectious process (429).

Several remarkable features of the experimental infection are peculiar to renal infections and mimic closely the clinical problem. First, despite the resistance of the intact unobstructed kidney to infection, an
small number of bacteria which would be incapable of establishing infection in most other tissues.

Furthermore, bacteria which are readily cleared within hours from sites such as blood, liver, spleen and muscle, once introduced into the kidney, establish an active infection which persists for long periods and may never be eliminated during the lifetime of the animal (430). There is little evidence for progressive loss of renal function in these animals, despite continuing infection; where untreated animals have been followed for up to six weeks after infection, renal function, although depressed initially, has returned to normal (431).

One widespread belief that has influenced the investigation of host defense mechanisms is that the renal medulla is usually susceptible to infection, and is the site of bacterial persistence in chronic infection. One mechanism that has been proposed to explain the apparent susceptibility of the medulla to infection is that the hypertonic region of the medulla causes a delayed granulocytic response that allows infection to become established in the medulla (432). However, subsequent events involving the spread of infection beyond the original lesion show that mobilization of phagocytic cells into adjacent infected but undamaged tissue does not occur and that the polymorphonuclear infiltrate remains confined to the initial inflammatory foci.
Evidence of neutrophilic exudation being mediated through the complement system (433) which is inactivated by renal tissue (434) is consistent with the phagocytic cell.

Bacterial persistence has been investigated experimentally in the rat kidney where the vascular cortical tissue can readily be differentiated macroscopically from the medulla and from the papilla.

Although the mobilization of polymorphonuclear leucocytes during renal infection has been studied, the function of other inflammatory cells forming the interstitial infiltrate have not been well characterized, although the morphological details have been known for many years.

Components of the host's defense in the kidney are likely to include non-specific phagocytosis, cell-mediated immune response and specific antibody production. In both acute and chronic renal infection the small lymphocyte has been found to be the predominant inflammatory cell even when numerous polymorphonuclear leucocytes are present in luminal casts.

In both animals and man, infection of the urinary tract may result in an increase in circulating antibody directed against the invading organism, although the protective value of this response remains to be established; as well as the systemic immune response to infection, a local immune response has been reported in pyelonephritis and in lower tract infection.
IgG with antibacterial activity has been found in the urine and increased immunoglobulin excretion in urinary tract infections has been reported in both animal and human studies.

Local antibody synthesis has been shown to persist for long periods following acute infections and clearly demonstrates that the kidney, a non lymphoid organ, is capable of local immunoglobulin synthesis during the course of an infection. The specific nature of the antibacterial antibody formed within the kidney has been confirmed at a cellular level and the cellular kinetics of the immune response have been established (435). In these studies the persistence of antibody forming cells in the pyelonephritic kidney was a feature of the immune response and suggested that continued local antibody synthesis may be an important component of the host defence mechanism in urinary tract infection.

Studies of autoimmune processes as a component of the host's response to infection followed the clinical observation that kidneys are frequently sterile in chronic pyelonephritis (436).

That progression of the lesion may not require the presence of viable bacteria is supported by the finding of alterations in tissue antigenicity produced by endotoxin so that antibody produced against "endotoxin modified renal tissue" could result in further tissue damage (437).
Alteration of the serum bactericidal ability has also been investigated as an aberrant host defence mechanism leading to the establishment of renal infection. It has been described an antibactericidal mechanism which has been associated with infection of the upper urinary tract and which possibly acts as a blocking factor preventing lysis of otherwise sensitive bacteria (438, 439).

Although many host factors have been examined experimentally in relation to the establishment and persistence of infection, the consistent and predictable pattern that emerges with infection of unobstructed kidney is that of an acute inflammatory nonprogressive lesion which heals with contraction and scarring and in which bacteria may persist despite an adequate host immune response. This situation is not uncommon in infectious diseases where the organisms are protected from the host's defence mechanism because of their intercellular location.

Current views of the host-parasite relationship in urinary tract infections have been influenced by studies of infections in the rat, where pyelonephritis has been induced unilaterally following direct inoculation of bacteria into one kidney only. The subsequent bacteriologic, immunologic and pathologic changes have then been followed in the contralateral, unmanipulated kidney as well as in the pyelonephritic kidney. Using this model it has been possible to investigate the relationship of the invading
bacteria in the kidney and the development of pathologic lesions (429). In the damaged kidney into which the bacteria had been injected, scarred and contracted kidneys were found showing the characteristic pathologic features of pyelonephritis. In the controlateral kidney, however, approximately the same number of bacteria were present in the kidney but the pathologic changes were minimal. When the distribution of bacteria within the uninjured kidney was examined, organisms were found to be present throughout the kidney and not simply confined to the areas showing pathologic lesions.

Once infection is established in the urinary tract, it appears that the host responds with a vigorous and well characterized specific immune response.

Some idea of the complexity of the host response to urinary tract infection and the difficulties facing both the clinical and experimental investigator will be apparent. Urinary tract infections are still a major cause of morbidity in man, so that a critical understanding of the basic host-parasite relationship should be a matter of concern to all nephrologists.

There seems to be general agreement that acute pyelonephritis is closely related to a bacterial infection of the kidney; in chronic pyelonephritis, however, there is considerable controversy about the
pathogenic mechanism responsible for the continuing destruction of kidney tissue, even in those cases where infection is no longer demonstrable.

The question was raised whether immune mechanisms might contribute to the progression of chronic pyelonephritis.

The first report concerning humoral immune mechanisms during urinary tract infection came from Pfaundler who demonstrated in 1898 (440) that sera from patients with chronic urinary tract infections combine with microorganisms originating from urine specimens of the same individual. It took several years until this reaction was identified as bacterial agglutination. This test, or some modification thereof, has been used frequently in many studies of the kidney and urinary tract.

In 1952, Neter et al. (441) described an indirect hemagglutination test which gained considerable popularity because of its simplicity and high degree of sensitivity.

During the last few years several authors have suggested the presence of autoimmune mechanisms in chronic pyelonephritis.

Kleeman, Hewitt and Guze (442) were the first to suggest that continuous liberation of renal antigens during pyelonephritis might trigger autoimmune phenomena. Such a process would explain the progression of this disease, especially in those instances where the bacterial infection
has disappeared. During the early phase, infection of the kidney would act as an adjuvant, stimulating autoantibody formation by releasing antigens from kidney tissue. This mechanism could then lead to a self-perpetuating disease.

It has been observed (443) that autoantibodies are directed against a kidney specific antigen or against an antigen present in kidney and liver.

Furthermore, antibodies could be demonstrated which are directed against an antigen of E. Coli, identical with a kidney antigen. These are obviously cross-reacting or heterophile antibodies. Such antibodies are produced after stimulation by a foreign antigen and combined with an identical antigen present in organs and tissues.

Heterophile antibodies can be of importance in the pathogenesis of certain diseases. This has been conclusively demonstrated by Kaplan and Meyerserian (444, 445); they found that infection with Streptococci lead to formation of antibodies, which cross-react with antigens of the heart muscle, thus leading to an immunologic reaction, known as rheumatic myocarditis.

Cross reacting antibodies occurring in pyelonephritis could also be demonstrated by some authors (446, 447), who found antibodies elicited by microorganisms during kidney infections in men; these antibodies reacted with human kidney tissue in vitro.
Such a mechanism could explain the progression of a parenchymal kidney disease, although bacteria as well as bacterial fragments have been eliminated.

Autoimmune reactions directed against tubular antigens of the kidney have been described (448-450); it has been demonstrated that immunization of experimental animals with tubular material elicits autoimmune reactions and that homologous autoantibodies can be formed against tubular antigen after kidney transplantation. However, a correlation between renal infections and autoimmune reactions against tubular antigens could not be demonstrated.

In an advanced stage of renal disease with destruction of tubules and increased liberation of tubular antigens, such autoantibodies could also be responsible for progressive glomerular damage, suggesting that liberation of tubular antigens might elicit autoantibody production followed by the formation of antigen-antibody complexes (451). Such complexes can be deposited at the glomerular basement membrane causing acute glomerulonephritis; this pathogenetic mechanism could explain how severe tubular damage might cause glomerular changes.

However, despite years of investigation, the cellular basis of the host-parasite relationship in acute and chronic pyelonephritis is still poorly understood.
It has been suggested that cellular mechanisms do contribute to host defence in pyelonephritis, but not in the early stage of the disease, when infection is established before a cellular response can be mounted (452); infection is established before inflammatory cells can intervene; this clearly limits the host-protective role of these components in the early stages of infection; cellular defence mechanisms therefore have a limited impact on the establishment of infection but do play an important role in containment.

The individual roles of the cellular components however, still need to be determined.

The degree of renal damage is determined by events in the acute inflammatory phase of infection (453, 454); the relationship between cellular factors and host resistance in chronic pyelonephritis still needs to be established; granulocytic cells limit bacterial replication in the chronically infected kidney (455), but further studies are needed to demonstrate how infection persists in the face of an effective defence component and the mechanism by which microorganisms avoid eradication.

The mononuclear cell infiltrate in chronic pyelonephritis has served as a stimulus for investigations into the role of lymphocytes in pyelonephritis. Coles and co-workers (456) studied the role of the T cell in
thymectomy had no effect on the microscopic or macroscopic appearance of the renal lesions 3 weeks after infection, thus concluding that the early lesions of experimental pyelonephritis are unaffected by the presence or absence of T cells.

It has been observed (457) that normally functioning T cells are an important host defence mechanism in chronic renal infection; it appears that they are important in clearing organisms from the kidney after several weeks of infection and are involved in the chronic scarring process.

Bacterial infection (including bacteria, polymorphonuclear leukocytes, or the initial inflammatory response) triggers the immune response, namely a B-cell antibody response which is influenced by and influences Th and Ts system.

This acute phase of the disease is followed by a stage of chronic pyelonephritis under the influence of Te cells; these effector cells are either induced by the original bacterial antigen or by the results and/or consequence of response thereto.

The role of antibody alone or in conjunction with T cells cannot be completely estimated; in the rat, infection persists for the life of the animal despite the continuous presence of both agglutinating and hemagglutinating antibacterial antibody (458). It has been observed that
infection was at its peak during the time of peak antibody production (457).

Heterotopic renal transplantation in the rat.

The techniques of microvascular surgery are becoming commonplace in many areas of clinical practice as well as in experimental research. Basic training and standardization in the microsurgical laboratory have spread to all surgical specialties, including reconstructive urologic surgery where experimental techniques have helped to augment clinical advances.

We wanted to use an experimental model of renal transplantation in the rat, to study the effect of infection on the expression of renal antigens.

Operative technique

Organ transplantation depends on the successful anastomosis of the relevant blood vessels, the diameter of which may be less than 1 mm.

To cope with such small vessels, very fine instruments are required; renal transplantation can be carried out either by an end-to-end anastomosis of the renal blood vessels, or by anastomosis of the ends of the donor blood vessels with the sides of the dorsal aorta and posterior
vena cava of the recipient; we have performed renal transplantation according to the second procedure.

Preparation of the donor kidney

After adequate induction of surgical anestesia (3.7% cloral hydrate: 300 mg/Kg body weight, i.p.), the rat is placed on its back with its tail toward the investigator (459).

The animal's ventral surface, groin and legs are shaved and then prepped with a povidine-iodine antiseptic solution.

A long midline incision is made into the abdominal cavity. The liver is retracted against the diaphragm and the gut is wrapped in a warm saline - moistened gauze pack and displaced to the left of the investigator, if the left kidney is to be prepared, outside of the abdominal cavity. The renal artery and vein are found, and any attached collateral blood vessels (e.g. the spermatic and adrenal veni) are ligated and cut. By careful blunt dissection, the renal artery and vein are separated from each other along their whole length and cleaned most thoroughly of adventitia and fat. This is an important and quite difficult step during which other small attached blood vessels may be encountered which must be ligated and cut. The dorsal aorta and posterior vena cava are also cleaned of fat and adventitia for 3-4 mm below and above the junction with the renal vessels. Care
must be taken in holding the vena cava which has a thin wall. The dorsal aorta is ligated 2-3 mm below the renal artery and clamped with artery forceps 3-4 mm above the renal artery, after first ligating any collateral vessels such as the artery of the opposite kidney and the superior mesenteric artery.

The kidney is perfused with cold heparinized saline via a 20-gauge needle inserted into the aorta, and the donor kidney is flushed in a retrograde fashion.

Immediately after the start of the perfusion, the vena cava is cut and perfusion continues until the renal venous effluent is clear.

The dorsal aorta is now cut cleanly across, just below the clamp, and also just below the ligature.

In this way a cuff of aorta is formed with the renal artery attached. Where the renal vein is attached to the vena cava, a small elliptical segment is cut out of the vena cava with curved scissors, after first clamping it posteriorly, so that this segment remains attached to the renal vein.

Excess fat is removed from around the kidney which is freed from its connective tissue attachments.
The ureter is located and cut a few millimeters above its entry into the bladder. It must not be stripped of its adventitia or fat otherwise necrosis can subsequentialy occur; the ureter must not be ligated.

**Preparation of the recipient**

After induction of anesthesia, the rat is placed supine on the operating board. The animal's ventral surface, groin and legs are shaved and then prepped with a povidine-iodine antiseptic solution. A right or left nephrectomy is carried out through a midline abdominal incision, depending on which kidney is being transplanted. The dorsal aorta and posterior vena cava are cleaned of fat and adventitia for a few millimetres posterior to the renal vein. This area of the aorta and vena cava is now completely clamped with a specially prepared curved haemostat. Blood flow in these vessels is usually completely stopped by this procedure but it is a good practice to attempt to clamp the two vessels in such a way that a small flow can still be obtained.

A sufficient amount of the aorta and vena cava must be available in the curve of the clamp for the subsequent anastomosis. A small elliptical opening is made with curved scissors in the dorsal aorta anteriorly and in the vena cava posteriorly in the clamped part of these vessels. The size of
the openings should match as nearly as possible the segments left on
blood vessels of the donor kidney.

The openings in the aorta and vena cava are irrigated with saline to
remove blood and small clots.

The donor kidney is placed in position and two sutures, at 180° to
each other using two separate curved atraumatic needles and 7/0 prolene,
are placed in the opposed dorsal aorta and donor renal artery. After tying
the knots, the free tail of each thread is clamped with small serrated
neurosurgical clips and used as the stay sutures to produce slight tension
on the vessel. The top of the anastomosis is sutured with a continuous
stitch using the right hand needle. The kidney is then flipped over to the
opposite side to expose the underside of the vessels which are now
sutured together using the left hand needle. A similar procedure is carried
out for the vena cava-renal vein anastomosis.

After suturing, the curved clamp is slowly removed while applying
pressure on the two anastomoses with a moist gauze pad.

The anastomosis of the ureter to the bladder is performed by
inserting the end of the donor ureter into the bladder of the recipient; for
this procedure the donor ureter is severed close to the bladder. A small
stab wound is made in the side of the recipient's bladder, and a small pair
of curved forceps is inserted and pierced through the posterior wall of the
bladder. The tip of the donor ureter is grasped with these forceps and is drawn into the bladder so that it fits comfortably without tension. Where the ureter passes into the bladder, a 7/0 nylon stich is placed in the wall of the ureter securing it to the bladder wall.

The abdomen can now be closed after replacing the gut in the correct anatomical position.

The total time of ischemia that the donor kidney undergoes must not exceed 45 min, otherwise the kidney may not function subsequently.

Rats carrying transplants do not require any special post-operative care except to be kept warm for an hour or two.

When transplantation is performed between members of the same inbred strain, the transplanted kidney may remain healthy and/or the recipient may show a normal blood urea nitrogen level. When different strains are used, rejection phenomena occur by about eight days and the kidney may cease to function.

**Experimental pyelonephritis in transplant kidneys in rats**

Host defence mechanisms in pyelonephritis have been the subject of detailed study and many aspects of the host-parasite relationship have been considered. There is ample evidence of a prompt and vigorous immune response to acute infection, with both systemic and local
Adult imbred Lewis (LEW - RT1) Sprang-Dawley rats were used in these experiments. An non allograft model was used because in this way the animals were not treated with immunosuppressive drugs, to avoid functional or morphologic changes occurring sometimes in kidneys of Cyclosporine-A treated rats.
antibody synthesis being demonstrated. The effect of infection on cell-mediated immunity and the role of the complement system have also been well documented.

Morphological observation have located neutrophils at the site of infection soon after challenge and T-lymphocytes have been identified in the lesion. It has been shown that tissue damage results from events in the early stages of infection.

One consistent finding in experimentally induced pyelonephritis is that infection persists for many months and is difficult to eradicate.

Some contributing factors have been proposed, such as the demonstration that phagocytosis and T-cell responsiveness are both inhibited in the kidney, and that cell-mediated immune mechanisms are depressed during the course of both experimentally induced and clinical renal infection.

Materials and methods

1) Experimental host: Adult Sprang-Dawley rats from an inbred colony, each weighing between 200 and 250 g, were used in these experiments. Neither donor nor recipient received any treatment to modify rejection; nevertheless, a high percentage of these transplants survived for many weeks, as already observed (460,
even if a small rise in the blood urea nitrogen level and histologic evidence of a cellular infiltrate have been demonstrated; the cellular infiltrate occurs at its highest level, about 7 days after transplantation, and recedes without treatment in most of cases.

2) Experimental infection: Pyelonephritis was induced by the direct inoculation of bacterial strains into the surgically exposed transplanted kidney, after the vascular and ureteral anastomoses have been completed, using a glass microcapillary (462), to inject 5 ml aliquots of inoculum into the kidney, giving a mean challenge of 1300 ± 250 bacteria per organ.

The animals were sacrificed at 7 and 15 days after the transplant, the transplanted kidneys were removed and sent partly for haematoxylin - eosine staining and partly frozen in liquid nitrogen and stored at -70°C for subsequent immunohistochemical staining.

A group of rats with kidney transplant but without infection induced in the transplanted organ was studied as control; the rats were sacrificed at 7 and 15 days after the transplant. A control group of non-transplanted kidneys were considered as well.

3) Preparation of bacteria

The following bacterial strains were used:

- Escherichia coli pili p+
- Streptococcus faecalis
- Pseudomonas aeruginosa.

To take out membranes of these rods, the following procedures have been applied:

- a culture of 10 mls of broth obtained from a plate after a one night incubation with addition of ampicillin 100 mg/ml has been obtained
- the resulting suspension has been diluted in 100 mls containing 100 mg/ml of ampicillin to allow the strains to grow for 2 or 3 hrs to reach an optical density O.D. = 0.7 - 0.8
- then centrifugated at 12,000 rpm for 10 mins
- then suspended in 10 mls phosphate buffered saline pH 7.00
- the resulting suspension has been sonicated for 30 sec. for 5 consecutive times with 1 min. intervals, in a centrifuge tube in polycarbonate in a baker of ice.
- then centrifuged at 4,000 rpm for 10 mins and then suspended in 150-200 ml of phosphate buffered saline

4) Evaluation of extent of pyelonephritis

- microscopic pathology: at the time of sacrifice a midcoronal 3-4 mm section was taken from the removed transplanted kidney for histologic examination. The formalin-fixed tissue slice was
processed for routine histologic study and stained with hematoxylin and eosin. The section were then stained by incubating in a solution of 3-amino-9 ethyl carbazole, post-fixed in 4% formaldehyde for 5 mins., counter stained with hematoxylin and mounted in Elvanol.

5) Immunohistochemistry

Tissues for immunohistochemistry were quick-frozen in liquid nitrogen and stored at -70°C. Cryostat sections, 5 mm thick, were cut at -20°C, thaw-mounted on glass slides, fixed in cold and stained by the avidin-biotin-complex method; sections were incubated for 1 and 1/2 hrs with the optimal dilution of mouse anti-rat monoclonal antibodies diluted in phosphate-buffered saline, pH 7.4, in a humidified chamber, followed by incubation with a 1/120 dilution of the avidin-biotinylated peroxidase complex; the binding of mouse antibodies was visualized by staining with fluorescein-labeled goat antimouse IgG diluted in normal rat serum to absorb antirat crossreactive antibodies. Cellular infiltration was graded semiquantitatively using a scale consisting of 0 (none), 1+ (occasional cells), 2+ (mild), or 3+ (moderate to severe). Control sections were incubated with fluorescein-labeled antimouse IgG without a primary antibody.
6) Antibodies

The monoclonal antibodies that were used are summarized as follows; they were purchased from Serotec / Italfarmaco S.p.a.:

- ED1: recognizes an intracellular antigen in blood monocytes, alveolar, peritoneal and tissue macrophages, and veiled cells in spleen and lymph nodes, as well as Class II-positive interdigitating cells in the T cell areas of lymphoid organs;

- W3/25: recognizes a determinant on the majority of thymocytes (90-95%), a subset of peripheral T cells and macrophages; the antigen recognized by W3/25 is a surface glycoprotein of 56,000 mw and is the homologue of the human CD4 antigens; the antibody labels the rat T helper subset, that mediates helper activity for B and T cells, graft versus host reactivity and produces IL-2 in the mixed lymphocyte reaction.

- MRC OX-8: recognizes a determinant on the majority of thymocytes (90-95%), a subset of peripheral T cells, the majority of NK cells and the granular intraepithelial leucocytes in the small intestine; the antigen recognized is a complex of surface glycoproteins of mw 34,000 and 76,000 and is the rat homologue of the human CD8 antigen; the antibody labels a T-cell subset which mediates suppression of antibody formation and the cytotoxic cell precursor.
- MRC OX-3: recognizes a polymorphic determinant of rat la antigen on B-cells, dendritic cells and certain epithelial cells.
- F17-23-2: reacts with rat Class II MHC antigens; it was originally used to define the localization of Class II MHC antigens in rat kidney and was also used to define the interstitial dendritic cells of the rat.
- MRC 0X-43: recognizes the endothelium of all rat blood vessels except capillaries in the brain.

Results

No microscopic abnormality was found in normal control kidneys; the differences in microscopic abnormality in grafts without infection and after infection were evident.

Within the first 2 weeks after transplantation, an inflammatory response developed within allografts; it has already been demonstrated that afterward it partially subsides (463); glomeruli, large vessels and small numbers of intertubular capillaries showed a dense leukocyte infiltrate; there is a tendency for development of cortical interstitial and tubular atrophy.

In grafts after infection, the pyelonephritic lesions were characterized by severe leucocytic infiltration, with partial involvement of tubules and destruction; the glomeruli seemed largely uninvolved; most lesions were in
the cortex; segments of kidney with nearly absent infiltration were present in all cases. The infiltrate in the interstitium consisted predominantly of mononuclear cells, most of which had the morphologic appearance of macrophages. Abscess formation was seen only in a few specimens. Many plasma cells were noted within the lymphoid interstitial infiltrate by day 7 and were abundant at day 15.

Table 31 summarizes the cellular infiltration pattern of normal kidney tissue, kidney graft removed without bacterial infection and after bacterial infection, as observed following application of monoclonal antibodies. The monoclonal antibody ED1 stained an occasional interstitial cell in a fine granular pattern in normal kidney tissues; between zero and few ED1-positive cells were found in normal renal glomeruli. Renal allografts removed from uninfected recipients showed many ED-1-positive cells in the intima and media of the vessels; the staining is much more pronounced in the second week after the transplant, and is strong in grafts after inoculation of bacteria; no difference has been demonstrated related to the injected bacterial strain.

Immunoperoxidase studies revealed that W3/25 monoclonal antibody did not stain normal kidney tissue, while most of the mononuclear cells stained for W3/25 in kidney grafts, both without and
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Normal renal tissue n. staining</th>
<th>Grafts without infection n. staining</th>
<th>Grafts with infection n. staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED1</td>
<td>4 ±</td>
<td>4 ++</td>
<td>12 +++</td>
</tr>
<tr>
<td>W3/25</td>
<td>4 −</td>
<td>4 +++</td>
<td>12 +++</td>
</tr>
<tr>
<td>MRC OX-8</td>
<td>4 −</td>
<td>4 ++</td>
<td>12 ++</td>
</tr>
<tr>
<td>MRC OX-3</td>
<td>4 +</td>
<td>4 ++</td>
<td>12 +++</td>
</tr>
<tr>
<td>F 17-23-2</td>
<td>4 −</td>
<td>4 ++</td>
<td>12 +++</td>
</tr>
<tr>
<td>MRC OX-43</td>
<td>4 ±</td>
<td>4 +</td>
<td>12 +</td>
</tr>
</tbody>
</table>

- negative
+++ many positive cells
after infection; the same can be observed for MRC OX-8 monoclonal antibody; generally, W3/25 cells were estimated to be three times more numerous than OX8+ cells.

In normal kidneys, staining with MRC OX-3 monoclonal antibody was confined to dendritic cells scattered throughout the interstitial tissue of the cortex and medulla; there was no staining of the tubular epithelium, nor was there detectable endothelial cell staining; very rarely, a glomerulus contained MRC OX-3 cells that appeared to be within the mesangium. In kidney transplants, although the dendritic cells of donor origin were still brightly stained, the tubular epithelial cells also showed patchy but intense staining, indicating significant local production of MRC OX-3-determined antigens. The distribution of the tubular staining indicated that proximal tubular cells were primarily involved; the antigen was also expressed on the parietal epithelium of Bowman's capsule. Staining with MRC OX-3 monoclonal antibody was much more intense in kidney graft after infection, but we were not able to discover any difference between the three bacterial strains.

By using F17-23-2 monoclonal antibody, no staining has been observed in normal kidneys, while a clear uptake of the antibody has been shown at 7 and 15 days after transplantation; the staining is more pronounced after experimental infection.
MRC-OX43 stained the arterial, capillary, and venous endothelium in normal rat tissues; the staining of the renal arterial endothelium was, however, very weak or absent. Kidney allografts showed a slightly increased reactivity pattern with respect to that of normal tissues, and additional staining was found of a few rounded interstitial and fibroblast-shaped cells.

SUMMARY OF SIGNIFICANT RESULTS

From our observations, it doesn't seem that experimental infection in renal transplantation provokes significant increase of expression of W3/25 and MRC OX-8 staining with respect to kidneys in which infection was not induced; it seems therefore that expression of CD4 and CD8 antigens is not increased by infection.

Staining with MRC OX-3 monoclonal antibodies, that recognizes mainly B cells, and with F17-23-2, that recognized class II MHC antigens, is much more intense in kidney graft after infection.
DISCUSSION

The success of renal transplantation depends on a compromise between achieving sufficient immunosuppression to avoid rejection of the graft and maintaining a level of immune competence sufficient to protect the recipient from infection (464). In the early years of transplantation the incidence of severe and lethal infections was high and discouraging, but in recent years a compromise has gradually been reached so that cadaveric renal transplantation now offers a good quality of life to patients in haemodialysis.

The problem of infection, however, remains of considerable concern and contributes substantially to the morbidity and mortality of renal transplantation.

Although most infections in the renal transplant recipient are caused by common pathogens, devastating opportunistic infections occur sufficiently frequently to require a multidisciplinary approach involving infections disease experts and sophisticated microbiological back-up (465).
In the first part of our study, we investigated the infectious complications of renal transplantation with regard to the recipient and donor factors, and the effects on patient and graft survival.

In our study, we have then taken into consideration a number of parameters, aiming to observe whether they could affect the incidence of infectious complications and graft and patient survival, and to which extent.

First, we considered patients age.

Younger patients experience the highest incidence of infections; this observation addresses our attention to the problem of pre-transplant evaluation of the potential recipient; in this group of patients a chronically infected native urinary tract (both due to reflux nephropathy or neurologic bladder voiding dysfunction) was the cause of E.S.R.F. In the majority of these cases, the transplant surgeons must keep into consideration the problem of sterilization of the native urinary tract, even doing pre-transplant nephrectomies if required; otherwise a long term antibiotic prophylaxis must be undertaken in patients awaiting for a kidney transplant and/or after transplantation. A neurologic bladder must be treated as necessary, and augmentation cystoplasty, or urinary diversion, may be the procedures to be performed in some cases.
The higher incidence of serious infectious complications in older patients can drive us to draw some considerations; the introduction of Cyclosporin and the subsequent use of lower doses of steroids have resulted in improved patient and graft survival in renal transplantation. An alternative to renal transplantation is hemodialysis. Patient survival on dialysis is equivalent to that with transplantation (466, 467). Given that survival percentage is satisfactory with either form of therapy, quality of life may be more important in choosing treatment modality. As would be expected, older patients have an high incidence of significant risk factors. Certainly, renal transplantation should not be denied on the basis of patient age alone; but a careful investigation and selection of recipients is mandatory, to avoid those complications that may be life threatening. In our experience, graft and patient survivals seem to be better in younger patients, but we do not believe that age may be discriminating. Fehrman et al. (468) reported 1 and 3 year actuarial patient and graft survival rates of 71%, 57%, 63% and 49%, respectively, in 55 recipients older than 65 years. Murie et al. (469) reported 1 year patient and allograft survival rates of 87% and 73% in 63 patients older than 55 years. These researchers failed to show any significant difference in allograft survival compared to younger patients. Death with a functioning transplant is a major cause of graft failure in elderly patients (467); it has observed that the chief causes
of death are cardiovascular disease and infection; these are inherent problems in this population of patients. The role of invasive pre-transplant cardiac assessment is debatable (470-472), but we believe that a careful screening of pre-existing infections and the prompt recognition of those infection that may occur after transplantation is mandatory to avoid patient death due to infectious complications.

Another factor that is important in determining the incidence of post-transplant infections is the type of pre-transplant dialysis. Dialysis *per se* make the patients more prone to infections (473). In fact in dialysis patients, there is impairment of several aspects of lymphocyte and granulocyte function; unidentified uremic toxins are thought to be responsible; malnutrition or vitamin D deficiency can sometimes be contributory factors. Much of the information about immune defects in chronic renal failure is based on research in hemodialysis patients; to what extent the observations hold true for patients treated with peritoneal dialysis is not always known. The higher incidence of infections in dialysis patients in addition may be related to frequent violation of normal skin and mucosal barriers (access site in hemodialysis patients and skin exit site in peritoneal dialysis patients).

In dialysis patients the incidence of urinary tract infections is high, especially in patients with polycystic kidney disease; a defunctionalized
bladder may be an unsuspected source of infection. Pneumonia is an important cause of mortality in this population. Diverticulosis and diverticulitis occur not uncommonly in dialysis patients and especially in those with polycistic kidney disease. The incidence of tuberculosis has been estimated to be as much as 10-fold higher among hemodialysis patients than among the general population; tuberculosis in hemodialysis patients is frequently extrapulmonary; disseminated disease may occur in the absence of chest x-ray abnormalities. Mortality in dialysis patients with tuberculosis has been reported to be as high as 40%. The incidence of hepatitis B infections among hemodialysis patients is high; it often runs a protracted course and in 50% of cases progresses to a chronic, hepatitis B surface antigen (Hbs Ag) - positive state. Currently most hepatitis in dialysis patients is due to hepatitis C.

Given the higher incidence of infections in dialysis patients, it is important to screen the potential recipient carefully with the aim of discovering those infections that can compromise graft and patient survival.

In our experience, we have observed that patients not yet on dialysis have a lower incidence of post-transplant infections complications; in particular only UTIs are present in these patients. Even graft and patient survival is better in patients not yet on dialysis. Certainly these
observations may be interesting, but providing a kidney to all patients before entering into dialysis can be a substantial problem.

We have then taken into consideration the kidney disease that lead to renal failure. Before 1980s, surgeons were reluctant to transplant kidneys in diabetics because of the prevailing belief at the time that post-transplant patient and graft survival was poor and rehabilitation was not possible. Morbidity and mortality however are substantially higher in diabetic patients maintained on dialysis then in their non diabetic counterparts, with cardiovascular disease and infection being the leading cause of death. Nowadays, it is commonly believed that a functioning kidney transplant offers the uraemic diabetic a higher probability for survival with good rehabilitation than does either C.A.P.D. or maintenance haemodialysis. Macrovascular disease, particularly of the coronary arteries, poses a threat to long-term survival of diabetic kidney recipients. Vigorous treatment of hypertension is a key component of management for diabetics at every stage of progressive nephropathy.

Urinary infections are not unexpected because of difficulties in bladder emptying associated with diabetic autonomic neuropathy (474). Although infections may not occur more frequently than in non-diabetic patients, they are more often due to Staphylococcus aureus or fungal infections (475).
The observation of the high incidence of UTIs in diabetic patients and in those with reflux nephropathy points out once again the problem of sterilization of the native urinary also in consideration of the observation that patients with reflux nephropathy suffer from severe infectious complications as well, such as lung, bacteraemic and renal infections; patients awaiting for a renal transplant must have a sterile urinary tract; but it is important to have repeated urine culture in the post-transplant period, to discover the early onset of UTIs.

We then considered pre-transplant predisposing conditions and the development of infections complications in the post-transplant period.

In particular, we can observe that the highest prevalence ratio for infectious complications are in patients with recurrent UTIs in the pre-transplant period, and also in patients with an abnormal lower urinary tract. An abnormal lower urinary tract may be defined as one in which abnormalities are the principle or major contributory cause of chronic renal failure (476).

The principle causes of an abnormal lower urinary tract are shown in table 32.

Figures from the European Dialysis and Transplant Association show that of all new patients commencing renal replacement therapy those with an abnormal lower urinary tract account for 7.6% of all adults,
but 24.7% of children (aged 15 or under at the start of renal replacement). Thus a significant number of patients are involved and it is essential to consider the special problems faced by this group of patients when discussing the place of renal transplantation in their treatment. Indeed, in many centres, patients are considered unsuitable for transplantation. It is not felt necessary to investigate all patients with chronic renal failure in terms of bladder function. Equally, patients with known lower tract abnormalities should all be fully investigated prior to transplantation.

<table>
<thead>
<tr>
<th>Table 32 - Causes of an abnormal lower urinary tract</th>
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<tbody>
<tr>
<td>Neuropatic bladder</td>
</tr>
<tr>
<td>Bladder extrophy</td>
</tr>
<tr>
<td>Posterior urethral values</td>
</tr>
<tr>
<td>Bladder neck obstruction (not prostatic)</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Prune Belly Syndrome</td>
</tr>
<tr>
<td>Vesico-ureteric reflux</td>
</tr>
<tr>
<td>Bladder tumour</td>
</tr>
</tbody>
</table>
Patients - especially younger ones - with a suggestive clinical history or with urological complications, and patients in whom the aetiology of chronic renal failure is unknown, should have investigations, proceeding as far as necessary to establish that bladder function is normal.

The basic investigation recommended for all patients in whom there is uncertainty about bladder function are measurement of the urinary flow rate and ultrasound examination of the bladder before and after micturition.

If results of these are normal, no further investigations are required unless the situation is known to be more complex. Further information is gained from simple cytogram and cystoscopy but these are less definitive than a full urodynamic videocystometrogram. From this is obtained data on the bladder capacity, end-filling pressure, detrusor activity, compliance and the bladder neck mechanism. Only with this comprehensive investigation it is possible to decide whether the bladder can be used safely following transplantation, whether (and how) an unacceptable bladder can be improved, and whether it is possible to offer "undiversion" to a patient with a urinary diversion.

Criteria for a "safe" bladder for transplantation have been established (table 33).
Table 33 - Criteria for a "safe" bladder for transplantation

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Good volume</td>
<td>&gt; 300 ml</td>
</tr>
<tr>
<td>2. Low end-filling pressure</td>
<td>&lt; 30 cm H₂O</td>
</tr>
<tr>
<td>3. Good flow rate</td>
<td>&gt; 18 ml/sec.</td>
</tr>
<tr>
<td>4. Absence of systolic detrusor contractions, normal compliance</td>
<td></td>
</tr>
</tbody>
</table>

In general terms, they define a good-volume, low pressure bladder with stable detrusor activity.

If, on urodynamic testing, a bladder is shown to fall outside the acceptable criteria, several options are available. Firstly, the use of a urinary diversion. Secondly, reconstruction and augmentation of the bladder in an attempt to increase the capacity and reduce the end-filling pressure. Finally, intermittent clean self-catheterisation and the artificial bladder sphincter may be of value.

It is often argued that the long-term prognosis (10-20 years) of kidneys draining into a conduit is not good and that if the patient's abnormal drainage (including the conduit) has resulted in destruction of the native kidneys after a number of years then the same is likely to occur to the transplanted kidney. However, this argument is flawed for several reasons.
Much comment has been made on the requirement for clearance of the upper tracts pre-transplant, especially in the presence of dilated infected kidneys; however, with current immunosuppressive regimens post-transplant and available antibiotics less problems are caused by grossly diseased upper tracts and unless repeated infection has been a relevant problem pre-operative nephrectomy is rarely indicated. If post-operative problems require nephrectomy it can be safely performed once the immediate post-transplant period has passed, usually at about three months.

If a dialysis patient still passes significant volumes of urine, construction of a useable bladder or conduit may be performed at any time; however, problems may occur with a "dry" conduit or reconstructed bladder if the patient is severely oliguric or anuric related in part to mucous secretion from the bowel segment used. Ideally, transplantation should be performed within a year of reconstruction of the bladder or elective construction of an iled conduit.

For obvious reasons, anastomosis of the transplant ureter to the augmented bladder or iled conduit may present a technical challenge.

In addition to the standard post-operative complications involving any transplant recipient, there are a number of specific problems to which patients with an abnormal lower urinary tract are at risk. These are
principally related to the risk of urinary infection and the effect of abnormal bladder function on renal function. Incomplete and inadequate bladder emptying together with the abnormal wall to which the transplant ureter is anastomosed result in considerable diagnostic problems in assessing both the site and the severity of possible obstruction, which may be functional rather than anatomical.

It is generally agreed, however, that it is possible and realistic to offer renal transplantation to the majority of patients with an abnormal lower urinary tract. Medium term (up to 10 years) results using an ileal conduit are acceptable, though more caution must be exercised over the use of the native bladder, even following reconstruction, in order to produce the high volume, low pressure bladder.

We have considered afterwards the complications of kidney transplantation and correlated them with the prevalence ratio of infectious complications in the post-transplant period; we have considered vascular, urologic and lymphatic complications.

Vascular complications are generally divided into early and late, based on their occurrence after transplantation; early complications include hemorrhage from the wound, from the transplanted kidney, or from the arterial and venous anastomosis, and in addition thrombosis of the renal artery or spontaneous rupture of the kidney; late complications
include the development of anastomotic or mycotic aneurism of the renal artery and renal artery stenosis.

Early urological complications after transplantation are most often technical and usually result from inadequate blood supply to the ureter or lower pole of the kidney, or from an imperfect ureteral anastomosis (477). The consequences of such technical errors are urinary leakage, ureteral necrosis, calicocutaneous fistula and urinary tract bleeding (478). Bleeding into the bladder and clot retention are uncommon but potentially serious complications that may result in graft loss; by using a multilayer bladder closure and adhering to the principle of hemostasis, bleeding, bladder leakage or diverticula formation should occur rarely.

Ischemic injury to the collecting system related to harvesting technique can result in urinary leakage, fistula formation, obstruction, ureteral necrosis and possible graft loss.

Late complications include ureteral obstruction secondary to ischemia, rejection, bladder outlet obstruction, urinary tract calculi, and hydronephrosis secondary to vesicoureteral reflux into the transplanted kidney or a noncompliant bladder.

Besides urological complications, patients may have post-transplantation urological problems, such as incontinence, infertility,
impotence and urological malignancy; of course, these last problems have not been considered in our series.

Perirenal fluid collections are mostly lymphocele; it is a collection of lymph surrounding the transplanted kidney; the source of lymph may come from divided lymphatics of the transplant itself. If the lymphocele becomes large it will present as ilial or abdominal mass; compression of the ureter may result in the deterioration of renal function. Edema of the ipsilateral leg may be present.

Patients with urologic complications experience the highest prevalence ratio of infectious complications; in particular, they have the highest incidence of UTIs and septicaemia. Although significant improvement in patient and graft survival have occurred in the last decade, urological complications continue to be an important source of morbidity and mortality in renal transplant recipients. A meticulous attention to surgical technique, focusing on gentle handling of the vessels, the kidney itself, ureter and bladder, cannot be overemphasised. To prevent urologic complications in renal transplantation, it is essential to identify all the factors responsible for the development of this problem.

It is of utmost importance to follow certain principles in donor nephrectomy in both cadaveric and living related donors to minimize urological complications; the goal is to obtain healthy kidneys with
minimal trauma and minimal warm ischemia time. The most important cause for ureteral complications is vascular insufficiency, as a result of excessive ureteral and hilar dissection at the time of nephrectomy.

While doing ureteroneocystostomy, many transplant surgeons prefer to create a submucosal tunnel at the time of ureteral implantation to prevent vesico-ureteral reflux.

In the dissection of the iliac fossa to accommodate the allograft, care should be taken to carefully control hemostasis and prevent in this fashion a post-operative hematoma that may result in ureteral compression, vascular occlusion or infection later in the post-operative course. Also, meticulous control of lymphatics vessels is an important step in the prevention of lymphocele.

Complications of the urinary tract are associated in an high percentage with mortality, secondary to sepsis; this can be avoided by the prompt diagnosis and management of these complications. Clinical signs and symptoms of urologic complications may be subtle, unless a urine leak is obvious. Ultrasound has proved a highly effective means of diagnosing even minimal degrees of obstruction or small urine collections and should be used liberally in the post-operative period.

Another aspect we have taken into consideration is the type of immunosuppression the patients received.
From the early 1960s, azothoprine and steroids provided the basis of immunsuppressive therapy in clinical renal transplantation. Over the next 25 years, a host of other immunosuppressants including drugs, a variety of methods of irradiation, thoracic duct drainage, thymectomy and antilymphocyte sera came and mostly went.

Today, however, the dominant role in maintenance therapy has clearly been challenged by the advent of Cyclosporine, and to a lesser extent the dominance of steroids in the treatment of rejection episodes is also under pressure from the newer preparations of antilymphocyte serum and the new monoclonal anti-T cell antibodies. Azathioprine and prednisolone, which in combination has often been referred to as "conventional immunosuppression", also served as the benchmark against which the newer agents were compared both for efficacy and complications. While Cyclosporine, either alone, or in combination with steroids, or in triple combination with predinsolone and azathioprine, has become the major form of immunosuppression in many centres, there remain many patients who are unable to tolerate Cyclosporine, and many other areas of the world where Cyclosporine is too expensive for long-term maintenance therapy. In all these instances, there continues to be a need for the judicious use of "conventional immunosuppression".
In our experience, it seems that the type of maintenance immunosuppression has not influence on the onset of infectious complications, except lung infections that are more frequent in patients who received ATG/ALG, and on graft and patient survival.

However, most of people involved in transplantation agree about the need of a better immunosuppression, that is not just the need of more potent immunosuppression but rather the development of protocols which will provide more specific immunosuppression, and perhaps eventually allow us to induce immunological tolerance in the clinical setting.

We have then considered immediate graft function post-transplantation in relation to infectious complications. It is interesting to observe that most of kidneys without immediate function experienced a rejection episode. Early rejection episodes that occur in the face of aggressive immunosuppression are the strongest predictors of subsequent graft survival identified to date. The remarkable advances in immunosuppression have dramatically improved graft survival rates, but there remain individuals for whom immunosuppression is inadequate, as evidenced by early rejections.

In our experience, the incidence of infections is higher in patients with delayed graft function; it is possible that a tailored antinfection prophylaxis protocol can play a role in reducing infectious complications
in this group of patients, also in consideration of the higher incidence of rejection episodes they encounter, with the need for further immunosuppressive therapy.

The following parameter we have taken into consideration is the cold ischemia time. When dealing with cold ischaemia time, it is necessary to mention the kidney preservation solution that can allow organs to maintain for longer periods.

The European Transplant Community has in the past used Euro-Collins solution almost exclusively for kidney preservation. Post-operative delayed graft function requiring post-transplant dialysis has been reported for kidneys stored in Euro-Collins for longer than 30 hours. The incidence of this failure has been observed to be as high as 30-40% (479). The University of Wisconsin (UW) solution has been shown to provide superior preservation of the pancreas, liver and kidney, when compared with Euro-Collins solution.

Since the UW solution was developed as an universal cold storage solution for all intraabdominal organs, it has been observed that it is a suitable solution and provides a better preservation of the kidney (480); its use resulted in a more rapid reduction in post-operative serum creatinine, higher creatinine clearance rate, and less post-operative
dialysis (21% vs. 31%) when compared with kidneys preserved in other solutions.

In our experience, kidneys with a cold ischaemia time more than 50 hours have a significantly lower 1-year graft survival (62.50%).

So, trying to reduce the incidence of post-transplant infectious complications, often linked to delayed graft function, and to prolong graft survival, it is important to preserve the kidney with the best available solution.

We have subsequently pointed out the problem of donor infection and contamination of the kidney via perfusion solution. Contamination of the donor kidney is an unwelcome technical complication of organ recovery procedures that reflects unfavourably on donor selection or preservation technique. More importantly, infection is the nemesis of the renal transplant recipient who is immunologically enfeebled by immunosuppressant drugs. In such a setting, invasive sepsis due to Gram-positive or negative bacteria or fungi may prove lethal or can lead to systemic or perinephric infection, anastomotic disruption or mycotic aneurysm of the renal allograft anastomosis. The fundamental surgical principles relevant to this problem include: a) avoiding contamination of donor kidneys by careful assessment of donors' potential for systemic or renal infection; b) careful donor nephrectomy and organ preservation
techniques to avoid nosocomial contamination; and c) prompt recognition and treatment of infection.

It has been observed that perioperative antimicrobial prophylaxis in the donor, at the time of nephrectomy, may decrease the incidence of infection in the preservation medium and in the recipient (481). Provided that prophylactic antibiotic therapy is employed, bacterial contaminations can be relatively insignificant in regard to the fate of the allograft survival and the patient survival rates, if contaminations are detected at an early stage, and prompt measures are taken to counteract the contamination with intensive antibacterial chemotherapy. Routine bacteriological sampling of the transplants is recommended, and establishment of proper antibiotic treatment when a contamination is detected should be used.

As far as Cytomegalovirus infection (CMV) is concerned, it has been observed that it is the most important virus infection affecting transplant recipients; in Western countries, approximately 50-60% of patients awaiting transplantation have been infected in the past and have antibodies to CMV. In normal people CMV infection uncommonly produces symptoms but the virus subsequently becomes latent in macrophages and poly-morphonuclear leucocytes and other tissue such as the renal tubules. CMV infection in renal allograft recipient is more often symptomatic and can be severe or even fatal. The infection is
"primary" in a previously seronegative recipient; "secondary" infection occurs in previously seropositive patients due either to reactivation of the patient's own latent virus or to re-infection, but it is not possible to distinguish clinically between these two possibilities. In all infections the severity is directly related to the degree of the patient's immunosuppression.

Primary CMV infection in seronegative recipients can be avoided if the transfused blood and especially the transplanted kidney both come from seronegative donors.

The morbidity associated with re-infection or reactivation in the severely immunosuppressed patient is considerable, especially when antilymphocyte globulin has been given. As morbidity is greatly reduced with more moderate immunosuppression, it is important to use the least aggressive immunosuppression regimen which does not compromise graft function and survival.

We have then considered donor age in relation to the onset of post-transplant infectious complications. The continued shortage of kidney for transplantation has led to increased utilization of nontraditional cadaver donors, including those at both extremes of the age spectrum. While most reports have recommended caution in using kidney from donors younger than two or older than fifty-five years of age, recent reports indicate that
these organs can function well after transplantation (482). The concern to use cadaver kidney from older donors for renal transplantation was based on structural and functional renal changes that are known to occur with senescence. These include progressive reduction in glomerular surface area and proximal convoluted tubular volume, a corresponding reduction in glomerular filtration rate, glomerular and tubular basement membrane thickening, and reduplication of elastic tissue with intimal thickening in small vessels. There does not appear to be any major difference in the immunogenicity of grafts from elderly donors.

The results of various studies indicate that well-functioning kidneys from older cadaver donors can be successfully used for transplantation. This is supported by the finding of a significant inverse correlation between the donor serum creatinine level at procurement and one-year allograft survival. Older donors with an elevated serum creatinine level (> 2.0 mg/dl) should not be employed for renal transplantation.

In recipients of older cadaver kidney, renal functional status at the time of procurement and subsequent ischemic damage are particularly important determinants of recipient allograft outcome. Pretransplant renal biopsy may be a useful tool for evaluating renal morphology in selected older donors with adverse characteristics.
Based on the findings reported here, we come to the following conclusions: 1) donor age is not important in determining infectious complications; 2) donor age should not be a decisive factor in selecting a potential donor for transplantation.

We have then considered the type of ureteric anastomosis and the incidence of infections. We have already discussed about transplantation in patients with an abnormal lower urinary tract. Although the occurrence of more dangerous urologic complications, a great deal of interest is also focused on the avoidance of vesicoureteral reflux after transplantation. When anastomosing the ureter direct to the bladder, the surgical problem could be whether using an antirefluxive ureteral implantation technique or a non antirefluxive method.

It has been observed (483) that the use of an antirefluxive ureteral implantation technique was of no advantage in preventing kidney graft recipients from ureteral reflux or UTI; besides, the presence or absence of reflux did not influence the incidence of UTIs.

We have then considered the HLA-matching in relation to the development of infectious complications in the post-transplant course. Whether HLA-matching should be used to improve the success rate of cadaver kidney transplants continues to be a matter of controversy. Since the HLA-match is only one of many factors that influence graft outcome,
it has been argued that it is necessary to analyze large transplant numbers to obtain valid answers concerning the role of HLA matching.

Before the introduction of Cyclosporine multi- and single-center studies generally reported a beneficial effect of HLA matching. However, improved results at some centers, irrespective of HLA matching and before Cyclosporine, initiated some controversy regarding the benefits of tissue matching.

The potential benefits of histocompatibility and organ sharing based on histocompatibility remains a hotly debated issue even in the Cyclosporine era; several large single-centers studies seem to refute the benefit of matching in patients treated with Cyclosporine.

The introduction of DNA typing as a method of identification of HLA pattern revealed an error rate of approximately 25% in the determination of HLA-DR by conventional serological technique (484).

It is obvious that failures do occur among "matched" transplants; prior sensitization by rejection of a graft is the most important factor that results in failure.

In our experience, we can say that HLA matching should be considered an important aspect of renal transplantation as far as the onset of infectious complication is concerned. Severe infectious complications (such as lung and systemic viral infections and septicaemia) do occur
more frequently in non-well matched kidney transplant, in which early rejection episodes are more frequent; infectious episodes seem therefore to be related to immunosuppression that has been given.

We have afterwards considered in our review genitourinary tract infections, the most common form of bacterial infection affecting renal transplant recipients. Although in the past technical complications of the transplant surgery and infection of the native urinary tract contributed significantly to the occurrence of UTIs, this is no longer the case because most transplant centers will eradicate all pre-transplant infections and urologic complications of transplant surgery now occur in less than 5 percent of cases.

Despite these advances, the incidence of UTI post-transplant is approximately 30 to 40 percent.

Also in our experience it is confirmed that Escherichia coli is the most common microorganisms isolated from urine (35.75%); other series have found similar data; but there is a high incidence of Pseudomonas infection, that contributes significantly to morbidity and can be difficult to eradicate. UTI presenting in the first 3 months post-transplant is frequently associated with overt pyelonephritis, bacteremia with the patiential for metastatic seeding of infection, and a high rate of relapse.
Therefore, care must be taken when diagnosis and treating UTI, also in consideration of the potential lethal consequence of it.

In conclusion, we can say that it is incumbent upon all of people involved with the medical side of transplantation to develop better methods for preventing and treating rejection and preventing, diagnosing and treating infectious complications of antirejection therapy.

The truism that infection and rejection are closely bound together and that progress in one area will affect the other remains as applicable today as it was 20 years ago.

As one approaches both our traditional forms of transplantation and the more experimental areas of transplantation, the following points relevant to infections disease complications should be kept in mind:

1) Infection may be divided into three general categories: those related to technical complications, those related to epidemiologic exposure, and those due to viruses present in the graft or his donor and that are rendered clinically manifest post-transplant. The modulation of these infection is accomplished by the dose, duration and type of immunosuppressive therapy being administered.

2) There is an expected timetable according to which particular infections occur at particular time in the post-transplant course.
Exceptions to this timetable are usually due to exposure to excessive environmental hazards.

3) The biggest challenge in approaching the infections is the prevention and treatment of those viral diseases that contribute so broadly to the morbidity and mortality still associated with clinical human transplantation.

4) Because of the impaired inflammatory respose of this patient population, signs and symptoms of infections may be greatly muted. Physicians caring for such patients must be alert and aggressive in their approach to "minor" skin lesions or radiographic findings.

5) Although the challenge of caring for these patients is great, the rewards are even greater.

Coming along with the infectious complications v.s. renal allograft rejection, we can make some considerations.

Unlike the cytomegalovirus infection, the role of other type of infectious complications in induction or promotion of renal allograft rejection has been investigated less frequently over the past 15 years. The possible role of bacterial and viral infection in the induction or promotion of renal allograft rejection has been a matter of interest and its possible role is supported by some and rejected by others (485).
Bacterial antigens could cross-react with mammalian HLA antigens, and infection and rejection can stimulate the secretion of similar cytokines: tumor necrosis factor, interferon gamma, and interleukin 6.

With these observations, once more it is imperative to keep careful attention to the infectious complication after transplantation, and to their prevention.

In the treatment of severe infection,

1) early diagnosis of the causative organisms,

2) selection of multiple drug combined therapy,

3) selective high-dose chemotherapy against isolated organisms are important.

After having considered the clinical aspects of infectious complications on renal transplantation, we then considered the immunohistology of the transplant kidney to show an eventual influence of infections on graft cellular infiltration; this part of the study has been performed by using monoclonal antibodies directed against antigenic determinants of the transplanted kidneys.

The production of monoclonal antibodies to specific cell-surface antigen has been described in 1975; this major development has had a profound impact in the field of transplantation and has led to a greater understanding of the process of graft rejection (486).
Commercial availability of monoclonal antibodies to previously undefined cell-surface markers provides a means of detecting alterations in the composition of the transplant infiltrate and the expression of parenchimal antigens.

Localization of antigen within a tissue relies on the detection of specific antibody bound to the cellular component of interest.

Early investigations of cellular infiltration in the transplant kidney were based on a morphological assessment of graft removed because of irreversible rejection and on needle-core biopsies of rejecting grafts in situ; in general, cellular infiltration was associated with graft rejection and little information was available regarding the type of cell in the infiltrate.

Leucocyte migration into the transplant kidney begins immediately after vascularization of the graft and significant numbers of cells can be detected in the interstitium within hours. However, the realization that marked leukocyte infiltration is found both in rejecting and in well functioning grafts occurred only after the introduction of the routine renal allograft biopsies in the days and weeks following transplantation. In grafts with clinically stable function, peak levels of infiltration are seen within 3 weeks after transplantation, before decreasing thereafter. Nevertheless, significant leucocyte infiltration is still present in a successful renal allograft several years after transplantation.
A similar occurrence has been reported in the rat renal allograft model. While this infiltrate could represent a low-grade host response against the graft, the infiltrate may not be indicative of graft rejection if the T lymphocyte component consisted of suppressor, rather than cytotoxic, cells.

Leucocyte infiltration is considerably greater in acute rejection than in well-functioning grafts. Immunohistology has shown that the cellular response of acute rejection is of similar magnitude regardless of when it occurs but, in the graft which has undergone multiple severe rejection episodes, cellular infiltration may be less marked than anticipated where interstitial structures have been replaced by fibrosis.

The magnitude of the interstitial infiltrate may be further influenced by the immunosuppressive regimen. Controlled studies have shown that the infiltrate in grafts conventionally treated with azathioprine and low-dose prednisolone have greater levels of leucocyte infiltration than grafts treated with Cyclosporine. Infiltration per se is not necessarily indicative of poor graft function.

In addition to the overall magnitude of the cellular infiltrate in transplant biopsies, the composition of the infiltrate has been evaluated as well, but the data from a number of studies are rather conflicting; in acute rejection some have found the macrophage to be the predominant cell...
type, but others have found the T lymphocyte to be the most abundant infiltrating cell. Both the magnitude of the cellular infiltrate and the phenotype of the infiltrating cells in the graft have been used to assess clinical rejection.

The high levels of leucocyte infiltration in grafts undergoing rejection may also be used to assess the likelihood of rejection. Although it has been established that the presence of activated T lymphocytes is an absolute requirement for acute cellular allograft rejection (487), it has also been shown conclusively that allospecific, cytotoxic T cells can reside within an allograft without causing demonstrable functional impairment (488).

The results of our study show that infection is responsible for the higher degree of cellular infiltration in rejecting kidneys. But it remains to be stated whether, from the pathological point of view, the infiltrate of mononuclear cells inside the grafts was important before the infectious process appeared clinically patent, indicating that the rejection process had already begun before the infection could act specifically at the cellular level, and therefore infection reinforce rejection, or whether the infection is the main responsible for rejection.

The association of transplant rejection with virus infection has been documented in the past. It is possible that the Class I or II antigen re-
expression on graft parenchymal cells, presumably induced by gamma-
interferon in response to virus infection, induces rejection. It is possible,
though less likely, that activation of graft (donor-derived) tissue
macrophages (dendritic cells) via gamma-interferon, also contributes. An
alternate possibility, though not mutually exclusive, is that interleukin-2
released by the virus-activated T cells provides a necessary co-stimulus.
Induction of inflammation by either mechanism, or by both, may generate
a vicious circle in the graft: gamma-interferon activates resting monocytes
into tissue macrophages which, in turn, release interleukin 1. Interleukin
1, together with increased antigen presentation, generates more immune
response and more immune response creates more inflammation - i.e.
rejection.

As far as bacterial infections can act on renal transplant by inducing
rejection, their possible role has been a matter of interest and supported
by some.

Bacterial antigens can cross-react with mammalian HLA antigens,
and infection and rejection can stimulate the secretion of similar
cytokines: tumour necrosis factor, interferon-gamma and interleukin-6. A
large scale, multicenter, prospective study to answer the question of
infection versus renal allo graft rejection is certainly very much needed.
The present results demonstrate that renal transplantation triggers a remarkable variety of inflammatory events.

Histopathological and immunoistochemistry studies of kidney allografts with or without clinical evidence of rejection have documented the presence of macrophages in such grafts (489, 490).

It has already been observed (491) that there exist numerous macrophage subpopulations in normal and allotransplanted tissues; if phenotypically different subpopulations have different functional characteristics, this indicate that the macrophages exert different functions in different types of allografts, which may explain, at least in part, some of the organ-specific features of transplant rejection.

The increased staining after allograft infection may support the view of different macrophages subpopulations, active in response to foreign antigens as well as during rejection.

It doesn't seem that infection can alter the expression of helper or cytotoxic lymphocytes; on the contrary, expression of MRC OX-3 and F17-23.2 is much more pronounced in kidneys subjected to experimental infection; they showed intense uptake in the graft, that was seen early after transplantation and was still present at 2 weeks afterward.

These findings were in agreement with previously reported data, especially those concerning induction and expression of donor Class I and
II MHC (492), that suggest that quantitative monitoring of Class I and II expression may be of value in judging the progress of rejection.

The use of the monoclonal antibody OX43, which is directed against vascular endothelium and a subpopulation of macrophages (493), identified multinucleated giant cells with lysozomes and filopodia inside them.

The increase in MHC Class I and II antigen expression after ischemic injury may explain the increased incidence of rejection in damaged renal transplant (494, 495). The induction of MHC Class I and II genes is accompanied by the induction of other components of the antigen-presenting machinery.

IFN-γ can significantly upregulate the basal expression of adhesion molecules on different cell types, including renal tubular epithelial cells (496); such effects could further contribute to the problems of controlling rejection after ischemia in renal transplants. The expression of Class II and other immune interaction molecules within the allogenic parenchyma could increase the probability of rejection, contribute to progression of rejection or increase the susceptibility of tissue to effector mechanisms.

MHC induction almost always accompanies acute T cell-mediated transplant rejection and autoimmune injury, and immunosuppressive
protocols that block MHC and cytokine induction usually block injury (497).

Cytokines and growth factors, among other soluble factors, coordinate the inflammatory response by controlling the nature of the infiltrate and the functions of inflammatory and immune effector cells at the site of injury, but the critical question here is the linkage between epithelial, endothelial and interstitial events which leads to inflammation. The elucidation of the pathway between epithelial injury and interstitial inflammation, both at the cellular and molecular level, will provide a better understanding of the relationship between nonspecific injury, which triggers inflammation, specific T cell mechanisms, and the specific immune response. It is important to recognize that neither inflammatory infiltrate nor the expression of any cytokine is a priori evidence of an antigen-specific immune response. Similarly, in immunologic disease, injury may be a cause of the expression of cytokines, rather than an effect that is often invoked to explain the association. Thus, the occurrence of injury can invite a response of inflammatory cytokines, which can profoundly alter the interpretation of the cause of the injury in immunologic diseases. Moreover, injury leading to inflammation may promote some specific responses in some cases, leading to a cycle of injury→inflammation→injury. This could be a factor in some forms of
progressive injury, particularly chronic rejection, and other forms of chronic progressive immune renal injury.

However, no simple cytokine "causes" chronicity or explains chronicity. Rather, the persistence of the cytokine should invite continued study of what is inducing it, and that will lead to the cause.
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