BACKGROUND AND PURPOSE

Pancreatic islets of Langerhans contain insulin producing beta cells that regulate the utilization of dietary sugars by all cells in the body. In persons with Type 1 diabetes mellitus (T1DM), most of the beta cells are destroyed by an autoimmune attack, resulting in the need for pharmaceutical insulin delivered by injection or pump to avoid diabetes-related illness and death. About 5% of the 29.1 million people in the US with diabetes have T1DM, or an estimated 1.5 million people. The only alternatives to daily insulin injections or pump currently available are solid organ pancreas transplant or transplantation of islets of Langerhans isolated from a donated pancreas.

Islet transplantation in the US is experimental and available only at sites that have received exemption from the US Food and Drug Administration (US-FDA) for clinical research of islet transplantation in T1DM. In the US, individual transplant centers may initiate their own independent research protocols or participate in Clinical Islet Transplant Consortium (www.CITIsletStudy.org) to advance the field of islet transplantation. At the Canadian, European and Australian sites, both research and standard of care protocols have been available. Research investigators in clinical islet transplantation and islet science at the various programs contribute data and collaborate on the data analysis to advance knowledge about the risks and benefits of islet transplantation. Each center may publish the results of their local protocols or aggregate experience, and disseminate information regarding their open and recruiting protocols through their own means and/or at the National Library of Medicine’s developed website www.clinicaltrials.gov. In addition, CITR maintains interactive maps of North American and JDRF European and Australian islet transplant programs at www.citregistry.org.

In 2001, the National Institute of Diabetes & Digestive & Kidney Diseases established the Collaborative Islet Transplant Registry (CITR) to compile data from all islet transplant programs in North America from 1999 to the present. The Juvenile Diabetes Research Foundation (JDRF) granted additional funding to include the participation of JDRF-funded European and Australian centers. The cumulated North American and JDRF European and Australian data are pooled into an annual report. CITR Annual Reports are publically available and can be downloaded or requested in hard copy at www.citregistry.org. This Scientific Summary highlights results from the CITR 2012 (8th) Annual Report, either by direct inclusion or by reference.

PATIENTS AND METHODS

At the time of their first Islet transplant, CITR allograft recipients were 7-72 years of age (mean 45±10SD), had T1DM for 2-61 (29±11) years, and had very poor diabetes control including hypoglycemia unawareness and severe hypoglycemic events. Poor glycemic control can manifest as frequent episodes of critically low blood sugar levels (which often result as a reaction to injected insulin, requiring the assistance of another person to avert a possibly life-
threatening loss of consciousness), wide swings in blood sugar levels (blood glucose lability), or consistently high HbA\textsubscript{1C} levels (>8% of total hemoglobin).

Data reported to the Registry are abstracted from medical information that is routinely collected by investigators in the course of their research protocols or clinical practice, and for reports to the multiple agencies and entities required by US-FDA regulated trials or according to the requirements of the respective nation.

Detailed follow-up data are abstracted pre-infusion and at Day 75, Month 6, and annually post infusion. At each new infusion, a new follow-up schedule is established.

All grade 3, 4 and 5 adverse events, according to the Clinical Islet Transplant Consortium (CIT) Terminology Criteria for Adverse Events (TCAE), and all serious adverse events (regardless of grade) are reported to CITR. A copy of the CITR data collection forms may be requested from the CITR Coordinating Center (citr@emmes.com), or viewed at the CITR Website (www.citregistry.org).

CITR utilizes the Coordinating Center’s (The Emmes Corporation, Rockville, MD) web-based data entry and management systems to capture data on recipients, donors and pancreata. Additional data have been obtained through data sharing agreements with the United Network for Organ Sharing (UNOS), the Administrative and Bioinformatics Coordinating Center (ABCC, 2001-2009) of the Islet Cell Resource Centers (ICR), and the Data Coordinating Center (DCC) of the Clinical Islet Transplant Consortium (CIT, 2008-).

The Registry data exists because of the voluntary participation of the transplanting centers, with written informed consent for participation in the Registry by the islet recipients. While the Registry represents the most comprehensive collection of the human islet transplantation experience since 1999, there may exist uncontrollable biases and imbalances including selective reporting and differences in clinical care and decision-making. Even with the diligent efforts of the participating centers, the total number of cases and outcomes remains relatively small. Hence, the aggregate results should be interpreted cautiously.

**Statistical analysis.** The database for the 8\textsuperscript{th} Annual Report was closed for analysis on December 17, 2013 for data on recipients that were transplanted as of December 31, 2012.

The major focus of the present analyses is to identify factors of patient selection, islet processing and islet transplantation management factors that result in the best possible clinical outcomes of islet transplantation. Reduced data reporting, particularly in long-term follow-up, has posed a challenge for the present analyses. The primary endpoints of insulin use, hence independence or not, and fasting C-peptide levels are the most completely available outcomes data. Monitoring site visits have been performed as scheduled and have included data audits for key recipient baseline and primary outcome data. Additionally, since 2008, site-by-site semi-annual reviews have been conducted by teleconference to maximize reporting of primary endpoints.

Descriptive analyses include tabular or graphical displays of sample means and their standard deviations (SD) or standard errors (SE), and whole-distribution statistics such as median, interquartile range and extremes. Primary outcomes -- analyzed at study time points post first or last infusion -- include percent insulin independent (≥14 consecutive days), C-peptide <0.3 ng/mL, HbA\textsubscript{1C} <6.5% or drop by ≥2%, fasting blood glucose of 60-140, and severe hypoglycemic events (Yes/No). First achievement and final loss of insulin independence, as well as complete graft failure, are analyzed by Kaplan-Meier time-to-event analysis with proportional hazards investigation of predictive factors, employing multivariate models to adjust for
correlated or confounding factors. Secondary outcomes include whole-distribution description of these and other laboratory measurements, metabolic test results, liver and kidney function measures, and complications of diabetes. Safety is monitored by incidence rates of adverse events classified by CIT-TCAE criteria and related to either infusion procedure or immunosuppression as determined by the local investigator.

Statistical comparisons are observational in nature: reported p-values are not based on controlled, experimental design but on the available data as a sample of convenience. The results should be used to direct future research as well as guide current clinical practice.

RESULTS

Islet Allograft Transplantation Activity 1999-2012. As of December 31, 2012, the CITR Registry included data on 864 allogeneic islet transplant recipients (686 islet transplant alone, ITA, and 178 islet after or simultaneous with kidney, IAK/SIK), who received 1,679 infusions from 2,146 donors (Exhibit A). The North American sites contributed 60% and the JDRF European and Australian sites contributed 40% of the recipients. Combining the ITA and IAK/SIK recipients, 28% received a single islet infusion, 49% received two, 20% received three, and 3% received 4-6 infusions.

Exhibit A
CITR Recipients, Infusions and Donors by NIDDK/JDRF Sites and by ITA/IAK-SIK Consented, Registered and First Infused in 1999-2012

<table>
<thead>
<tr>
<th></th>
<th>Islet Transplant Alone (ITA)</th>
<th>Islet After Kidney or Simultaneous Islet-Kidney (IAK-SIK)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>North America</td>
</tr>
<tr>
<td>Recipients</td>
<td>686</td>
<td>461</td>
</tr>
<tr>
<td>Infusions</td>
<td>1,356</td>
<td>879</td>
</tr>
<tr>
<td>Donors</td>
<td>1,785</td>
<td>944</td>
</tr>
</tbody>
</table>

Exhibits B1 and B2 display the data collected from the islet transplant programs in North America and the JDRF European and Australian sites from 1999 through 2012. Of the 602 total North American recipients reported by general survey of the sites to have received an islet allograft in 1999-2012, 516 (86%) consented to and were registered in CITR. Detailed data was available on 501 of these recipients, representing 83% of the overall 602. Of the 362 total reported JDRF European and Australian recipients, 96% (348) were consented and registered in CITR and 78% (283) have detailed data available. Both North American and JDRF sites saw a decline in new recipients around 2007, followed by an increase in following years. In 2012, North American sites again saw a decline while JDRF sites increased the number of new recipients.
Exhibit B
Total Number of Islet Allograft Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion

1. Allograft recipients at CITR North American Centers 1999-2012

Islet Transplant Recipient Characteristics. Over the eras of the Registry, the following trends are observed for recipients of allogeneic islets:

- Recipients have been selected at older age (42±0.6* to 48±0.9) and longer wait time (236.7±21.4d to 367.6±68.6d) at initial transplant
- Recipients have been selected with higher HbA1c (7.9±0.1 to 8.4±0.1), increased use of insulin pump (30% to 53%), and higher prevalence of hypoglycemia unawareness (58% to 79%)
• Greater proportions had positive GAD65 autoantibody (17% to 24%) and lower proportions had positive insulin autoantibody (32% to 11%)
• Recipients had lower levels of total cholesterol (181.3±2.8 to 163.7±5.6) and LDL cholesterol (98.5±2.5 to 86.4±4.7) in recent eras
• Recipients had somewhat higher initial levels of estimated GFR (82.1±2.1 to 87.7±2.9))

*Mean±SE

There were also notable differences in medical characteristics between ITA and IAK/SIK recipients, most notably, a much lower initial eGFR in the IAK/SIK (57.8±2.6 vs. 91.9±0.9) recipients.

Donor Information. All donors were deceased, at a mean age that rose from 43.5±0.7 SE to 44.5±0.5 years from the first to third era and decreased to 42.4±1.0 in the most recent era. “Infusions” (all infusions given to a single recipient on a given day) were comprised of about 58% all male donors, 37% all female donors, and 5% mixed male and female donors. Less than 10% of “infusions” were comprised of all Hispanic donors and 89% were comprised of all white donors. About 59% of the donors had cerebrovascular accident/stroke as their cause of death while 29% experienced trauma. Approximately 36% of the donors had a history of hypertension and 18% had a history of alcohol dependency.

Thirty-one percent (31%) of the donors received a transfusion during their terminal hospitalization, while only 6% received a transfusion intraoperatively. Sixty-one percent (61%) of the donors received steroids and 97% received at least one vasopressor during the terminal hospitalization. A total of 11 donors tested positive for anti-HBC, one tested positive for RPR-VDRL and one for HCV. Mean serum creatinine of the donors remained steady around 1.05 mg/dL, while the mean maximum stimulated blood glucose decreased from 244±6.4 SE to 202.4±6.4 mg/dL throughout the eras.

The following trends are observed among donors of allogeneic islets over the eras:

• Substantial increase in donor weight and BMI (26.7±0.4 to 34.4±2.2)
• Lowered use of transfusion during hospitalization (34% to 12%)
• Increased of steroids and insulin during hospitalization (62% to 77%)
• Increased use of insulin to donor during hospitalization (34% to 49%)
• Donor serum creatinine (1.1±0.05 to 1.0±0.1) and stimulated blood glucose (244±6 to 202±6) have declined substantially over the eras

Pancreas Procurement and Processing. Mean time from cross clamp to pancreas recovery was 50.4±62 SD minutes while mean cold ischemia time was 7.5 hours. Over the eras, pancreas preservation with UW-only fell from 48% to 11% while HTK use rose from 0% to 17.5% and preservation other than UW, 2-layer, HTK, Eurocollins and Celsior rose from 30% to 68%. For digestion, use of Liberase HI dropped from 75% in 1999-2002 to 11% in 2011-2014, while Serva/NB1 use rose from 0% to 20%, and other collagenase rose from 0.3% to 4%. Thermolysin use increased from 0% to 7% and pulmozyme use rose from 14% to 30%. Culturing of the islets for >6 hours rose over the eras from 24% to 41%, with mean culture time rising over the eras. All of the pancreata processed used a density gradient for islet purification. Of the 2,146 islet preparations, 17 (0.8%) showed a positive aerobic culture, 7 (0.3%) showed a positive anaerobic culture, 10 (0.5%) showed a positive fungal culture, and 1 (0.05%) tested positive for mycoplasma.
The following trends were observed among islet preparations:

- UW (48% to 11%) and 2-layer solutions (12% to 1%) use have declined appreciably over the eras.
- Islet preparations were cultured more frequently and longer (10.9±17.4 to 25.3±10.7) in the recent eras.
- Pulmozyme use increased substantially in the recent eras (14% to 30%).
- Mean time from brain death to pancreas recovery was about 3 hours longer for ITA than IAK/SIK, and has increased over the eras by 4 hours.

**Islet product characteristics.** Mean total islet equivalents (1000s) per infusion rose from 412±10 SD IEQs in the first era to 423±9 in the third, then decreased to 411±11 in the most recent era. Total Beta cells and β-cells/kg were higher for IAK/SIK (5.5±0.7 vs. 3.4±0.2) and have increased over the eras (2.9±0.3 to 3.9±0.5). Endotoxin (both total and /kg) has declined sharply over the eras (0.4±0.1 to 0.1±0.05). Stimulation index was higher for ITA than IAK/SIK, and has declined over the eras (3.7±0.3 to 2.7±0.2).

**Immunosuppression therapy.** Induction with IL2R antagonists only, which comprised about 57% of all initial infusions in 1999-2002, was replaced or supplemented with regimens that included T-cell depletion with/without TNF antagonists in about 60% of the new infusions performed by 2011-2014. In 1999-2002, maintenance immunosuppression was predominantly (66%) calcineurin (CNI)+mTOR inhibitors. It was increasingly replaced or supplemented throughout the eras by a CNI and IMPDH-inhibitor combination; in the most recent era, CNI+mTOR inhibitors were used in 31% of new infusions while CNI+IMPDH inhibitors were used in about 46%.

**Graft Function.** First achievement of insulin independence measured from initial islet infusion (Exhibit C), with or without subsequent infusion, is an indicator of the rate of engraftment under the real-time conditions of competing events including early graft loss, islet resource availability, patient/doctor decisions and myriad other factors, some of which are characterized in the CITR data and others not. It is notable that the cumulative rate of achievement of insulin independence follows the general shape of engraftment curves for solid organs, but with a slower initial slope, indicative of multiple infusions. Among the most predictive factors of first achievement of insulin independence were negative IA-2 autoantibody at baseline, shorter average cold storage time, ≥500K IEQs infused overall, and immunosuppression with IL2RA and mTOR-inhibitor (Exhibit C).
**Exhibit C**
First Achievement of Insulin Independence
Post First Infusion (Censored at final graft loss or end of follow-up)

---

**IA2 autoantibody (negative is favorable)**

**Cold storage time (shorter is favorable)**

**IEQs infused (≥500K favorable)**

**Induction IS (IL2RA is favorable)**

**Maintenance IS (mTOR is favorable)**

Among factors potentially predictive of successful long-term islet function are induction and maintenance immunosuppression; 5-year insulin independence rates are greatly improved for recipients using, as compared to those not using, T-cell depletion (p=0.001) and/or TNF-α inhibitors (p=0.02) for induction and calcineurin inhibitors (p=0.001), mTOR inhibitors (p<0.001), and/or deoxyspegiualin (p=0.004) for maintenance (Exhibit D1-5). Improved insulin independence rates at annual follow-ups post last infusion are also seen with older recipient age (p<0.001, Exhibit D6) and lower insulin requirements (p<0.001, Exhibit D7), even in this patient population with high rates of hypoglycemia unawareness and severe hypoglycemic events. In a subgroup analysis of recipients over age 35, on less than 43 units per day of insulin at baseline,
and managed with TCD/TNF-a inhibition, 5-year insulin independence rates are more than double recipients without these favorable factors (p=0.001, Exhibit D8).

Additional beneficial factors include baseline HbA1c<8.5% (p=0.005), negative IA-2 autoantibodies (p=0.001), positive microinsulin autoantibody (p=0.01), baseline LDL<75 (p<0.001), baseline triglycerides <30 mg/dL (p<0.001), baseline cholesterol <150 (p=0.004), ABO blood type A (p=0.03), donor transfused (p=0.04), thermolysin (p=0.001), UW (p=0.01), 2-layer (p=0.03), and/or HTK preservation (p=0.001), islets cultured>6 hrs (p=0.05), donor BMI<25 or >32 (p=0.05), death-to-recovery>24 hrs (p=0.02), islet stimulation index≥1.5 (p=0.03), IEQ/islet particle ratio>0.83 (p=0.04), DNA content>4 (p=0.04), and total IEQs over all infusions≥500K (p<0.001).

### Exhibit D

**Percent insulin independence post last infusion by predictive factors**

<table>
<thead>
<tr>
<th>Predictive Factor</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. TCD favorable</td>
<td>0.001</td>
</tr>
<tr>
<td>2. TNFa-Inh favorable</td>
<td>0.02</td>
</tr>
<tr>
<td>3. Calcineurin inhibitor favorable</td>
<td>0.001</td>
</tr>
<tr>
<td>4. mTOR inhibitor favorable</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5. Deoxyspegualin favorable</td>
<td>0.004</td>
</tr>
<tr>
<td>6. Recipient age≥35 favorable</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Similarly, graft function is lost over long-term follow-up, although it too varies substantially according to various factors. By Kaplan-Meier and Cox proportional hazards analysis, retention of graft function (C-peptide ≥0.3 ng/mL) post last infusion is maximized by recipient age ≥35 years (Exhibit E1, p<0.001), baseline LDL <75 (Exhibit E2, p=0.008), ≥500K IEQs infused (Exhibit E3, p=0.01), use of Serva/NB1 (p=0.002), and calcineurin inhibitors (Exhibit E4, p<0.001). With these factors combined, graft retention rates remain at 80% for 7-8 years (Exhibit E5).

**Exhibit E**
Time to complete graft failure post last infusion

1. Recipient age ≥35 (p<0.001)

2 ≥500K IEQs infused (p=0.03)
The higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c<6.5% or drop by 2%, FBG of 60-140, and the lower the likelihood of severe hypoglycemia (Exhibit F). Even partial graft function, i.e., fasting C-peptide of 0.3-0.5 ng/mL, is associated with lowered insulin use, improved HbA1c, greater glycemic control, and lower levels of severe hypoglycemia, which is drastically reduced over all follow-up even with C-peptide<0.3 ng/mL. While these strong associations among the co-primary outcomes are highly significant, any causal relationships cannot be deduced just from the associations; a temporal analysis is a separate focus topic.
Exhibit F
Insulin independence (1), HbA1c <6.5 or drop by 2% (2), FBG 60-140 (3) and Absence of severe hypoglycemic events (4)
By concurrent C-peptide level, at annual follow-up post last infusion
Adverse Effects. ALT and AST levels typically rise after islet transplantation, then level off. Serum creatinine rose over years of follow-up after initial islet transplant, in both ITA and IAK/SIK. The decline in eGFR after islet transplantation is both statistically significant and clinically important. The differences by era are due to both higher pre-transplant levels and a more blunted decline in the most recent era (Exhibit G1, p<0.001). IAK/SIK had much lower pre-transplant levels than ITA, which then declined at a slower rate (Exhibit G2, p<0.001). Importantly, there were no differences in initial levels or subsequent decline over follow-up by immunosuppression regimens. Compared with an age-unadjusted cohort of 1,141 T1D followed by the Diabetes Control and Complications Trial and then by the Epidemiology of Diabetes Interventions and Complications (EDIC) (The DCCT/EDIC Research Group, 2011) who started with mean eGFR levels of 126 ml/min/1.73m³, CITR allograft recipients had much lower mean eGFR (92±20.5 SD for ITA and 58±31 for IAK/SIK) at their first transplant. CITR ITA recipients exhibited a decline in eGFR of 12.4±19.2 and IAK/SIK experienced a mean decline of 0.8±32.3 ml/min/1.73m³ in 5 years from first infusion, compared to a mean decline of about 9 ml/min/1.73m³ over the first 5 years in the DCCT.

Exhibit G
Chronic Kidney Disease Collaboration (CKD-EPI) Estimated GFR (mL/min/1.73m²)

Neoplasms. A total of 41 instances of neoplasm have been diagnosed in 32 of the 864 islet recipients who collectively represent a total of 5,762 person-years of observed follow-up. This equates to about 0.007 neoplasms per person-year. There were 21 instances in 17 patients (1 in 15 recipients, 2 in 1 recipient, and 4 in another) of basal or squamous cell carcinoma of the skin. Of the 15 patients with a single instance, 11 recovered, 1 recovered with sequelae, 1 is
recovering, and 1 has an unknown recovery status. The recipient with 4 instances recovered with sequelae and the recipient with 2 instances has not recovered.

There were 6 instances of malignant ovarian cysts, 4 instances of breast cancer (2 instances in 1 recipient), 2 instances of lung cancer, 2 instances of thyroid cancer, and 3 instances of PTLD. Of these 14 recipients with non-skin cancers, 8 recovered, 2 recovered with sequelae, 5 have not recovered, and 1 died (lung cancer).

For 3 instances of cancer, there were no types specified (2 instances in 1 recipient). Both of these recipients have recovered.

Deaths. There have been 25 reports of death to the Registry for islet allograft recipients, for 2.4% crude mortality over a mean of 6.7 years elapsed follow-up per patient (including periods after complete graft failure and loss to observed follow-up). Causes of death were (# cases): cardiovascular (5), hemorrhage (3), pneumonia (2), diabetic ketoacidosis (1), infection (1), respiratory arrest (1), acute toxicity (1), pneumopathy (1), multi-organ failure of unknown etiology (1), viral meningitis (1), and lung cancer (1). The remaining 7 deaths did not have a cause specified.

CONCLUSIONS

In the years since 2005, fewer North American centers performed islet transplantation, with the number of centers decreasing rapidly until 2007, briefly increasing in 2008, then leveling off until 2012. With the continuation of Clinical Islet Transplantation (CIT) Consortium protocols that began in 2008, the number of new islet cell recipients rose somewhat in North America through 2011. New allograft recipients at European and Australian JDRF sites remained fairly steady between 2006 and 2008, but have seen an increase in more recent years.

The safety-risk profile indicates that over 1999-2012, recipients of allogeneic islet transplantation were much more impacted by their disease than either of the DCCT-EPIC T1D cohorts, being substantially older, having diabetes for many more years, exhibiting much more impaired kidney function at initial transplant, and suffering from very poor glycemic control marked by frequent episodes of severe hypoglycemia. Despite the burden of immunosuppression, CITR allograft recipients exhibited substantial benefit with acceptable risk as evidenced by low levels of infusion-related complications, and relatively few events of immunosuppression-related cancer and death. Increased cancer risk is associated with both diabetes (Hemkens, et al., 2009; Suh, 2011; Noto, Osame, Sasazuki, and Noda 2010) and solid organ transplantation (Engels, et al., 2011), making it difficult to predict expected rates of neoplasm in T1D islet transplant recipients. Declining kidney function, while of concern, is not comparable to the full DCCT-EPIC cohorts: in CITR allograft recipients, eGFR started much lower relative to the DCCT-EPIC cohorts, declined at higher rates in the ITA group and declined at similar rates in the IAK/SIK group, which were very low to start with.

Islet transplantation continues to show improved long-term benefits of insulin independence, normal or near normal HbA1c levels, sustained marked decrease in severe hypoglycemic episodes and a return of hypoglycemia awareness. The accumulated experience in islet transplantation indicates that the best candidates for islet transplantation are recipients ≥35 years of age in relatively better glycemic control. The infusion of >500k IEQs over all infusions, as well as use of T-cell depletion with TNF antagonism for induction, and CNI and/or mTOR inhibitors for maintenance immunosuppression, are associated with improved outcomes.
Acknowledgments and Disclaimers

The Collaborative Islet Transplant Registry is funded by the National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, USA, and by a supplemental grant from the Juvenile Diabetes Foundation International. Additional data is made available through cooperative agreements with the US United Network for Organ Sharing, Alexandria, VA, and the Administrative and Bioinformatics Coordinating Center of the City of Hope, Duarte, CA (1999-2009). The CITR investigators (roster available at www.citregistry.org) have contributed data used in this report. The principal investigator and biostatisticians of the CITR Coordinating Center (roster available at www.citregistry.org), had full access to all the study data and assume responsibility for the integrity of the data, the accuracy of the data analysis, and the overall results and conclusions presented. Members of the CITR Publications and Presentations Committee over the life of the Registry (roster available at www.citregistry.org) contributed substantially to the analysis of the data and interpretation of the results. No collaborator discloses any conflict of interest in reporting the results presented in the CITR Annual Reports or the Scientific Summary. The voluntary participation of the islet transplant recipients is gratefully acknowledged.

REFERENCES


