Schistosomiasis: What 200 million people have that you don’t

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UGA

Voices from the Vanguard
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Center for Tropical and Emerging Global Diseases at UGA

- **CTEGD**: 19 interdisciplinary faculty and their laboratories

- **CTEGD’s Mission**: Pursue cutting edge research on tropical and emerging global diseases, and train students in this field

**CTEGD’s Goals**
- Become an remain a preeminent center for research and education in parasitic and other global infectious diseases
- Turn research into medical and public health interventions
- Promote global research and education at UGA and in Georgia

**CTEGD’s training mission**
- CTEGD has 5 Training Grants to fund students & postdocs
  - 1 T32; 1 in Argentina; 1 in Brazil; 1 in Kenya; 1 for student travel (EMF)
- CTEGD has 6 PIs with field programs in endemic countries
<table>
<thead>
<tr>
<th>Faculty</th>
<th>College/School</th>
<th>Department</th>
<th>Scientific Area</th>
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<tbody>
<tr>
<td>Steve Hajduk</td>
<td>Arts and Sciences</td>
<td>Biochem/Mol Biol</td>
<td>Molecular biology</td>
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<td>Bob Sabatini</td>
<td>Arts and Sciences</td>
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<td>Molecular biology</td>
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<tr>
<td>Dan Colley</td>
<td>Arts and Sciences</td>
<td>Microbiology</td>
<td>Immunology</td>
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<tr>
<td>Jessie Kissinger</td>
<td>Arts and Sciences</td>
<td>Genetics</td>
<td>Bioinformatics</td>
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<td>Roberto Docampo</td>
<td>Arts and Sciences</td>
<td>Cellular Biology</td>
<td>Biochemistry</td>
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<tr>
<td>Silvia Moreno</td>
<td>Arts and Sciences</td>
<td>Cellular Biology</td>
<td>Biochemistry</td>
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<tr>
<td>Kojo Mensa-Wilmot</td>
<td>Arts and Sciences</td>
<td>Cellular Biology</td>
<td>Biochemistry/Cell biology</td>
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<tr>
<td>Boris Striepen</td>
<td>Arts and Sciences</td>
<td>Cellular Biology</td>
<td>Molecular biology/Cell biology</td>
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<tr>
<td>Rick Tarleton</td>
<td>Arts and Sciences</td>
<td>Cellular Biology</td>
<td>Immunology</td>
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<tr>
<td>Pat Lammie (CDC)</td>
<td>Arts and Sciences</td>
<td>Cellular Biology</td>
<td>Immunology/Public Health</td>
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<td>Harry Dickerson</td>
<td>Veterinary Medicine</td>
<td>Infectious Diseases</td>
<td>Immunology</td>
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<tr>
<td>Julie Moore</td>
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<td>Immunology</td>
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<tr>
<td>David Peterson</td>
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<td>Infectious Diseases</td>
<td>Molecular biology</td>
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<tr>
<td>Don Harn*</td>
<td>Veterinary Medicine</td>
<td>Infectious Diseases</td>
<td>Immunology *(in 02/09)</td>
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<tr>
<td>Pejman Rohani</td>
<td>School of Ecology</td>
<td>Ecology</td>
<td>Mathematical modeling/Ecology</td>
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<td>Don Champagne</td>
<td>Agri.&amp; Environ. Sci.</td>
<td>Entomology</td>
<td>Vector biology/Immunology</td>
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<tr>
<td>Mike Strand</td>
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<td>Entomology</td>
<td>Molecular biology</td>
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<tr>
<td>Mark Brown</td>
<td>Agri. &amp; Environ. Sci.</td>
<td>Entomology</td>
<td>Molecular biology/Biochemistry</td>
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</tbody>
</table>

4 Colleges or Schools
8 Departments

CTEGD applies these different disciplines to many different parasites and the diseases they cause. Interdisciplinary; Interactive

www.ctegd.uga.edu
Diseases Studied by those in CTEGD

<table>
<thead>
<tr>
<th>Disease</th>
<th>Fields of Study</th>
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<tbody>
<tr>
<td>Malaria</td>
<td>Immunology, molecular/cell biology, vectors</td>
</tr>
<tr>
<td>African trypanosomiasis</td>
<td>Biochemistry &amp; molecular</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Cell biology, drug development</td>
</tr>
<tr>
<td>Cryptosporidiosis</td>
<td>Cell biology, drug development</td>
</tr>
<tr>
<td>Cyclosporiasis</td>
<td>Biochemistry, molecular &amp; cell biology</td>
</tr>
<tr>
<td>Chagas’ Disease</td>
<td>Immunology/molecular/vectors/Dx/Drugs</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>Biochemistry &amp; molecular biology</td>
</tr>
<tr>
<td>Cysticercosis</td>
<td>Biochemistry &amp; molecular biology</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>Immunology &amp; operational/control</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>Immunology &amp; control</td>
</tr>
<tr>
<td>Ich</td>
<td>Immunology &amp; molecular biology</td>
</tr>
<tr>
<td>Vector biology</td>
<td>Culicine, anopheline &amp; ixodid vectors; parasitoid wasps</td>
</tr>
</tbody>
</table>

- Occasionally transmitted or important in USA;  **Frequently transmitted or important in USA;
- Biodefense Priority Pathogen;  **Major global problem, especially in the tropics
Schistosomiasis

- Worm infection of ~ 200 million people
- Mostly: Africa > Asia > South America
- Worms live in blood vessels & produce eggs
- Global distribution depends on certain snails and living conditions (sanitation, occupation, etc.)

- Chronic infection – it lasts for many years
  - 5%-10% will die if untreated – HS disease; PP fibrosis
  - Most have subtle morbidity & moderate learning and physical deficiencies

- Good drug (praziquantel) available, but people get reinfected – need ongoing control

- No vaccine
Schistosome Life-cycle

- Immature worms; schistosomula
- Cercariae
- Specific snails
- Miracidium
- Eggs
- Adult worms
Composite schistosomiasis life-cycle
**Adult worms:**

**Males & Females**

They live in your blood vessels

**Mean life-span:**

~ 5-10 years; 40yr longevity record

How do they stay in there so long?

Why don’t you reject them?
Global Schistosomiasis: Prevalence, Morbidity, Mortality

- 20 Million - severe disease (HS, varices, carcinomas, calcification) (20K – 200K deaths/Yr)
- 100 Million - “moderate” morbidity - developmental deficits, GI disfunction, hydroureter, polyposis, dysuria, hematuria
  -- new term: Subtle Morbidity
- 80 Million - “asymptomatic”
- 200 Million infected
Schistosoma mansoni egg-induced granuloma in a mouse liver

Gross liver pathology:

Human hepatosplenic schistosomiasis mansoni

Demonstrating advanced peri-portal fibrosis (Symmer’s clay pipestem fibrosis)

This is severe disease
IP C
Pt 042

Moderately Bad Schistosomiasis
X-rays of urogenital morbidity due to *S. haematobium*; Ultrasound is even better

Three main species infect people: *S. haematobium*, *S. japonicum*, *S. mansoni*

Obstructive uropathy

Calcified bladder
Egyptian boy with hepatosplenomegaly, ascites fluid build-up and superficial collateral circulation (NAMRU-3 clinical ward)

The Faces of Schistosomiasis

Schistosomiasis at the Egyptian village level – moderate or subtle morbidity
How do you measure “subtle morbidity”???

Reassessment of the “subtle morbidity” in chronic schistosome infections by “meta-analysis”  
*King, Dickman & Tisch: Lancet 2005; 365: 1561*

**What is a meta-analysis, or “Cochrane review”?**  
Systematic review and critical appraisal of multiple studies

- Screened 482 published & unpublished reports (1921 – 2002)  
- Selected 135 for inclusion in the meta-analysis  
  - 14 *S japonicum*  
  - 60 *S mansoni*  
  - 44 *S haematobium*  
  - 17 multiple species

Presentation of results – Graphic display (*forest plot*) gives individual studies + Confidence Intervals as boxes and horizontal lines; The vertical line drawn at “1” represents “no effect”
Effect of schistosomiasis (infection) on Hemoglobin Concentration

*S. haematobium* doesn’t quite make it statistically alone

*S. mansoni* and *S. japonicum* do

In the aggregate schisto does

People with schistosomiasis had significantly less Hb than did non-infected people
The effect of TREATMENT for schisto on [Hb]

These are all randomized control trials; and they show significant homogeneity – either when pooled or categorized by species

Specific treatment for schistosomiasis with PZQ significantly improved measures of anemia in all studies
Diagnosis of Schistosomiasis

Microscopic fecal or urine examinations

- Thick smear (Kato/Katz)
- Concentration techniques (sediment/filter)
- Polycarbonate filters (urine; S. haematobium)

Antibody assays (measure exposure)

Antigen assays (measure active infection & and quantify intensity)

The standard is egg counts… but….sensitivity & how???
Where in the world do you get schistosomiasis???

Almost 90% of the world’s 200 million cases of schistosomiasis are now in subSaharan Africa.
**Main intermediate snail hosts that transmit human schistosomiasis**

<table>
<thead>
<tr>
<th>S. mansoni</th>
<th>S. haematobium</th>
<th>S. intercalatum</th>
<th>S. japonicum</th>
<th>S. mekongi</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Biomphalaria)</td>
<td>(Bulinus)</td>
<td>(Bulinus)</td>
<td>(Oncomelania)</td>
<td>(Tricula)</td>
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<table>
<thead>
<tr>
<th>Africa</th>
<th>Africa</th>
<th>Asia</th>
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<tbody>
<tr>
<td>B. pfeifferi</td>
<td>B. truncatus</td>
<td>O. hupensis</td>
</tr>
<tr>
<td>B. alexandrina</td>
<td>B. globosus</td>
<td>T. aperta</td>
</tr>
<tr>
<td>B. sudanica</td>
<td>B. forskalii</td>
<td></td>
</tr>
<tr>
<td>B. africanus</td>
<td>B. forskalii</td>
<td></td>
</tr>
</tbody>
</table>

**Americas**

| B. glabrata |
| B. straminea |
| B. tenagophila |

**Schistosomiasis is also a disease of SNAILS**
Factors Contributing to Transmission of Schistosomiasis

- **Human & animal (Sj) reservoir hosts**
  - Contamination & Contact Patterns; Occupational aspects
  - Age/Prevalence & Age/Intensity Curves
    - Immunity?

- **Water -- Uses & Abuses**
  - Development (Dams; Irrigation), Socioeconomic (Sanitation)

- **Snail hosts**
  - Habitat (geography & weather), Dams, Marshes

- **Adult worms -- Longevity & Fecundity**

- **Focal Transmission sites**
  - Rural -- and now Urban/peri-urban settings
  - Location, Location, Location……
Schistosomiasis Transmission Dynamics

Possible Points of Attack
- Sanitation, Water Supply & Education
- Snail Control
- Chemotherapy (Prevalence/Intensity/Morbidity)

Current Control Initiatives Are Focused on Morbidity Control:
- WHA Resolution 54.19; The Schistosome Control Initiative (Gates $)(USAID $)

We will come back to this public health/control part, 1st some research
As an immunologist – there are LOTS of fascinating aspects to this host/parasite relationship that need research --- even if it did not cause a bad disease in 200 million people

**What are the big basic biomedical research questions in human schistosomiasis?**

A. **What are the correlates and mechanisms of resistance to reinfection?**
   This is what we are doing – can we do it better?

B. **What are the correlates and mechanisms of subtle morbidity?**
   This could follow on the heels of the anemia study.

C. **What are the correlates and mechanisms of severe morbidity?**
   This is what we did 15-30 years ago (Brazil; Egypt) – can we do it better now, and better than others?

D. **Does schistosomiasis prevent autoimmune diseases and atopic allergy (yes – experimentally); and if so how?**
   Requires a combination of epidemiologic, clinical and immunologic skills

E. **Does treatment alter immune responses and immunoregulatory responses, and if so how?**
   This is, in part, what we are doing – can we do it better?

So what is our lab’s current research?
The immunology of schistosomiasis in western Kenya

Resistance and Susceptibility to Reinfection in People Who are
Occupationally Exposed to Schistosomiasis

A collaboration of UGA, KEMRI & CDC scientists

Kisumu

ctegd
Global Health Through Research
Main Collaborators:

**UGA:** Carla Black; Jen Carter; Michael Gatlin

**KEMRI:** Diana Karanja; Pauline Mwinzi

**CDC:** Evan Secor
If he gets treated for his schistosomiasis, how many exposures will it be before he gets re-infected, in this high transmission situation?

Based on longitudinal studies
Characteristics of the initial cohort study

- 5 year study period
- 96 individuals (adults) followed for >1 years
  - Treated, cured, followed every ± 4 weeks, retreated with Pzq if egg positive; Egg negativity noted; Followed – again/again/again….  
  - Exposure by # of cars washed per week

Resistance:
- Increases with increased CD4+ count in men co-infected with HIV-1
- Increases with decreased water contact
- Increases upon multiple infections, treatments, cures and reinfections

Karanja, et al., Lancet 360:592, 2002
Does repeated cure & reinfection “immunize” some people against reinfection?
If it does “immunize,” what parallel immunologic change occurs?
The hypothesis is:

During chronic infection the immune system is continuously exposed to some schistosome antigens, but;

On worm death (natural 5-10 years into infection and occasionally thereafter – or upon being murdered) some “resistance-inducing antigens” are exposed/released in sufficient quantity, and in the “right” manner, to lead to resistance (after sufficient worm deaths)

We and others have reported multiple immune changes upon treatment – some of which correlate with resistance to reinfection
How do we do this research? What do we do?

1. Work with the people and explain what you want to do, and get their consent — everything is multiply approved early on
2. Diagnose them for schisto, other worms, malaria and HIV
3. Bleed them, take the blood to the laboratory, and process their blood for a wide variety of immunologic and genetic assays — most in the KEMRI lab, some here at UGA
4. Get the data and analyze in many different ways
5. Try to figure out what it all means, publish scientific papers
6. Get more funding to do more of this — better and better, based on what you (and others) found
Summing-up the longitudinal immunology studies so far...

We think that by killing worms each time someone gets infected we are simply ‘speeding up’ the natural process

- Eosinophils – resistance
- Mast cell precursors – susceptibility
- T reg cells – ??
- T subsets in children with coinfections – ??
- Anti-SWAP IgE antibody – resistance
- CD23+ B cells – development of resistance
- Cytokine gene polymorphisms – resistance
- Cytokine production – (IL-5, IL-13, IFN-γ) resistance

SO WHAT ???
Good Question!

We hope to learn enough to form a composite of what is needed to mount a substantial protective response, and......some day that might be what we want to try to induce with a vaccine

Also – IMMUNOLOGY IS IMMUNOLOGY

What we learn here may be useful in studying other diseases and conditions, such as allergies, other infections, transplants and autoimmunity
The heart of our research in Kenya.....
Another hat, not as a basic immunologist, but as a global health researcher and someone involved in the other end of the “Research to Control” spectrum

At the far end of this spectrum:

Levels of Limiting Parasitic Diseases or their Consequences

- **Control** (Infection/Transmission vs. Morbidity)
- **Elimination of disease** (as a public health problem)
- **Elimination of infections** (in a defined geographic area)
- **Eradication**
- **Extinction**

Conceptual (and practical) differences:
Existence vs. Transmission vs. Morbidity
Current Status of Global Worm Infections
Erad/Elim/Cont Efforts

Fully ongoing
- Dracunculiasis (Guinea Worm) – Eradication
- Onchocerciasis – Control
- Lymphatic Filariasis – Elimination

Now at the country level
- Schistosomiasis – Morbidity control
- Soil-transmitted helminths – Morbidity Control

Possibles some day
- Taeniasis & Cysticercosis – Eradication
- Echinococcosis; Elimination
WHA 54.19: Morbidity Control of Soil-transmitted Helminths & Schistosomiasis

• **Burden of disease** (2 billion+200M, developmental impact)

• **Country & Global Partners commitment**
  – Organizational; Financial capacity; Human capacity

• **Strategy:**
  – School-based, school-age, Pg women, occupationally exposed: annual or bi-annual treatment
    – Albendazole/Mebendazole (Industry partner) & Praziquantel
  – School & Community health promotion/education
  – Organization & Management
  – Schistosome Control Initiative (Gates Fdn, $40M)
  – Operational research – SCORE (Gates Fdn, $18.7M at UGA)
  – President’s Initiative on NTDs (USAID) (DFID)

• **Capacity building**
The Schistosome Control Initiative (SCI)

(Gates/; now USAID funded; at Imperial College, London)

Started in 2002

1. Donate Praziquantel and Albendazole to Ministries of Health (MOHs) in Africa (based on an Action Plan competition)
2. Develop distributions systems with MOHs
3. Provide treatment and health education
4. Monitor and evaluate effectiveness

Facilitated over 50 million treatments with PZQ and many more deworming doses of albendazole – Helping 6 countries establish national control programs and several others start smaller pilot projects

Burkina Faso; Mali; Niger; Tanzania; Uganda; Zambia; and some in Rwanda and Burundi
Schistosomiasis Consortium for Operational Research & Evaluation

SCORE

Bill and Melinda Gates Foundation funded at UGA

A consortium to do operational research – defined as finding out what current and future program managers need to do the job (mass drug administration) better – both programmatically and in terms of tools.

It will be run out of UGA, but involve investigators from across the globe – through subawards to many partners.

Developed with assistance by the President’s Venture Fund
SCORE:

Ground rules established early on by the Foundation

1. Operational research only – defined as what do current and future program manager need to do the job better; programmatically and in terms of tools
2. No S. japonicum studies
3. No drug development
4. No vaccine studies
5. Work with existing control programs, when possible
6. Work with the schisto community, when possible

Remember: Schistosomiasis control is MDA with PZQ

Studies will be Collaborative or at least Complementary, part of a whole (a platform approach)
Objective 1. **Evaluate alternative approaches to control schistosomiasis, and to eliminate schistosomiasis in settings with low or seasonal transmission**

**Activities:**

- Analysis of existing data
- Qualitative evaluations to define critical barriers and success factors
- Field research on how best to sustain control: CDI vs. School; etc.
- Field research on how best to achieve elimination
  - Low transmission area: intense coverage, 2 Rx, snails, latrines
- Field research to increase program effectiveness
  - CDI ± < 5s vs. School ± non-enrolled; Health clinics
  - Diagnostics; population genetics; morbidity; indicators

All with community health education and cost-accounting
Objective 2. Develop the tools needed for a global effort to control and eliminate schistosomiasis

Activities:

- Evaluate a CCA urine test for rapid assessment of *S. mansoni* prevalence: quality & impact
- Develop the bases for other survey tools for *S. mansoni* (if needed)
- Develop and evaluate diagnostic tests for *S. haematobium* and *S. mansoni* in snails and people: from product profile to assay
- Monitor genetic changes in schistosome populations under MDA
- Evaluate and compare current measures of subtle morbidity and well-being as outcomes of MDA
Objective 3. Assist in maximizing the global schistosomiasis control and elimination effort and its integration into broad-based NTD control programs

Activities:
- Encourage the use of SCORE and other data in development of guidelines
- Assess remaining barriers to integration of schistosomiasis control into other broad-based NTD control programs and ways to address those barriers

SCORE Management structure
3 components:
- a secretariat of 4 - 5 people at the University of Georgia
  - Colley, Binder, King, Assoc Dir Mgmt, Admin Asst
- a technical working group (~ 15 PIs of SCORE projects)
- an outside advisory group of 5 or 6 people

This is now a whirlwind of activity............
How is SCORE going to work?

Invited meetings to develop common research protocols
    How will we actually ask each of the activity questions?

Selective solicitations of proposals to do those research protocols

Some proposals will be approved and subawards funded

Annual meetings and site visits will determine progress on the protocols and the data will be analyzed and published

There will likely be 20 or so subawards to keep up with and then translate the findings into policy

On to some stuff that might be helpful in thinking about careers in Global Health
GLOBAL HEALTH & GLOBAL HEALTH RESEARCH

“A healthy world is a good thing for America.”
“Health diplomacy must be the foundation of our foreign policy.” Senator Arlen Specter Senate Appropriations Committee Hearing “FY2008 Budget for Global Health”

How do I get to work in global health?
How did Dan Colley get to work in global health?

Do you know these public health workers?
How did I get wherever it is I am?

- Small high schools in Western New York
- Smaller college in central Kentucky (Centre College of Kentucky)
  - Married the right woman from Kentucky
- Graduate school at Tulane – in transplantation immunology & microbiology
- Post-doc at Yale – in very basic immunology
  --- progressing nicely to be an immunology professor and researcher of basic immunology

Brazil – teaching and reorganizing some research SCHISTO
A real job – VAMC & Vanderbilt University School Medicine
  Asst Prof/Assoc Prof/Prof

CDC – Director, Division of Parasitic Diseases
UGA – Director, CTEGD & Professor of Microbiology

Do you see a well thought out path here?

I don’t!
How do I get to work in global health?

What kinds of opportunities are there for people like me in global health?  *Remember the continuum!*

What education and training do I need to work in global health?

**Treat people** — Medical School, House Staff training; Fellowship (medical, research, CDC, etc.)

**Do research** — Graduate School *(in lots of things)*; Postdoctoral training

**Set policy** — MD, PhD, Masters, experience

**Teach** — Depends on the level

How do you want to make your contribution to improving global health???
• Turn research into medical and public health interventions

• Promote global and biomedical research and educational programs at the University of Georgia

We in CTEGD are doing global health

Along with many others at UGA we make the types of contributions for which we are trained

It takes lots of people with lots of different talents
Back briefly to schistosomiasis ---

200 million people suffer from having these worms in their blood vessels for years and years

- We can do something for many of them now
- Research is needed for better understanding and for better tools
- The Research to Control Continuum needs to be real – this means people with many different skills need to work with each other and respect each other’s contributions
And now...... a couple of shots to prove it’s not all work and no play !
This was last week at Lake Tahoe, California..... as I worked on this presentation
On yet a different day…..
Kenyan elephants and a Tanzanian mountain - Kilimanjaro
THANKS for listening… Thaaaaat’s all folks……

THANKS for listening…