# The Epidemic of Chronic Kidney Disease in USA and in the World: Causes and Prevention

**Vito M. Campese, M.D.**
Professor Emeritus of Medicine
Division of Nephrology and Hypertension
Co-Director USC/UKRO Kidney Research Center
Keck School of Medicine of USC
Los Angeles

May 10, 2021

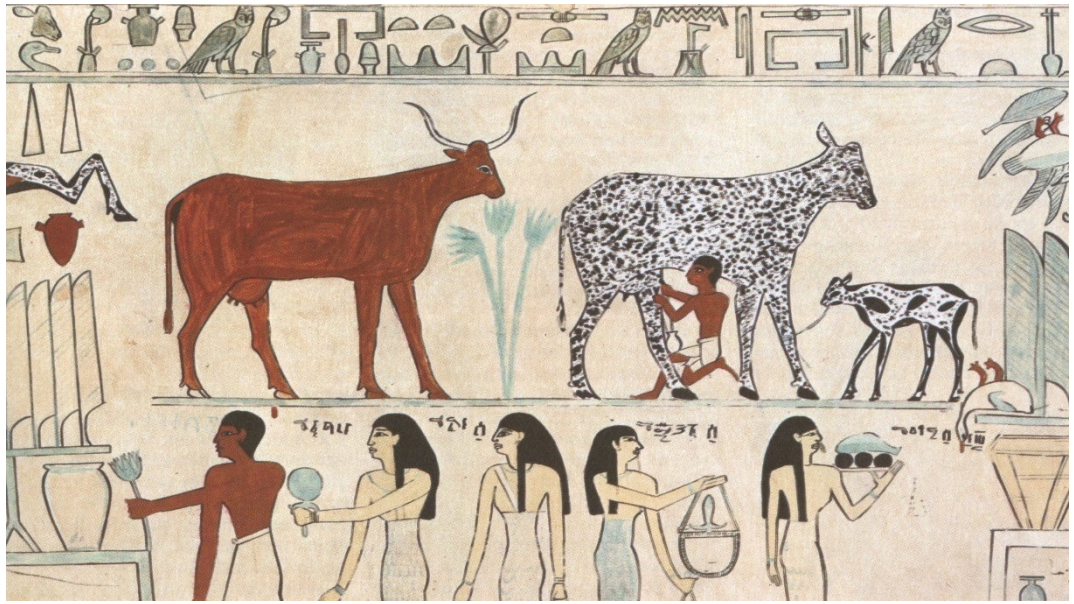
# Evolution and Survival

- Human being and environment are inter-related in a dynamic but fragile equilibrium.
- Humans have always struggled for survival facing environmental challenges, adversities, epidemics, and exposure to toxins.
- On the other hand, human beings have had a tremendous impact on the environment, magnified in recent times

# Hunter Gatherer to Agriculture

~10,000 years ago

Mesopotamia



Sheep, Cattle Goats

# The Development of Relationship between Human and Geography

- ***The second stage* (from 250 years ago)**
- in the 18th century, the second revolutionary leaps occurs with the development of machineries to help in the production chain. It is **the beginning of the industrial civilization)**.
- The 19th century, is marked by the development of internal combustion engine and the use of electricity**.**

# The Development of Relationship between Human and Geography

- **The third stage**: With the 20th century, mankind started the third technological revolution.
  - Non-renewable fossil fuel energy (coal, oil, nuclear energy)
  - Electronic computers, and space technology
- From manual labor to machine production.
- From agriculture and animal husbandry to the commodity economy.
- This resulted in an unprecedented increase of productivity, and wealth, but also in new forms of environment pollution, such as plastic, space junk, nuclear radiation, noise pollution, automobile exhaust, light and electromagnetic pollution, **and a more sedentary life-style**

# The GREEN Revolution or Third Agricultural Revolution (1950-70)

- The key leader was Norman Borlaug (Nobel Peace Prize 1970)
- Introduction of chemical fertilizers and agro-chemicals (Pesticides, and herbicides)
- Improved irrigation and mechanization
- High yielding hybridized seeds for a varieties of cereals
- This initiative increased supply of grain, has led to cheaper livestock and is credited with saving over a billion people from starvation
- **But, at what cost for the environment and the human species?**

# Agricultural Dust Exposure

# Humans and the Environment

- Continuous and increasing rate of exploitation of natural resources, industrialization, technological growth, and unplanned urbanization are responsible for grave environmental crisis and ecological imbalance (Ex. Global Warming).

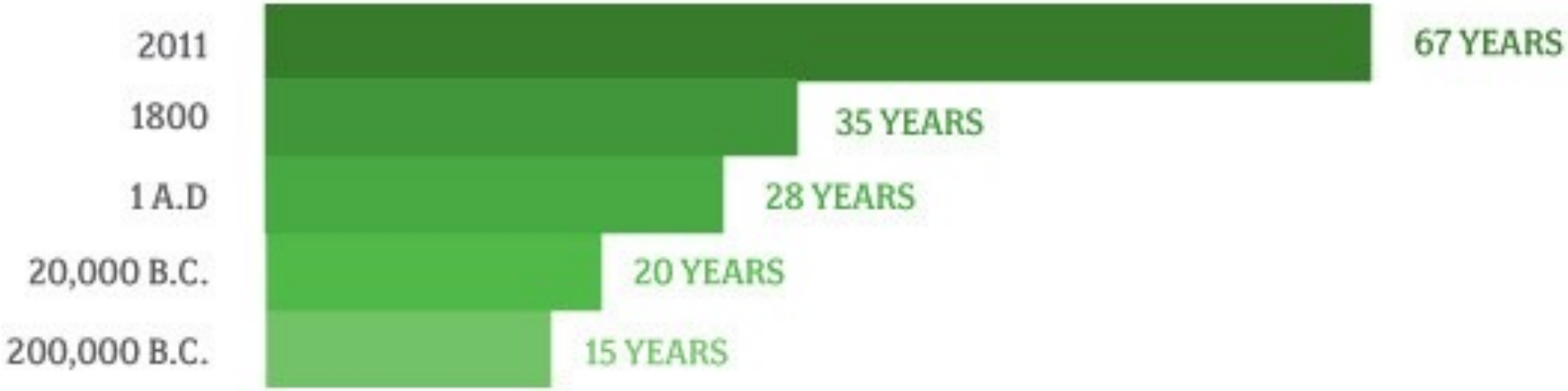
# But Careful !!!

- Nature is vengeful against those that try to subvert it.
- Many animal species have been wiped out from earth. Even the powerful dinosaurs.
- **Humanoids are no exception. !**

# What has been the Impact of these Revolutions on Public Health?

# Total World Population

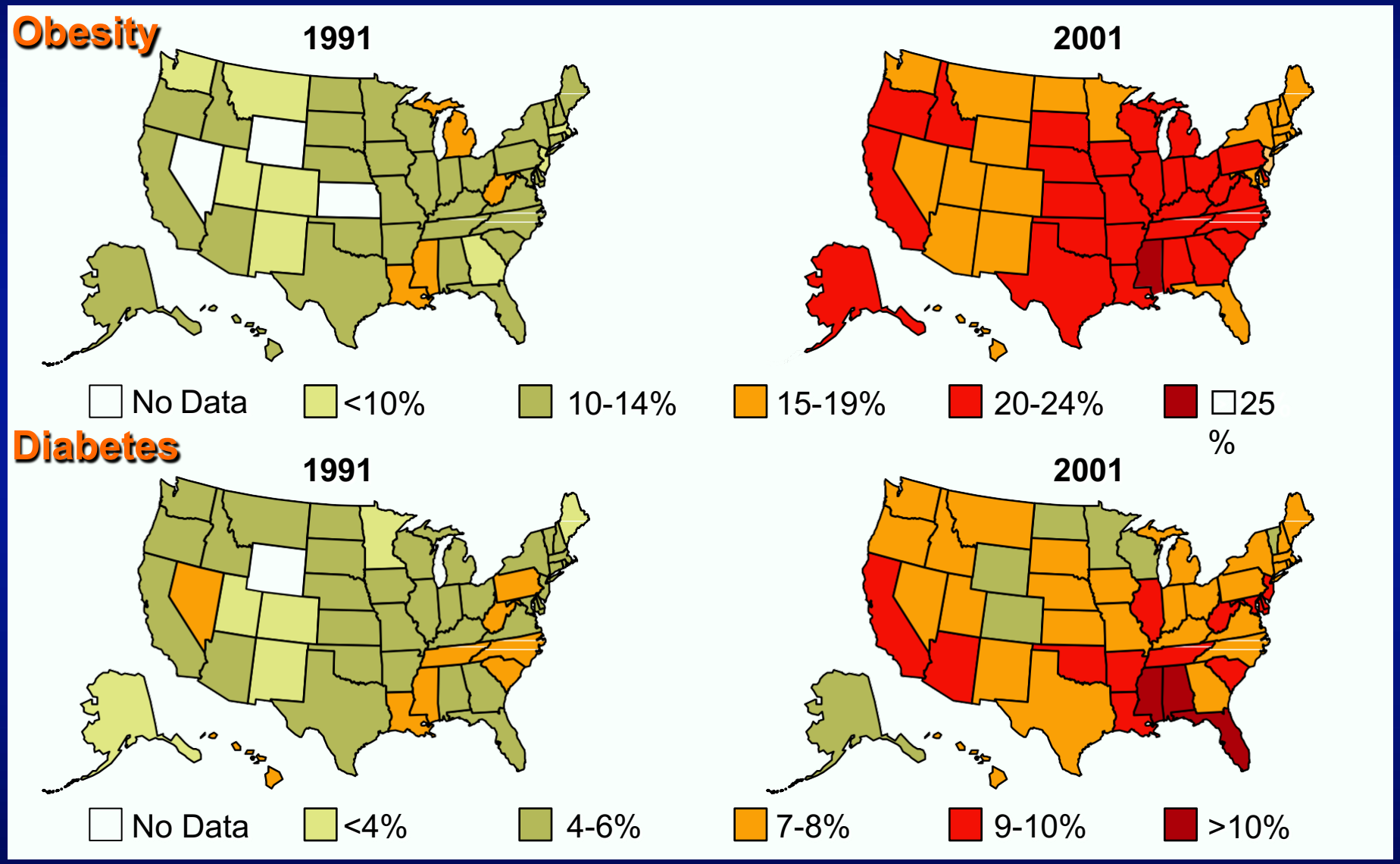

# Average Life Expectancy



# Three Major Consequences

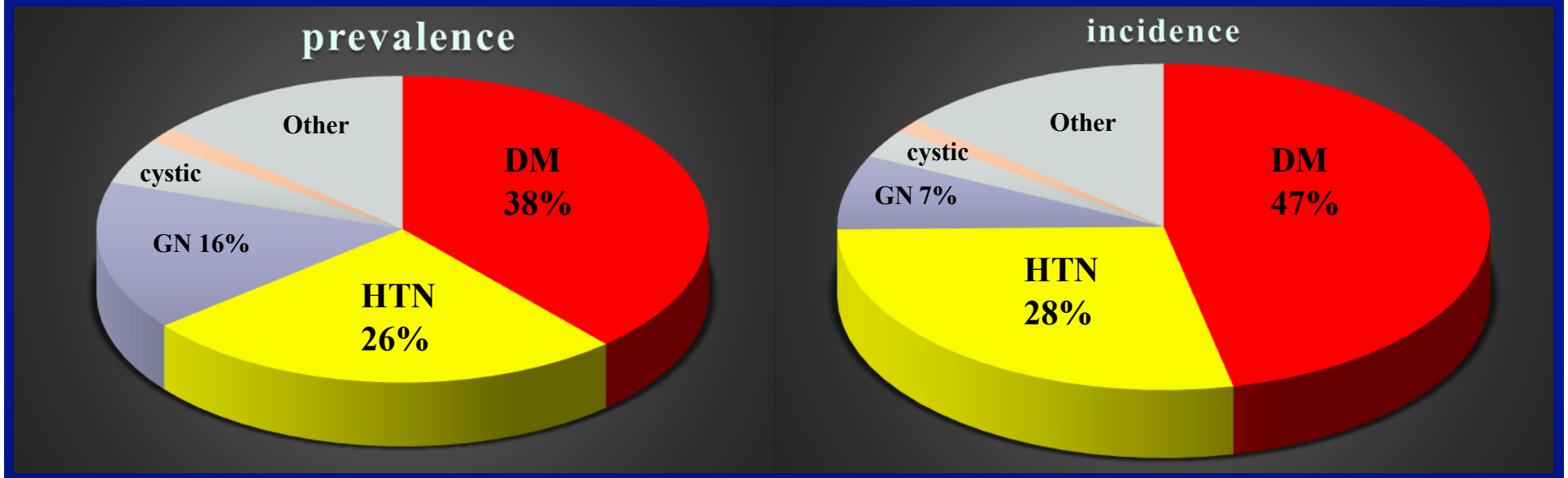
1. Transformation from manual labor to machinery and computers → *More sedentary life*
2. Increased availability of cheap and abundant food → *Increased food intake*
3. Increased pollution of the environment → *increased exposure to poisons*
4. *The use of new medicines and diagnostic agents* have contributed to prolonging life, but have introduced a new array of poisons that adversely affect health

# Obesity and Diabetes Trends in the US




Mokdad. *JAMA*. 2003;289:76-79.

# Primary Diagnoses For Patients Who Are On Dialysis Or Start Dialysis




USRDS 2016

# Definition of CKD (NKF-DOQI)

- Condition that affects the kidney, with the potential to cause either progressive loss of kidney function or complications resulting from decreased kidney function such as CVD

| Working criteria. One of the following: |
| --- |
| Kidney damage for 3 months, as defined by structural or functional abnormalities of the kidney, manifest by either:<br>- Pathological abnormalities; or<br>- Markers of kidney damage (abnormalities in blood, urine, or imaging tests) |
| GFR < 60 mL/min/1.73m$^2$ for 3 months |

*www.kidney.org/professionals/KDOQI*

# National Kidney Foundation: Stages of CKD*

| Stage | Description | GFR (mL/min/1.73 $m^2$) | Clinical Term |
|---|---|---|---|
| 1 | Kidney damage with normal or ↑ GFR | ≥90 | |
| 2 | Kidney damage with mild ↓ GFR | 60-89 | |
| 3 | Moderate ↓ GFR | 30-59 | CKD |
| 4 | Severe ↓ GFR | 15-29 | Advanced CKD |
| 5 | Kidney failure | <15 (or dialysis) | ESRD |

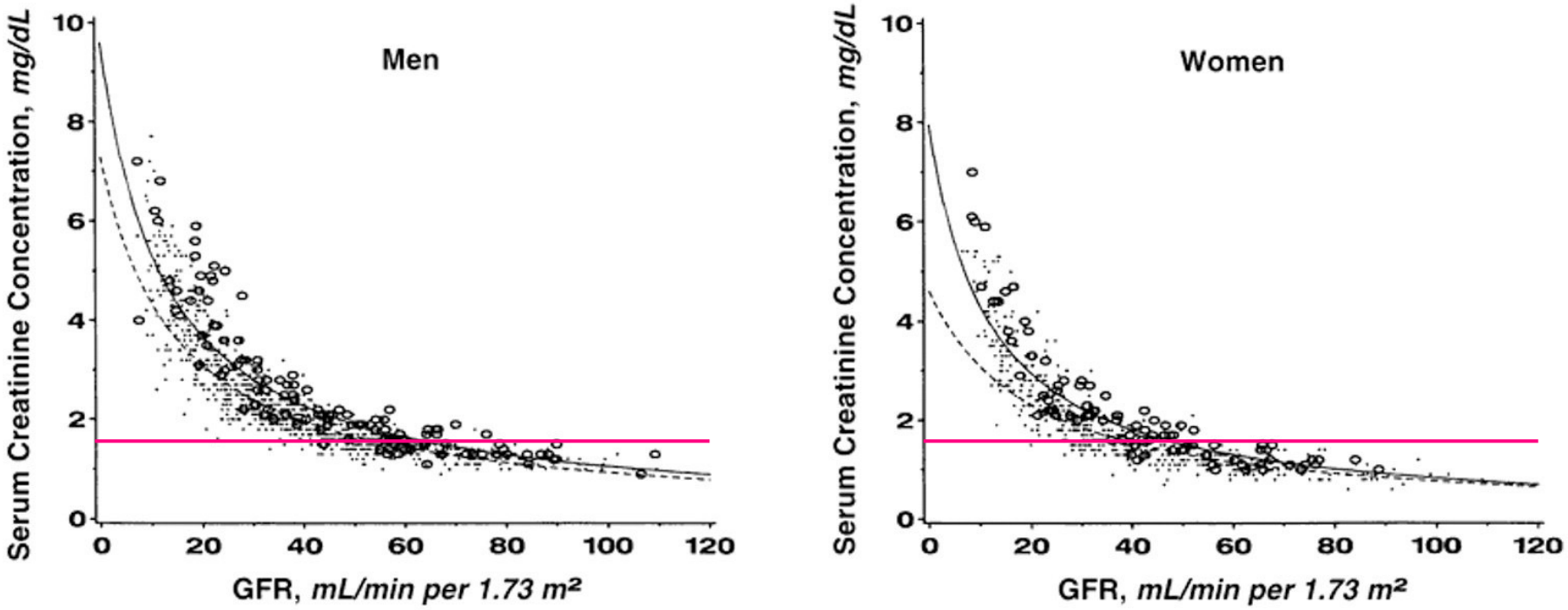
*In patients >20 years of age

National Kidney Foundation. *Am J Kidney Dis.* 2002;39(suppl 1):S1-S226.

Are we using the right sensors to detect CKD?

# Serum Cr is insensitive marker of reduced GFR

MDRD: cohort of 1628 pts aged 18-70 with chronic renal disease not on dialysis who underwent GFR measurement by $^{125}$I-iothalamate clearance




Levey 1999, Ann Int Med 130:461

# Limitations of isolated, unstandardized serum Cr

- $GFR = U_{Cr} \cdot V / S_{Cr}$ Highly lab dependent

# Fallacies of Serum Creatinine

## *Three Patients with Creat = 1 mg/dL*

1. Patient weighs 50 Kg and produces 1 g of creatinine/24 h → GFR = 70 ml/min
2. Patient weighs 75 Kg and produces 2 g of creatinine → GFR =140 ml/min
3. 3. Shaquill O Neal 100 Kg and produces 3 g of creatinine → GFR = 210 ml/min

# Limitations of isolated, unstandardized urine Cr

- $GFR = U_{Cr} . V / S_{Cr}$

= Cr generation rate

Depends on age, gender, muscle mass, diet and Urine collection

# 24 hour urine Cr clearance to estimate GFR

- Inaccuracy linked to method used to measure creatinine
- Inaccurate urine collection
- Overestimates GFR due to tubular secretion of creat.
  - Can correct by averaging creat. and urea clearance

# Direct measurement of GFR

- $^{125}$I-iothalamate
- Inulin clearance
- $^{99m}$Tc-DTPA radionuclide scan

# Estimates of Renal Function

- **Cockcroft-Gault:**
  - CrCl: [(140-age) x Weight (kg)] /SCr x 72 (x 0.85 if female)

- **MDRD*:**
  - GFR: $(SCr)^{-0.203}$ x $(Age)^{-0.176}$ x (0.742 if female) x (1.210 if AA)
  - Example:
    - 67 y.o. white male with serum creatinine 1.4 has estimated GFR of 55 by MDRD (Average GFR for age 60–69 yrs is 85)

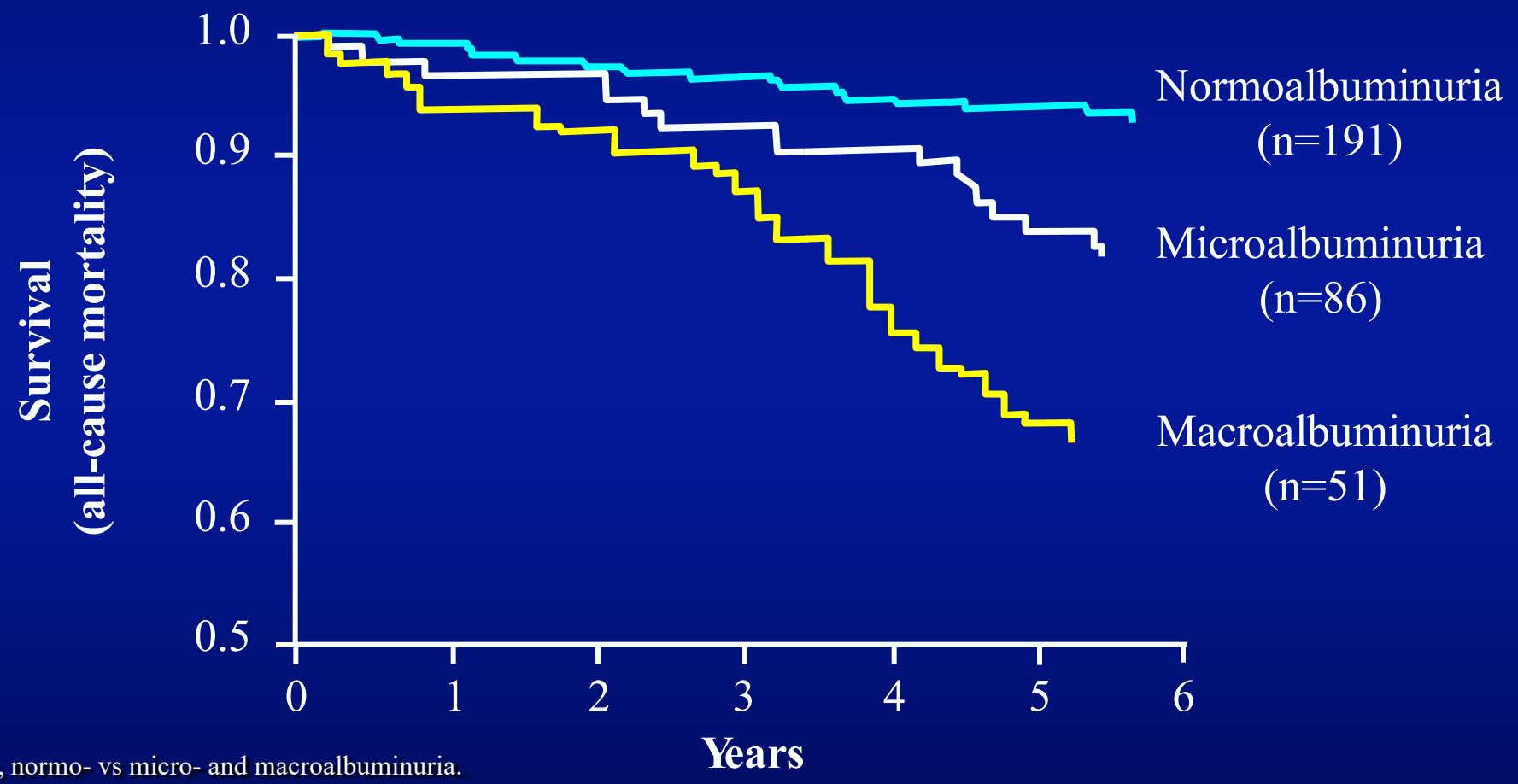
*Clinicians are often unaware of the degree of renal insufficiency by looking at SCr alone.*

*MDRD formula recommended for use by the National Kidney Disease Education Program www.nkdep.nih.gov.

# Microalbuminuria: Does it predict CKD?

- Microalbuminuria is considered a predictor of subsequent kidney disease
- In Type 1 diabetes, microalbuminuria predicts progression in ~ 90%
- In type II only 35-40% of pts with microalbuminuria develop overt proteinuria over 10 years
- In non-diabetic patients the predictive value of microalbuminuria for progressive kidney disease is not well established

# Proteinuria Is an Independent Risk Factor for Kidney disease,, CVD and Mortality



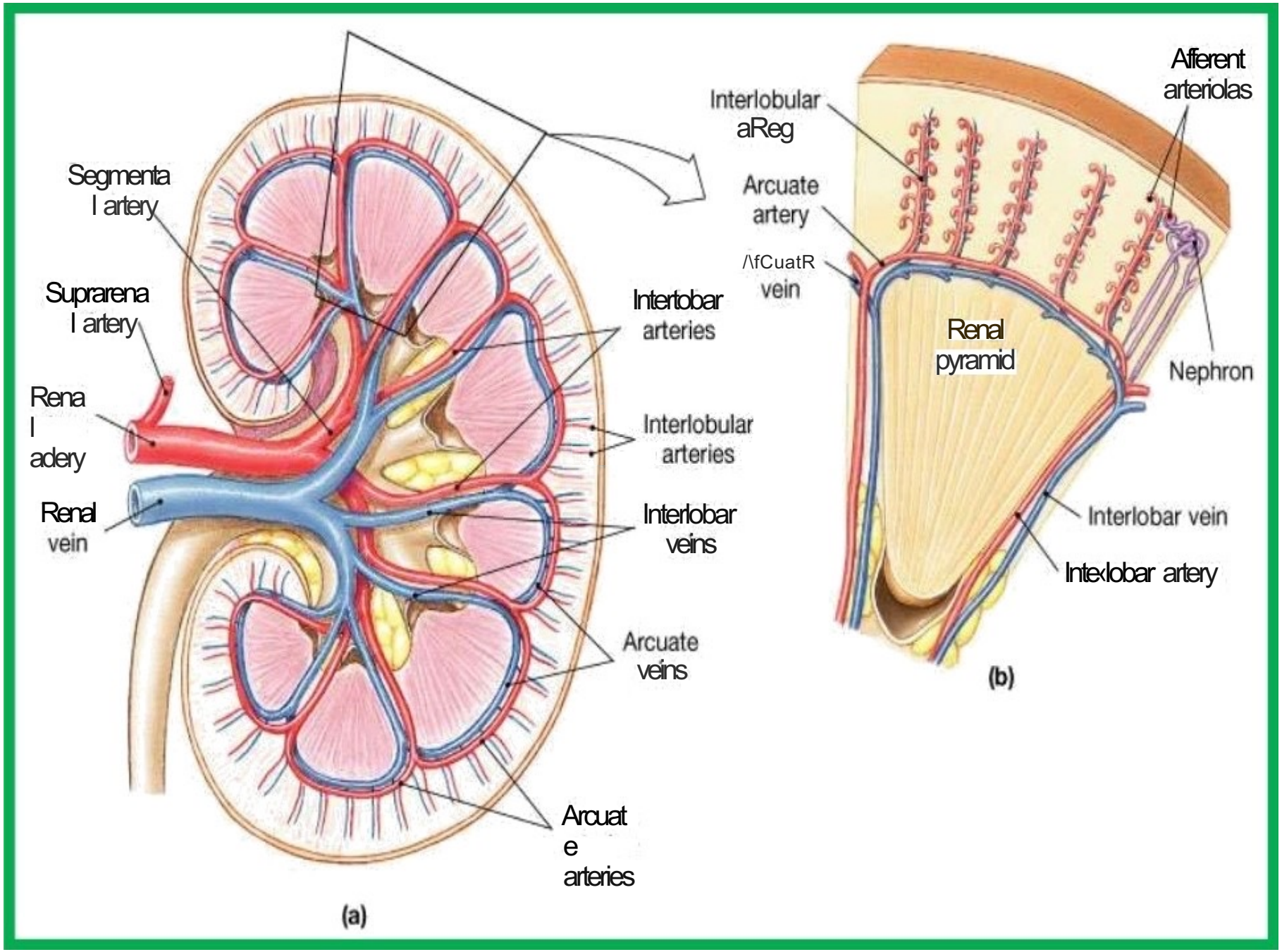

*P*<0.01, normo- vs micro- and macroalbuminuria.
*P*<0.05, micro- vs macroalbuminuria.

Gall et al. *Diabetes*. 1995;44:1303.

# Take home messages

- CKD is defined by GFR < 60 or other evidence of renal damage for ≥ 3 months
- GFR should be estimated from serum Cr by the MDRD equation but clinicians should be aware of overestimation when GFR is near or > 60 and in Asians
- The prevalence of CKD is uncertain, but it is probably 10-13% in the adult population
- Although microalbuminuria is associated with increased risk of CVD and CKD, it should not be used to define CKD
- CKD is associated with increased risk of death, CVD
- CKD is also a risk factor for progression to ESRD but 1/4 of patients do not progress and 90% die before reaching ESRD due to CV disease

# The Kidneys are particularly Susceptible to Environmental Factors


Segmenta
l artery
Suprarena
l artery
Rena
l
adery
Renal
vein
Intertobar
arteries
Interlobular
arteries
Interlobar
veins
Arcuate
veins
Arcuat
e
arteries
(a)
Interlobular
aReg
Arcuate
artery
/\fCuatR
vein
Afferent
arteriolas
Renal
pyramid
Nephron
Interlobar vein
Inte‹lobar artery
(b)

# Renal Blood Flow and its Regulation

- High blood flow: 1200 ml/min, 25% of cardiac output, 50x higher than to other organs
- A high blood flow is necessary for glomerular filtration
- Distribution
  - Cortex 90%
  - Outer medulla 9%
  - Inner medulla 1%

*Vasa rect are 40 mm long*
*Low hidrostatic pressure*
*High viscosisty*

# Smog and Mortality

- WHO estimates that 92% of the world's population lives in places where air quality levels exceed WHO limits.
- In Europe, it is estimated that exposure to excessive particulate matter > 2.5 □m ($PM_{2.5}$) causes more than 400,000 premature deaths/year.
- In China, in 2010 excessive $PM_{2.5}$ caused more than 1.2 million premature deaths, 42% higher than the level in 2000.

# Susceptibility of the kidney to environmental attacks

- Given their secretory and excretory functions, and hyperosmolarity in the medulla, the kidneys are commonly victimized by:
  - circulating antibody/antigen complexes
  - environmental toxins
  - Drugs ingested for *therapeutic* reasons (non-steroidal anti-inflammatory agents, antibiotics, lithium, platinum, immunosuppressive and anticancer agents), or *recreational* reasons (heroin, cocaine and amphetamines).
  - Diagnostic agents (such as contrast agents).

# The association between urbanization and reduced renal function: the China Health and Nutrition Survey (BMC Nephrol. 2017; 18: 160.)

- The prevalence of reduced kidney function was 8.1% among 3644 men and 4154 women, aged 18 to 94 years
- Using a validated, multi-component urbanization index, a *positive association was found between urbanization and reduced kidney function*.

# Prospective associations between environmental heavy metal exposure and renal outcomes in adults with CKD in Taiwan (doi: 10.1111/nep.13089)

- From January 01, 2003 to June 30, 2015, the authors retrospectively identified 2343 CKD patients with an eGFR of <60 mL/min/1.73 $m^2$ at one tertiary care center, in Taiwan.
- Patients were followed for 3.49 ± 2.27 years, until death or initiation of maintenance dialysis.
- *There were high correlations among the concentrations of eight metals (arsenic, cadmium, chromium, mercury, copper, lead, nickel, and zinc) and the risk of ESRD.*

# JASN 2018; 29:218-230

- A study, from St. Louis VA Medical Center, looked at 2.5 million veterans who did not have kidney disease when they were screened in 2003 and 2004. Their cases were "followed" across the country for an average of 8.5 years and compared to air pollution levels across the country being monitored by the Environmental Protection Agency (EPA) and the National Aeronautics and Space Administration (NASA). For accuracy, researchers also took into account other risk factors (age, race, sex, heart disease, lung disease, diabetes, high blood pressure, smoking, obesity, and poverty).

# Particulate Matter Air Pollution and the Risk of Incident CKD and Progression to ESRD

## METHODS

Observational cohort of 2,482,737 US Veterans followed for 8.52 years

Fine particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$) exposure data:

EPA ground-based air monitoring stations

NASA satellites spaceborne sensors

## OUTCOMES

**Increase in Risk of Kidney Outcomes for Every 10 Increase in $PM_{2.5}$ (μg/m³)**


**National Burden of Incident CKD Attributable to $PM_{2.5}$ Exposure Above the EPA recommended level of 12 μg/m³**


**CONCLUSION** Our findings demonstrate a significant association between exposure to ambient $PM_{2.5}$ and risk of incident CKD, eGFR decline, and ESRD.

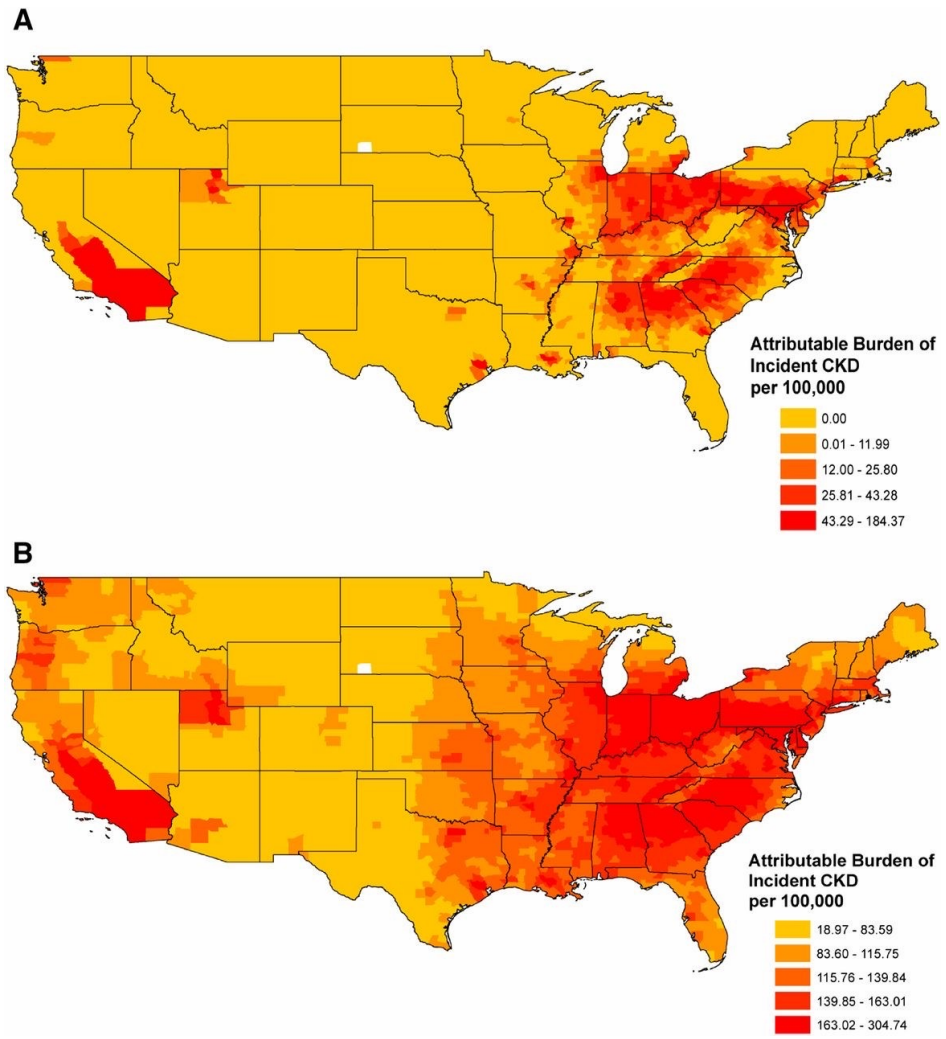
doi.org/10.1681/ASN.2017030253

JASN

Benjamin Bowe et al. JASN 2018;29:218-230

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

## Geographic distribution of the national burden of incident CKD attributable to air pollution in the United States.




Benjamin Bowe et al. JASN 2018;29:218-230

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

# Balkan Nephropathy

- BN is an endemic chronic tubulointerstitial nephritis affecting residents of rural villages located in valleys near tributaries of the Danube River in *Bosnia, Bulgaria, Croatia, Romania, and Serbia*.
- Epidemiologic features:
  - focal occurrence in certain farming villages, with unaffected villages located in close proximity;
  - a familial but not inherited pattern of disease;
  - occurrence only in individuals older than 18 yr
  - strong association with upper urinary tract transitional cell (urothelial) cancer

JASN **November 2007 vol. 18 no. 11 2817-2823**

# Balkan Nephropathy

# ARISTOLOCHIC ACID AND ENDEMIC NEPHROPATHY

- Jelaković (Zagreb) drew attention to the the fact that in Croatia nephrotoxicity common in horses that ingested hay contaminated with ***Aristolochia clematiti*** plant containing aristolochic acid.
- *In 1967 Ivić formulated an intriguing hypothesis (Lijetč Vjes* ***91 : 1278 –1281, 1***
  - Since seeds of *A. clematitis commingled with wheat grain during the annual harvest, a toxic co this plant might be inadvertently introduced into home-baked bread*
- Remarkably, during the next 35 yr, no attempt was made to confirm or follow u this hypothesis.

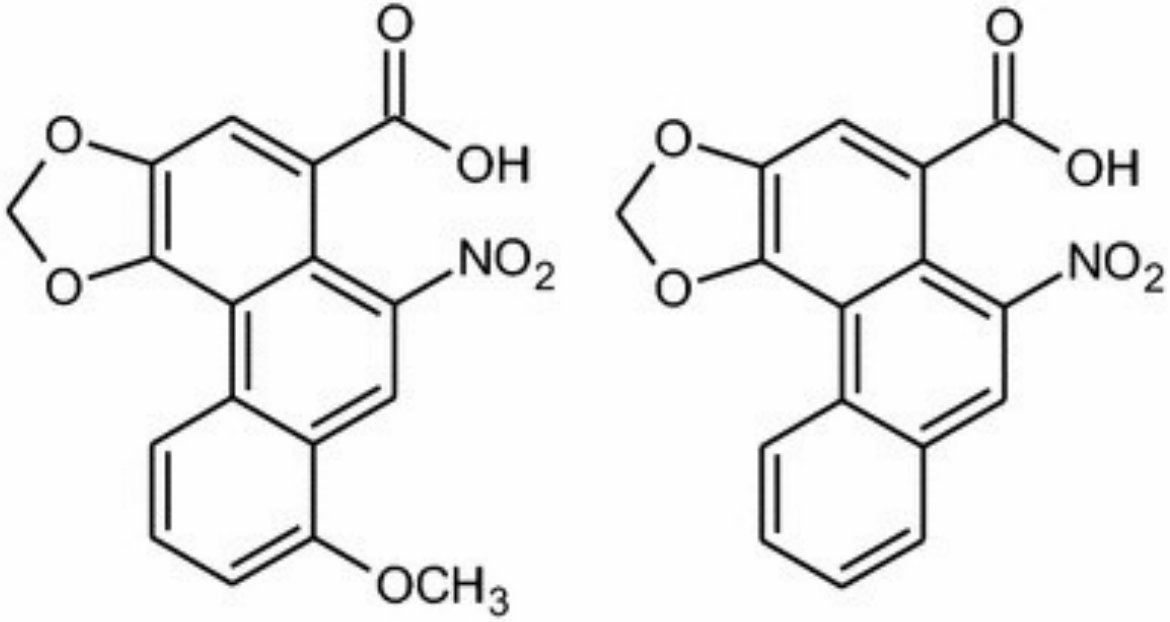
# ARISTOLOCHIC ACID AND ENDEMIC NEPHROPATHY

- Grollman et al at Stony Brooks, NY, (*Proc Natl Acad Sci U S A* ***104 : 12129 –12134, 2007***) used ultrasensitive, quantitative 32P-postlabeling methods, in conjunction with HPLC and mass spectroscopic techniques, to quantify dA-aristolactam (dA-AL) and dG-aristolactam (dG-AL) adducts in the renal cortex of patients with endemic nephropathy and in urothelial cancer tissues of residents of endemic villages.
- In urothelial cancers cells removed at surgery from patients residing in the endemic region he demonstrated that A:T→T:A mutations were dominant in the p53 gene.

# *Aristolochia clematitis and* Aristolochic Acid Formula

A

B




AAI AAII

# CHINESE HERBAL NEPHROPATHY = ARISTOLOCHIC ACID NEPHROPATHY

- *Aristolochia species have been used widely for more than 2000 years in Chinese medicine as well as in Europe, Latin America, and the United States.*
- Herbal recipes used in Roman-Greco times contained *Aristolochia in amounts estimated to be highly nephrotoxic.*
- *The potent toxicity of Aristolochia in humans was appreciated only in the early 1990s.*
- Nortier (*N Engl J Med* ***342 : 1686 –1692, 2000),*** described 112 patients with a diagnosis of Chinese herb nephropathy, with renal failure. Among the latter, removal of the native kidneys and ureters revealed a high prevalence (>40%) of urothelial cancer in the upper urinary tract, a highly unusual site for transitional cell cancers.
- *Subsequently, additional cases of so-called Chinese herb nephropathy were reported worldwide.*

# Epidemiology of CKDu in the World

- In the last 2-3 decades there has been an unexplained increase in the incidence of CKD, in some regions of Central America, India, Africa and Asia.
- This epidemic does not appear to be linked to cardio-metabolic causes and is called **CKD of uncertain origin (CKDu)**

# World Epidemic of CKDu

# Epidemiology of ESRD in Central America

- The first formal mention of the possible presence of a new pathologic entity was published in 2002 by Trabanino et al. (Rev Panam Salud Publica 2002;12:202-206), who reported that 67% of patients with advanced CKD in El Salvador had a disease of unknown origin.
- Subsequently, several other investigators have reported a high incidence of CKD in various regions of Central American for which the cause(s) remain unknown.

# Distribution of CKDu

# Mesoamerican Nephropathy


- Occurs predominantly along the Pacific coast, much less in the hills (?)
- Affects primarily young men working in sugar cane fields, miners, construction workers, fishing industry, port workers, brick-makers.
- It may affect women and children

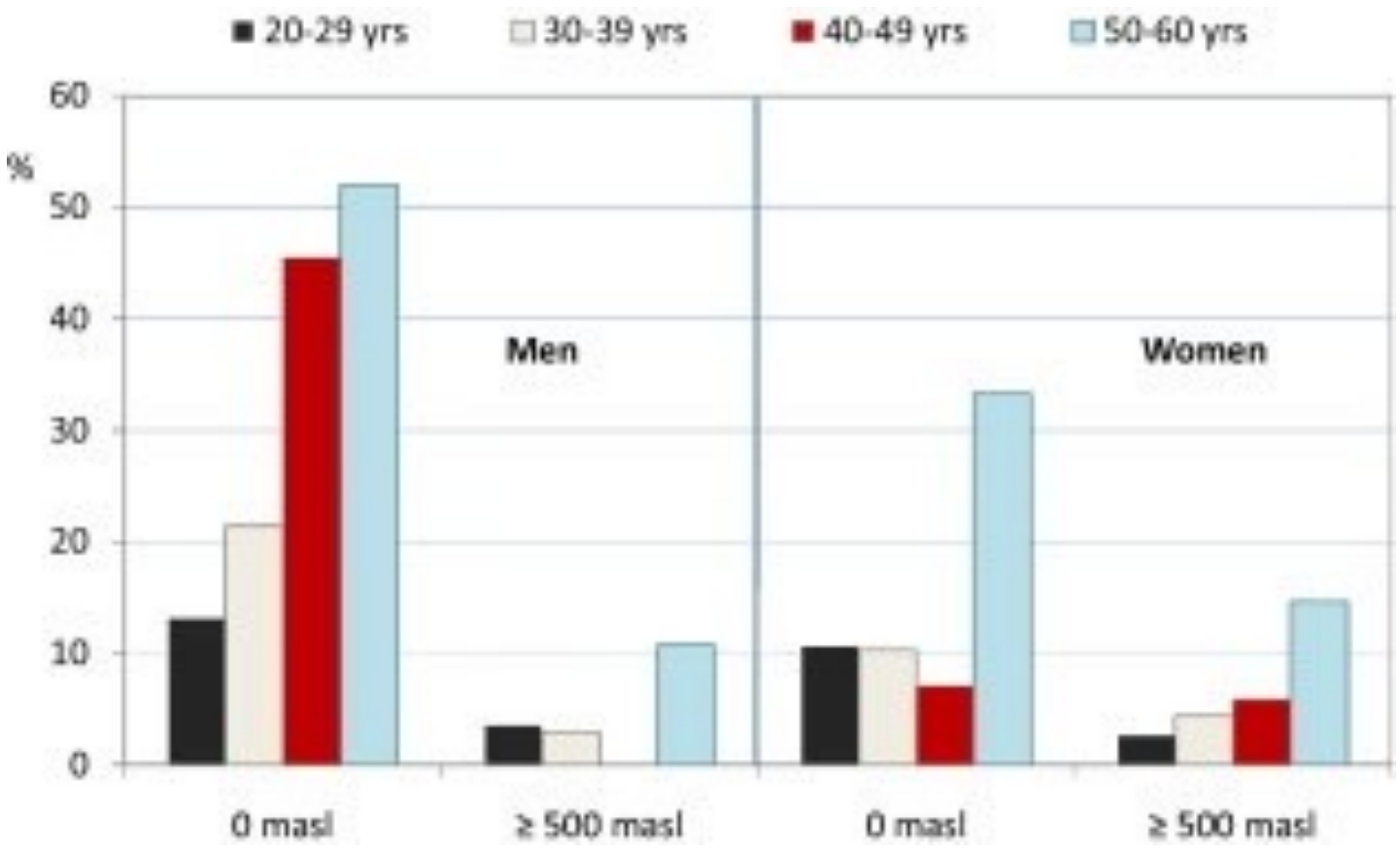
# Sugar-Cane Harvesting

# Meso-American Nephropathy Presenting as CKD

- A randomized (unpublished) survey of 10% of the general population in MalPaisillo (Leon, Nicaragua); 26,000 people
  - 27% of the screened participants manifested abnormal serum creatinine;
  - 35% had hyperuricemia.
- Urinalysis showed minimal proteinuria, some leukocytes

*Bigazzi and Bianchi, unpublished data*

Prevalences of serum creatinine levels greater than the upper limit of normal (men, 1.2 mg/dL; women, 0.9 mg/dL) in communities at sea level and communities at 500 meters above sea level or higher by sex and age.




Sea level

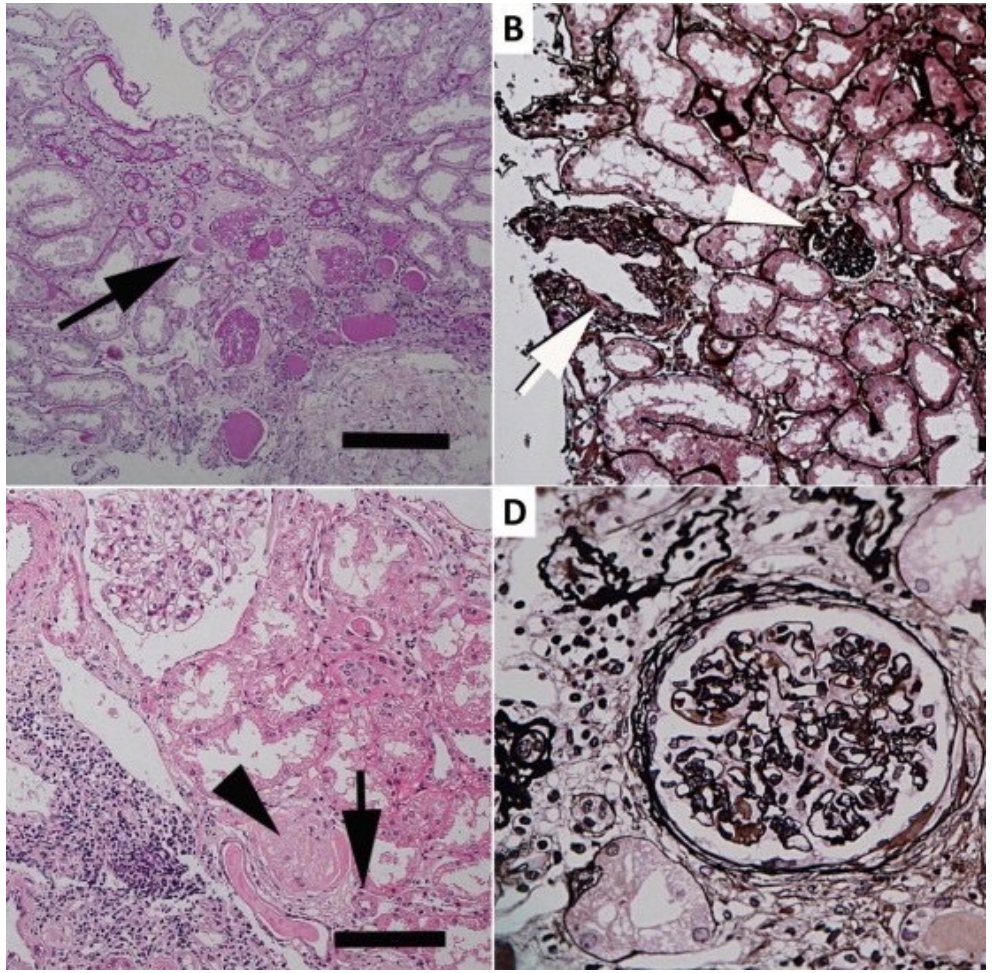
500 mts altitude

*Peraza S, et al. AJKD 2012; 59:531–540*

# MeN
# Clinical Presentation of CKD

- Patients usually present with:
  - Asymptomatic yet progressive reduction in eGFR
  - Normal or mildly elevated BP,
  - Low-grade non-nephrotic proteinuria
  - Often hyperuricemia
  - Often hypokalemia.

# Mesoamerican Nephropathy




- **Tubulointerstitial inflammation and fibrosis**
- **Secondary glomerulosclerosis**
- **Glomerular isch**emia

# Meso-American Nephropathy

- Clinical Presentation:
  - CKD (most common presentation)
  - AKI
  - ESRD

# Tropical Medicine Mystery:

## What is Killing Young Workers in Central America?

# Possible infectious etiologies

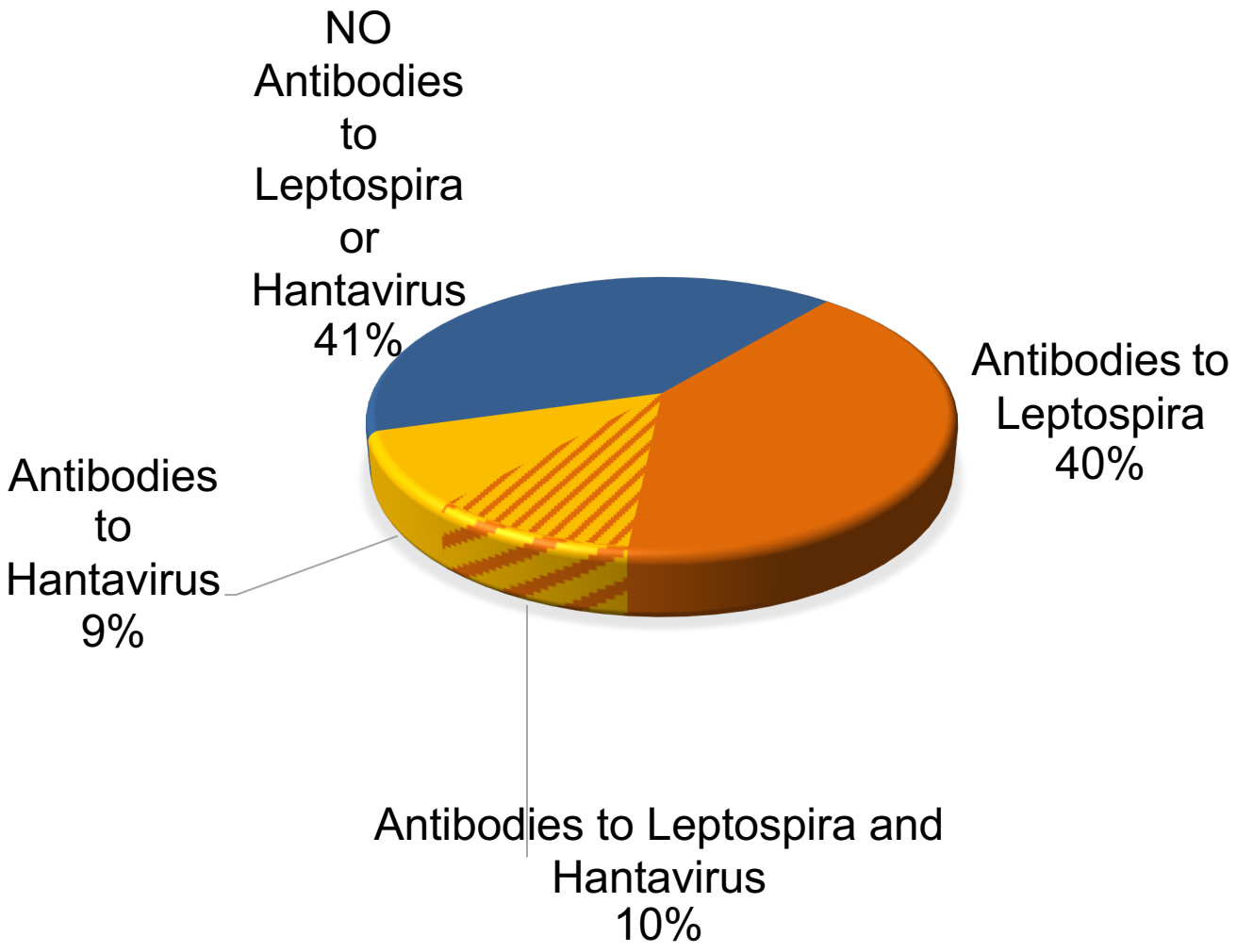
- **Leptospirosis**
- **Hantavirus**
- Malaria
- Dengue (rare: ARF due to rhabdomyolysis)
- Cytomegalovirus
- *Mansonella ozzardi/perstans* (common in sugar cane workers)
- Hepatitis B (membranous nephropathy, mesangiocapillary glomerulonephritis); Hepatitis C (cryoglobulinemia-mediated glomerulonephritis); Hepatitis E (acute tubular necrosis)
- *Streptococcus*
- *Leishmania*
- HIV

# Preliminary Epidemiologic Investigation

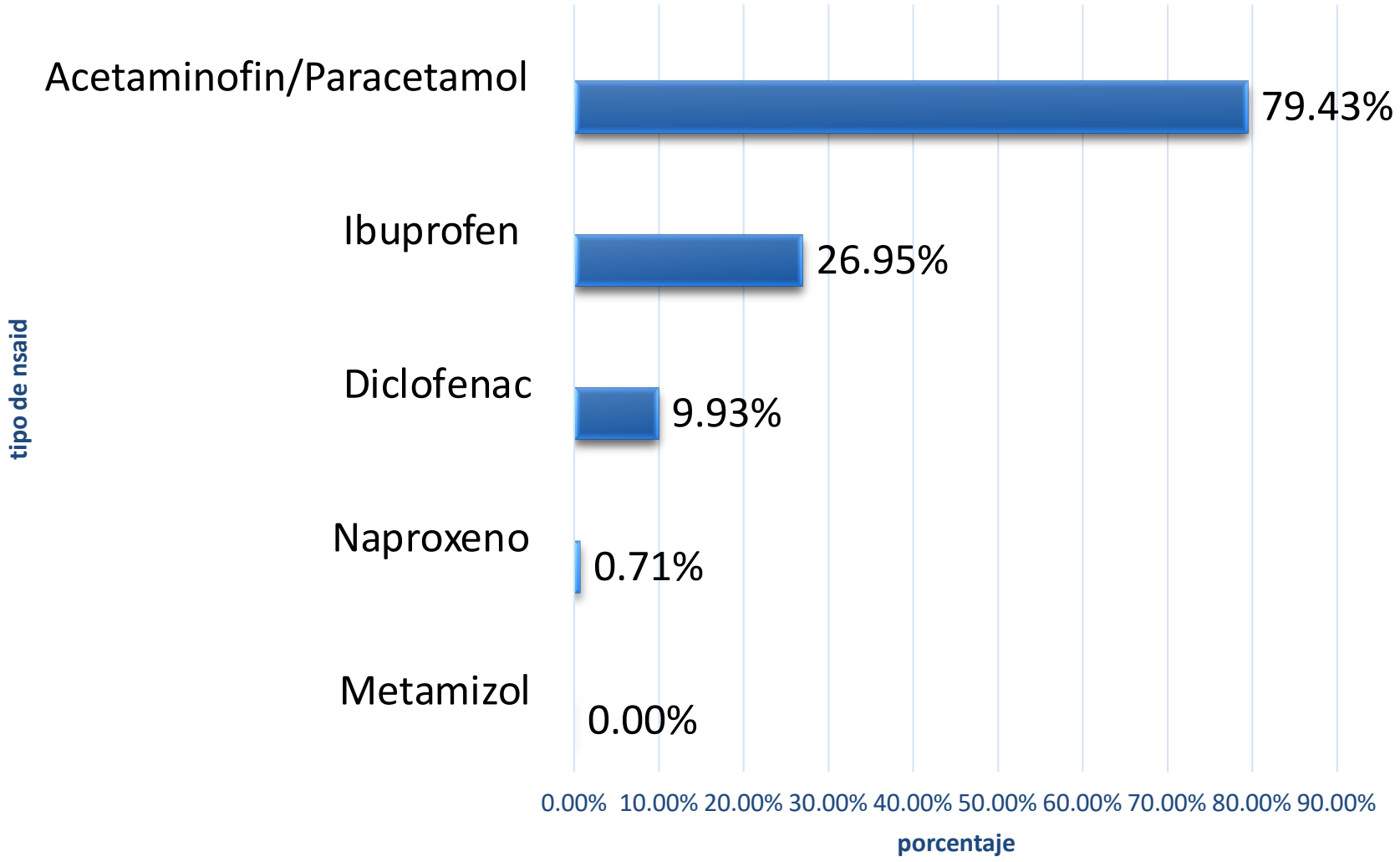
<u>Hypothesis:</u>

An infectious agent, possibly a zoonotic pathogen could be transmitted through water/soil in field, vectors, or contact with animals. Reservoir hosts may play an important role in maintaining the epidemic.

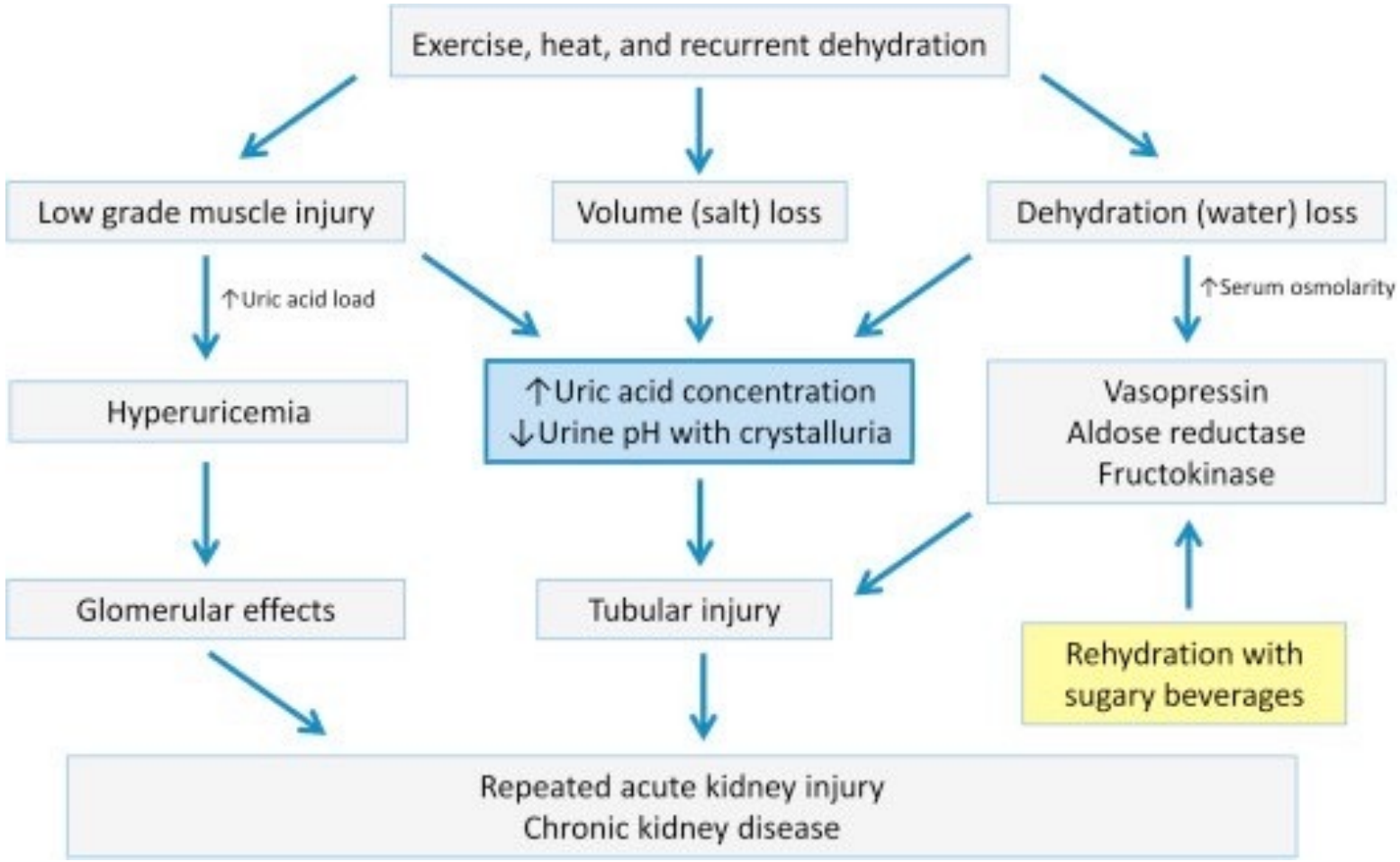
# Findings in 93 patients with MAN



# Concomitant Medications



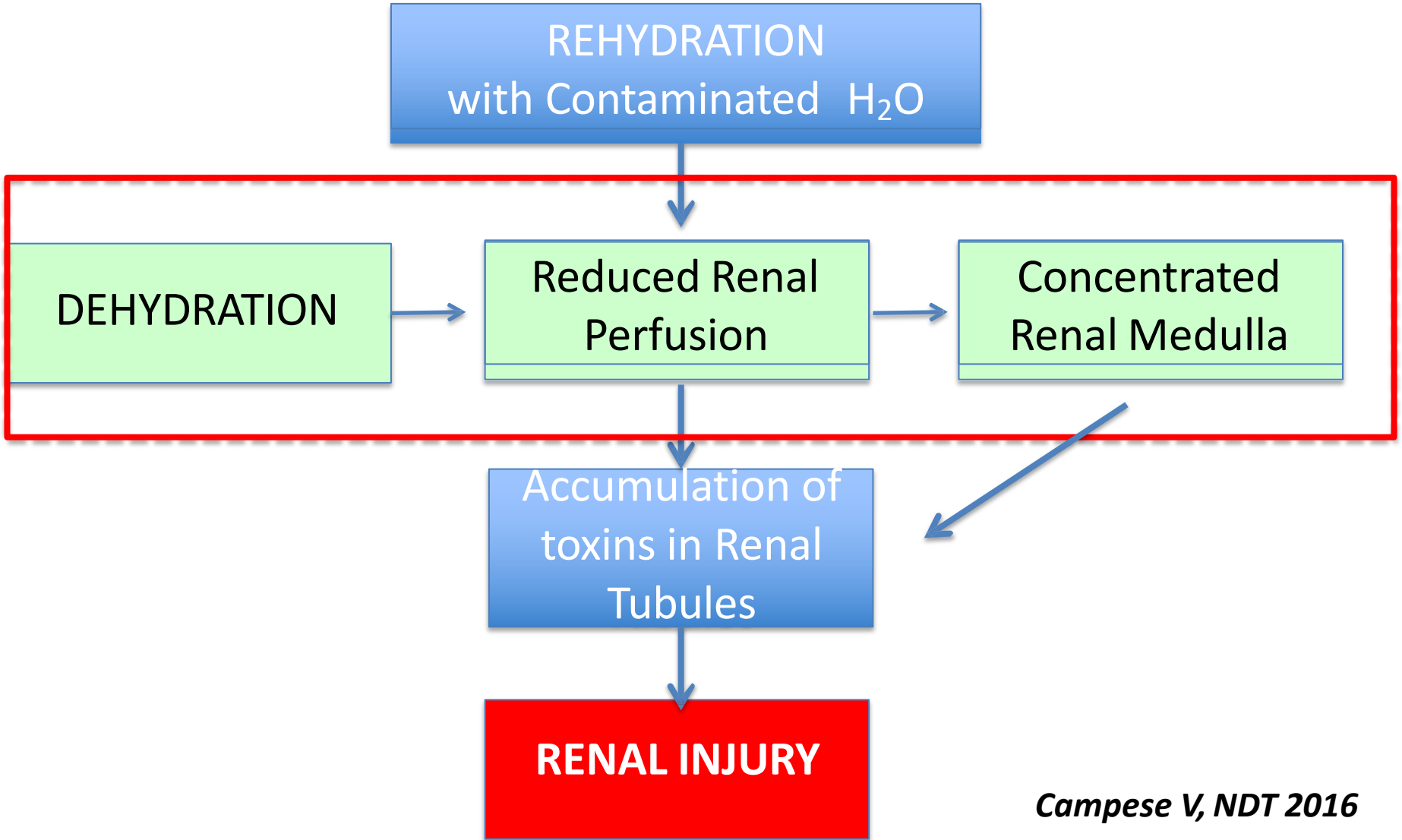
# Proposed mechanism for Mesoamerican nephropathy




Am J Kidney Dis. 2016;67(1):20-30

# Meso-American Nephropathy (MeN): Is the Problem Dehydration or Rehydration?

# MESOAMERICAN NEPHROPATHY

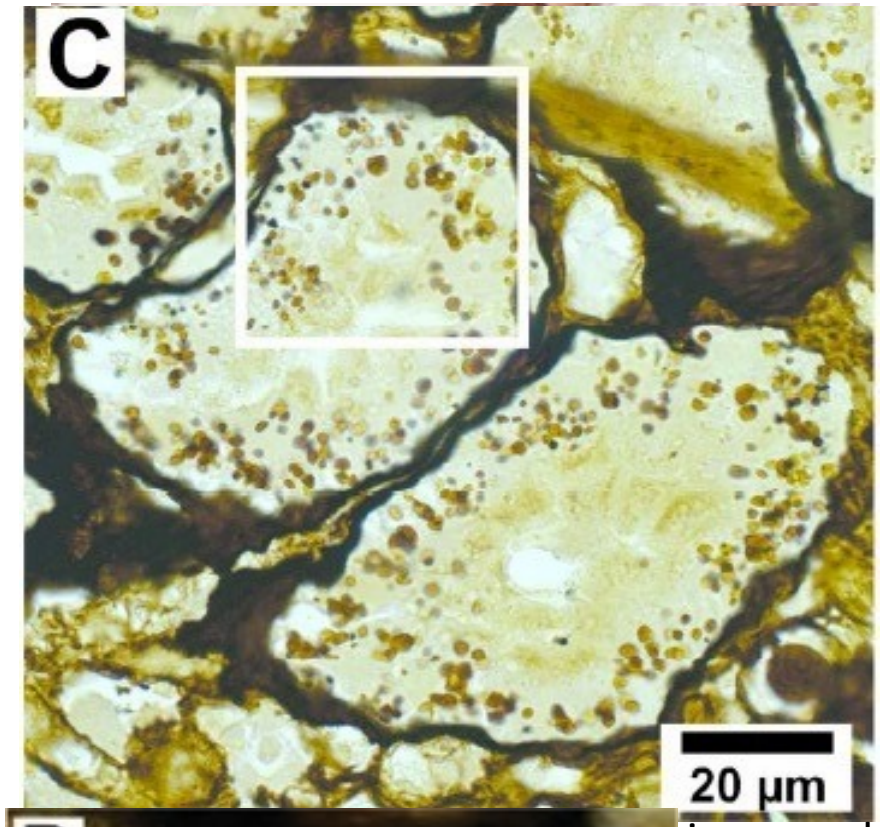


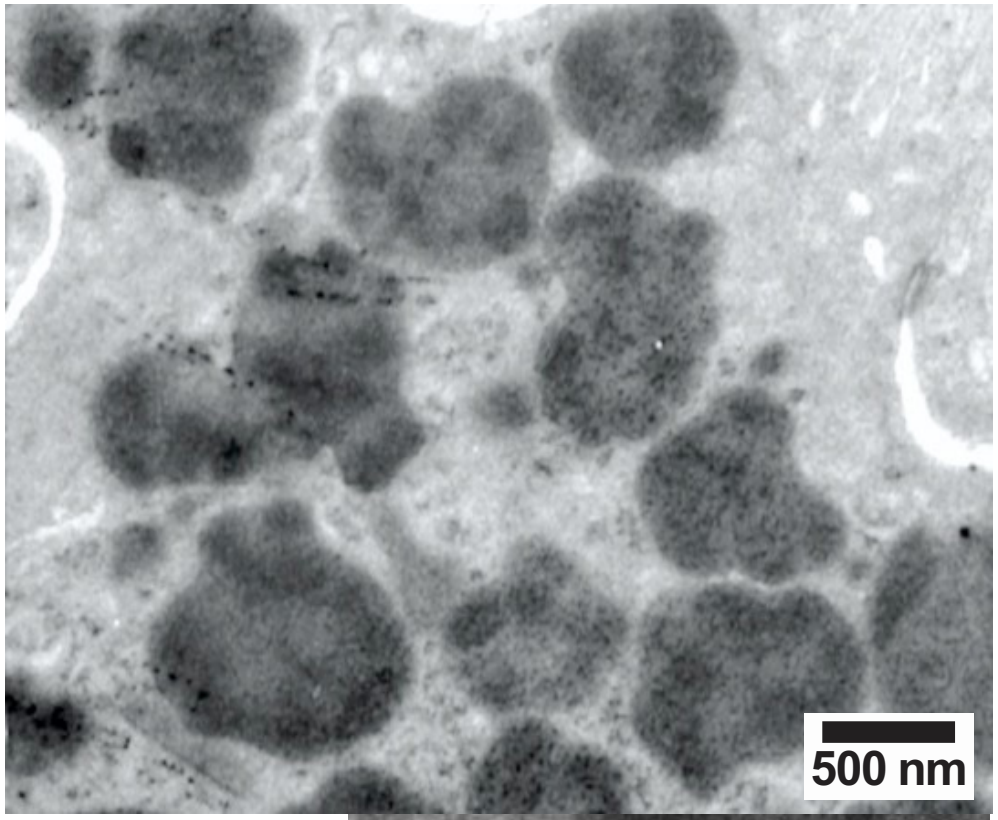

*Campese V, NDT 2016*

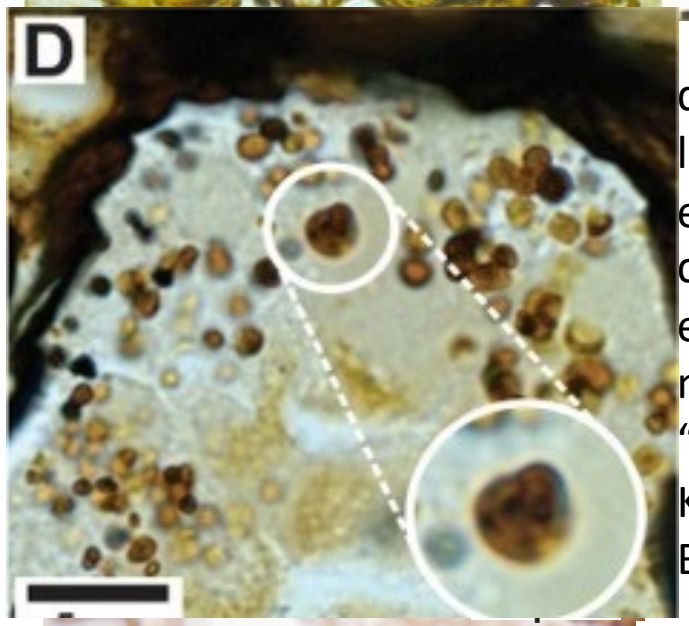
# Are the lesions seen in MaN linked to Calcineuri Inhibition?

- **EM shows big and dysmorphic lysosomes with light medium uniform electron dense matrix containing disperse dark electron dense deposits**
- **Cyclosporin LM causes similar lysosomal injury**
- **Aristolochic acid does not cause this type of lesions.**
- **Is this autophagy? Like seen with cyclosporin A?**
- **In Country that produce wine and use pesticides they have CINAC**
- **There is certainly in Europe a relationship between development of that lesion and use of pesticides**
- **In rats, dehidration did not cause these lesions, but when dehidration was accompanied with cyclosporine then the lysosomes lesions would appear**

*De Brod 2018*



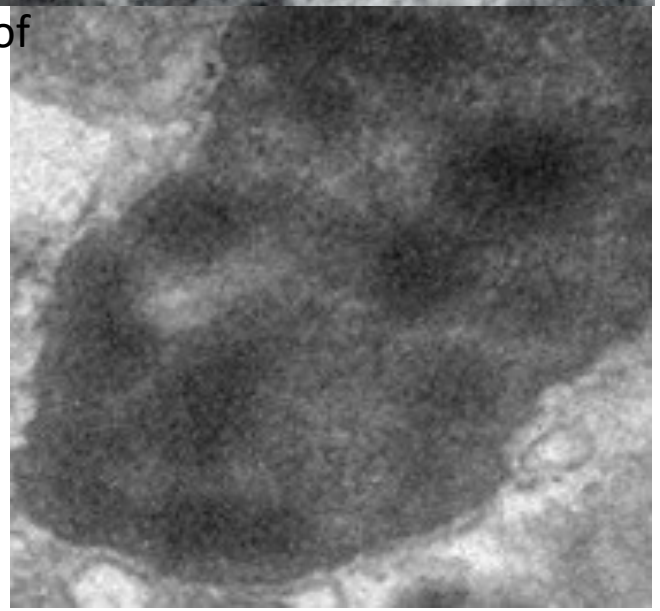



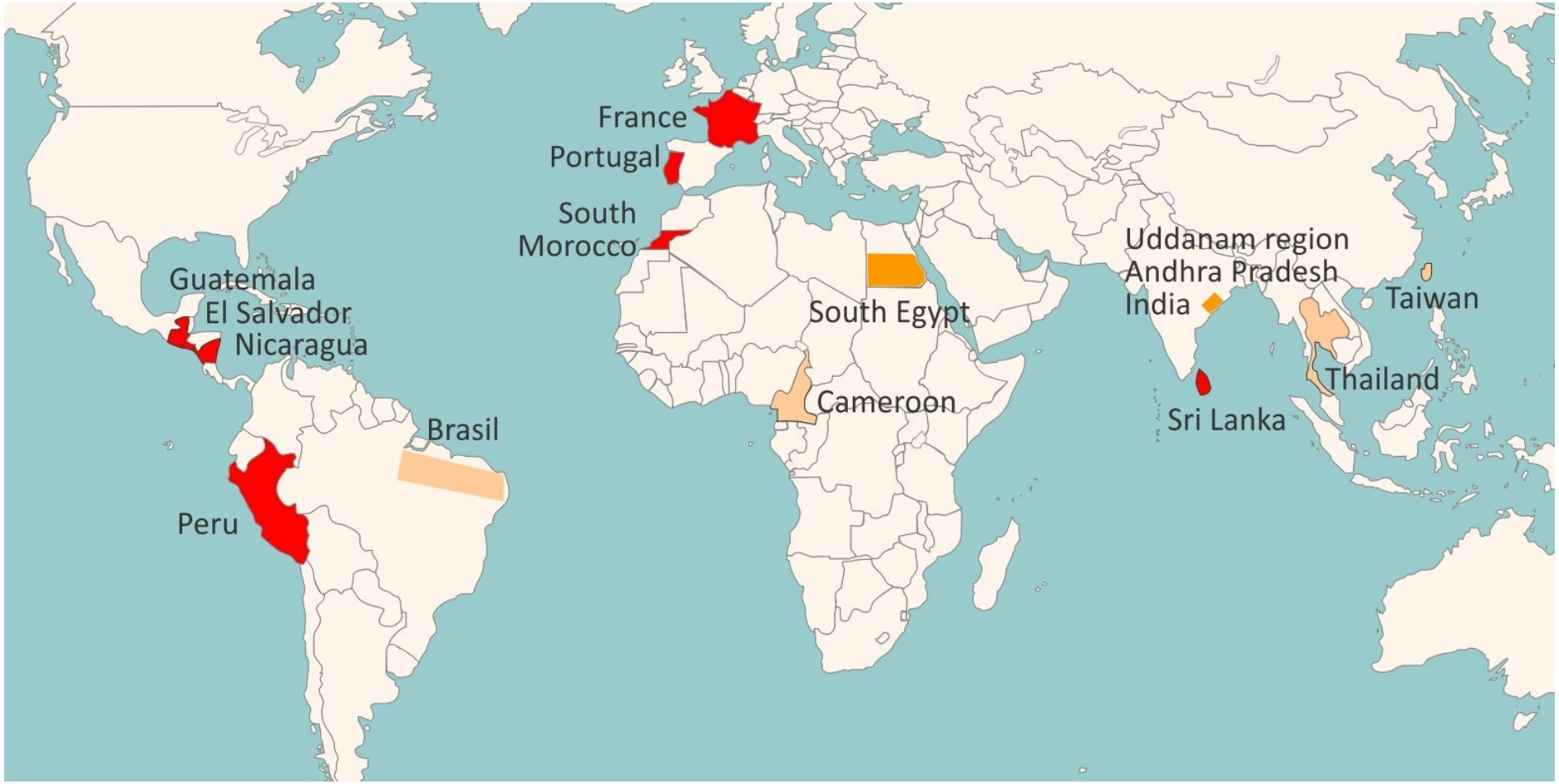

increased size and number of dysmorphic lysosomes with light-medium uniform electron-dense matrix containing dispersed dark electron-dense non-membrane bound “aggregates”.

Kidn Intern in rev oct 2018

B Vervaet, M De Broe et al



# Chronic Interstitial Nephritis in Agricultural Communities (CINAC) 1995-2018




Red: countries were these typical proximal tybular lesions were indentified in renal biopsies odf patiets with CINAC
Yellow under investigation , in India we have very recently also found these lesions

# Enan E, et al. Biochem Pharmacol 1992;43:1777

- All insecticidal Type II pyrethroids (cypermethrin, deltamethrin and fenvalerate) are potent inhibitors of isolated calcineurin from bovine brain.
- Herbicides, such as Paraquat, stimulate $H_2O_2$ production. This, in turn, inhibit calcineurin phosphatase activity and can cause AKI as well as CKD.
- Lomustine and Clomiphene (chemotherapeutics) are calcineurin type inhibitors and cause the same lesions

# Summary and Conclusions

- The symbiosis between human and environment has become precarious.
- A growing number of diseases are caused by environmental factors
- The kidney is particularly susceptible to environmental insults
- An epidemic of CKD of enormous proportion is affecting several regions in Central America, Asia and Africa
- The disease affects primarily young workers subjected to strenuous heat and working conditions
- The disease can progress rapidly
- The cause(s) remain unknown but environmental toxins in conjunction with dehydration appear to be critical factors