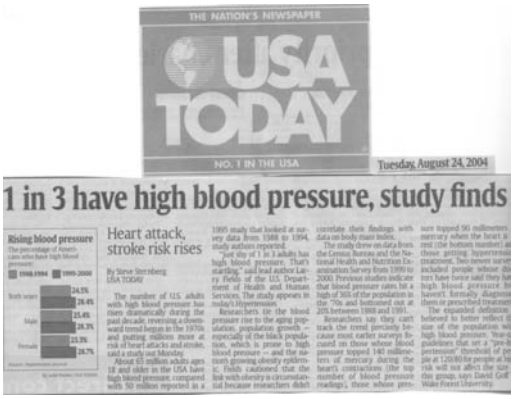
Vascular disease and the kidney

Case 1

- A 28 yo AA M presents with acute low back pain following weekend basketball game
- Has no other complaints; states he was told of HBP during college sports but never followed up.
  BP: 148/90 mm Hg (first reading)
  146/88 mm Hg (second reading- end exam)
  - Height: 6'0"; weight: 218 lb
  You treat the acute low back pain and ask the patient to return.

  BP on return when he feels well is from 150/92 to148/90 mm HG.
- Family Hx significant for HBP in both parents.
- Laboratory : BUN 13 mg/dl, creatinine 0.9 mg/dL; Fasting glucose: 96 mg/dL
  - U/A 2+ prot, 0 heme
  CXray normal, EKG borderline LVH.


THE NATION'S NEWSPAPER

USA TODAY

NO. 1 IN THE USA

Tuesday, August 24, 2004

1 in 3 have high blood pressure, study finds

Rising blood pressure

Heart attack, stroke risk rises

By Steve Sternberg
USA TODAY

The number of U.S. adults with high blood pressure has risen dramatically during the past decade, reversing a downward trend begun in the 1970s and putting millions more at risk of heart attacks and stroke, said a study out Monday.

About 65 million adults ages 18 and older in the USA have high blood pressure, compared with 50 million reported in a 1995 study that looked at survey data from 1988 to 1994, study authors reported.

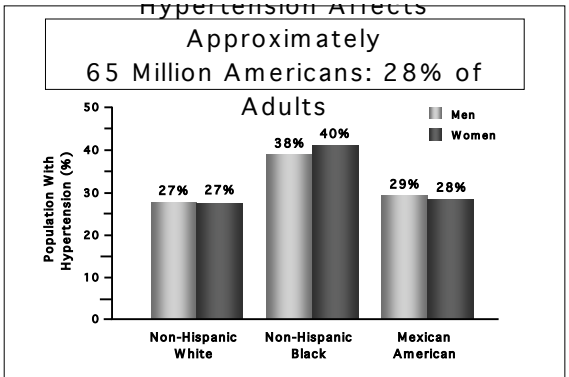
"Just shy of 1 in 3 adults has high blood pressure. That's startling," said lead author Larry Fields of the U.S. Department of Health and Human Services. The study appears in today's Hypertension.

Researchers tie the blood pressure rise to the aging population, population growth — especially of the black population, which is prone to high blood pressure — and the nation's growing obesity epidemic. Fields cautioned that the link with obesity is circumstantial because researchers didn't correlate their findings with data on body mass index.

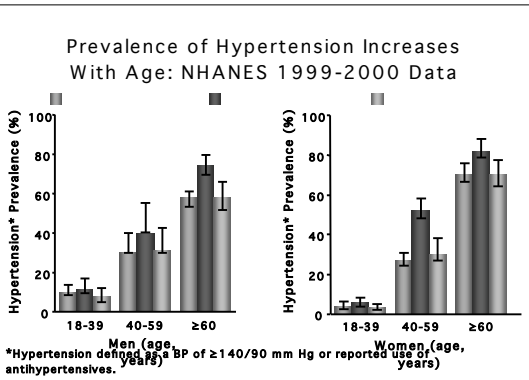
The study drew on data from the Census Bureau and the National Health and Nutrition Examination Survey from 1999 to 2000. Previous studies indicate that blood pressure rates hit a high of 36% of the population in the '70s and bottomed out at 25% between 1988 and 1991.

Researchers say they can't track the trend precisely because most earlier surveys focused on those whose blood pressure topped 140 millimeters of mercury during the heart's contractions (the top number of blood pressure readings), those whose pressure topped 90 millimeters of mercury when the heart is at rest (the bottom number) are those getting hypertension treatment. Two newer surveys included people whose doctors have twice said they have high blood pressure but haven't, formally diagnosed them or prescribed treatment.

The expanded definition is believed to better reflect the size of the population with high blood pressure. Researchers say new guidelines that set a "pre-hypertension" threshold of people at 120/80 for people at high risk will not affect the size of the group, says David Goff of Wake Forest University.



Fields LE et al. *Hypertension.* 2004;44:398-404.

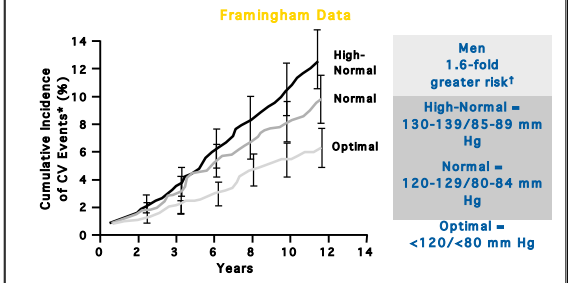


*Hypertension defined as a BP of ≥140/90 mm Hg or reported use of antihypertensives.

Error bars indicate 95% confidence intervals. Data are weighted to the US population.

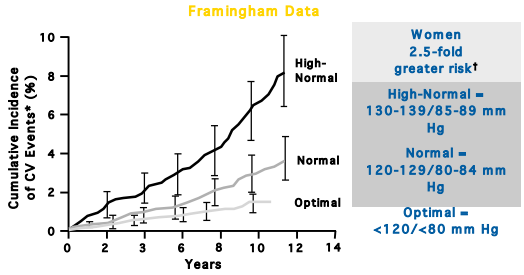
Adapted from Hajjar I, Kotchen TA. *JAMA.* 2003;290:199-206.

"High-Normal" BP in Men is Not Benign



*CV death, MI, stroke, heart failure. †Adjusted for concomitant CV risk factors.
Vasan RS et al. *N Engl J Med.* 2001;345:1291-1297.

"High-Normal" BP in Women is Not Benign



*CV death, MI, stroke, heart failure. †Adjusted for concomitant CV risk factors.
Vasan RS et al. *N Engl J Med.* 2001;345:1291-1297.

JNC 7: Lifestyle Modifications to Prevent and Manage Hypertension

Modification	Approximate SBP reduction
Weight reduction	5-20 mm Hg/10 kg
DASH diet	8-14 mm Hg
Sodium reduction	2-8 mm Hg
Physical activity	4-9 mm Hg
Moderate alcohol consumption	2-4 mm Hg

DASH = Dietary Approaches to Stop Hypertension.
Chobanian AV et al. *JNC 7: Complete Report.*
Available at: http://hyper.ahajournals.org/cgi/content/full/42/6/1206.

Walking the dog

My Doctor said "Only 1 glass of alcohol a day". I can live with that.

1 drink
= 250 ml beer
= 100 ml wine
= 35 ml liquor

Case 1

- Lifestyle modifications alone may be sufficient for a 28 yo patient with mild hypertension and no other CV risk factors.
- If do not achieve goal BP within 3-6 months, pharmacologic therapy can be prescribed.
- Excellent data prove that lowering BP with several classes of drugs, including ACEIs, ARBs, β-blockers, CCBs, and thiazide-type diuretics, will reduce the complications of hypertension.
- WHAT IS HAPPENING IN THE

Case 1

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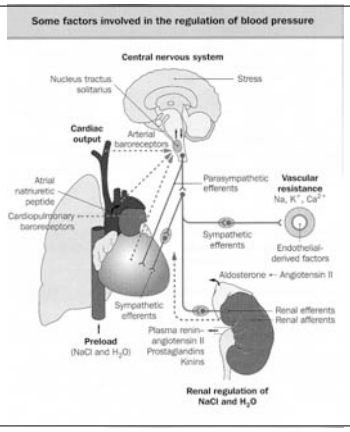
- WHAT IS HAPPENING IN THE KIDNEYS?

Pathology of hypertensive kidney disease (arterionephrosclerosis)



Hypertension and the kidney

Renal disease causes hypertension

↓ ↑

Hypertension causes renal disease

Renal disease causes hypertension

↓ ↑

Hypertension causes renal disease

↓

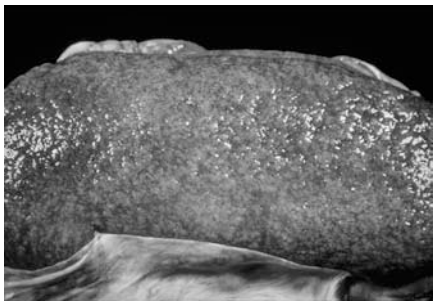
Hypertensive arterionephrosclerosis

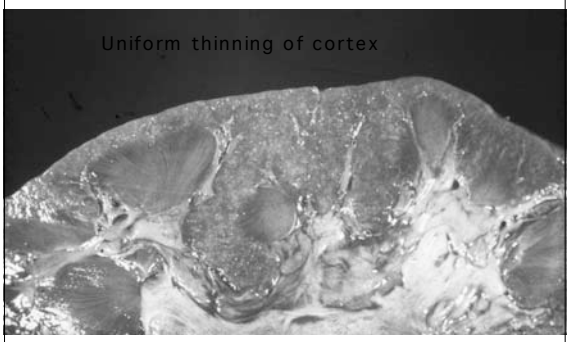
Clinical features of hypertensive arterionephrosclerosis

Most patients are asymptomatic

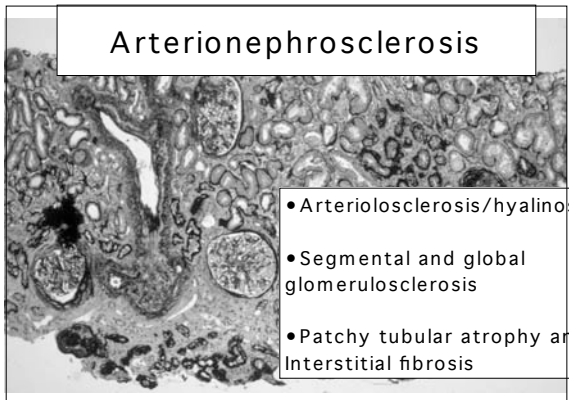
A minority develop chronic renal failure, with/without proteinuria

Arterionephrosclerosis:
Bilateral, small kidneys, granular surface



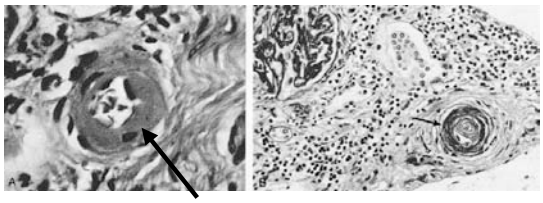


Arterionephrosclerosis

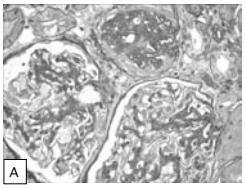


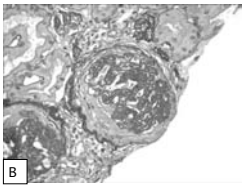
- Arteriolosclerosis/hyalino
- Segmental and global glomerulosclerosis
- Patchy tubular atrophy ar Interstitial fibrosis

Arterionephrosclerosis



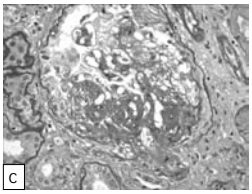
Arteriolar sclerosis and hyalinosis:
= Insudated palsma proteins and degenerating medial myocytes





Arterionephrosclerosis-
Glomerular changes

- Glomerulomegaly
- Global sclerosis
- Perihilar FSGS



Case 2:

- **60 yo AA M with Hypertension presents to ER with severe head aches over few weeks, and chest pain and SOB of 2 hrs duration.**
- **He has a BP of 190/130 mm HG, P84, R 18/min, blurring of disc margins on eye exam, S4G, Rales at both bases, and no edema.**
- **Lab: Bun 38 mg/dl, creatinine 2.4 mg/dl, U/A 2+ prot, 2+ heme 10-15 rbc no casts. CXray cardiomegaly . EKG shows LVH + evidence of an acute inferior MI.**
- **BP is controlled with IV labetalol, he is given ASA and plavix, and of bare-metal cardiac stent is placed in his R coronary artery.**
- **Over next few days BP is controlled with a beta blocker, ACE inhibitor and diuretic. He feels much improved, but BUN and creatinine only change slightly.**
- **USG shows 10 cm echogenic kidneys.**

Case 2

- What are the consequences of severe (accelerated, malignant) HBP?
- What is likely to happen to his kidney function if he stops his BP medications after hospital discharge?
- What is likely to happen to his kidney function if he stays on BP medications?
- How many BP medications will it take to control his hypertension?
- If this patient had died from his myocardial infarct, what would his kidneys likely show at autopsy?

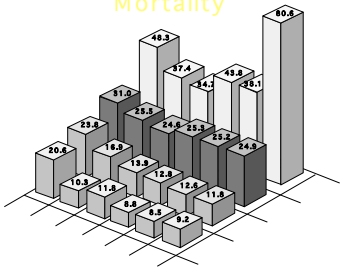
Many Patients in the US Are Not at JNC-Recommended BP Goals

NHANES (1999-2000)

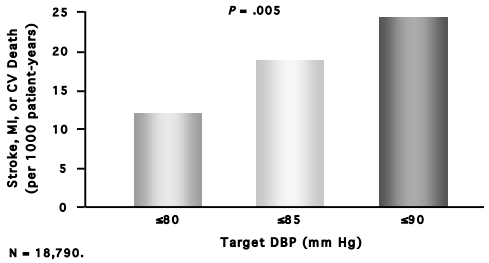
Patient Type	Goal BP (mm Hg)	% Not at Goal* Systolic BP	Diastolic BP
Total hypertensives	<140/90	57%	26%
African American	<140/90	60%	32%
Mexican American/ Hispanic	<140/90	63%	30%
Older patients (≥60 yr)	<140/90	71%	9%
Symptomatic CHD	<140/90	47%	4%
Patients with diabetes	<130/80†	81%	24%

*

MRFIT: Effect of Systolic BP and Diastolic BP on Age-Adjusted CHD Mortality

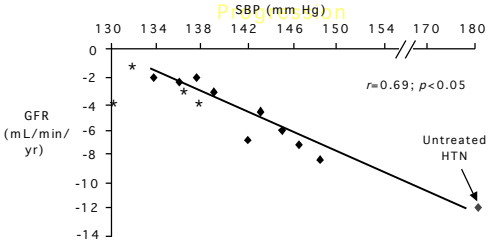


HOT Study: Fewer Major CV Events in Patients With Diabetes Randomized to Lower BP Goal



N = 18,790.
HOT = Hypertension Optimal Treatment.
Adapted from Hansson L et al, for the HOT Study Group. *Lancet.* 1998;351:1755-1762.

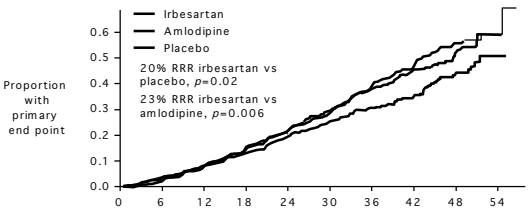
Summary of Studies on Nephropathy Progression



Parving HH et al. *BMJ.* 1989.
Viberti G et al. *JAMA.* 1994.
Klahr S et al. *N Engl J Med.* 1994.†
Hebert L et al. *Kidney Int.* 1994.
Lebovitz H et al. *Kidney Int.* 1994.
Maschio G et al. *N Engl J Med.* 1996.†
Bakris GL et al. *Kidney Int.* 1996.
Bakris GL. *Hypertension.* 1997.
GISEN Group. *Lancet.* 1997.†
*Estacio. *Diabetes Care.* 2000;23(suppl 2):B54-B6
*Schrier RW. *Kidney Int.* 2002;61:1086-1097.

†Nondiabetic renal disease patients.
Adapted from Izbar M, Bakris GL. In: Antman EM, ed. *Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease.* 2nd ed. New York, NY: W.B. Saunders Company; 2002:chap 35.

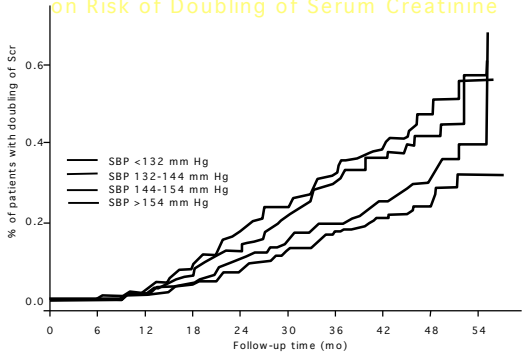
IDNT: Renal Outcome End Point—Time to Doubling of Serum Creatinine, ESRD, or Death



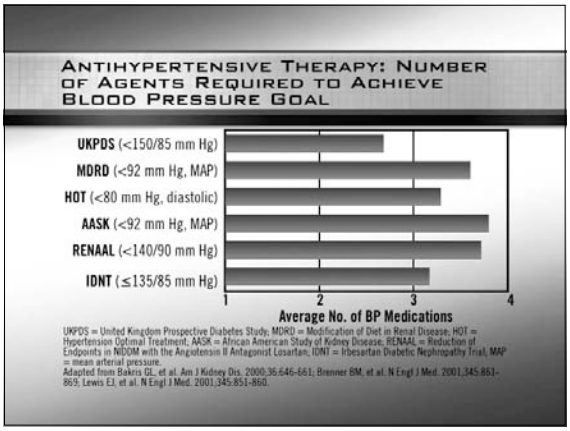
No. at risk									
Irbesartan	579	555	528	496	400	304	216	146	65
Amlodipine	565	542	508	474	385	287	187	128	46
Placebo	568	551	512	471	401	280	190	122	53

Lewis EJ et al. *N Engl J Med.* 2001;345:851-860.

IDNT: Impact of 12-Month Seated Systolic BP on Risk of Doubling of Serum Creatinine



Pohl MA et al. *J Am Soc Nephrol.* 2002;13:644A. (Poster #SU-P0853)



Case 2: Pathology of malignant (accelerated) hypertension

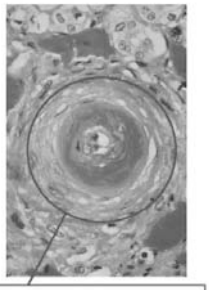
Accelerated/Malignant Hypertension

WHO definition:
Severe HT plus Bilateral fundal haemeorrhage & exudates

N.B. papilloedema NOT required for the diagnosis.

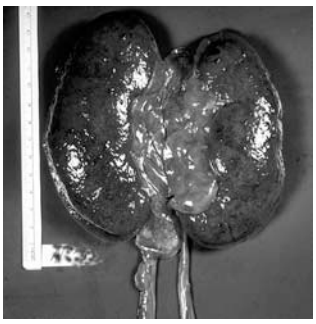
Following may be present but not diagnostic:

- DBP usually >130 mm Hg
- Renal failure
- Microangiopathic Haemolysis



Hallmark pathology - Fibrinoid arteriolar necrosis

Malignant nephrosclerosis

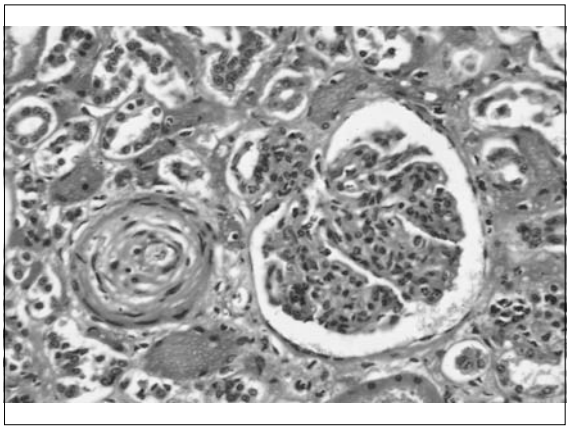


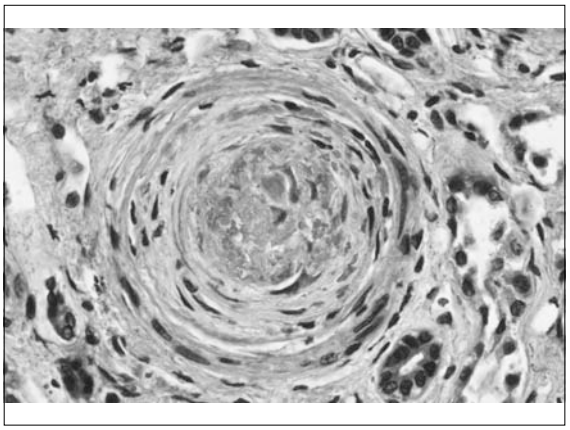
Normal size kidney*

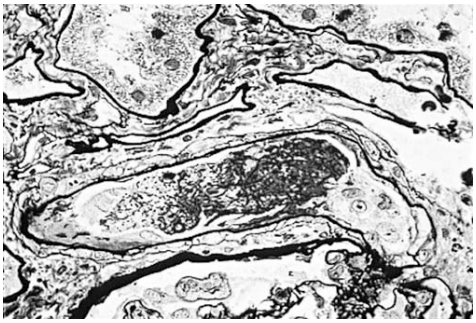
Smooth surface*

Petechial Hemorrhages

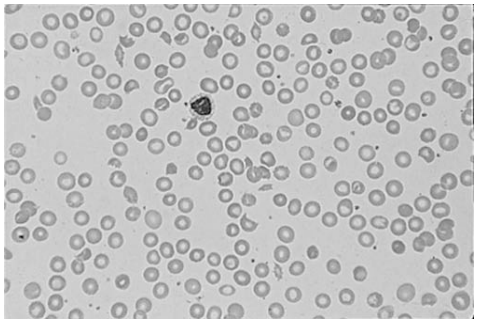
*(*Unless underlying essential HTN)*



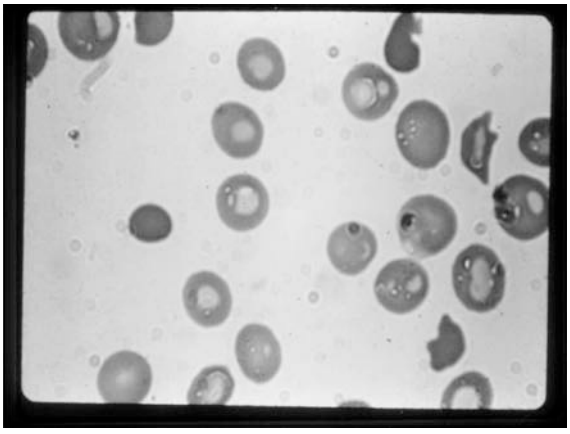




Arteriole with fibrin thrombus

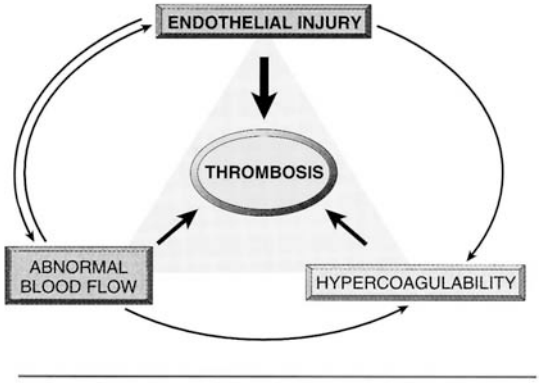


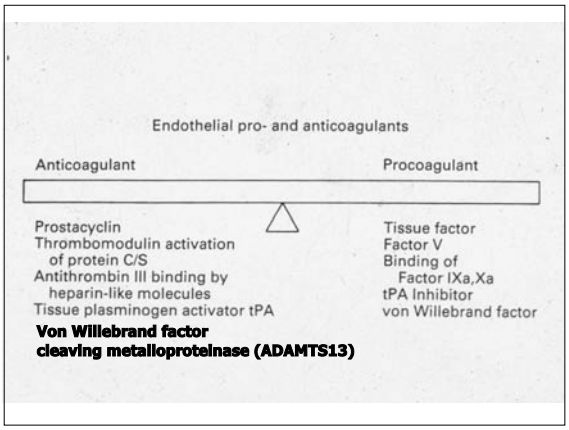
Schistocytes in hemolytic anemia

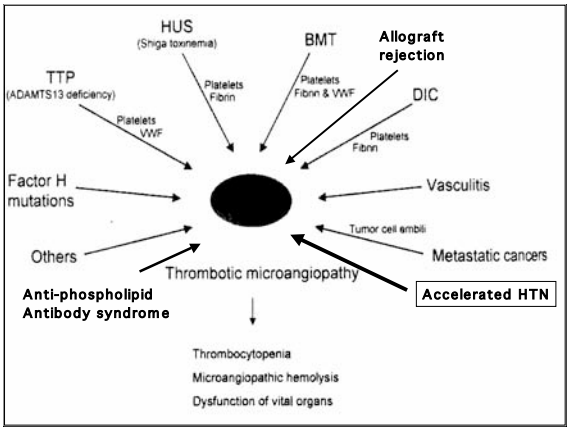


Severe endothelial injury leads to thrombotic microangiopathy

1. Acute renal failure
2. Microangiopathic anemia
3. Thrombocytopenia







Case 3

- 68 yo WM retired construction worker transferred for eval vasculitis and ARF.
- Excellent health – golfer and bowler.
- 5/95 loss of appetite, temps to 102, rash on back, cough Adm Hosp
- B13 mg/dl Cr 1.1 mg/dl WBC 2.9 Hct 33, plts 49 K. Rx antibiotics No dx disch
- 2 days later readm for temps .Hosp x 10 days Cr ↑ to 3.6 mg/dl, aDNA -, ANA + 1:400, ESR 68-145, U/A 2+ prot, 2+ heme, several rbc ? rbc casts?

  Urinary protein 784 mg /day
- WBC 10.0, Hct 35%, plts 142,000

Case 3

- Transfer to CUMC Px WD,WN, NAD, BP 170/84, Cor-Chest neg, Abd 2 Fb L, no edema, no rash.
- BUN 97 mg/dl Creatinine 4.0 mg/dl Palb 3.5, ALT 60 other LFTs nl

WBC 11.2K Hct 37% plts 114 K , Pt 14 PTT 49 U/A 1+ prot +rbc no casts

ANA + 1: 40 Hep BV,HCV neg, HIV-, ANCA – , CH50 and C3 nl

Anticardiolipin antibody strong positive

Antiphospholipid Antibodies

- Family of Antibodies (IgG, IgM, IgA) aganist negatively charged phospholipids
- Lupus Anticoagulant - Abs that prolong lipid dependent coag tests, interfere with phospholipid of the prothrombin activator complex.
- Anticardiolipin antibodies - Abs that bind to cardiolipin (phospholipid antigen used in tests for syphilis)
- False + VDRL
- Procoagulant Effect in vivo

Underlying Conditions with Antiphospholipid Antibodies

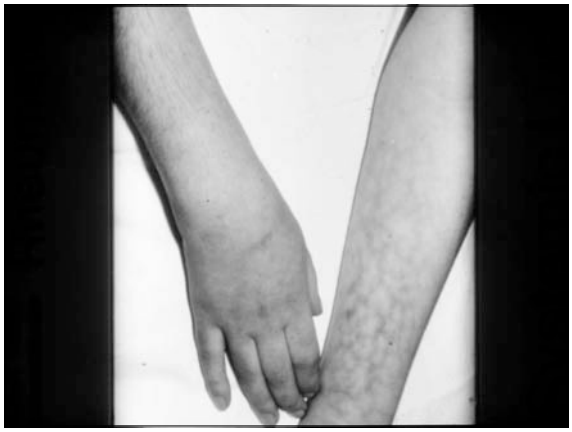
- Systemic Lupus Erythematosus
- "Lupus-Like" Syndrome
- Primary Anti-phospholipid Syndrome

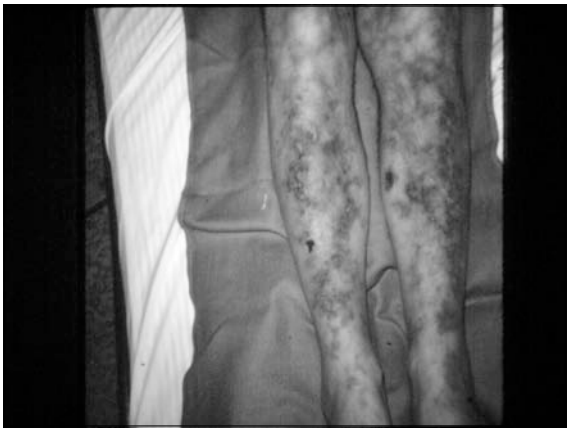
Clinical Manifestations Related to Anticardiolipin Antibodies

- Recurrent arterial and venous thromboses
- Placental thromboses and spontaneous abortions
- Livedo reticularis
- CNS complications
- Pulmonary Hypertension

Extrarenal Manifestations of APLS (65%)

• CNS disease	8
• Deep vein thrombosis	6
• Myocardial infarction	4
• Pulmonary embolism	4
• Livedo reticularis	4
• Adrenal disease	3
• Other (aortic thrombosis with RAS, bowel infarction, miscarriage)	3
Total	17/26





Serologies and Lab Data

• Prolonged PTT	12/26 (46%)
• Thrombocytopenia	9/23 (38%)
• +ANA	15/26 (58%)
• +AntiDNA	2/24 (8.3%)
• Low complement	7/24 (29%)
• False positive VDRL	6/11 (55%)

Clinical Presentation at Biopsy

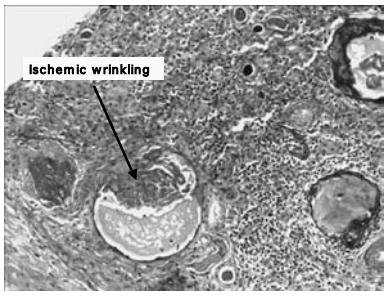
• Hypertension	16/26 (62%)
• Active urine sediment	10/26 (38%)
• Serum creatinine (mg/dl)	2.0 +/- 0.22
• Proteinuria (g/day)	4.4 +/-0.87
• Nephrotic Syndrome	15/26 (58%)

Course of APLS Patients

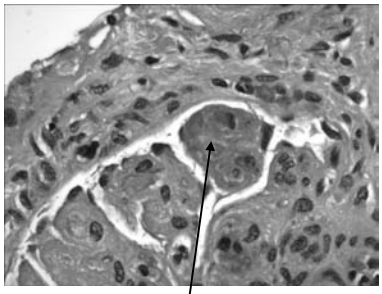
• Follow up	10 mo. - 10 yrs.
• True SLE	1 patient
• Improved renal function	10/19 (53%)
• Remission of N.S.	7/10 (70%)
• Worsening renal function	7/26 (27%)
• ESRD	4/26 (15%)

Case 3:Antiphospholipid antibody syndrome

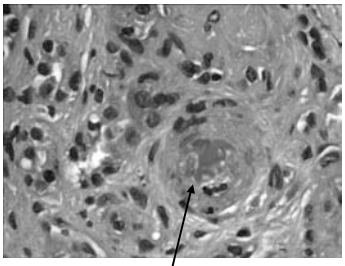
Pathologic findings



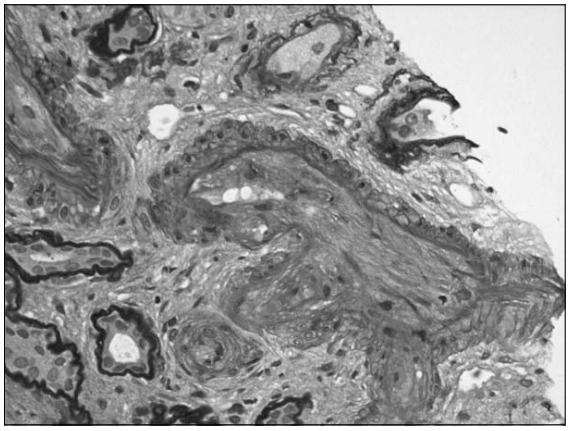
Glomeruli show ischemic changes (global wrinkling of glomerular basement membranes, tuft retraction, and cystic dilation of Bowman's space)

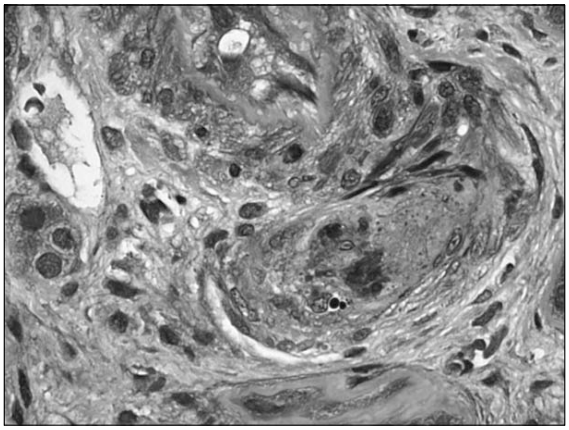


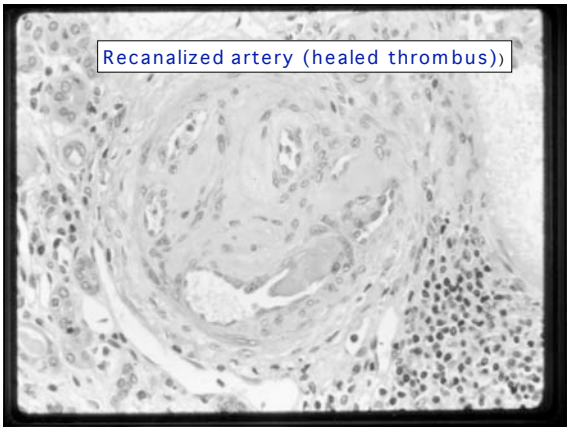
Glomeruli show segmental intracapillary fibrin

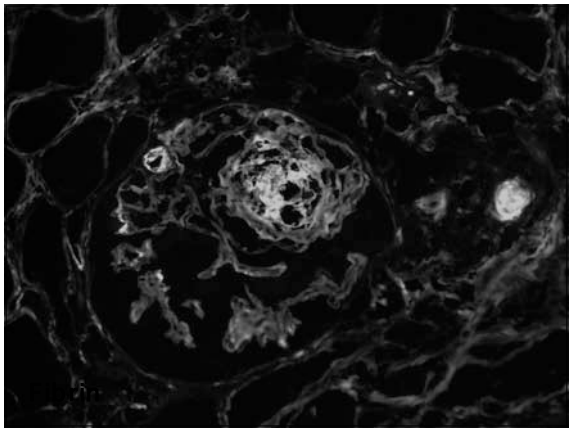


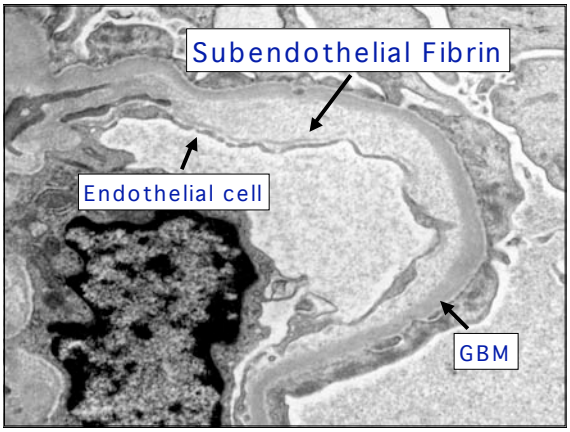
Arteries show widespread luminal narrowing with extensive subendothelial hyalinosis, endothelial swelling, focal myocyte dropout, focal mucoid intimal fibroplasia, and focal intramural fibrin with entrapped red blood cells.











Case 4

- A 4 yo girl presents with diarrhea and acute renal failure.
- She was in good health until 3 days PTA when went to neighbor's Bar-B-Q and had a hamburger. Over 24 hrs developed abdominal cramps, N/V, and bloody diarrhea. She became lethargic took in less fluids and her parents brought her to ER.
- BP 70/45 mm Hg, P130 /min, T 101, Cor-Chest -, Abd diffuse mild tender , increased BS, ext- no edema, + petechiae on legs.
- WBC 12.2K, Hct 28%, plts 52K, smear with schistocytes.
- BUN 45 mg/dl, creatinine 3.1 mg/dl.
- U/A 2+ prot. 3+ heme, +rbc TNTC, + rbc casts.

From the Centers for Disease Control and Prevention

Leads From the Morbidity and Mortality Weekly Report
Atlanta, Ga 3-3-93

Preliminary Report: Foodborne Outbreak of *Escherichia coli* O157:H7 Infections From Hamburgers—Western United States, 1993

THE GLOBE AND MAIL
SATURDAY, SEPTEMBER 16, 2006

Consumers warned not to eat fresh spinach imported from U.S.

BY MARTIN MITTELSTAEDT

Canadians shouldn't eat any fresh spinach imported from the United States until further notice, a precautionary step to avoid contracting E. coli contamination, says the Canadian Food Inspection Agency.

The agency issued the call yesterday afternoon, prompting grocery chains across the country to pull all U.S. spinach and any prepared salad containing the vegetable from U.S. sources off store shelves.

Companies supplying the restaurant trade with fresh salad ingredients have also stopped shipments.

The action was taken even though there have been no confirmed cases of E. coli poisoning in Canada from eating fresh spinach.

This is unlike in the United States, where a deadly E. coli outbreak believed to be associated with eating fresh spinach has caused one death and sickened at least 94 people.

Reports of illness are coming

Produce wholesaler Joseph Mercurio looks over bags of spinach

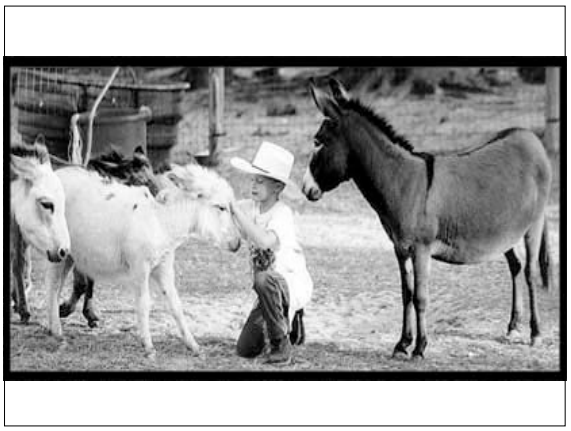
Sid Cardinal, a CFIA spokesman, who called the step a precaution, "Currently, there are no illnesses reported in Canada that are directly linked to this outbreak in the U.S.," he said.

At this time of year, Canadian grown spinach is also on the market and it is not affected by the advisory. Bags are supposed to carry a country of origin, allowing consumers to identify their source.

The effort to pull spinach from store shelves began at about 2:30 yesterday afternoon, when major grocery chains started removing the product, according to Justin Sherwood, a spokesman for the Canadian Council of Grocery Distributors, a trade group that represents most of the country's major supermarket chains, as well as companies that service the restaurant trade.

"Everyone feels it's better to be prudent," Mr. Sherwood said.

Eating food contaminated with



The New York Times

NEW YORK, SATURDAY, MARCH 26, 2005

Florida Officials Seek a Link in 15 Cases of a Kidney Illness

By DONALD G. McNEIL Jr.

Petting zoos may be the source of a disease cluster.

Childhood HUS

- STx Associated
- 2.1per 100,000 /yr peak < 5 yo
- Warm summer months
- Onset GI sx, cramps, diarrhea, n/v, fever
- 70% bloody diarrhea w/i 2 days
- E.coli 0157 3-7%sporadic, 20%epidemic
- STx – E coli in stool for wks

Role of Shiga Toxin

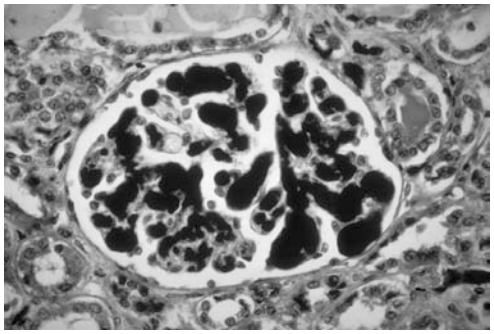
- Epidemics with hemorrhagic colitis +/- HUS
- Epidemics in fast food outlets
  E. coli 0157:H7
- Sporadic HUS same
- A filterable agent in stool causes Hem. Colitis & cytopathic to green monkey kidney cells (verotoxin)
- E. Coli 0157:H7 produce both STX1 and STX2

Transmission of E. Coli - STX

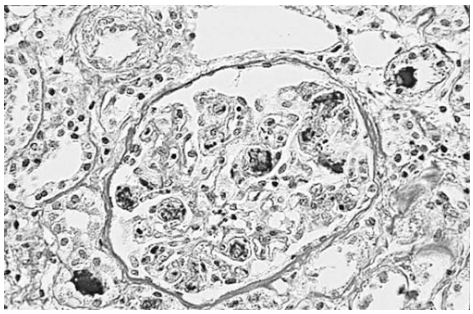
- E. coli in cattle (& other animals) – manure, water troughs, farms
- Transmit by food or water
- Usually beef contaminated at slaughter
- Also raw milk, fruit & veg, apple cider, apple juice
- Person to person – day care centers

Case 4: E.coli-associated HUS

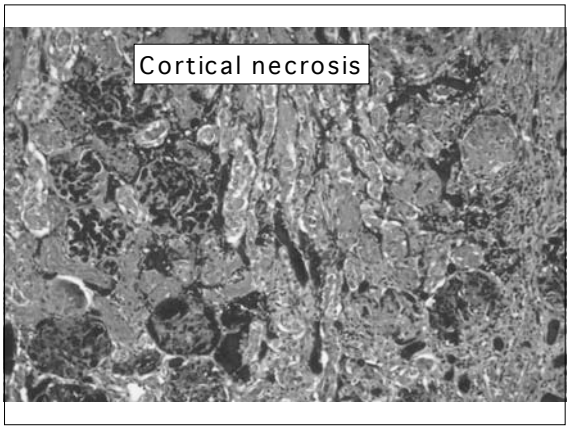
Pathologic findings

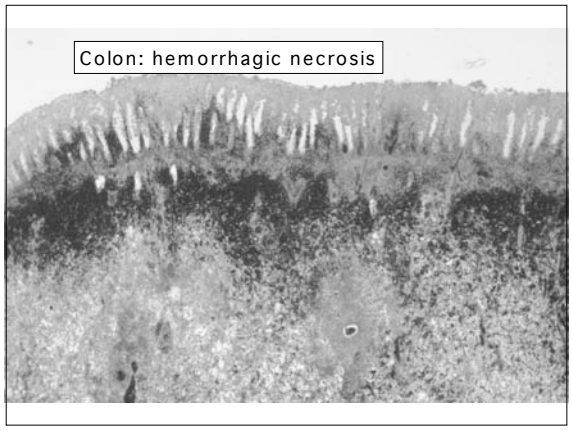


Fibrin thrombi in TMA



thrombi in glomerular capillaries





Shigatoxin-1 and Endothelium

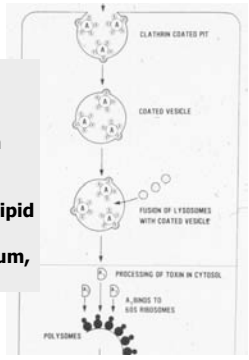
- Binds to Gb3 on glomerular endothelium
- Gb3 expression equal in children vs. adults
- Mechanism for childhood susceptibility remains undetermined

Ergonul, Clayton, Fogo, Kohan, 2003

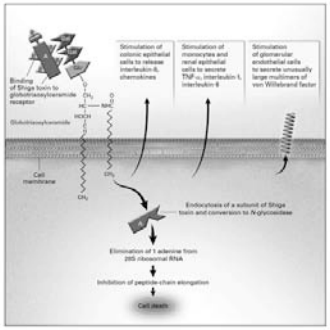
Verotoxin

•A subunit binds 60S Ribosomes, inhibit protein synthesis

•5 B subunits binds glycolipid receptors (gb3) on surface of colonic epithelium, endothelium, and WBCs



Shiga Toxin and Cell Injury



Moake, NEJM 2002

Higher Risk HUS

- Antibiotics
- Bloody diarrhea
- Fever, vomiting
- Leukocytosis
- < 5 yo
- females

Course ARF Childhood HUS

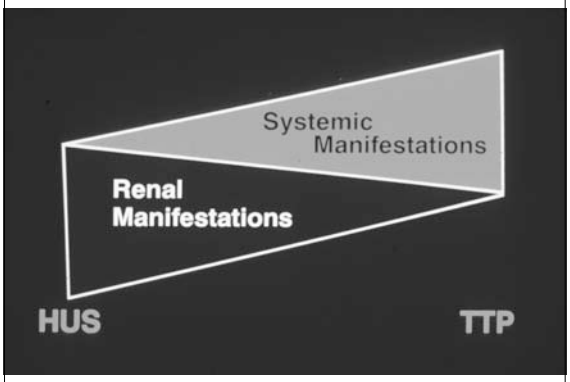
- 50% dialysis
- 75% transfusions
- 25% Neuro sx (CVA, sz, coma)
- 3-5% die in acute phase
- Long term renal dysfunction common

Residual Renal Disease in Childhood HUS

- 3-18% ESRD
- 10-40% low GFR, proteinuria, CRF, HBP
- Duration anuria predicts dysfunction

  7.5 % anuria < 10 days low GFR

  42.5% anuria > 16 days low GFR



Thrombotic thrombocytopenic purpura (TTP)

- Familial or acquired
- Single episode, or relapsing
- F:M 3: 2
- Peak in 3rd decade
- CNS, other extrarenal signs often predominate (e.g. fever; purpura; heart failure; lung edema; elevated LDH)
- Acute renal failure; microangiopathic hemolytic anemia; thrombocytopenia

ADAMTS 13

A disintegrin and metalloprotease, with TSP-1-like domains

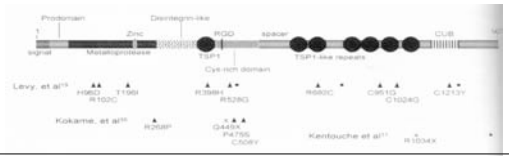
(aka vWF-clearing protease)

Protease, normally degrades vWF multimers

Deficiency →

platelets GPIbα ↔ vWF multimers

Mutations or autoAb



Criteria for Inclusion of TTP Cases

Presence of thrombocytopenia & microangiopathic hemolysis

No plausible causes

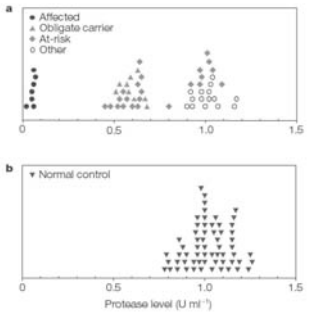
No features suggestive of typical or atypical HUS

Age > 10 yr

127 Cases in 4 yrs – All severe ADAMTS 13 deficient

Tsai H-M. JASN 14: 1072-1081, 2003.

ADAMTS and TTP



Levy et al, Nature 2002

ADAMTS13

- A disintegrin and metalloprotease, with TSP-1-like domains
  (aka vWF-clearing protease)
- Protease, normally degrades vWF multimers
- Deficiency →
  platelets GPIbα ↔ vWF multimers
- Mutations or autoAb