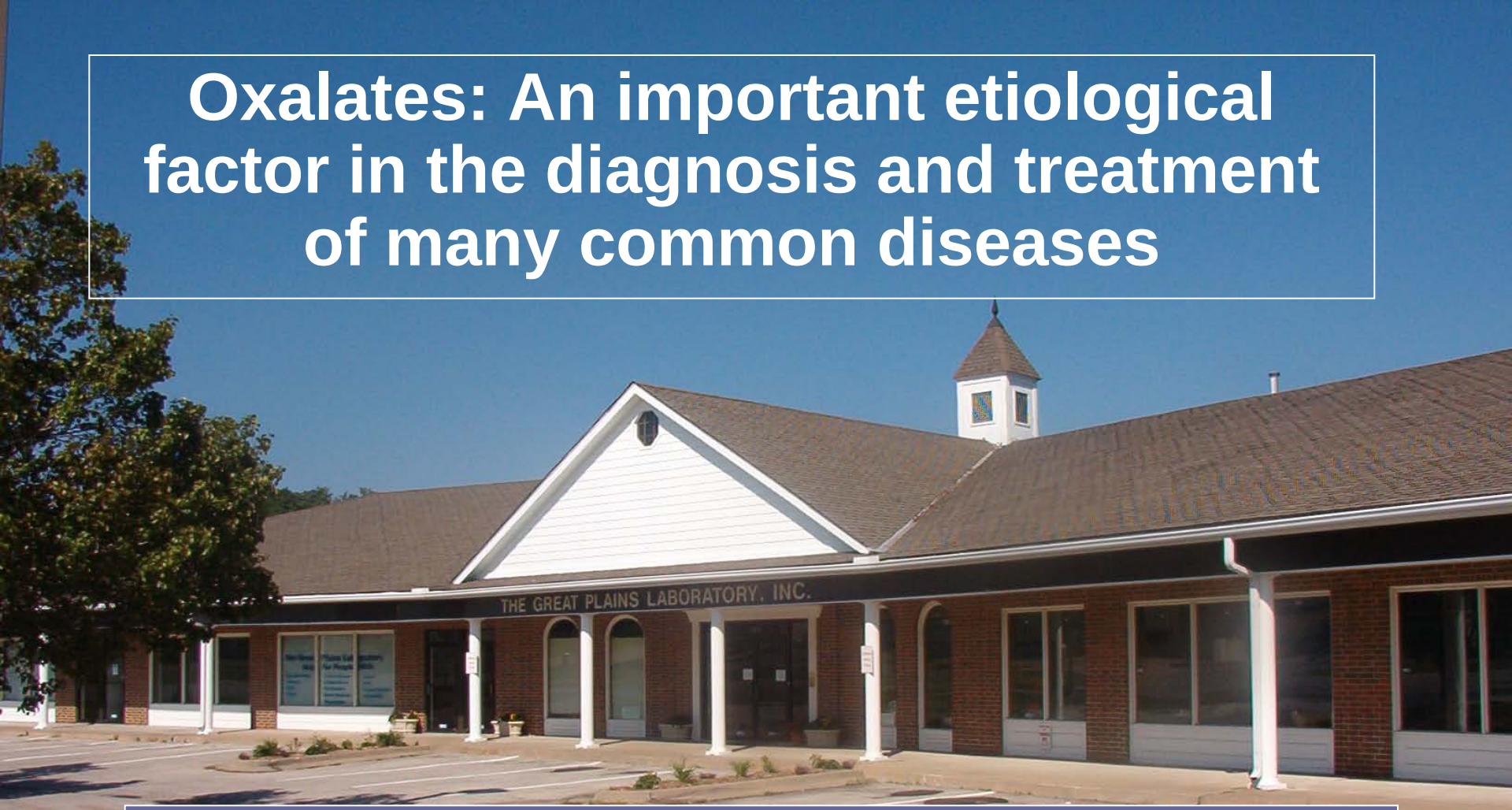
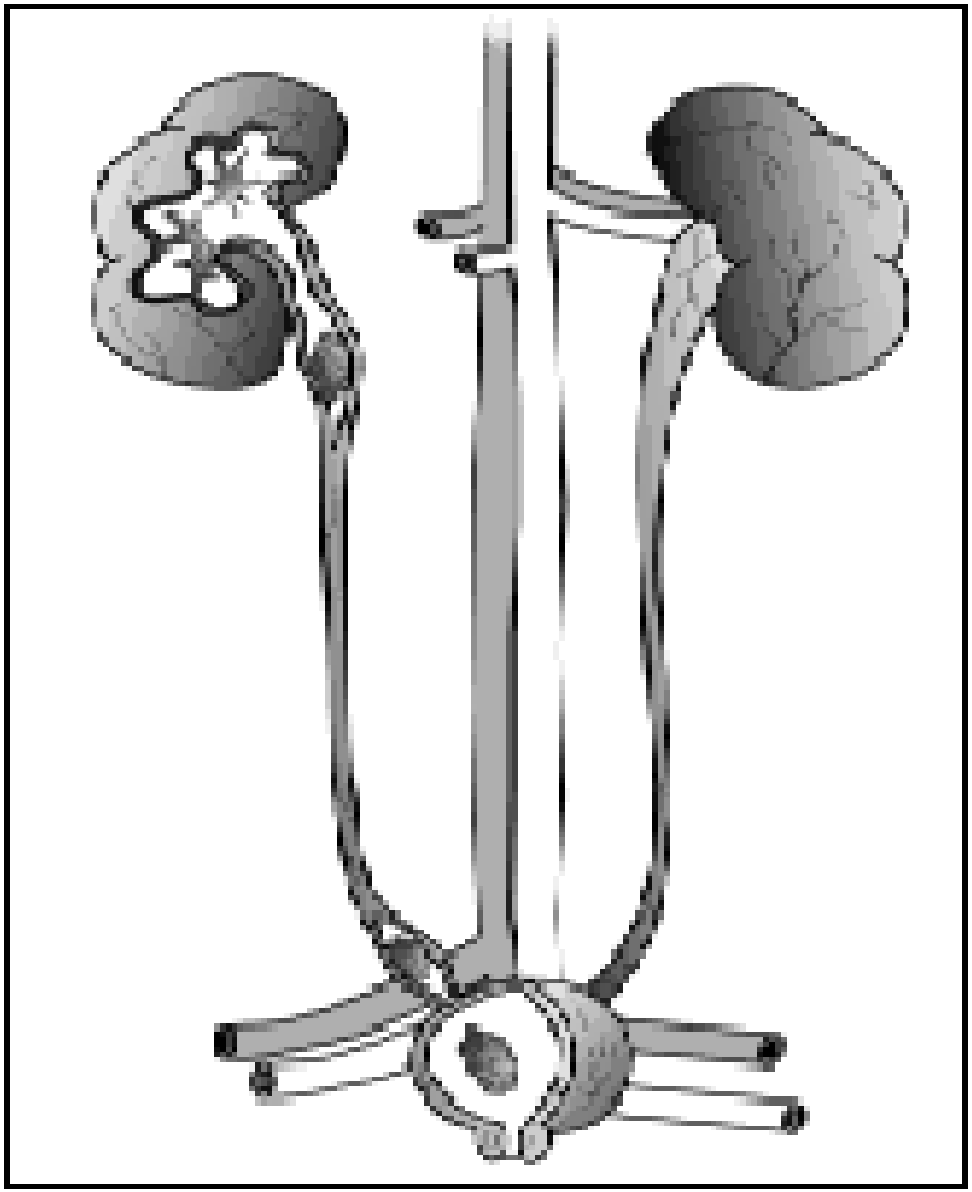
Oxalates: An important etiological factor in the diagnosis and treatment of many common diseases



William Shaw Ph.D.
The Great Plains Laboratory, Inc.
913 341-8949

Oxalate stone from mummy 800 AD

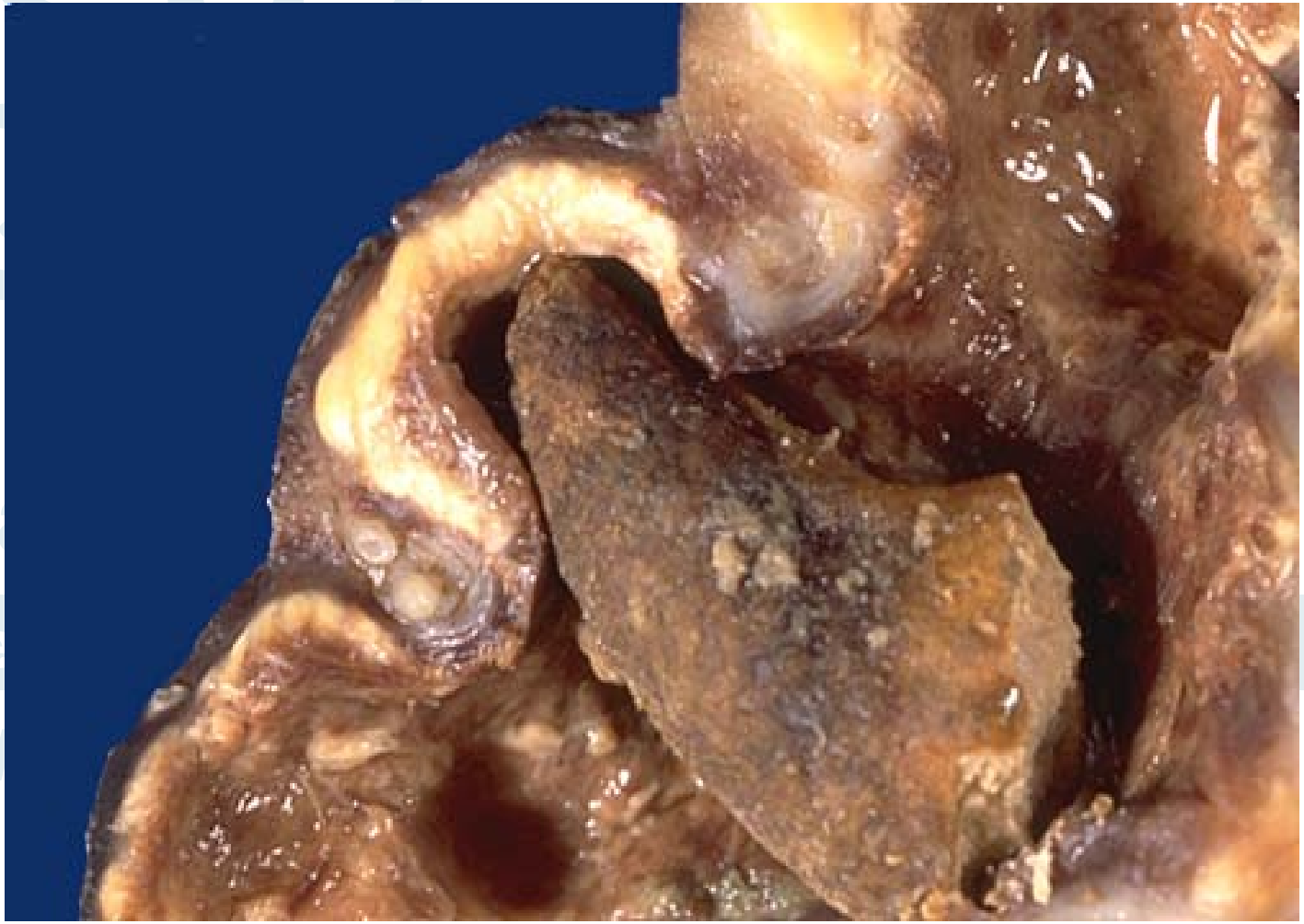


Oxalate staghorn in kidney x-ray

Size of oxalate crystals

Normal kidney

Staghorn oxalate crystal in kidney



Black oxalate crystals

Oxalates and kidney stones (mercola.com)

- 10-15 percent of adults will be diagnosed with a kidney stone in their lifetime.
- 1 million Americans develop kidney stones each year.
- Once you have had one kidney stone attack, your chance of recurrence is about 70 to 80 percent
- 75-90% of kidney stones are oxalatesPain in your side and back, below your ribs
- Episodes of pain lasting 20 to 60 minutes, of varying intensity

Oxalates and kidney stones (mercola.com)

- Pain “waves” radiating from your side and back, to your lower abdomen and groin
- Bloody, cloudy or foul-smelling urine
- Pain with urinationNausea and vomiting
- “Urgency” (persistent urge to urinate)
- Fever and chills (indicates an infection is also present)

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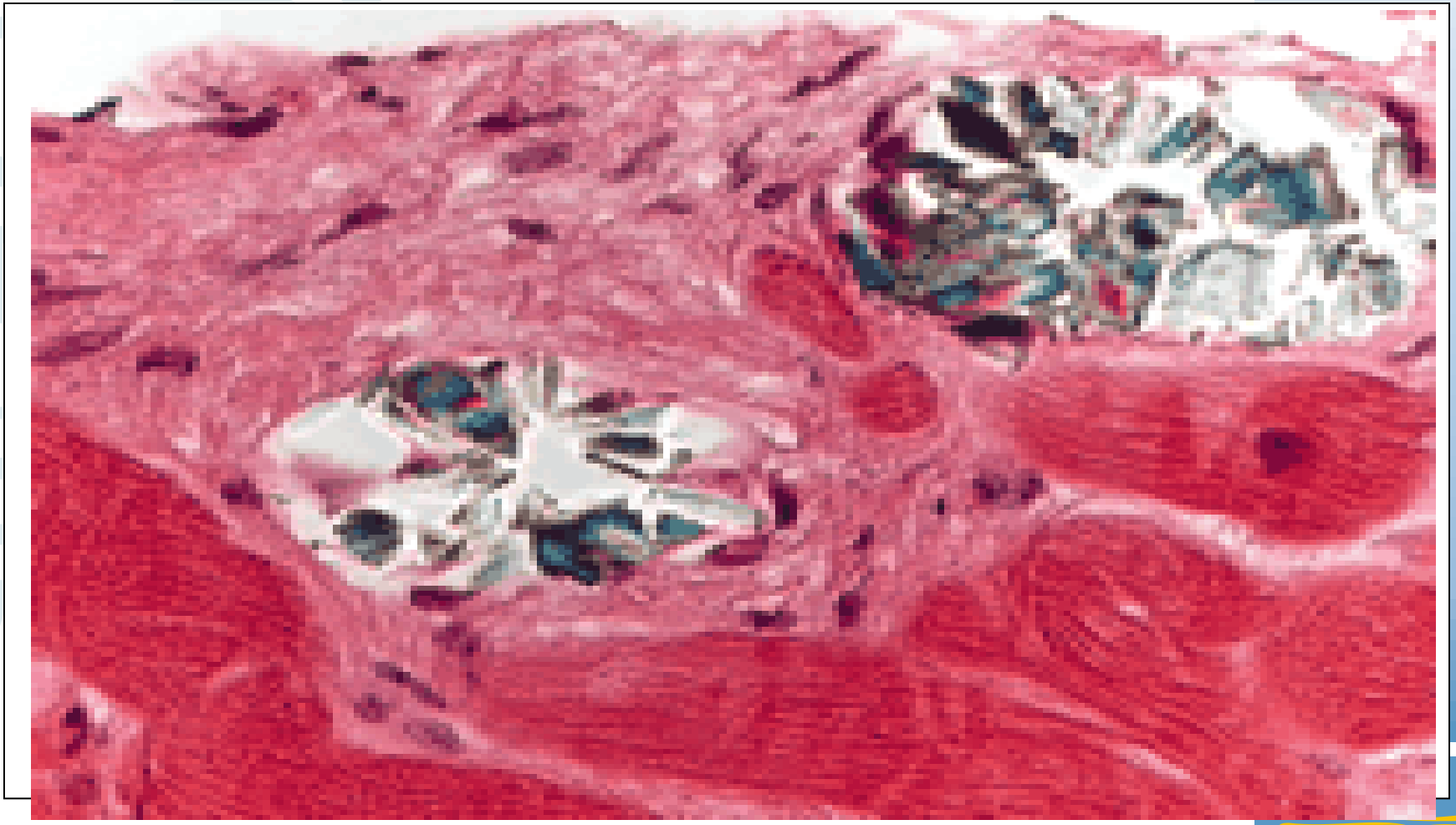
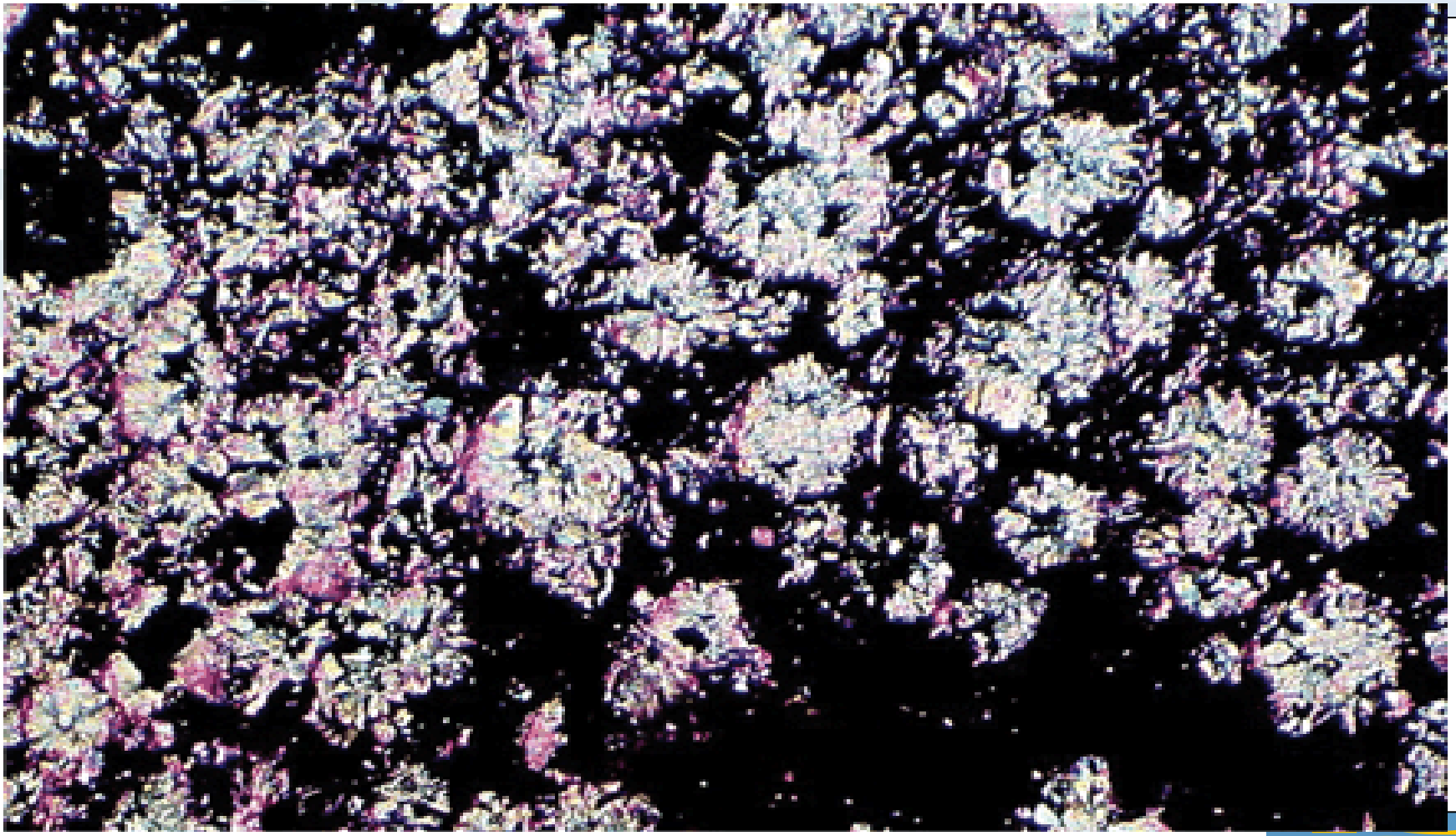
Oxalate crystals in the heart



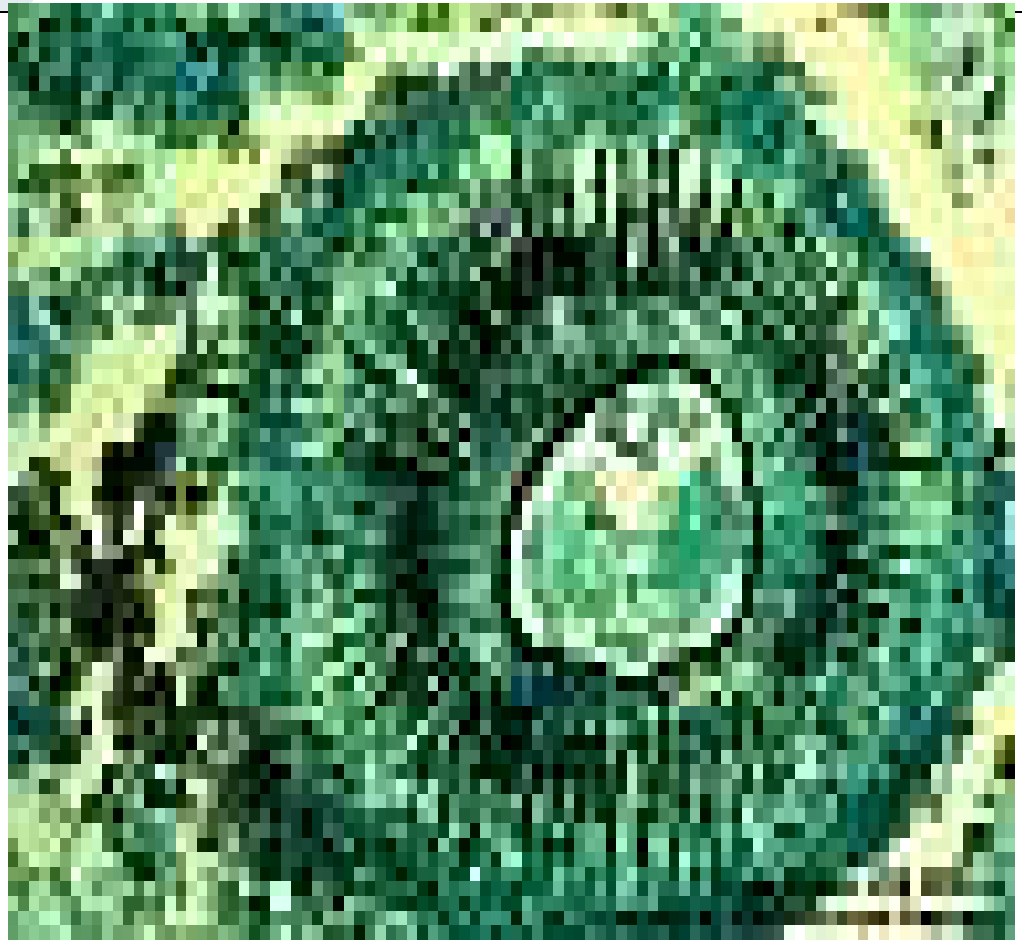
Oxalate crystals in bone



Oxalate crystals in brain

Fig. 3 *Crystals in brain* × *350.*

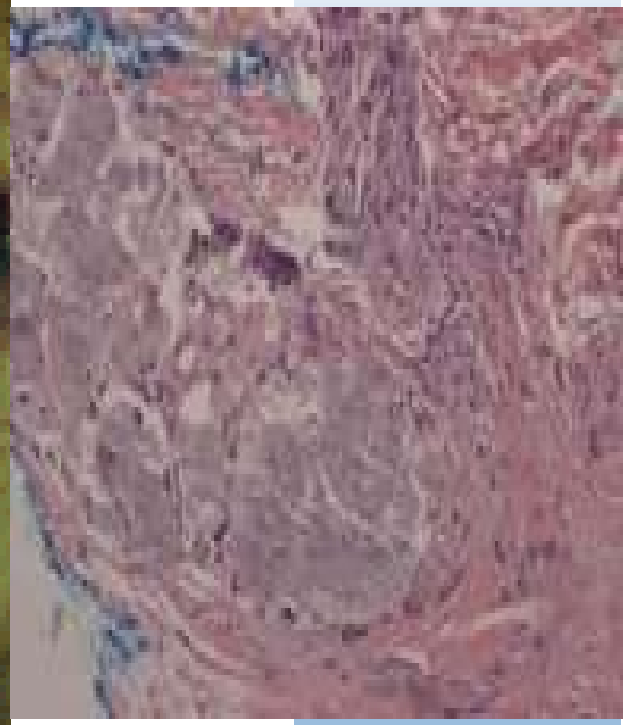
Oxalate crystals in Aspergillus



Oxalate deposits from fungus on tree

Oxalate crystals in skin

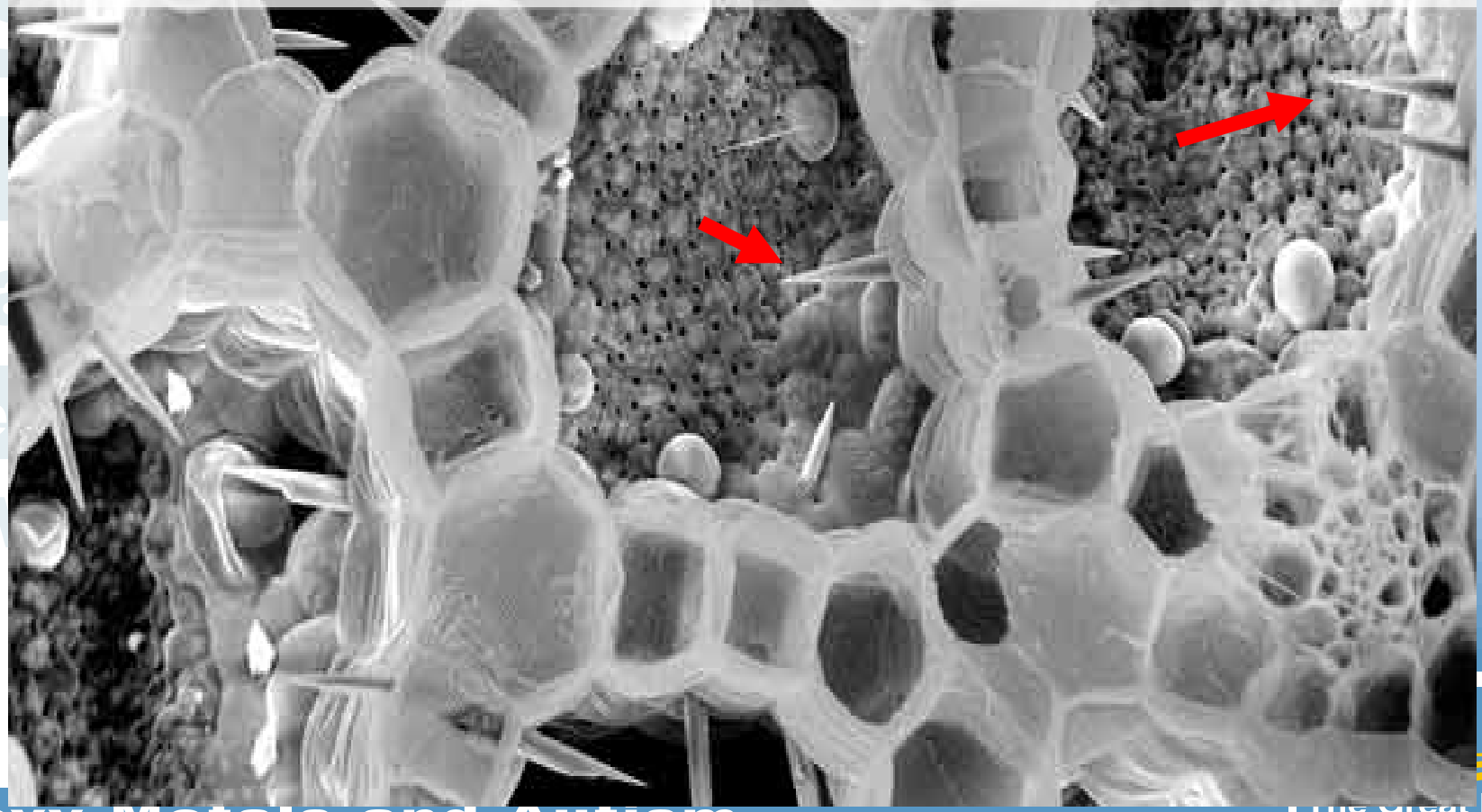
Oxalates in skin of leg



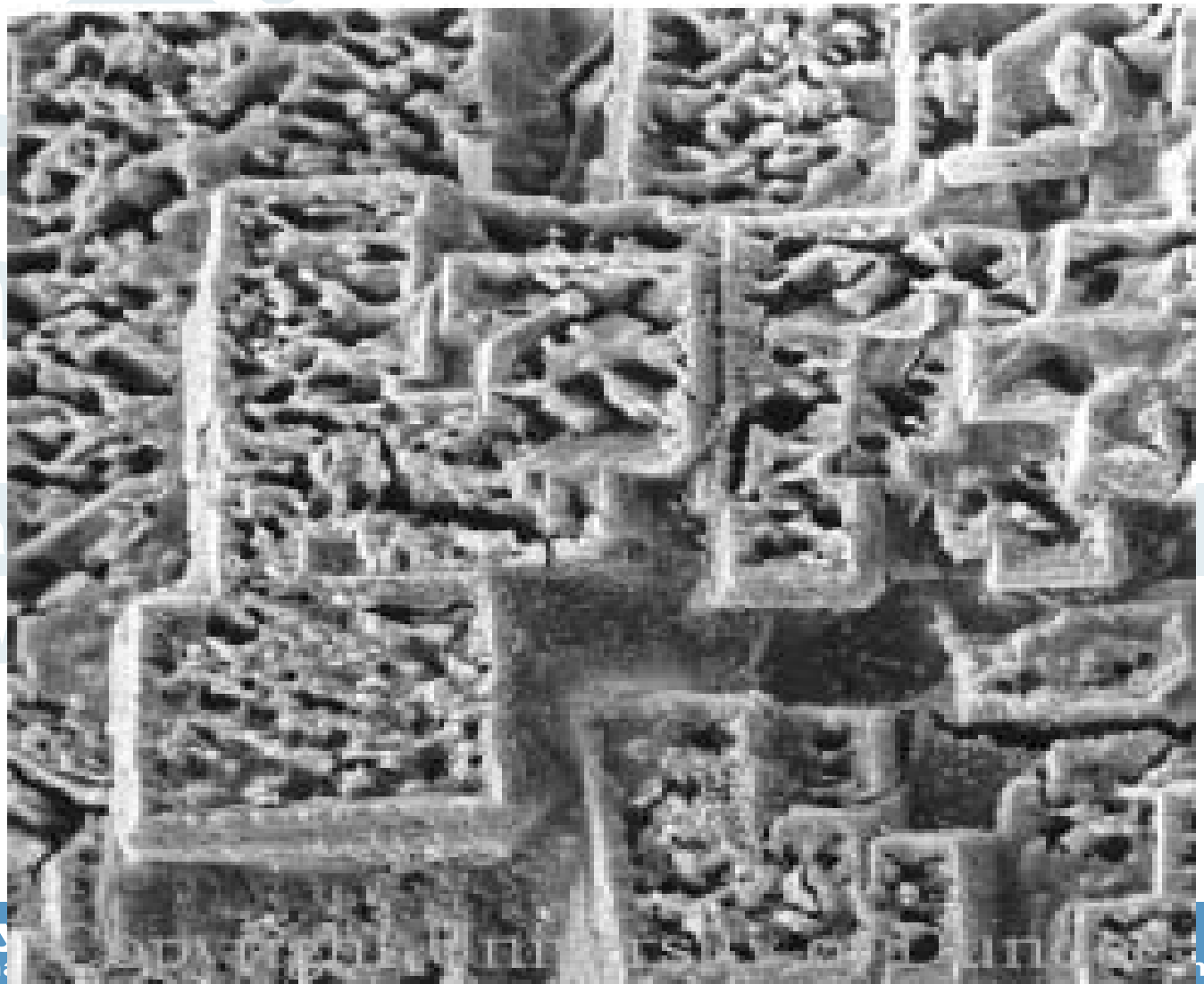
Oxalates from water hyacinths

Hidden in tiny airspaces within the petioles, or tiny stems of leaves, on an *Eichhornia crassipes* (water hyacinth) plant are these styloids, one of the more fearsome-looking shapes of calcium oxalate crystals in plants.

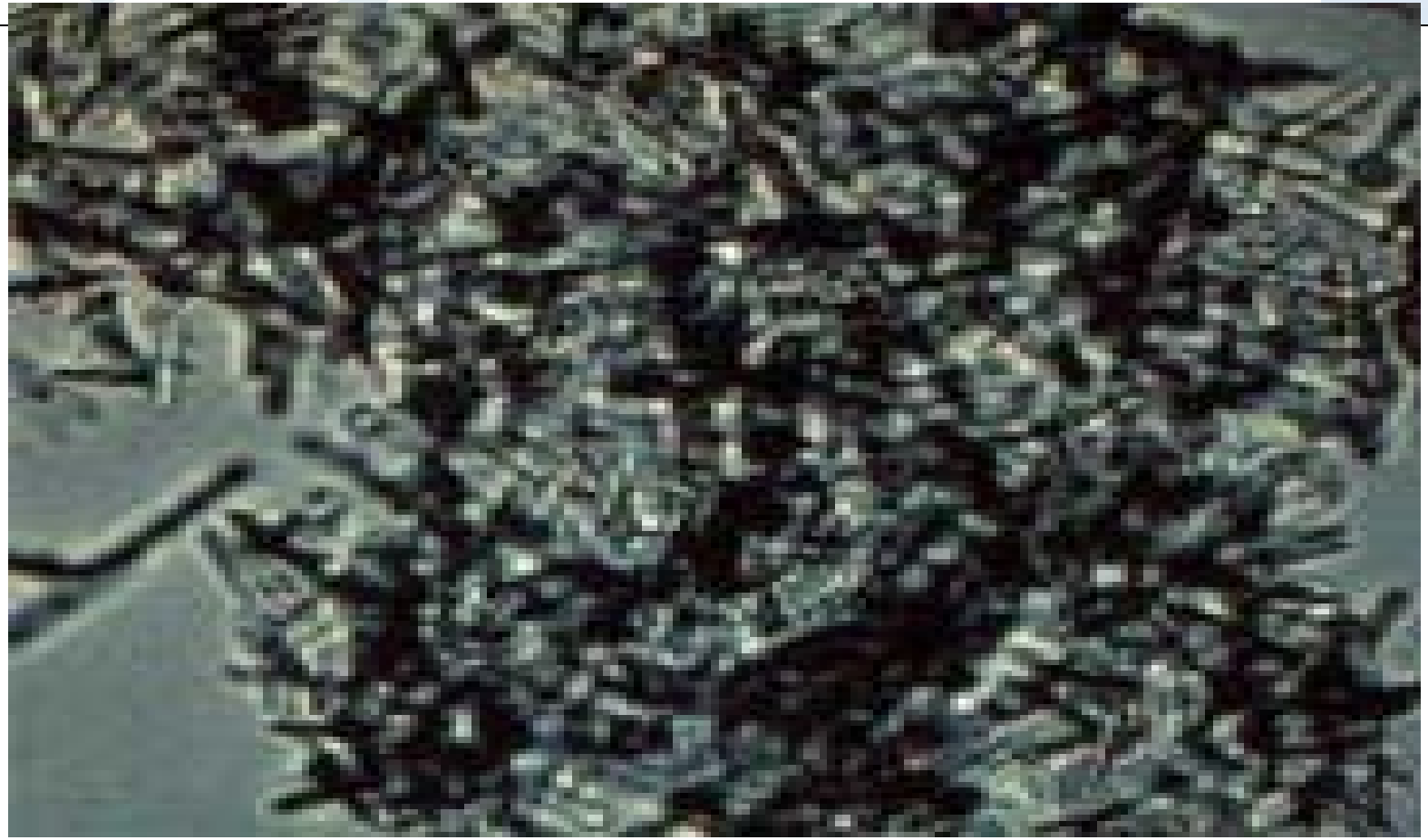
SCANNING ELECTRON MICROGRAPH BY HARRY T. (JACK) HORNER



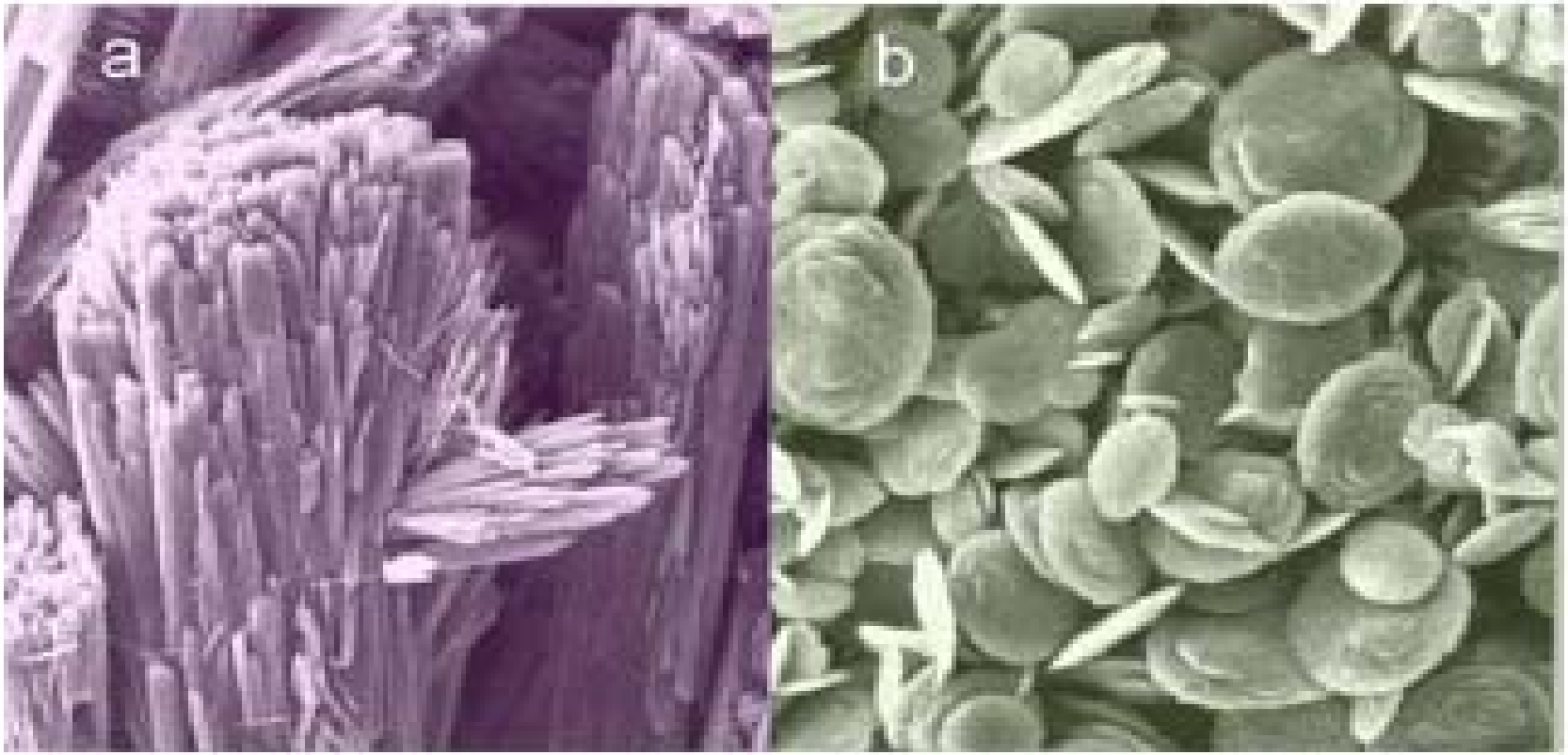
Cobalt oxalate crystals from Aspergillus



Oxalate monohydrate



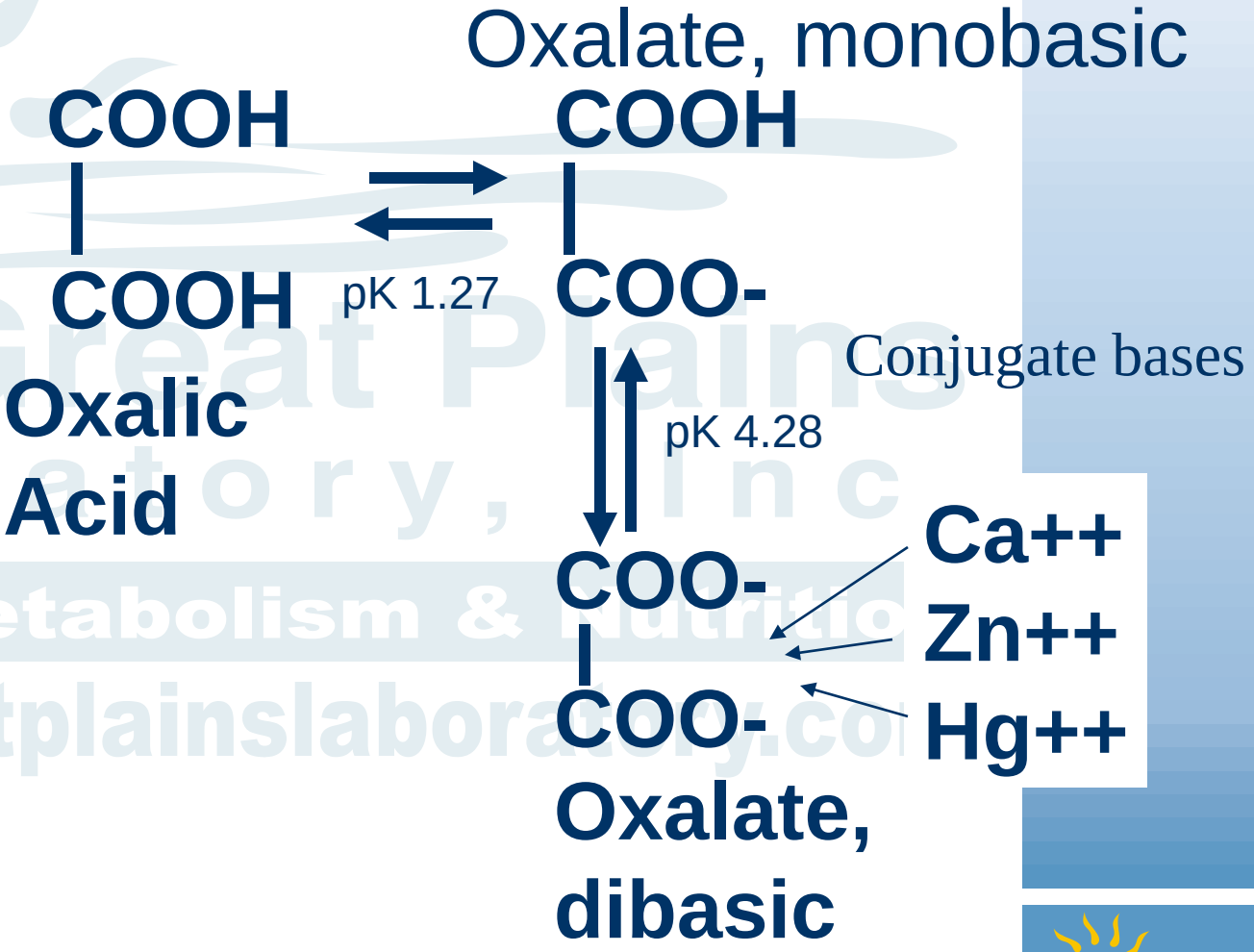
Oxalate metal complexes from Aspergillus



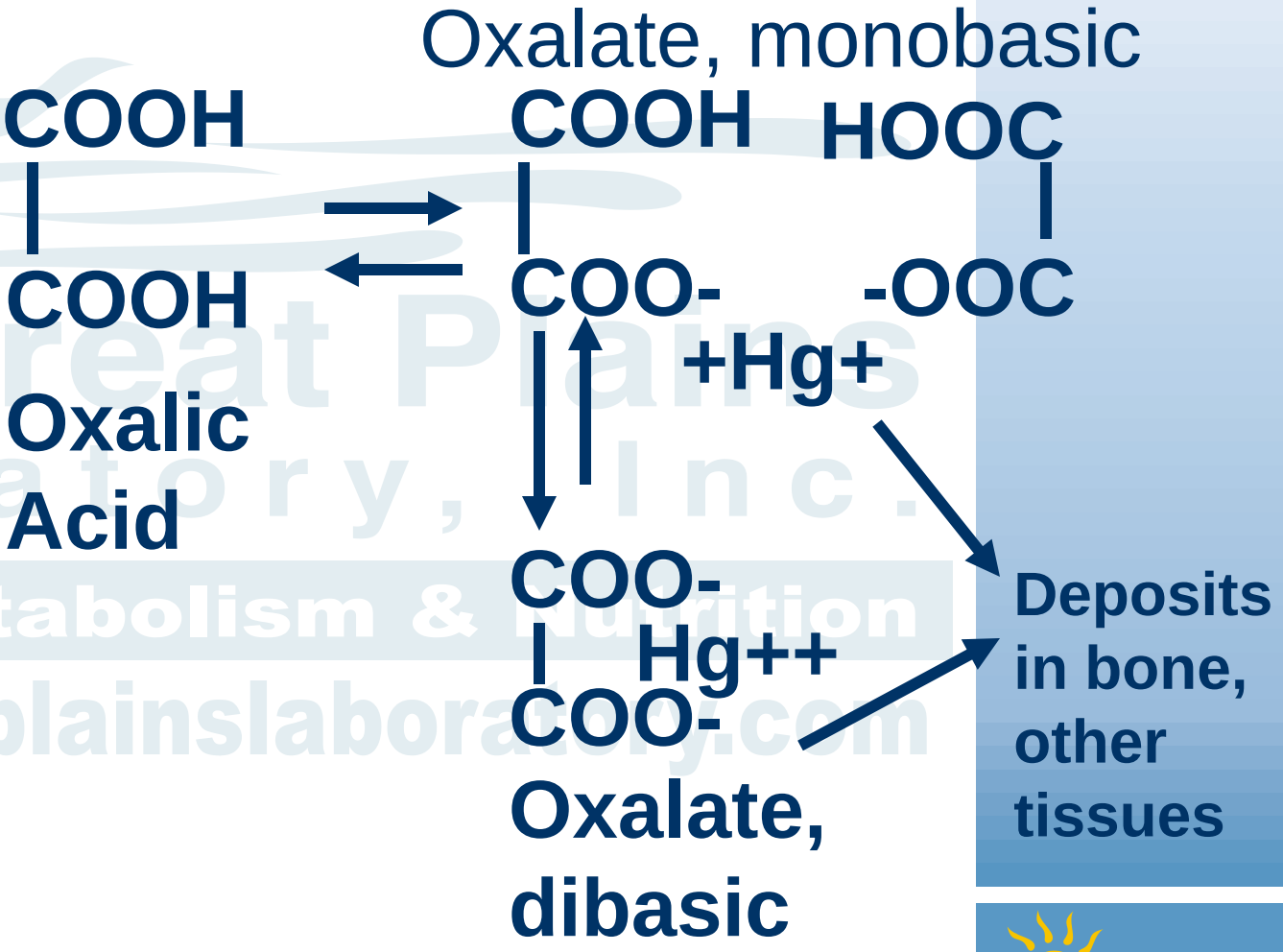
Scanning electron micrographs of crystals of (a) cobalt oxalate and (b) zinc oxalate produced by the soil fungus Aspergillus niger *during the solubilization of*

Oxalate crystals in tree fungus

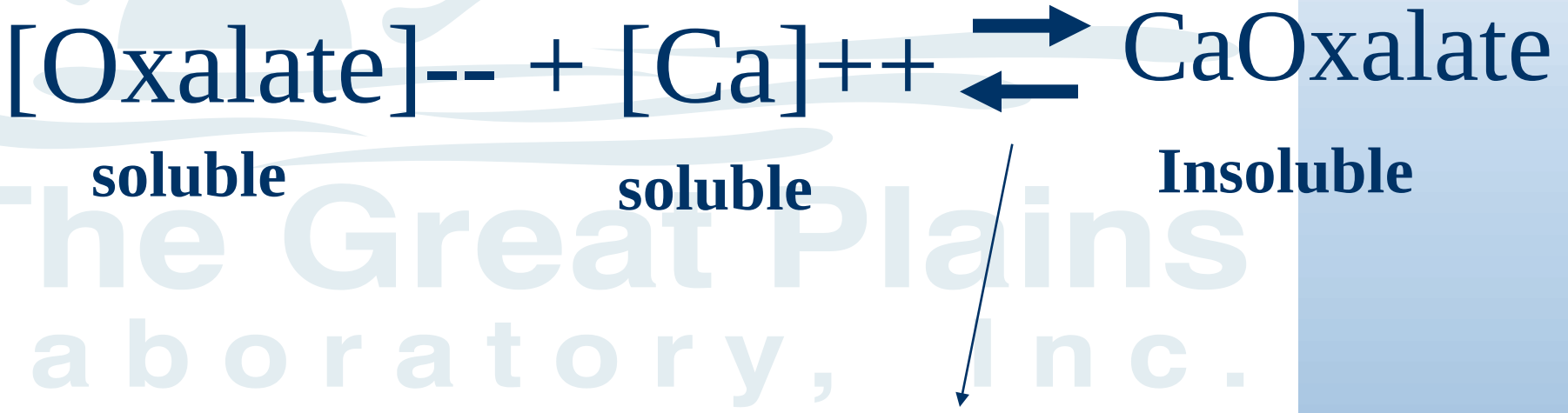
Oxalate interconversions



Oxalate chelates mercury



Solubility problems with oxalates



Solubility is major factor that determines oxalate and heavy metal toxicity

Salt	Ksp (solubility product constant)
Mercury I	1.75 X 10-13
Lead	8.6 X 10-10
Copper II	4.4 X 10-10
Zinc	1.4 X 10-9
Cadmium	1.42 X 10-8
Calcium	1.5 X 10-8
Magnesium	8.5 X 10-5

Improvements noted in autism according to Susan Owens

- Loss of numerous GI symptoms: diarrhea, etc
- Loss of urinary tract problems: frequent urination
- Improved cognitive, academic, and motor skills
- Loss of pain in legs, feet, urinary tract, genitals
- Reduction in abnormal behavior and self abuse

Vulvodynia

- It is a syndrome of unexplained vulvar pain, frequently accompanied by physical disabilities, limitation of daily activities, sexual dysfunction and psychological distress.
- The patient's vulvar pain usually has an acute onset and, in most cases, becomes a chronic problem lasting months to years.
- The pain is often described as burning or stinging, or a feeling of rawness or irritation.

Vulvodynia JULIUS F. METTS, M.D. Ref:Vulvodynia and Vulvar Vestibulitis: Challenges in Diagnosis and Management. March 15, 1999 - American Academy of Family Physicians

- Cyclic vulvovaginitis is believed to be a reaction to yeast, which may be detected at times and not detected at other times with KOH preparation or fungal cultures.
- Because of the link with Candida, treatment for cyclic vulvovaginitis may include anticandidal medication even if cultures are not positive.
- Other treatments that have been helpful in patients with vulvodynia are a low-oxalate diet and, in some cases, the addition of oral calcium citrate (Citracal), two tablets (200 mg/950 mg each) orally three times a day to neutralize oxalates in the urine.

Evaluation of antifungal therapy for chronic fatigue and fibromyalgia

- **Teitelbaum: Improvement in 14 of 21 with yeast**
- **Eaton in England: Fermentation of sugar to alcohol was treated in 42% of patients by sugar restriction.**
- **78 % of patients controlled yeast by antifungal drugs and sugar restriction.**
- **Jessop- 84% of 1100 patients had clearing of symptoms after the antifungal ketoconazole--only 12 of 685 on disability stayed on disability**

Predictive Factors of Oxaliplatin Neurotoxicity: The Involvement of the Oxalate Outcome Pathway
L. Gamelin, et al Clin Cancer Res 2007;13:6359-6368

- Oxaliplatin displays a frequent dose-limiting neurotoxicity due to its interference with sodium channels through its metabolite, oxalate, a calcium chelator.
- In 10 patients, urinary excretions of oxalate and cations increased significantly within hours following oxaliplatin infusion, accompanied by increased excretions of glycine, alanine, serine, and taurine linked to oxalate

Predictive Factors of Oxaliplatin Neurotoxicity: The Involvement of the Oxalate Outcome Pathway
L. Gamelin,et al Clin Cancer Res 2007;13:6359-6368

- In a further 135 patients, a minor haplotype of AGXT (alanine glyoxylate amino transferase) was found significantly predictive of both acute and chronic neurotoxicity.
- When treatment with oxaliplatin is continued, a persistent sensory peripheral neuropathy can develop, causing superficial and deep sensory loss,sensory ataxia, and functional impairment.
- Effect on sensory neurons and muscle cells has not previously been described with other platinum agents

Mol Genet Metab. 2006 Aug;88(4):346-50. High incidence of hyperoxaluria in generalized peroxisomal disorders. Van Woerden CS, et al

- The Zellweger syndrome is characterized by a generalized loss of peroxisomal functions caused by deficient peroxisomal assembly.
- Hyperoxaluria was present in 19/23 patients with Zellweger syndrome (83%).
- The presence of hyperoxaluria was statistically significant correlated with the severity of neurological dysfunction.

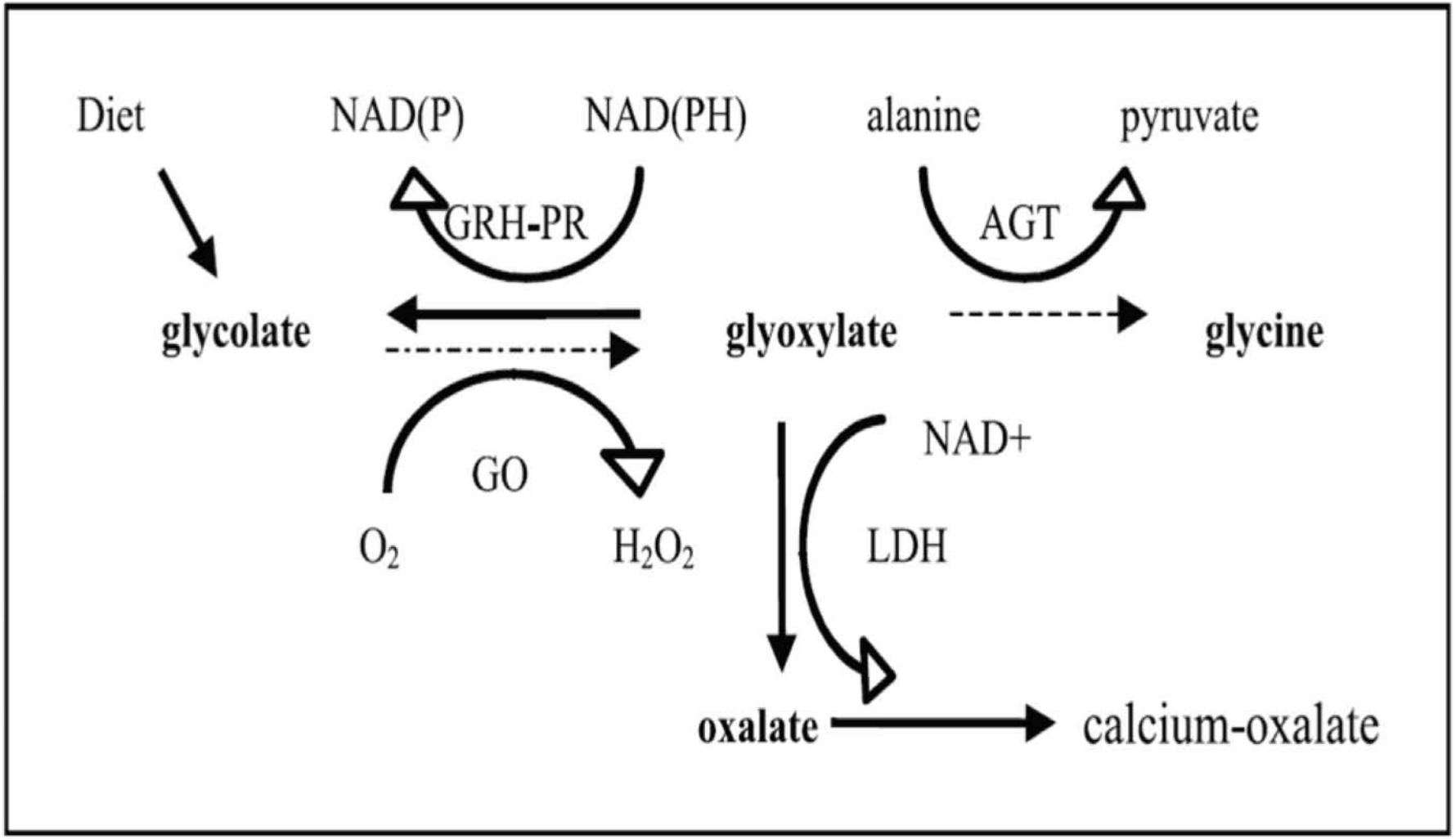


Fig. 1. The metabolism of oxalate and glyoxylate. The implications of enzymes and links with certain amino acids. GO, glycolate oxydase (EC 1.1.3.15); LDH, lactate dehydrogenase. Solid arrows, cytosol; dashed arrows, peroxisome.

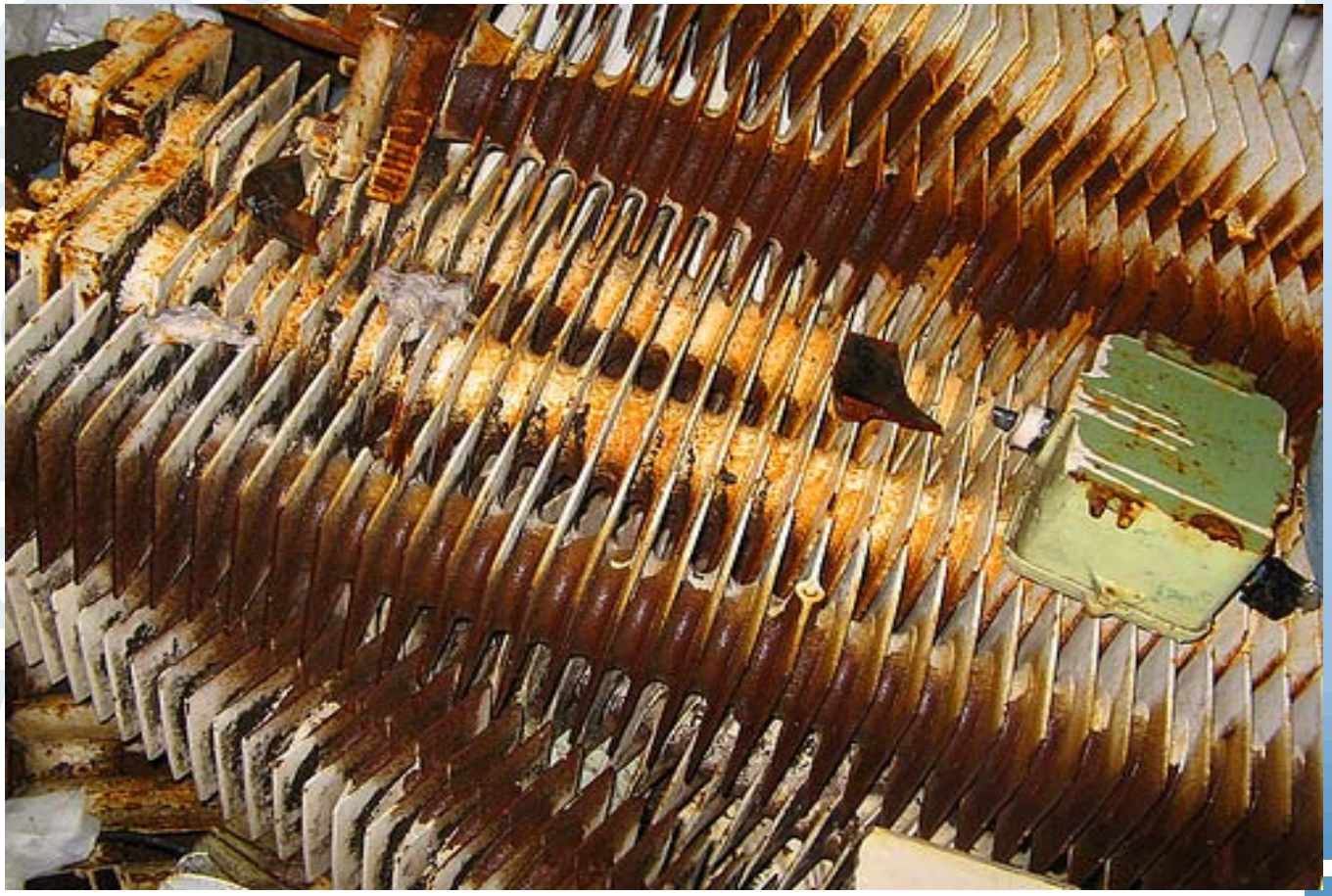
Predictive Factors of Oxaliplatin Neurotoxicity: The Involvement of the Oxalate Outcome Pathway
L. Gamelin,et al Clin Cancer Res 2007;13:6359-6368

- 32% of patients presented minor haplotype of AGXT, with 4.7% being homozygotes.
- Variant 154C>T (Pro11Leu) located on exon 1 plays a major role in the reduction of AGXT activity, being 30% less than baseline due to a location error of the enzyme in mitochondria rather than in the peroxisomes .
- Patients with the minor allele AGXT haplotype were at significantly higher risk of acute neurotoxicity, 53.4% versus 4.3%, despite calcium and magnesium infusions.

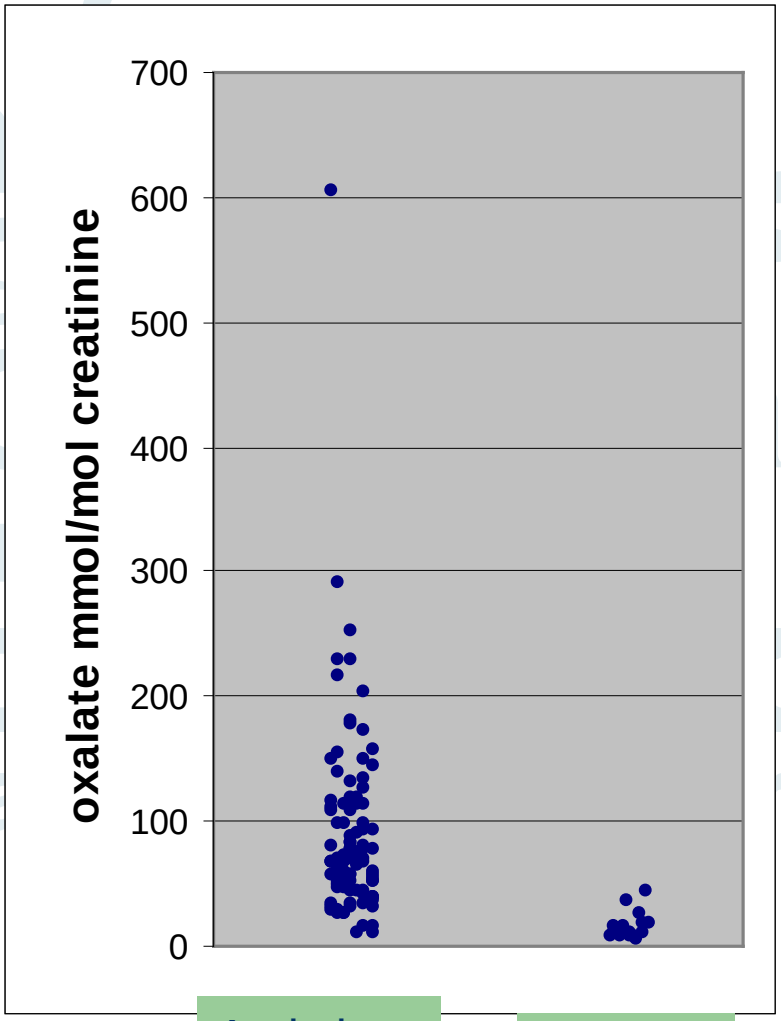
Other diseases in which oxalates may play a role

- Arthritis
- Joint pain
- Interstitial cystitis
- Vegetarianism
- Osteoporosis
- Heart disease
- Heavy metal toxicity
- Thyroid disease

Oxalic acid used to clean rusty radiator



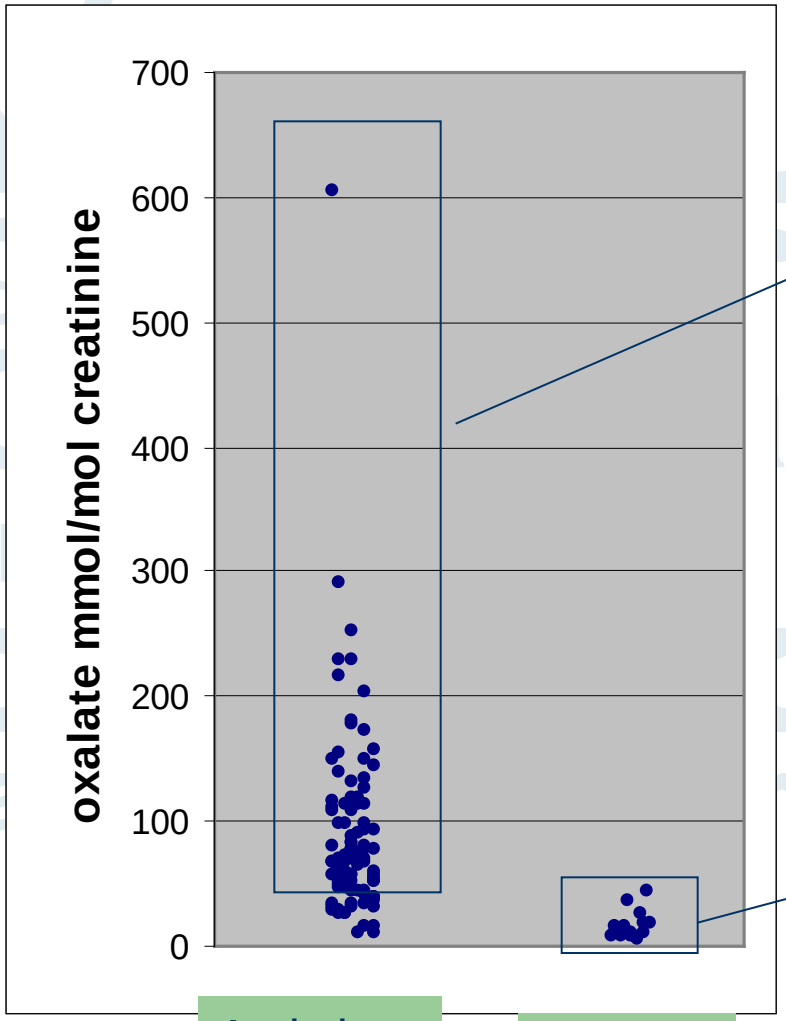
Comparison of urine oxalate in autistic spectrum and normal children



t-test

$p < 10^{-16}$

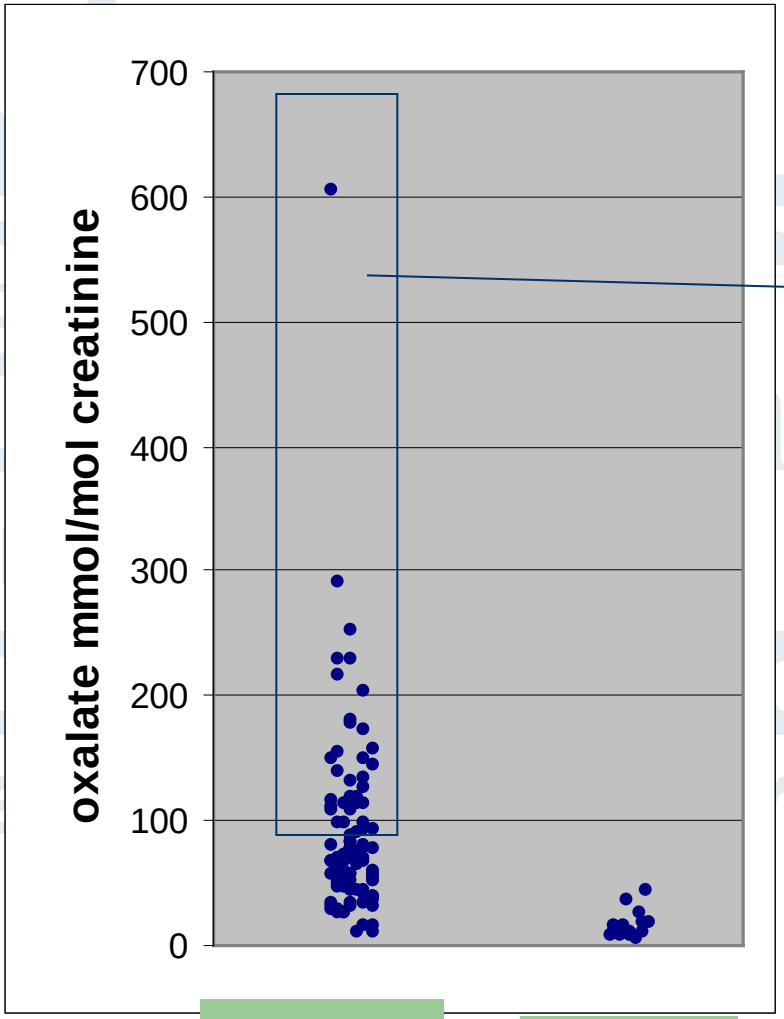
Comparison of urine oxalate in autistic spectrum and normal children



84% of individuals with autism are outside the normal range
Mean 2 sd

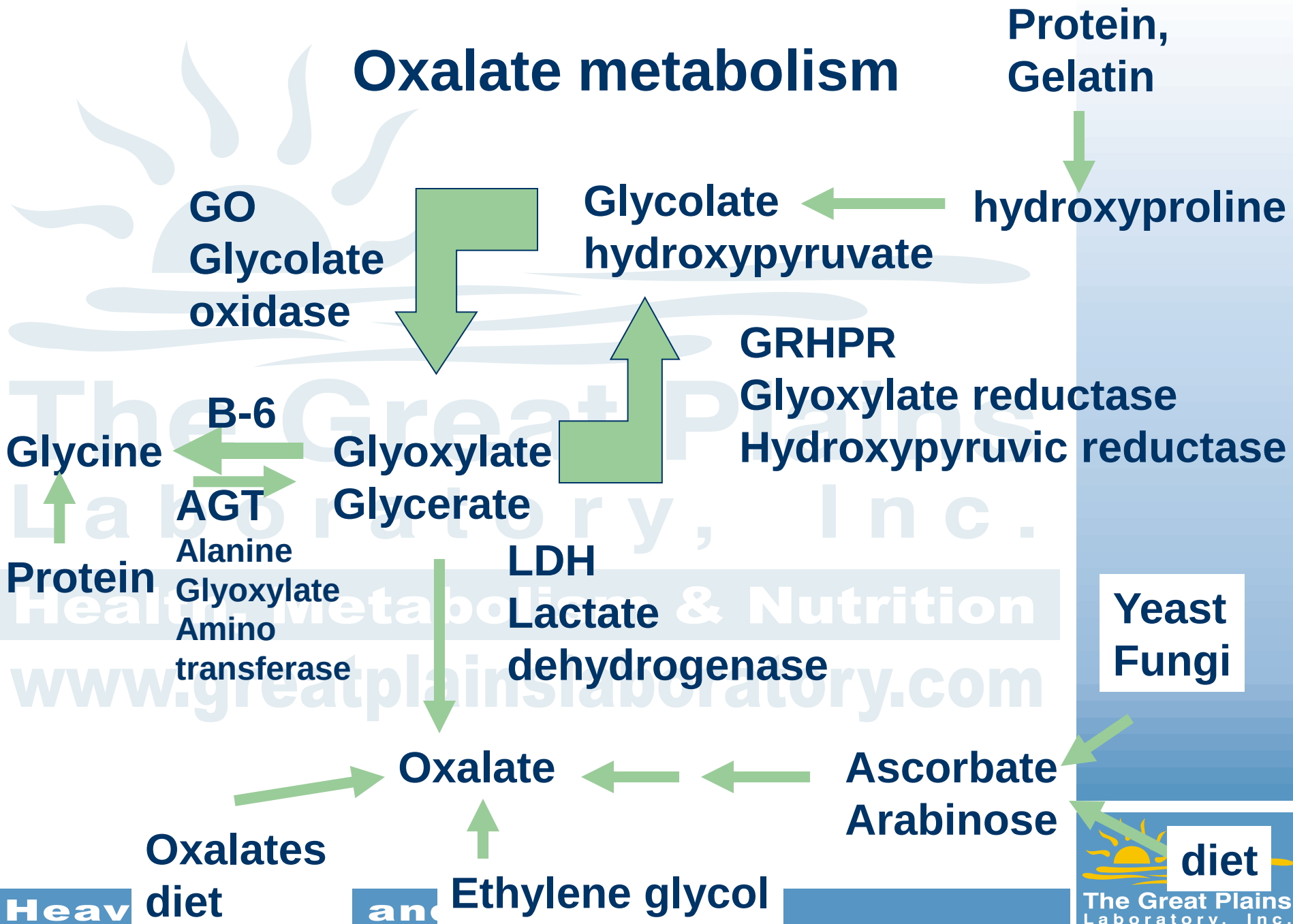
Normal range 0-36 mmol/mol creatinine

Comparison of urine oxalate in autistic spectrum and normal children



Range of oxalates in genetic diseases of oxalate-36% of people with autism in this range

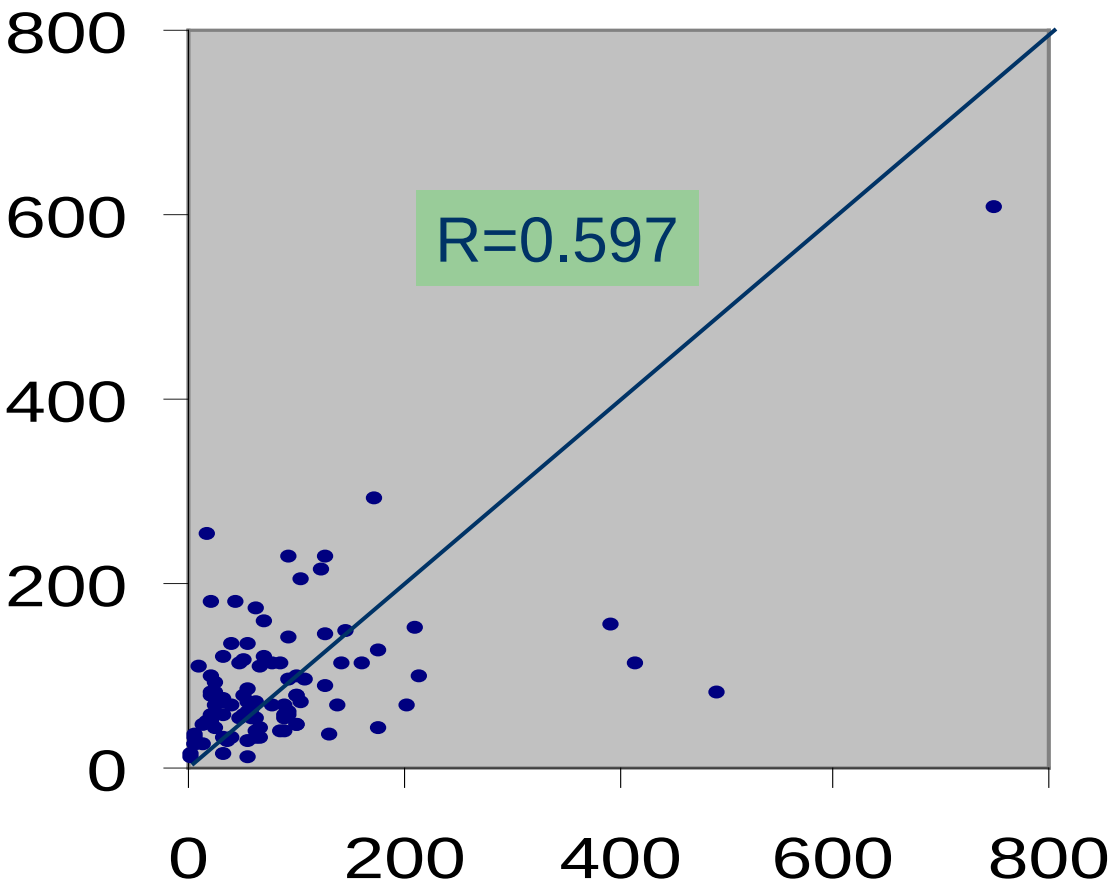
Oxalate metabolism



Primary Hyperoxalurias
Ref: Metabolic Basis of Inherited Disease

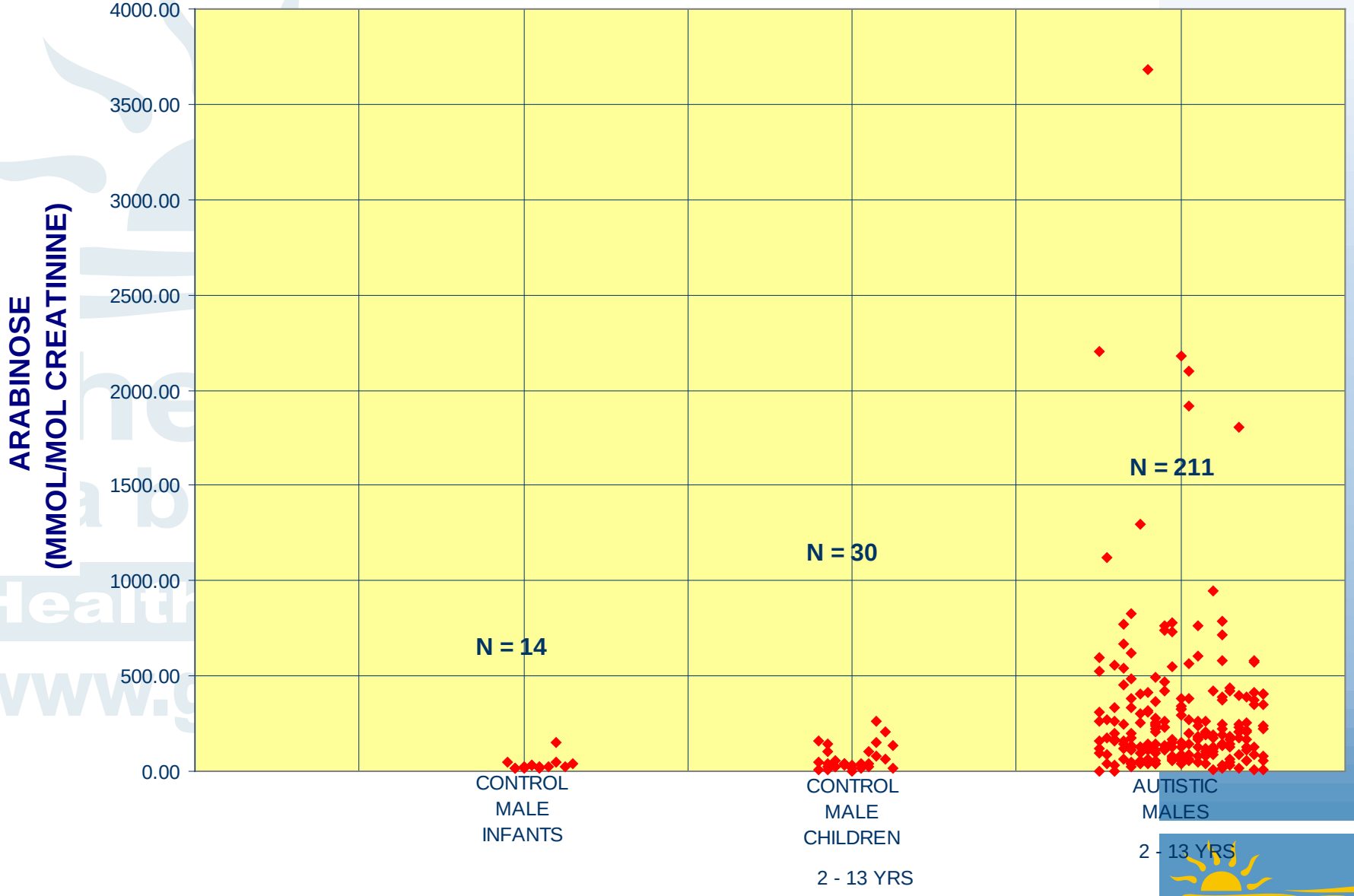
- Frequently fatal diseases that require combined liver and kidney transplants
- Considerable number of failures because oxalates deposits are considerable and cause severe damage for many years after transplants.
- 10% cases diagnosed <1 yr age
- Most cases 5-40 years
- 80% of diagnosed patients die before age of 20 yrs
- May be misdiagnosed as gout or arthritis

Correlation between urine arabinose and oxalate

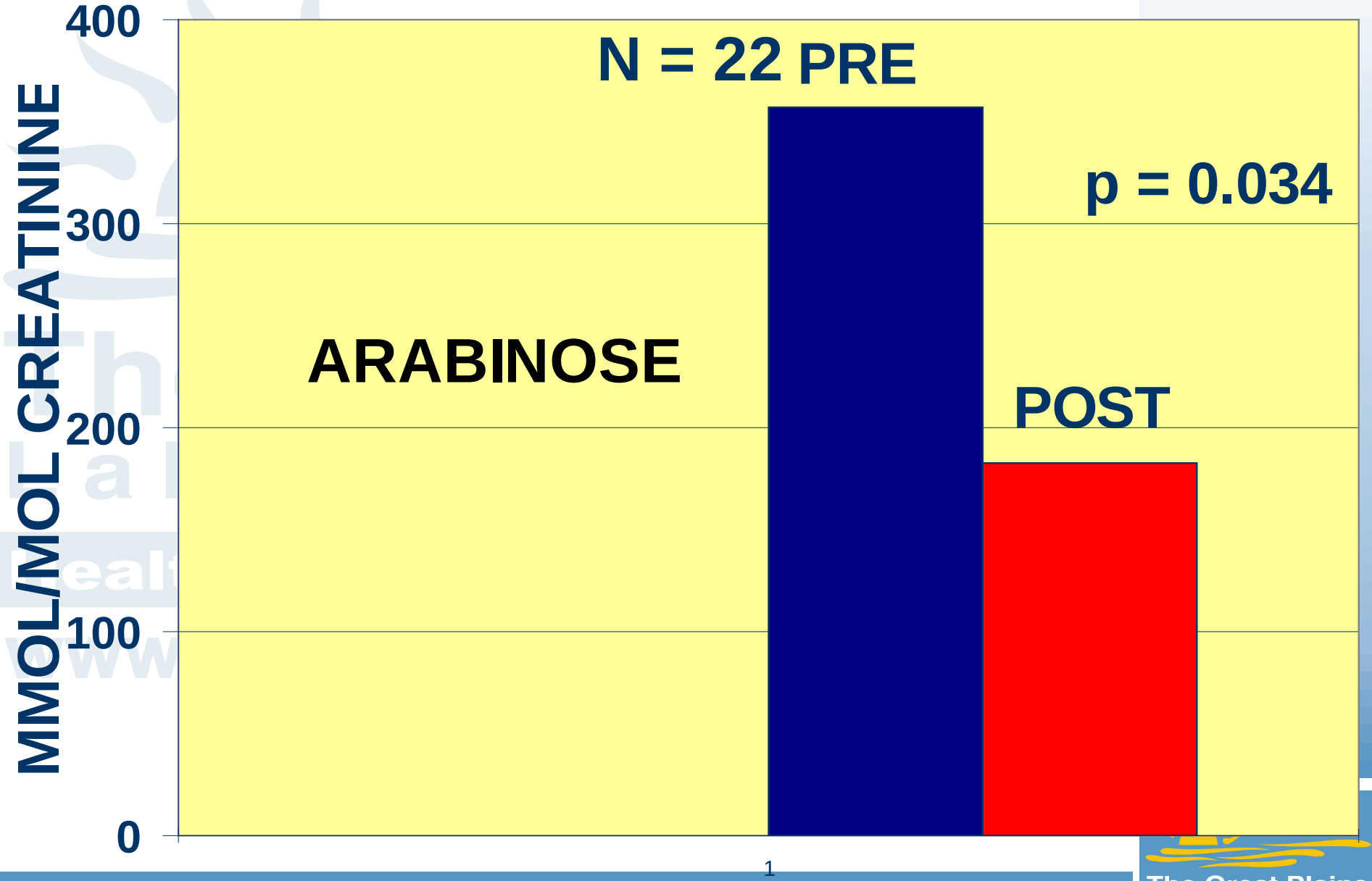


Where are oxalates deposited

- Bones
- Joints
- Blood vessels
- Lungs
- Eyes
- Skin
- Heart
- Thymus
- Skeletal muscle
- Joints
- Fat
- Teeth
- Mouth
- Nerves
- Brain
- Bone marrow
- Kidney
- Vagina
- Thyroid
- Blood brain barrier


ARABINOSE
(MMOL/MOL CREATININE)
4000.00
3500.00
3000.00
2500.00
2000.00
1500.00
1000.00
500.00
0.00
N = 14
N = 30
N = 211
CONTROL
MALE
INFANTS
CONTROL
MALE
CHILDREN
2 - 13 YRS
AUTISTIC
MALES
2 - 13 YRS

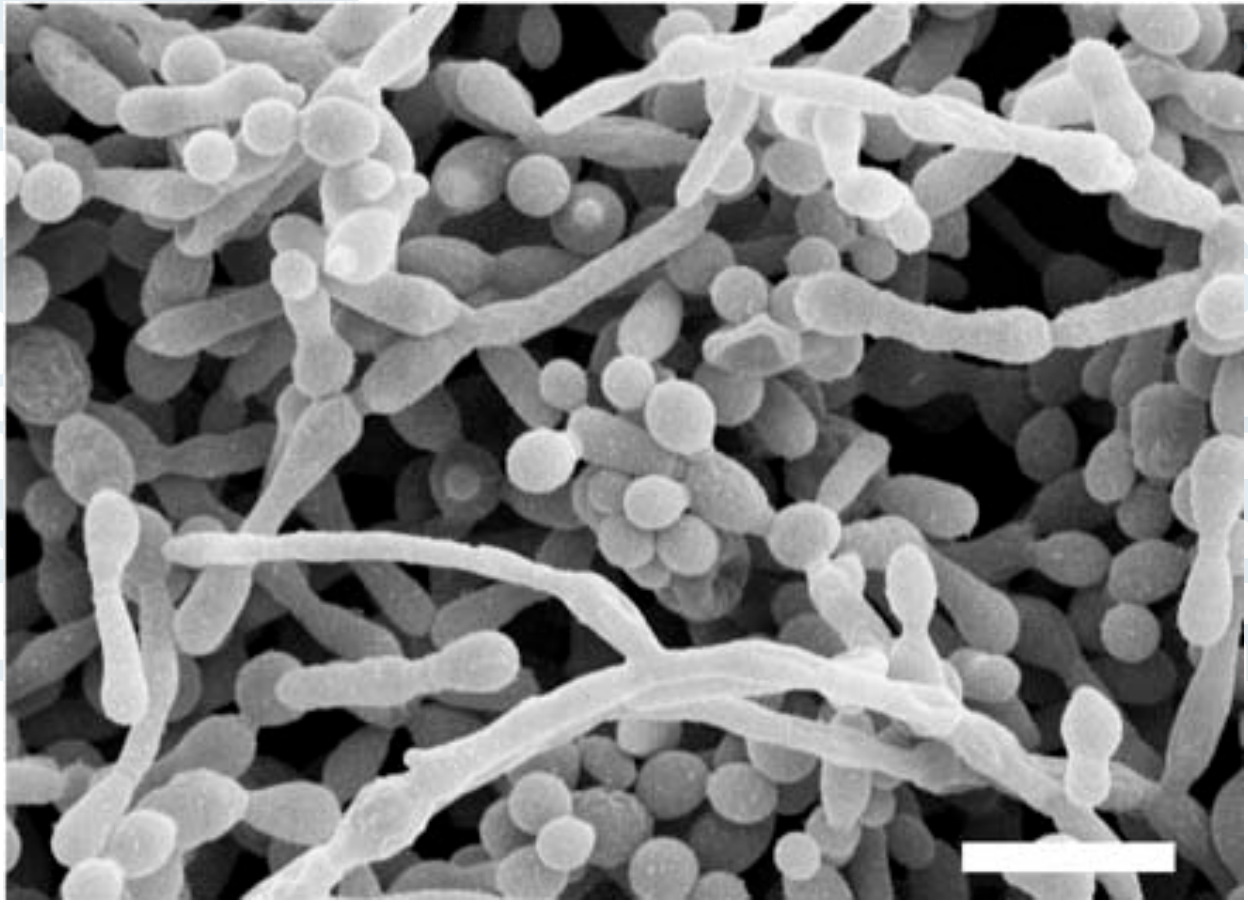
EFFECT OF 10 DAYS OF NYSTATIN



Urology. 1989 Dec;34(6):385-7. Detection by light microscopy of Candida in thin sections of bladder stone. Takeuchi H, et al Dept Urology, Shiga University of Medical Sciences, Japan

- We detected fungi morphologically resembling Candida albicans in an infected bladder stone by light microscopy of thin sections.
- The fungi were found in the layers precipitated with oxalate crystals and were invading the interstices surrounded with apatite or struvite crystals as in tissue infection.
- This presumably represents a superimposed infection due to changes in flora following treatment with antibiotics.

Candida biofilm-can trap oxalates and cause extreme oxalate corrosiveness



Ear Nose Throat J. 2004 May;83(5):331-3.
Isolated nasopharyngeal aspergillosis caused by A flavus and associated with oxalosis.
Dogan M, et al
Department of Otorhinolaryngology Head and Neck Surgery, Dokuz Eylul University School of Medicine, Izmir, Turkey.

- Biopsy analysis of the nasopharyngeal lesion revealed the presence of a mycelium made up of septate hyphae and associated oxalosis.
- Mycologic examination confirmed that Aspergillus flavus was the responsible pathogen.
- We treated the patient with a 4-week course of itraconazole.
- At the end of therapy, she exhibited no evidence of A flavus on physical and mycologic examinations.

Pol Merkuriusz Lek. 2006 Feb;20(116):159-63. The concentration of plasma anion oxalate in children treated with antibiotics Porowski T, et al.

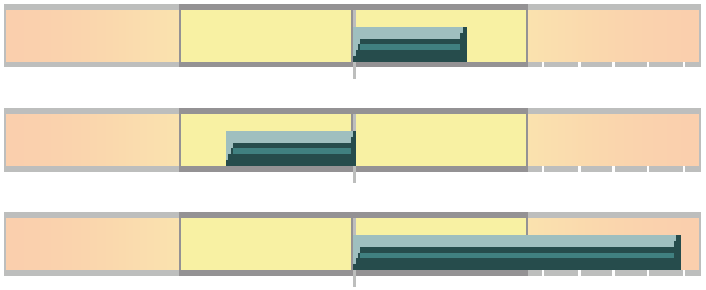
- 80 children, without nephrolithiasis, aged 10.1 +/- 4.3 years with bronchopneumonia, were treated with beta-lactam antibiotics. The children were divided in two groups: oral or IV antibiotics
- Plasma oxalate concentration increases during oral administration of antibiotics caused by increased intestinal absorption, as a result of saprophytic microflora deterioration.
- However intravenous administration of the same antibiotics does not change the concentration of plasma oxalate

Organic acid test-dysbiosis markers

Compound	Reference Range mmol/mol creatinine	Patient Value		Reference Interval Low Normal High
Yeast/Fungal				
citramalic	0.0 - 2.0	17.82	H	
5-hydroxymethyl-2-furoic	0.0 - 80.0	8.56		
3-oxoglutaric	0.0 - 0.5	0.27		
furan-2,5-dicarboxylic	0.0 - 50.0	6.98		
furancarbonylglycine	0.0 - 60.0	1.19		
tartaric	0.0 - 16.0	4.48		
arabinose	0.0 - 47.0	956.97	H	
carboxycitric	0.0 - 46.0	10.00		

Organic acid test-oxalate related

Oxalate Related					
glyceric	0.0	-	10.0	8.41	
glycolic	0.0	-	100.0	10.58	
oxalic	0.0	-	37.0	359.09	H



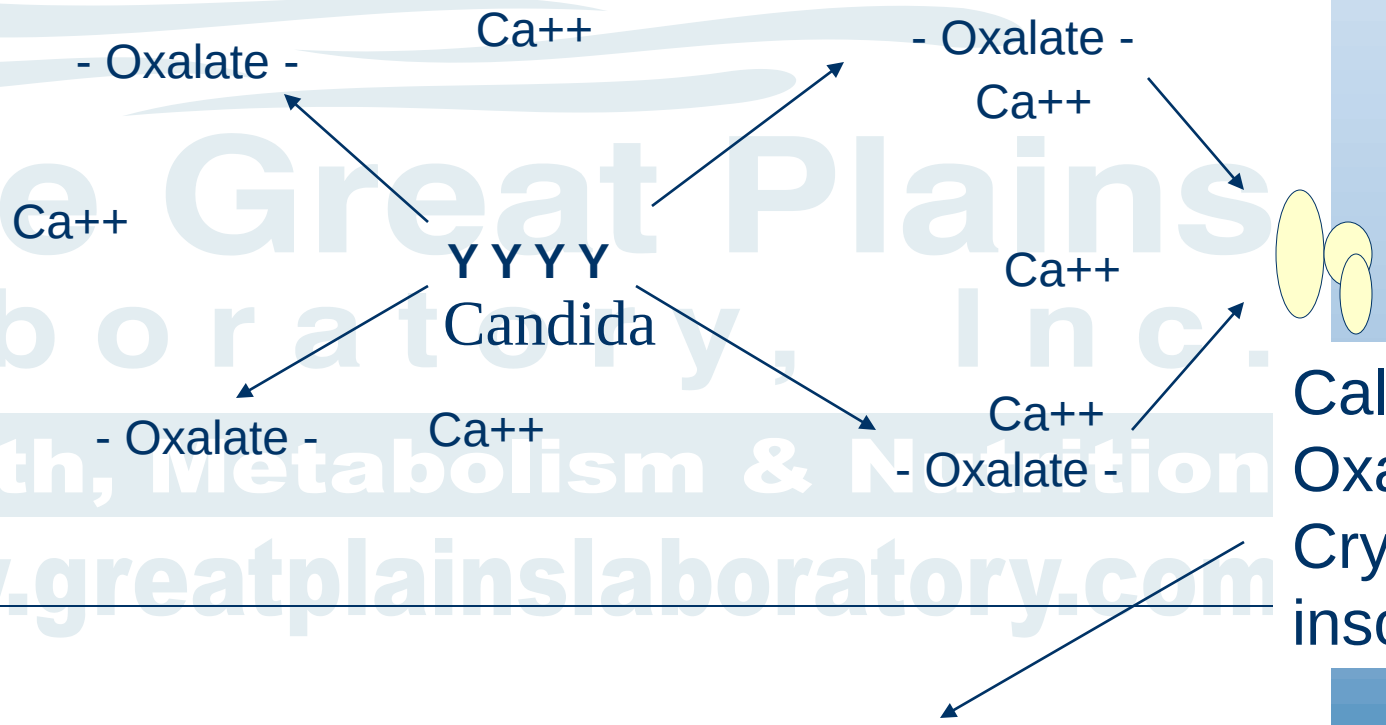
Organic acid test- vitamins

Low vitamin C indicates vitamin C not a problem

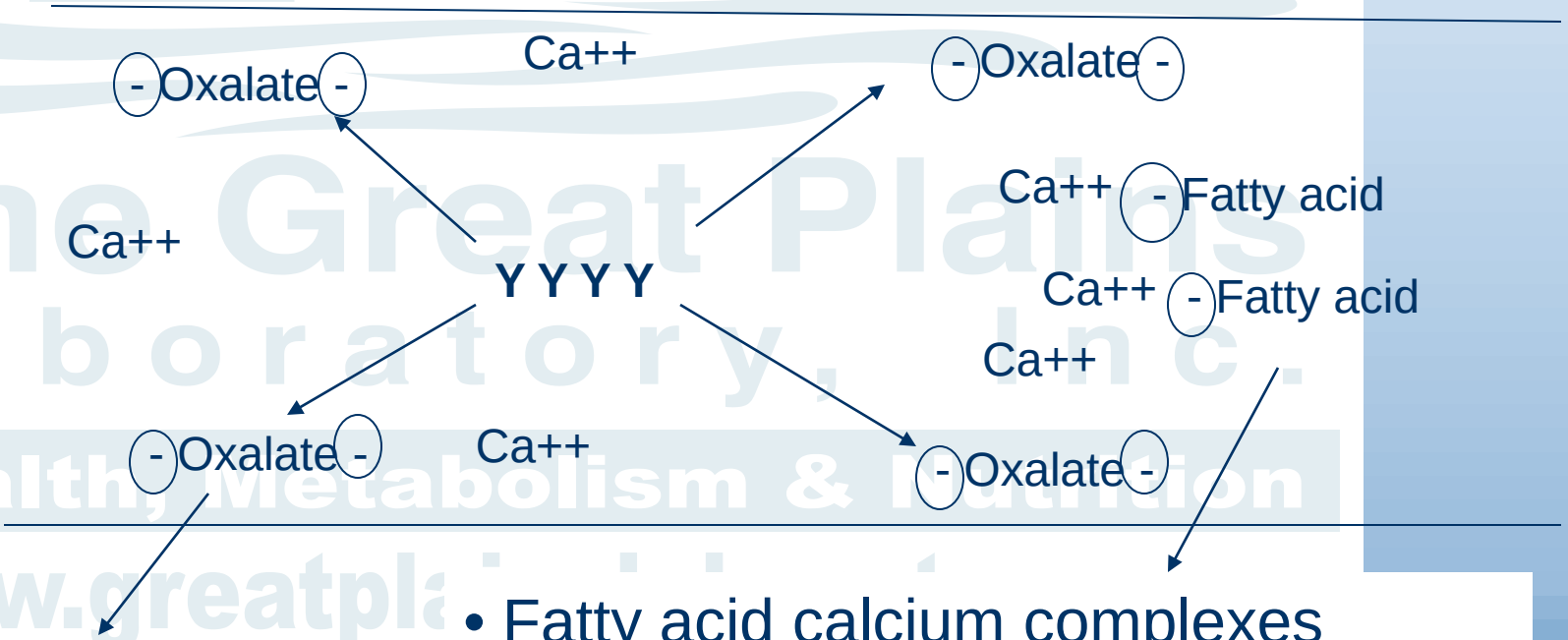
Vitamin Indicators				
methylmalonic	0.0 - 5.0	1.71		
ascorbic	10.0 - 200.0	1.72	L	
kynurenic	0.0 - 2.0	0.31		
methylcitric	0.0 - 12.0	0.16		
pyridoxic	2.0 - 26.0	1.50	L	
pantothenic	1.0 - 4.0	1.53		

Low vitamin B-6-reduces oxalate breakdown

Oxalate crystal formation in GI tract



Oxalate crystal formation in GI tract when fatty acids are high and/or poorly absorbed



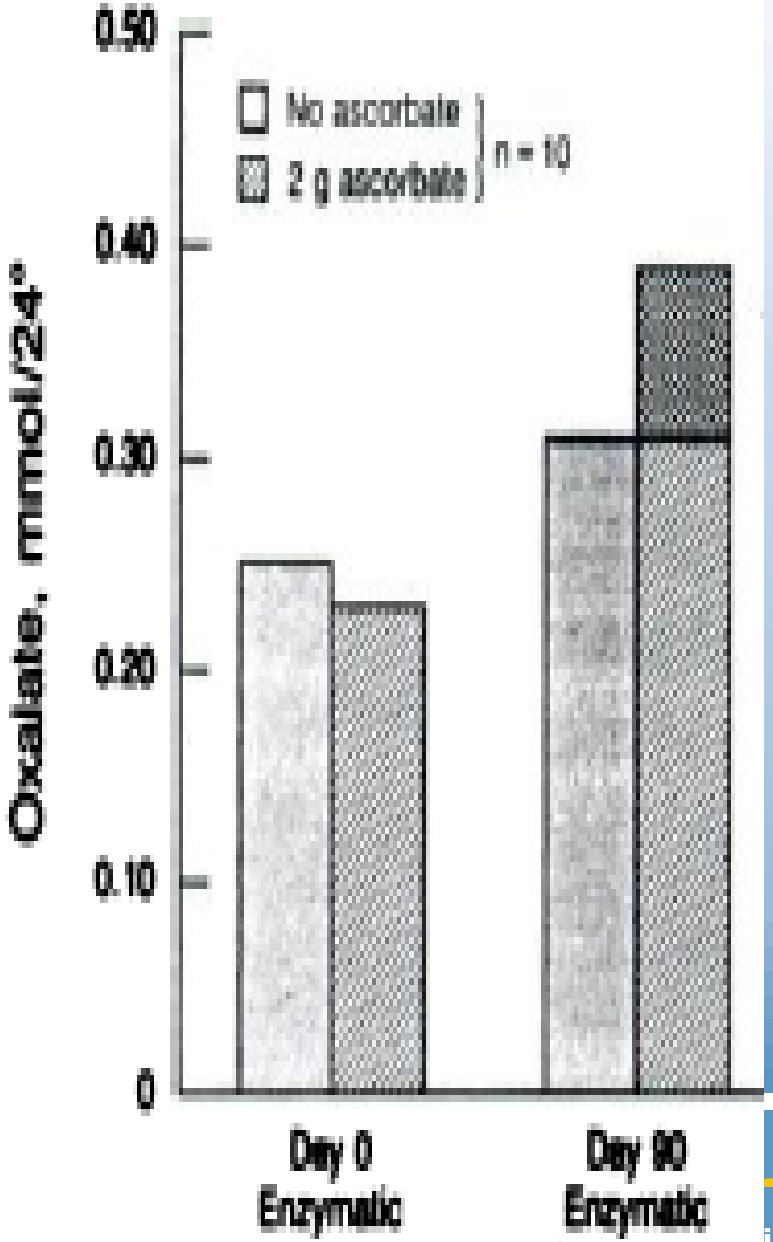
- Fatty acid calcium complexes form insoluble soaps
- Calcium not available to combine with oxalate
- More oxalate absorbed from GI tract

Dolske MC, Spollen J, McKay S, Lancashire E, Tolbert L. A preliminary trial of ascorbic acid as supplemental therapy for autism. Prog Neuropsychopharmacol Biol Psychiatry. 1993 Sep;17(5):765-74.

- 30-week double-blind,placebo-controlled trial of the effectiveness of ascorbic acid **(8000 mg/70kg/day)** for autistic children
- Pacing, rocking, flapping, and whirling behaviors responded especially well to this high dose vitamin C regimen.

No effect of vit C on oxalate excretion CLIN.CHEM.37/7, 1229-1235(1991)

Figure **6 shows that** ingestion **of** ascorbate **(2000 mg** daily) had **no** significant effect **on 24-h** oxalate excretion **in 10** normal subjects **when** measured **on the day of** collection.



A prospective study of the intake of vitamins C and B 6, and the risk of kidney stones in men **GC Curhan,et al Journal of Urology, June 1996, 155:6**

- Prospective study of the relationship between the intake of vitamins C and B6 and the risk of symptomatic kidney stones in 45,251 men 40 to 75 years old with no history of kidney calculi.
- During 6 years of followup 751 incident cases of kidney stones were documented. Neither vitamin associated with the risk of stone formation. For vitamin C the age-adjusted relative risk for men consuming 1,500 mg. daily or more compared to less than 250 mg. daily was 0.78

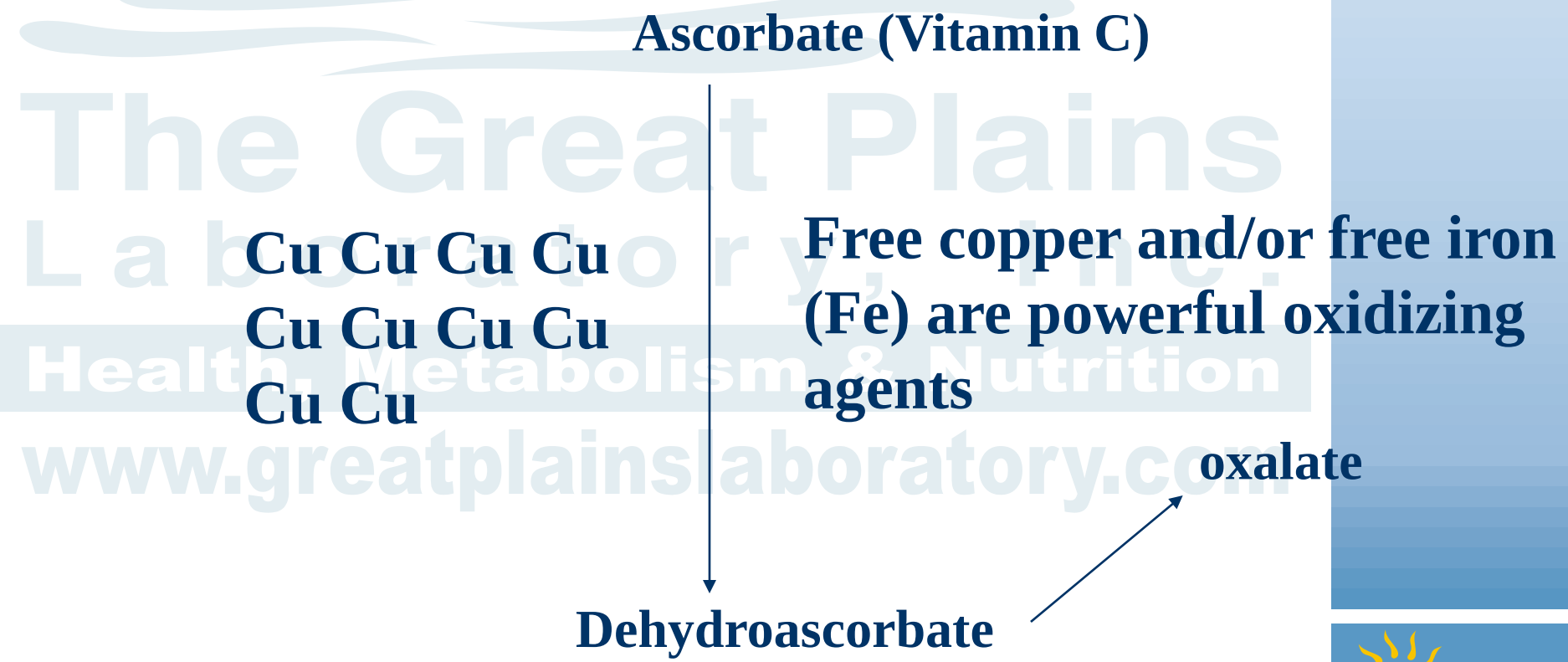
Nutrition. 1998 Nov-Dec;14(11-12):836-9. Oxalogenesis in parenteral nutrition solution components. Rockwell GF, et al

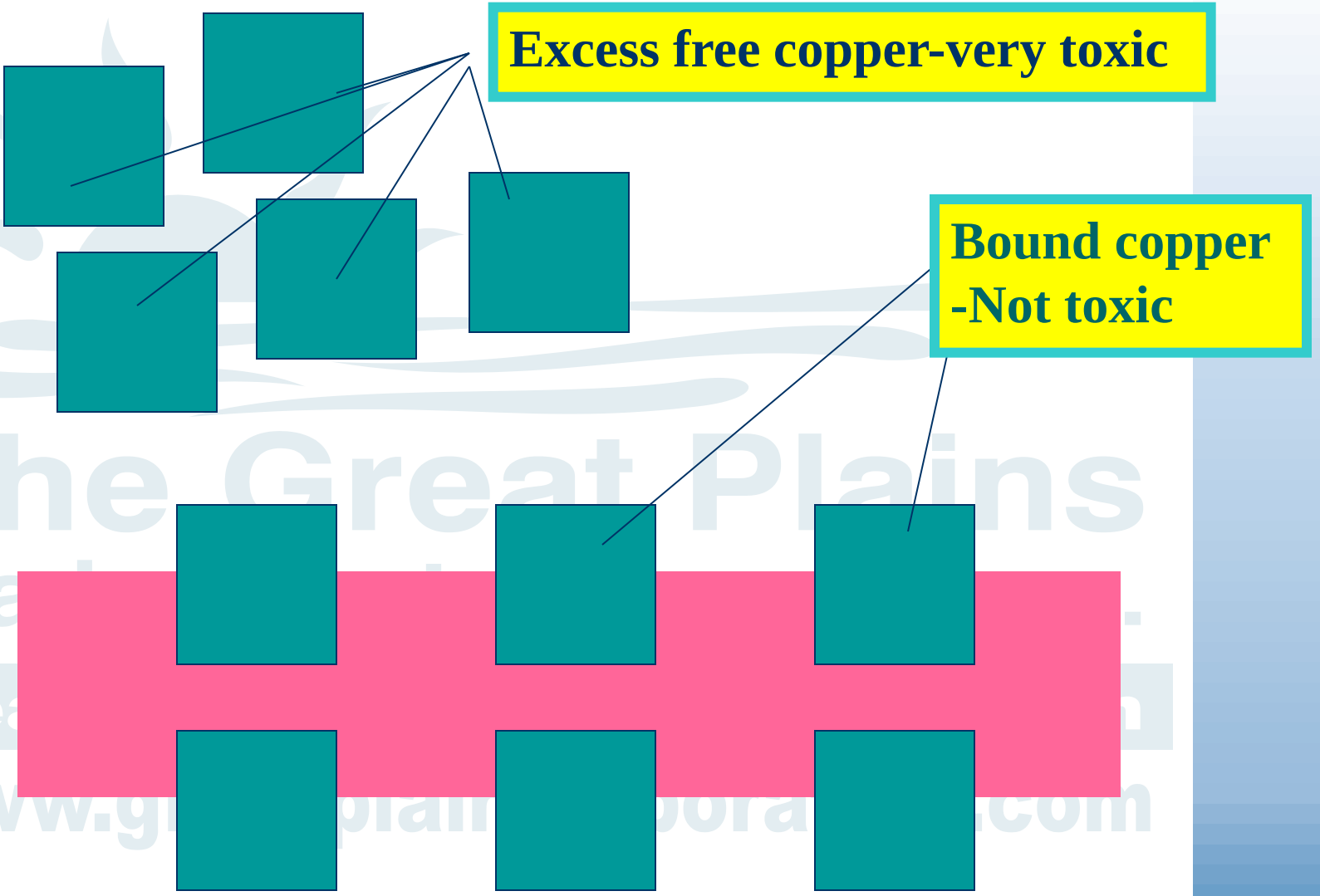
- Oxidation of ascorbate to oxalate, especially in the presence of catalysts such as copper and iron, has been implicated in formation of these precipitates.
- Oxalate is present in one TPN mixture at concentrations up to 8 ppm.
- The addition of ascorbate to an aqueous solution of trace metals may promote oxalogenesis.

Biol Psychiatry. 2008 Jul 15;64(2):89-97. Epub 2008 Jan 11. Shared gene expression alterations in schizophrenia and bipolar disorder. Shao L, Vawter MP. Department of Psychiatry and Human Behavior, Functional Genomics Laboratory, School of Medicine, University of California, Irvine, CA 60,

- Schizophrenia and bipolar disorder together affect 2.5% of the world population, and etiologies involve multiple genetic variants and environmental influences
- RNA samples from the dorsolateral prefrontal cortex
- (Brodmann area 46) consisting of individuals with schizophrenia (SZ), bipolar disorder (BPD), and control subjects were tested on the Codelink Human 20K Bioarray platform.
- 3 genes were highly enriched in brain expression (AGXT2L1, SLC1A2, and TU3A).
- AGXT2L1 expression in control subjects versus BPD and SZ was highly significant , $p < 10(-06)$).

Destruction of vitamin C by free copper ions





Ceruloplasmin

The Great Plains Laboratory, Inc.

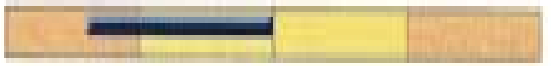
William Shaw, Ph.D., Director 11813 W. 77 Street, Lenexa KS 66214 Tel: 913-341-8949 Fax: 913-341-6207

Patient ID
Patient Name
Patient Age
Sex

Physician Name
Date of Collection
Time of Collection
Report Date

Advanced Metallothionein Profile

Compound	Reference Range	Patient Value		Reference Interval (Low / Normal / High)
Metallothionein (Whole Blood)	0.0 - 50.0 nmol/l	51.87	H	
Metallothionein (Red Blood Cell)	0.0 - 135.0 nmol/l	95.07		
Glutathione	800.0 - 1400.0 umol/l	2536.00	H	
Ceruloplasmin	1.5 - 4.5 umol/l	2.02		
Ceruloplasmin-Copper	9.0 - 27.0 umol/l	12.09		
*Copper Serum	12.0 - 23.0 umol/l	28.59	H	
*Zinc Serum	10.0 - 17.0 umol/l	8.56	L	
Plasma Metallothionein	0.0 - 2.8 nmol/l	23.07	H	
Plasma Metallothionein/Red Blood Cell	0.0 - 0.1 Ratio	0.24	H	
NonCeruloplasmin-Copper	0.0 - 1.6 Ratio	16.50	H	
Copper/Zinc	0.9 - 1.2 Ratio	3.34	H	
RBC Metallothionein/Zinc	To Be Determined Ratio	11.10		
Metallothionein/Glutathione	To Be Determined Ratio	0.20		
NonCeruloplasmin:Copper/Metallothionein(P)	To Be Determined Ratio	0.72		

Compound	Reference Range	Patient Value	Reference Interval: Low / Normal / High
Metallothionein (Whole Blood)	0.0 - 50.0 nmol/l	51.87 H	
Metallothionein (Red Bloo	0.0 - 135.0 nmol/l	95.07	
Glutathione	800.0 - 1400.0 umol/l	2536.00 H	
Ceruloplasmin	1.5 - 4.5 umol/l	2.02	
Ceruloplasmin-Copper	9.0 - 27.0 umol/l	12.09	
*Copper Serum	12.0 - 23.0 umol/l	28.59 H	
*Zinc Serum	10.0 - 17.0 umol/l	8.56 L	
Plasma Metallothionein	0.0 - 2.8 nmol/l	23.07 H	
Plasma Metallothionein/Red Blood Cell	0.0 - 0.1 Ratio	0.24 H	
NonCeruloplasmin-Copper	0.0 - 1.6 Ratio	16.50 H	
Copper/Zinc	0.9 - 1.2 Ratio	3.34 H	

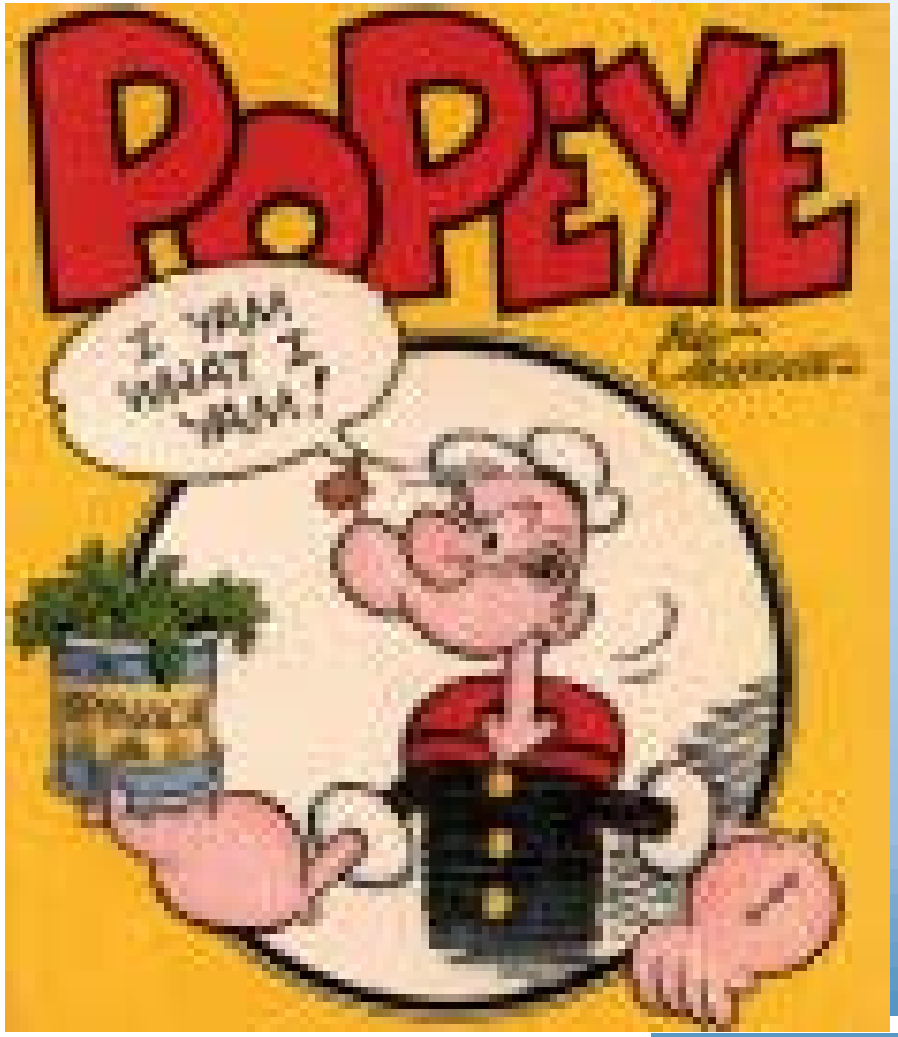
How does calcium citrate eliminate oxalate

- Calcium part of calcium citrate binds oxalates and causes them to precipitate, reducing absorption
- Citrate part of calcium citrate competes with any soluble oxalate at the intestinal mucosa, preventing absorption of oxalate
- Thus, calcium citrate is best form of calcium supplement

Supplements to reduce oxalates

- Probiotics-Help to control Candida and have enzymes that destroy oxalates
- Supplement with arginine, an amino acid that reduces oxalate crystal deposition in tissues and reduces oxidative damage to kidney cells
- Supplement with fish oil or cod liver oil
- Reduce arachidonic acid (omega-6)
- Supplement with B-6


Allens
POPEYE
SPINACH
NET WT. 13.5 OZ. • 383 g


POPEYE
I YAM WHAT I YAM!

High oxalate food list

- - kiwi
- - lemon peel*
- - lime peel*
- - orange peel
- - raspberries
- - rhubarb*
- - strawberries
- - tangerines
- - chocolate milk
- - almonds
- - baked beans in tomato sauce
- - cashews
- - tomato soup
- - vegetable soup
- - watercress
- - yams
- - cinnamon, ground-
- - eggplant
- - escarole
- - kale
- - leeks*
- - mustard greens
- - okra*
- - parsley
- - parsnips
- - peppers, green
- - pokeweed*
- - rutabagas
- - sorrel
- - spinach*
- - summer squash
- - sweet potatoes*
- - Swiss chard*
- parsley, raw*
- - pepper, > 1 tsp/day*-

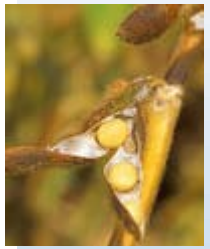
High oxalate food list

- - Fig Newtons
- - fruit cake
- - graham crackers
- - grits, white corn
- - kamut
- - marmalade
- - soybean crackers*
- - wheat germ*
- - blackberries
- - blueberries
- - red currants
- - dewberries
- - figs, dried
- - grapes, purple
- - gooseberries
- ginger
- - soy sauce
- - green beans
- - peanut butter*
- - peanuts*
- - pecans*
- - sesame seeds
- - sunflower seeds
- - soy protein
- - tofu (soybean curd)*
- - walnuts
- beans (green, wax, dried)
- - beets (tops, roots, greens)
- - celery
- - chives
- - collards
- - dandelion

Super high oxalate food list

- Spinach
- Soy protein
- Tofu
- Peanuts
- Peanut butter
- Pecans
- Lemon, lime peel
- Rhubarb
- Swiss chard
- Parsley, raw
- Sweet potatoes
- Pokeweed
- Black pepper
- Chocolate
- Instant coffee
- Leeks
- Tea
- Okra
- Wheat germ

Soy protein is probably not a good food for humans-Linda Massey, Ph.D., at Washington St. U.



• During their testing, the researchers found the highest oxalate levels in textured soy protein, which contains up to 638 milligrams of oxalate per 85-gram serving.

• Soy cheese had the lowest oxalate content, at 16 milligrams per serving.

• Spinach, measured during previous research, has approximately 543 milligrams per one-cup (2 oz. fresh) serving.

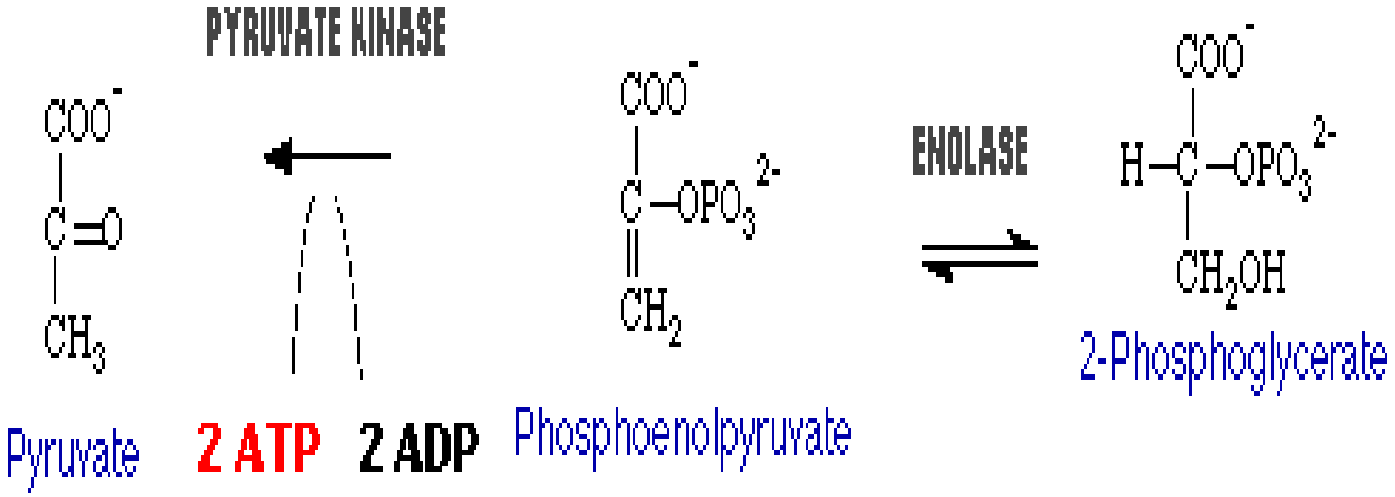
How much oxalate is in the diet and will be absorbed?

- A typical adult diet contains 97-930 mg per day
- < 30-50 mg per day to reduce stones
- 2.3% -12% is absorbed
- 2.2 mg-112 mg per day absorbed
- Sodium oxalate is very soluble and will be absorbed much more readily than calcium or magnesium oxalates
- Almost no oxalate is eliminated in stool so that stool is mainly an indicator of intake and/or microbial production
- Reference: Primary hyperoxalurias. Metabolic Basis of Inherited Disease:pg 937,1989

Last step in glycolysis inhibited by oxalate

Enzyme affected in Tourette's syndrome

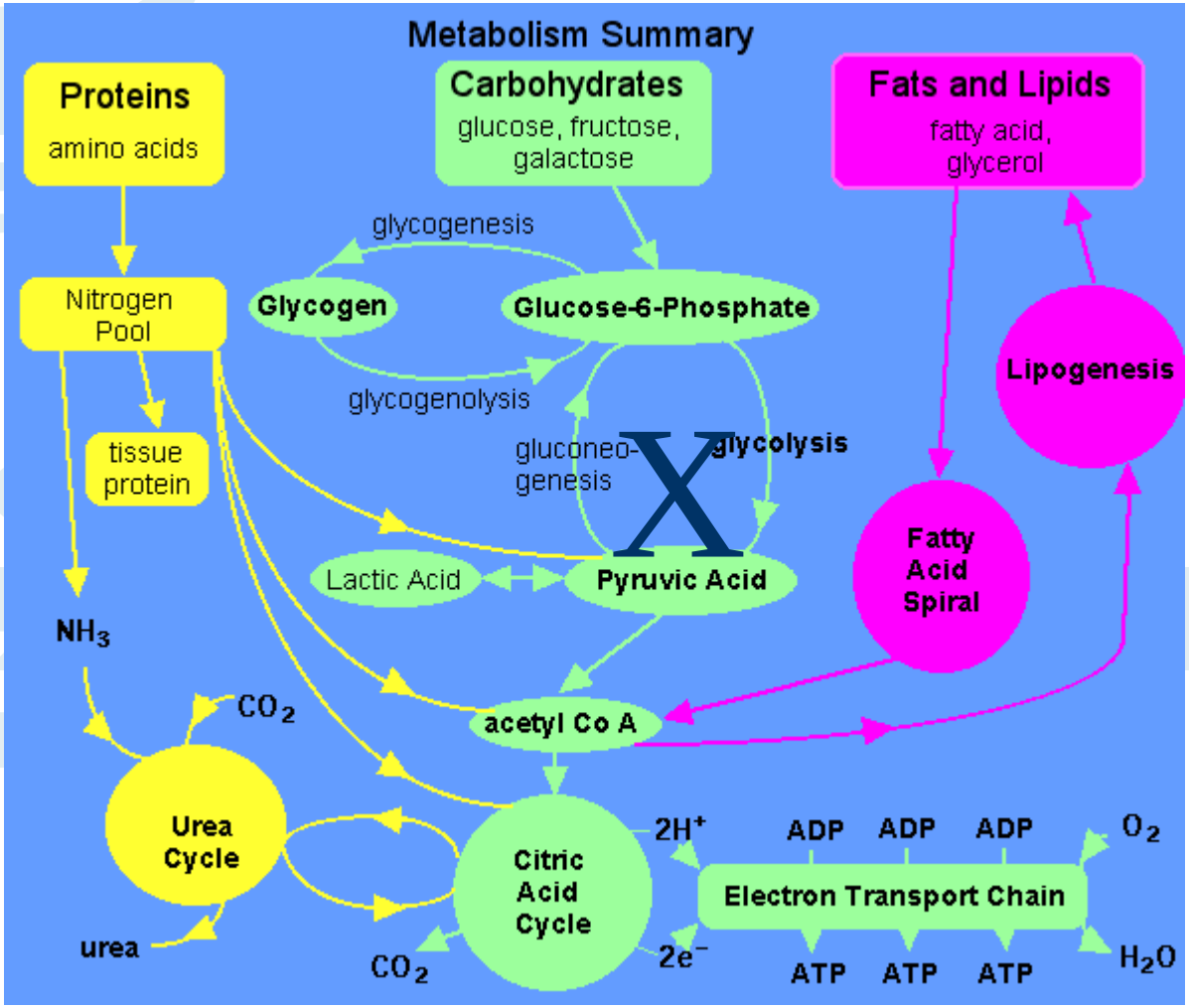
Inhibited by oxalate



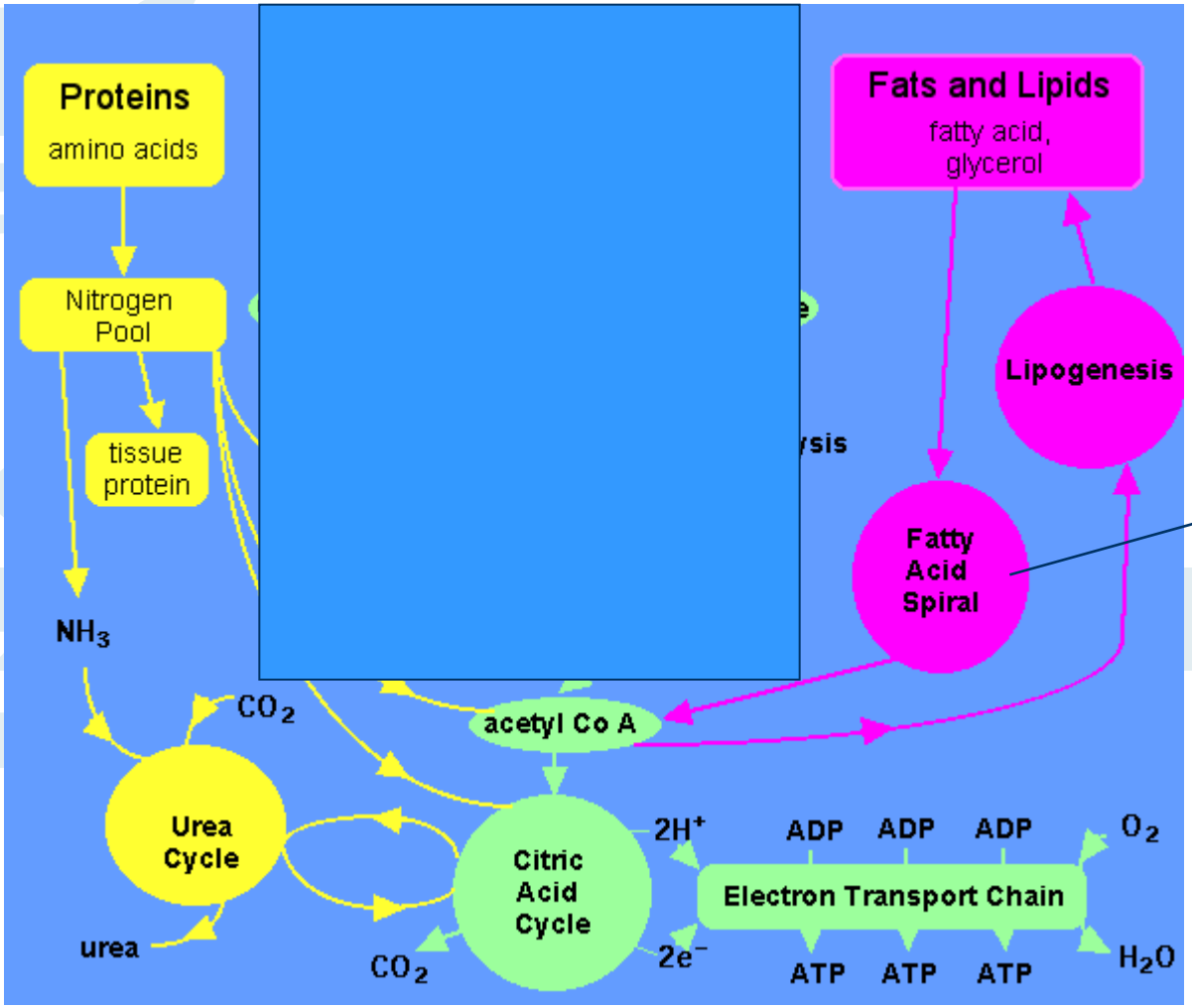
Meikai Daigaku Shigaku Zasshi. 1990;19(2):185-96. Studies on pyruvate kinase from pig dental pulp and brain Ozawa S, Ozawa K, Nakanishi N.

- Oxalate showed inhibitory activity against dental pulp and brain pyruvate kinase
- The Ki value was determined to be 50 microM and 80 microM, respectively.
- The inhibition of dental pulp and brain enzyme activity by oxalate was competitive with respect to phosphoenolpyruvate.

Importance of pyruvic acid in metabolism



What happens when pyruvic acid formation is blocked?



Ketosis

Summary

- Oxalates cause severe symptoms due to crystal deposition in virtually all tissues of the body including brain and blood brain barrier
- Oxalates in the GI tract bind essential elements like calcium, magnesium, zinc, and others, preventing their absorption
- Oxalates are powerful chelating agents that bind heavy metals but trap them in the tissues, preventing their release from the body
- Oxalates can cause significant damage by their sharp edges and are oxidizing agents as well

Summary

- Use calcium and magnesium citrate to prevent oxalate absorption
- Keep Candida under control all of the time
- Use low oxalate diet or at least eliminate foods highest in oxalates
- Vitamin C is not significant problem in producing oxalates unless free copper or iron is elevated
- Test for free copper and iron as soon as possible

Thank you

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