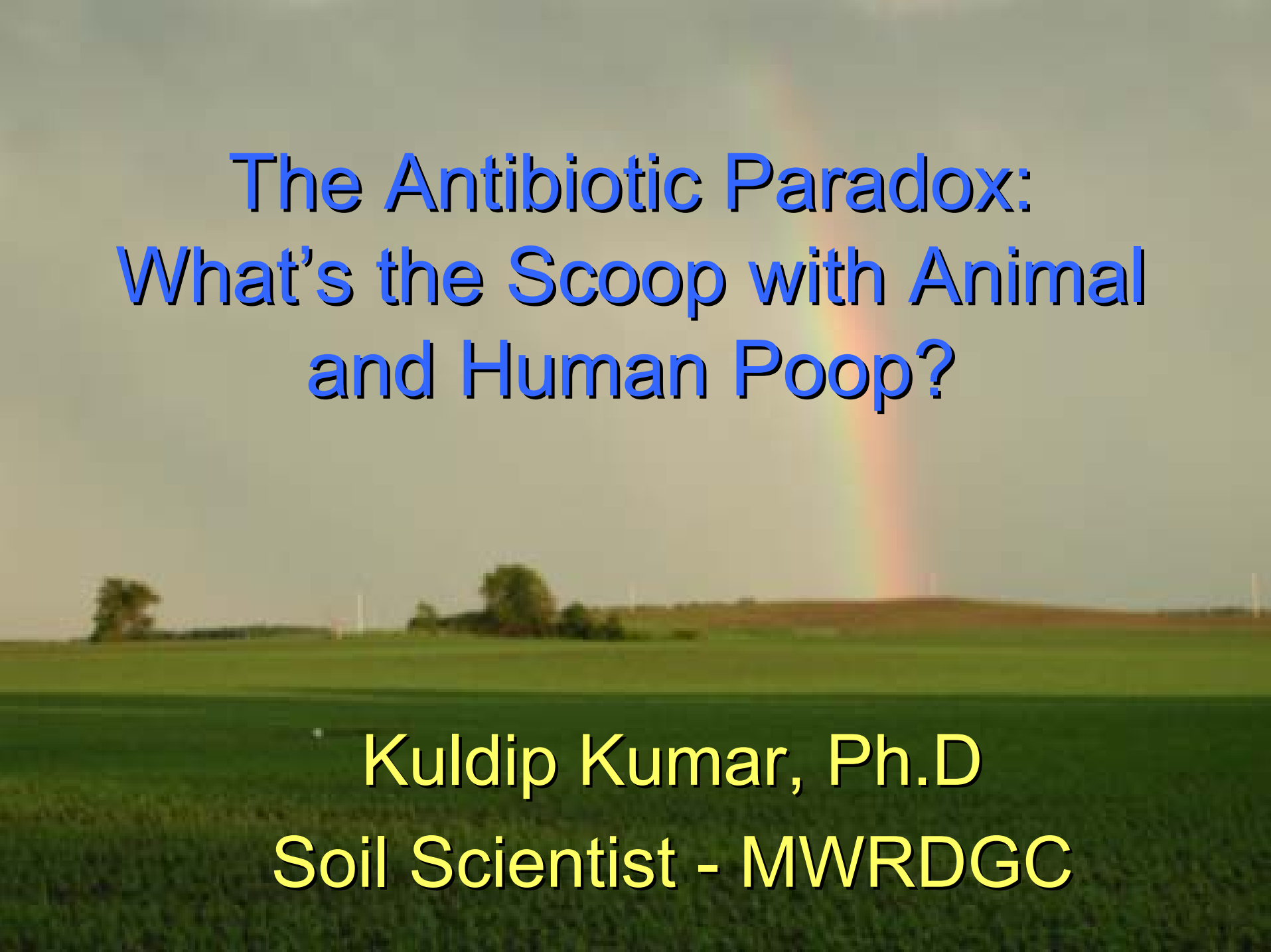


The Antibiotic Paradox: What's the Scoop with Animal and Human Poop?

Kuldip Kumar, Ph.D
Soil Scientist - MWRDGC

Pharmaceuticals in Environment

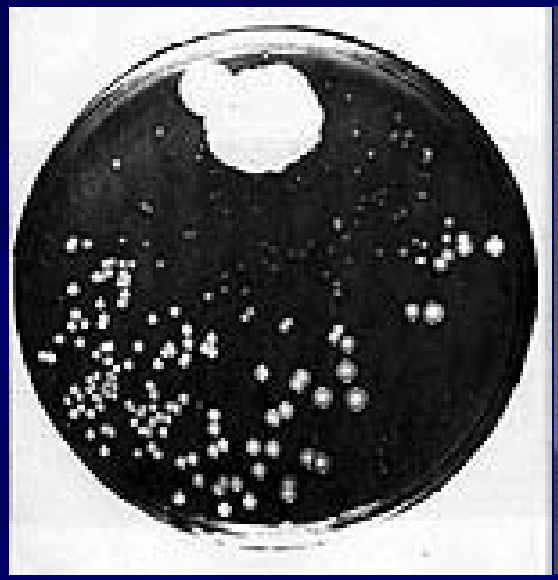
- Antibiotics – Therapeutic or Non Therapeutic
  - Antibacterial Compounds in PCPs
  - Steroid Hormones
  - Drugs – Prozac,……Antidepressants
  - Contraceptive pills
  - Blood Lipid-Lowering Agents
  - Beta Blockers

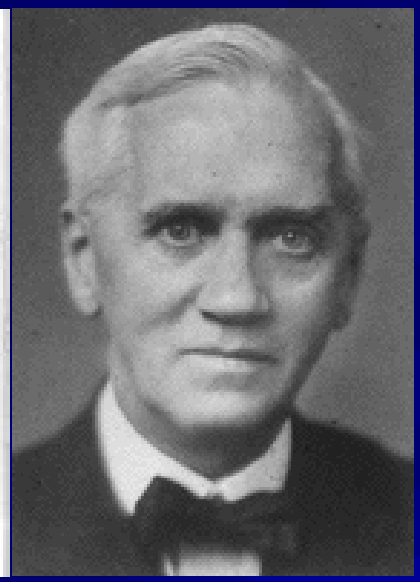
What Is An Antibiotic?

Antibiotics are powerful medicines that can kill bacteria and **only** bacteria.

Antibiotics do not work against viral infections like colds or the flu.

Discovery of penicillin





Alexander Fleming
1928
Nobel Prize, 1945

Discovery of sulfa drugs

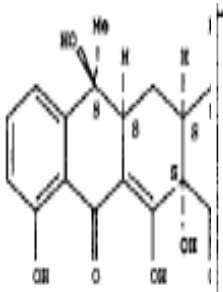
Gerhard Domagk
1932
Nobel Prize, 1939

Structure and Chemical Properties of Few Antibiotics

Tetracycline

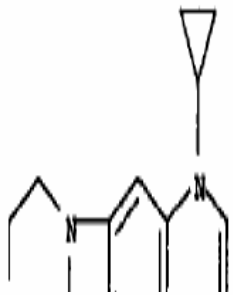
60-54-8

MW: 444.43



Ciprofloxacin

85721-33-1



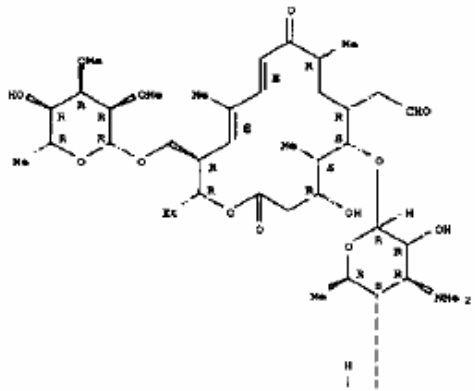
log K_{OW}: 0.4 [9]

S: 30 g/L [7]

Tylosin

1401-69-0

MW: 917.14



log K_{OW}: 3.5 [1]

S: 5 g/L [18]

pK_a: 7.1 [1]

Metal complexation: n.a.

$pK_{a,2}$: 7.65 [1]

Mode of Action of Different Antibiotics and Modes of Resistance

Class/Group	Mechanism of Action	Mechanism of Resistance
Aminoglycosides, Tetracyclines	Inhibits protein biosynthesis	Inactivation of antibiotic by enzymic modification
β-Lactums, Glycopeptides	Inhibits cell wall biosynthesis	Reduced permeability Reduced affinity for target Hydrolysis
Macrolides, Chloramphenicol	Inhibits protein biosynthesis	Reduced affinity for antibiotic target
Fluoroquinolones	Inhibits DNA replication	Alteration in target Decreased cell permeability
Sulphonamides	Inhibits folic acid biosynthesis	Metabolic bypass of inhibited reaction Overproduction of antibiotic target
Rifampin	Inhibition of RNA synthesis	Antibiotic inactivation
Polymixins	Disruption of bacterial membranes	Altered cell permeability

Chander… Kumar, 2007: Antibiotics: Has the Magic Gone? J Sci Food Agric 87, 739-42.

Pre-antibiotic age

- Tuberculosis and pneumonia responsible for 25% of deaths in US (1900)
- More people died in wars due to infection than to actual traumatic injury

Life Magazine (Aug. 14, 1944)

- "…the greatest news event of World War II may well be the discovery and development…of penicillin."

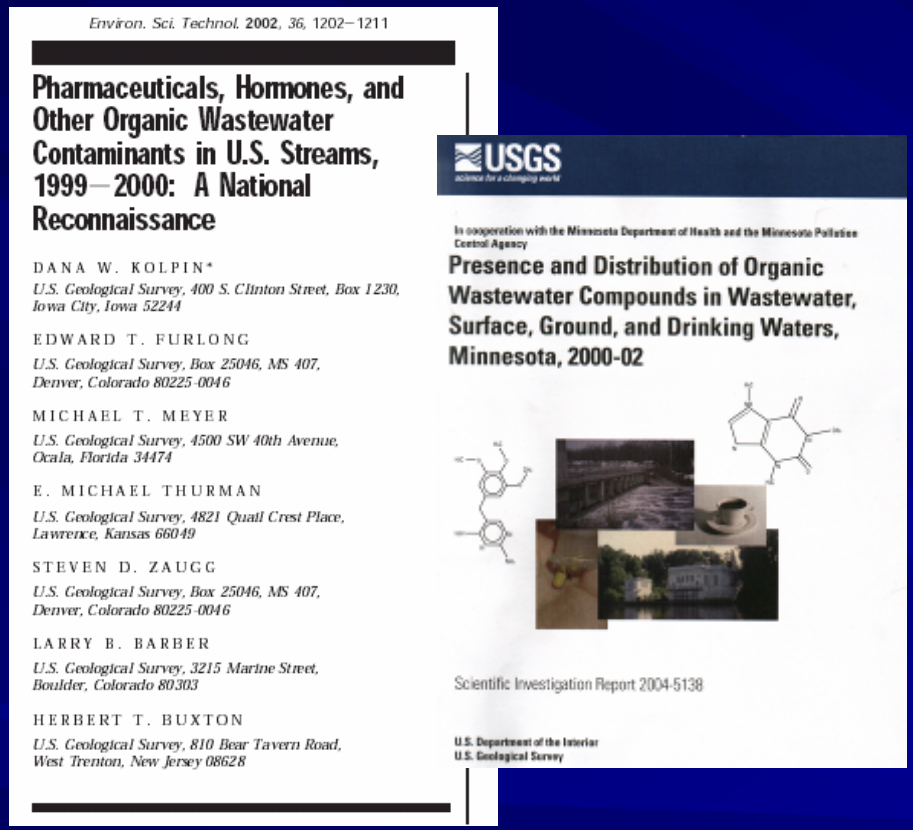
- "miracle drugs"
- "wonder drugs"
- "magic bullets"

⇨ **The Golden Age**

Nebraska Farmer ad for Penicillin from the mid-1940s.

- 1940s: Limited to therapeutic usage
- Late 1940s and 50s: Moore et al. (1946), McGinnis (1950), and others
  - Improve feed efficiency
  - Increase growth rates
- Antibiotic use in livestock production
  - Therapeutic
  - Growth promotion
  - Prophylactic

Antibiotics in the Environment



Environ. Sci. Technol. **2002**, *36*, 1202–1211

Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999–2000: A National Reconnaissance

DANA W. KOLPIN*
U.S. Geological Survey, 400 S. Clinton Street, Box 1230, Iowa City, Iowa 52244

EDWARD T. FURLONG
U.S. Geological Survey, Box 25046, MS 407, Denver, Colorado 80225-0046

MICHAEL T. MEYER
U.S. Geological Survey, 4500 SW 40th Avenue, Ocala, Florida 34474

E. MICHAEL THURMAN
U.S. Geological Survey, 4821 Quail Crest Place, Lawrence, Kansas 66049

STEVEN D. ZAUGG
U.S. Geological Survey, Box 25046, MS 407, Denver, Colorado 80225-0046

LARRY B. BARBER
U.S. Geological Survey, 3215 Marine Street, Boulder, Colorado 80303

HERBERT T. BUXTON
U.S. Geological Survey, 810 Bear Tavern Road, West Trenton, New Jersey 08628

USGS
science for a changing world

In cooperation with the Minnesota Department of Health and the Minnesota Pollution Control Agency

Presence and Distribution of Organic Wastewater Compounds in Wastewater, Surface, Ground, and Drinking Waters, Minnesota, 2000-02

Scientific Investigation Report 2004-5138

U.S. Department of the Interior
U.S. Geological Survey

- National and local reconnaissance surveys
- 200 sites
  - 50% of surface water samples contained 1^{+} antibiotic
- Source?

Antibiotics Detected in Drinking Water (Khetan and Collins, 2007)

Concentration	Antibiotics	Water	City/Country
165 ng/L	Clofibric acid	Tap	Berlin, Germany
258 ng/L	Carbamaepine	Finished	Atlanta, USA
ng/L levels	Sulfonamide, tetracycline, macrolides, quinolones	Point-of-use	10 cities in Canada
ng/L levels	Several antibiotics like fluro-quinolones, sulfonamides, tetracyclines etc.	Finished	North Carolina, USA


AIR
WATER

Antibiotics n

swissinfo, April 27, 200

Des Moines Regi

e

, to

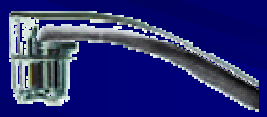
water

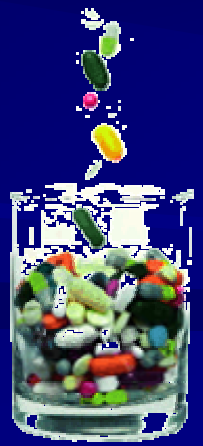
/services/prpressespi

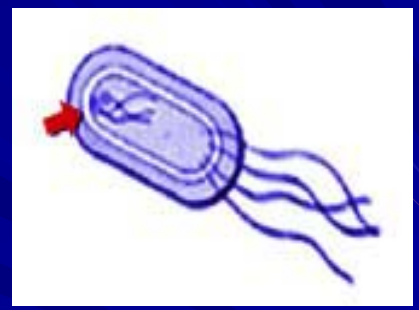
sinfo2_1.pdf

Major Concerns Regarding Antibiotic Usage

- Antibiotics appearing in potable waters
- Antibiotics appearing in food supply
- Emergence of Antibiotic resistant bacteria







The major pathway is thru the land application of manure or biosolids.

Antibiotic Production and Use

- Institute of Medicine
- 50 M pound produced per year
  - 60% Human medicine
  - 40% Agriculture uses
    - 32% Non-therapeutic
    - 8% Therapeutic

- Union of Concerned Scientists
- 35 M pound produced per year
  - 13% Human medicine
  - 84% Agriculture Uses
    - 78% non-therapeutic
    - 6% Therapeutic
  - 3% Pets

K.M. Shea, 2003

Antibiotics Approved by the FDA for Subtherapeutic Livestock Usage

- Amprolium
- **Bacitracin**
- Bambermycins
- Carbadox
- **Chlortetracycline**
- **Erythromycin**
- Laidomycin
- Lasalocid
- **Limcomycin**
- Monensin
- **Oxytetracycline**
- **Penicillin**
- **Sulfonamides**
- Roxarsone
- Tiamulin
- **Tylosin**
- **Virginiamycin**

=identical/similar to human drugs

Kumar and Gupta, 2003
USGS Report

Shea, K.M. 2003. Antibiotic resistance: what is the impact of agricultural uses of antibiotics on children's health?

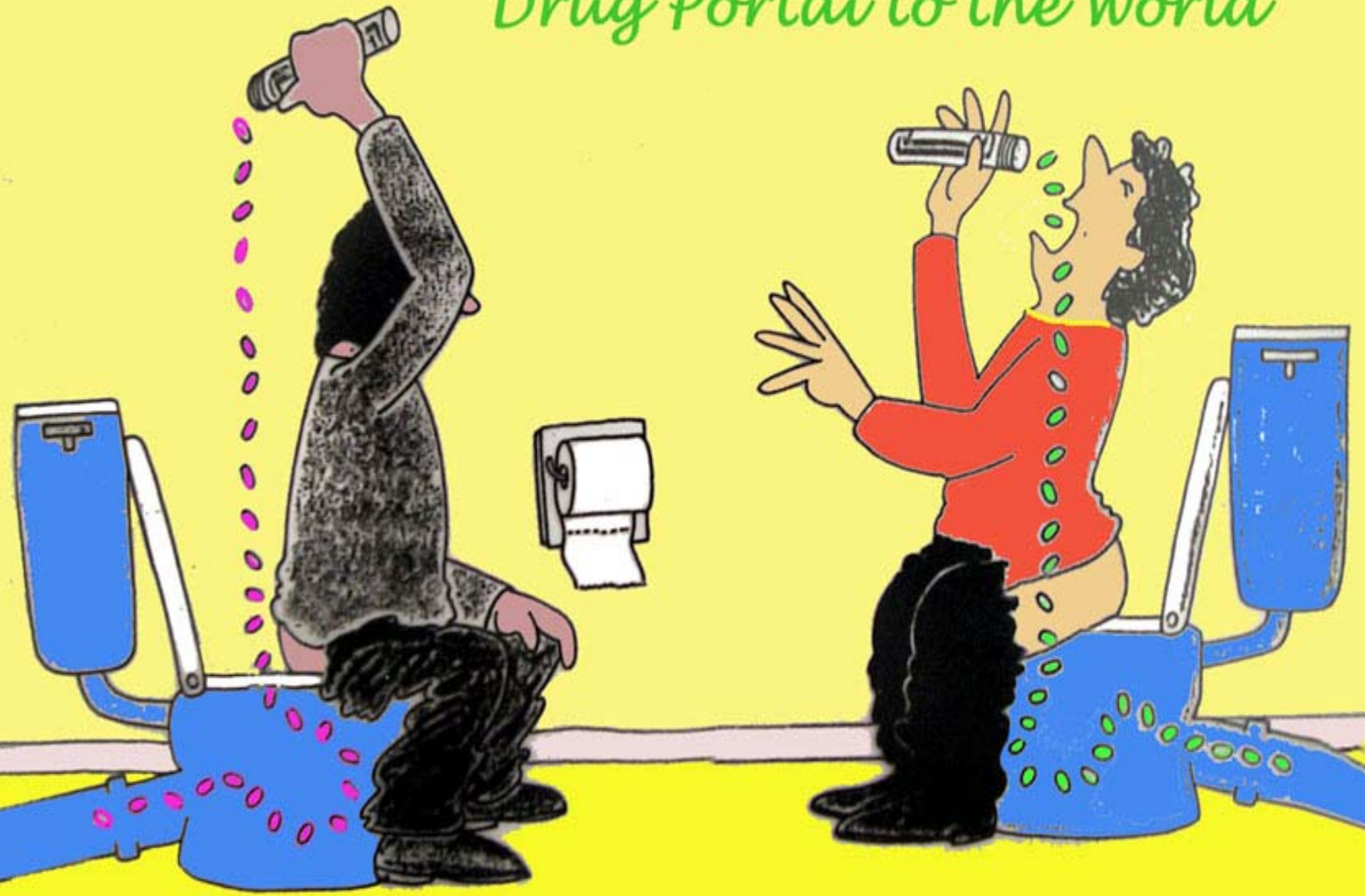
Non-therapeutic Use of Antibiotics in Animal Production

- Dose: 1-400 g/ton of feed

- Purpose:
  - To increase the ability of animal to absorb nutrients
  - To reach the market weight on time
  - To prevent the outbreak of diseases

Kumar et al., 2004; J. Environ Quality

Drug Portal to the World



adapted by Daughton from Ternes (April 2000)

Proportion of Antibiotics Excreted in Urine and Feces

Antibiotic	% Excreted
Tetracyclines	75-80
Lincomycin	60
Quinacrine	10
Metronidazole	40
Tylosin, Monensin, Erythromycin	50-90

Kumar et al., 2005; Adv Agron., Vol. 87

Concentration of Antibiotics in Different Manures

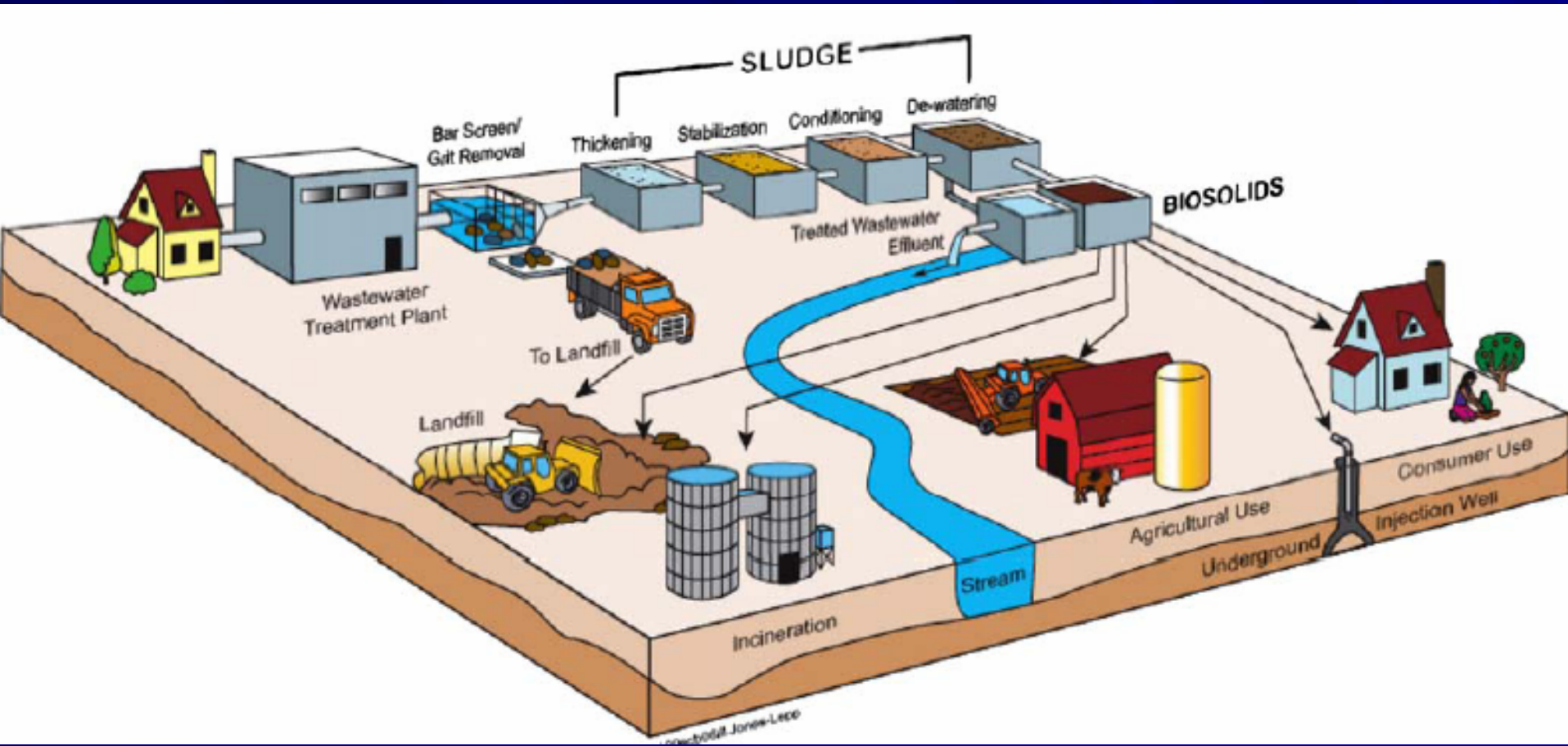
Antibiotics	Conc. mg/kg or mg/L
Tetracyclines (Chlor, Oxy, Tet)	0.1-200
Tylosin	0.1 – 7.9
Monensin	1.0-5.0
Sulfamethazine	3.3-8.7
Penicillin	0.2-5.0
Nicarbazine	35.1-152.1
Sulfathiazole	0.1-12.4

Kumar et al., 2005; Adv Agron., Vol. 87

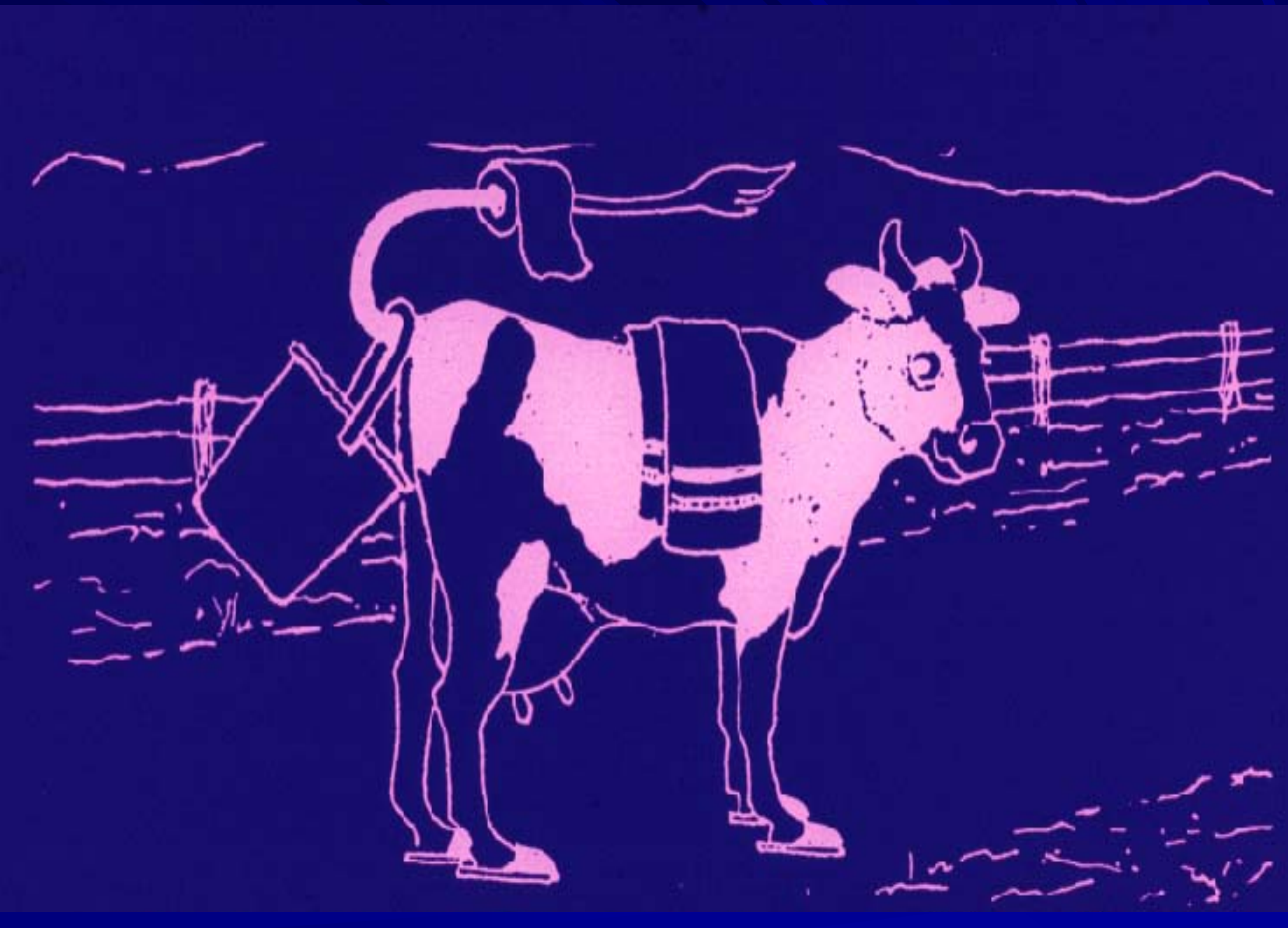
Concentration of Antibiotics in Biosolids and Sewage sludge (Jones-Lepp and Stevens, 2007)

Antibiotics	Media	Amount detected (mg/kg dry weight)
Fluoroquinolones		
Ciprofloxacin	Sewage sludge	2.3-2.4
Norfloxacin	Sewage sludge	2.1-2.4
Macrolides		
Azithromycin	Sewage sludge	0.001-0.16
	Millorganite	0.014
Clarithromycin	Sewage sludge	0.0003-0.063
	Millorganite	0.0009
Erythromycin	Class A & B biosolids	nd-0.041
Sulphonamides	Sewage sludge	nd – 0.197
Trimethoprim	Class A & B biosolids	nd – 0.133
Tetracylines (District)	Class A & B biosolids	nd – 0.171

nd-not detected


SLUDGE
Bar Screen/
Grit Removal
Thickening
Stabilization
Conditioning
De-watering
BIOSOLIDS
Treated Wastewater
Effluent
Wastewater
Treatment Plant
To Landfill
Landfill
Consumer Use
Agricultural Use
Injection Well
Underground
Stream
Incineration

Swine Facility-CAFO (Concentrated Animal Feeding Operation)



Relative Use of Biosolids, Manures, and Fertilizer (million tons dry weight) in US.

	Biosolids	Manure †	Fertilizers
Produced	6.9	133	50
Land Applied	2.8	120	50
Fecal Coliform	~500,000 MPN/g	5-30 million colonies/g	-
Salmonella	< 7 MPN/4g	3100 organisms/g	-

†Kumar, K., et al. 2005.
Antibiotic use in agriculture and its impact on the terrestrial environment. Adv. Agron. 87:1-54

“Risks” – 40 times greater manure than biosolids ?

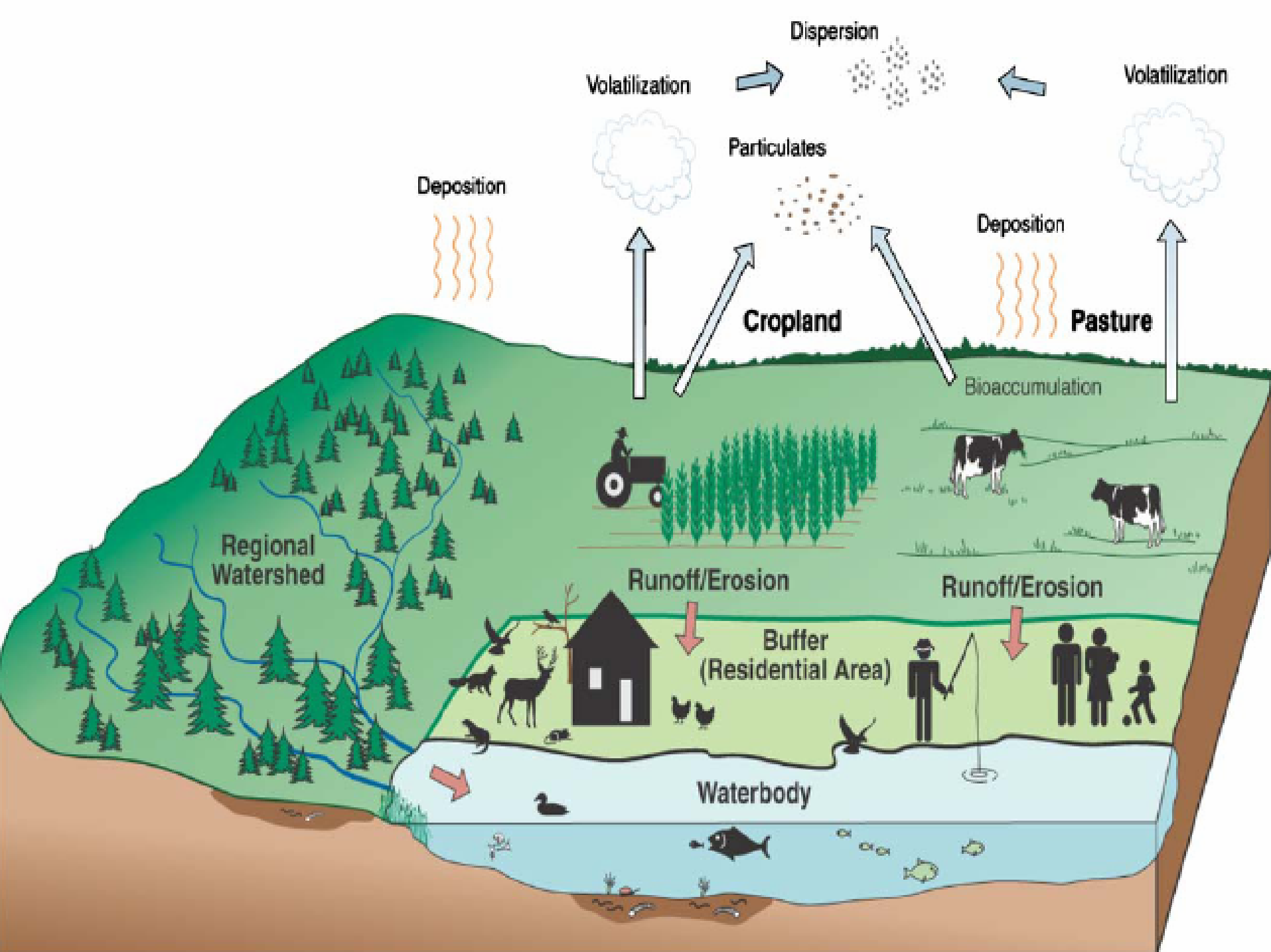
- Manure

“Manures have been used since beginning of time, and they have been used for so long that people don’t think about comparing risks and benefits – ***manures are simply accepted and they have been for over 2000 years***”

- Biosolids

YET “***for biosolids, it appears that risks associated with their use are no greater than – and, in many cases , may in fact be less than – risks associated with manure use”***

Finally, may be the solution lies in MTPs (Manure Treatment Plants) just like we have WWTPs (Waste Water Treatment Plants)


Dispersion
Volatilization
Volatilization
Particulates
Deposition
Deposition
Cropland
Pasture
Bioaccumulation
Regional Watershed
Runoff/Erosion
Runoff/Erosion
Buffer (Residential Area)
Waterbody

Fate and Transport of Veterinary Antibiotics in the Environment

Solid Beef Manure

Liquid Hog Manure

University of Minnesota has been in the lead

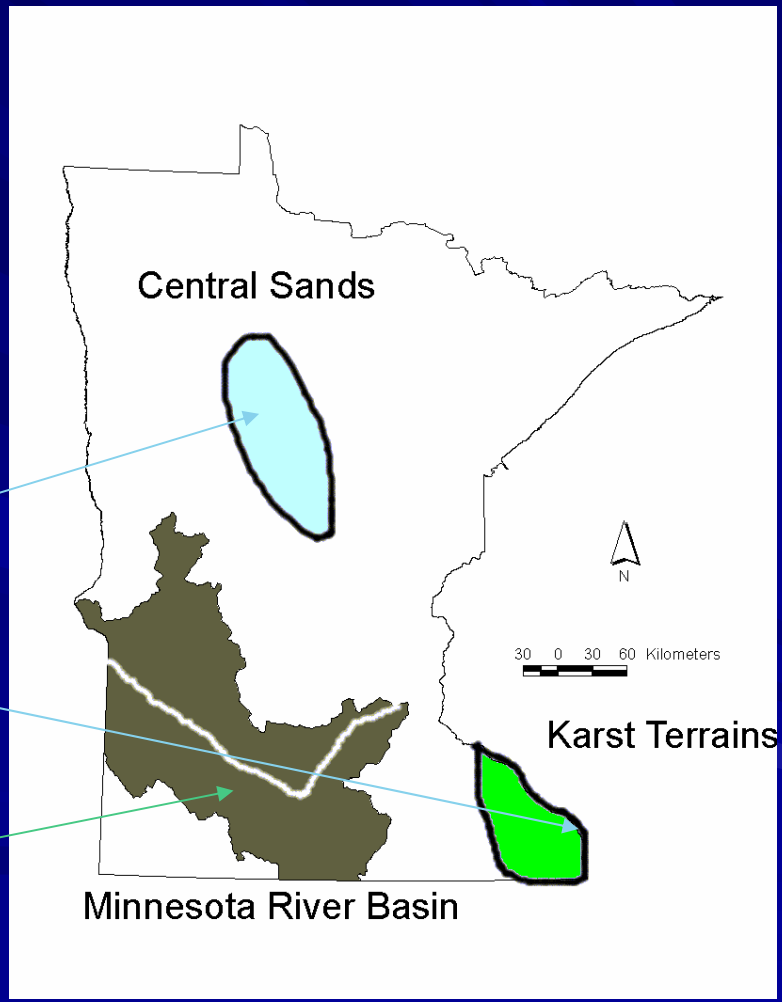
Antibiotic Losses from Manure Application

- Surface runoff
- Leaching

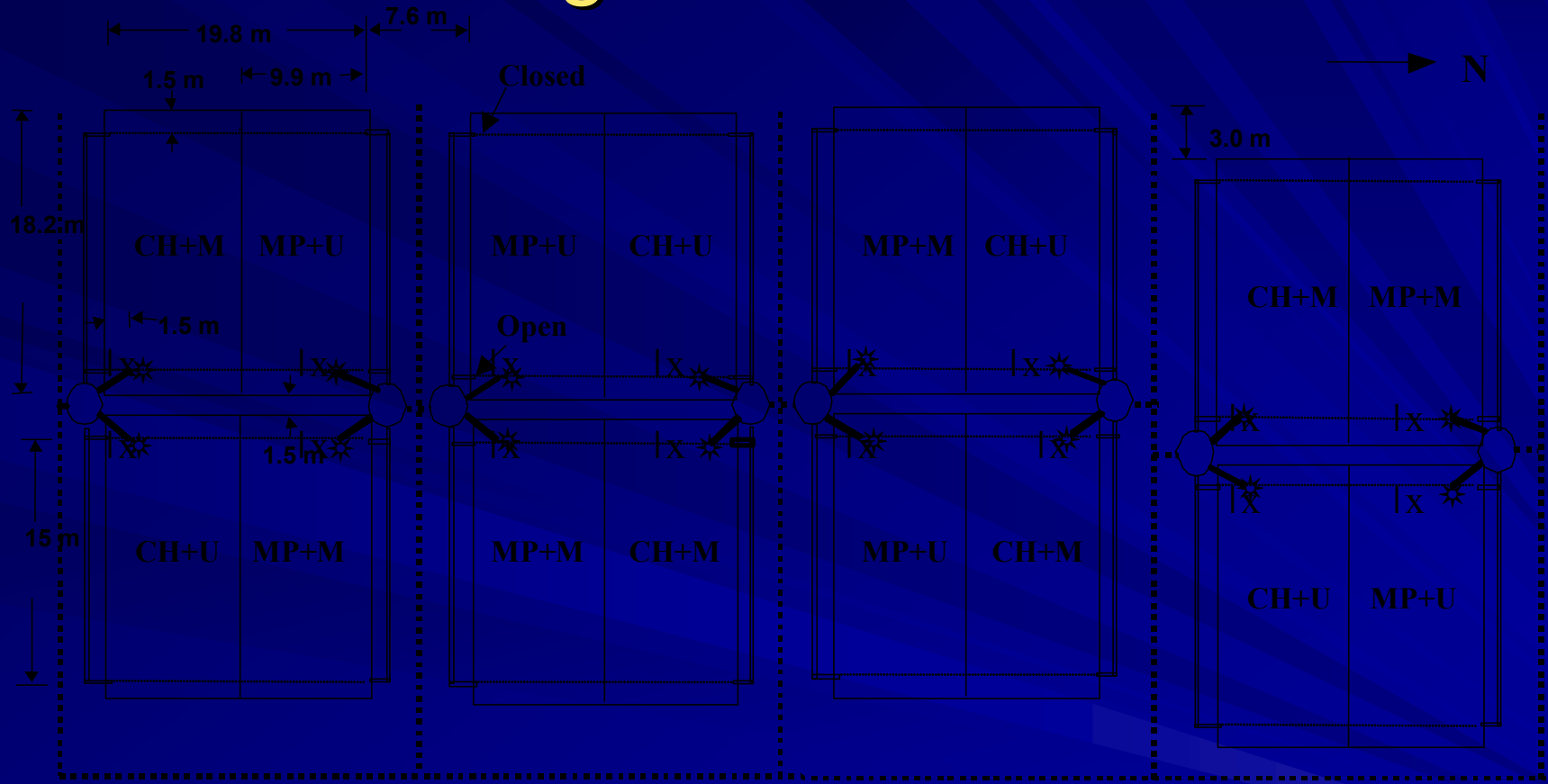
Staples (turkey and swine)

Lancaster, WI (swine and beef)

Lamberton (swine)



Drainage and Runoff Plots



Legend:

- Primary tile line (Diameter=10.2 cm)
- Second tile line (Diameter=12.7 cm)
- Non-porous tile line (Diameter=10.2 cm)
- Berm and plastic barrier
- Surface inlet
- Monitoring wells

MP+M: Moldboard plow & Manure
MP+U: Moldboard plow & Urea
CH+M: Chisel plow & Manure
CH+U: Chisel plow & Urea

Surf-N-Sub Plot Set-up

Monitoring Well


Equipment shelter
ISCO

Winter and Snowmelt Scenes

Antibiotics Applied in Manure

- Manure applied=46.23 m^3/ha
  (4000 gallons/ac)
- Chlortetracycline=5.0mg/L of manure
  =231 grams/ha (0.21 lbs/ac)
- Tylosin=5.6 mg/L of manure
  =259 grams/ha (0.23 lbs/ac)

Antibiotic Losses

- No losses of dissolved chlortetracycline in surface runoff or through tile drainage
- No losses of dissolved tylosin in tile drainage

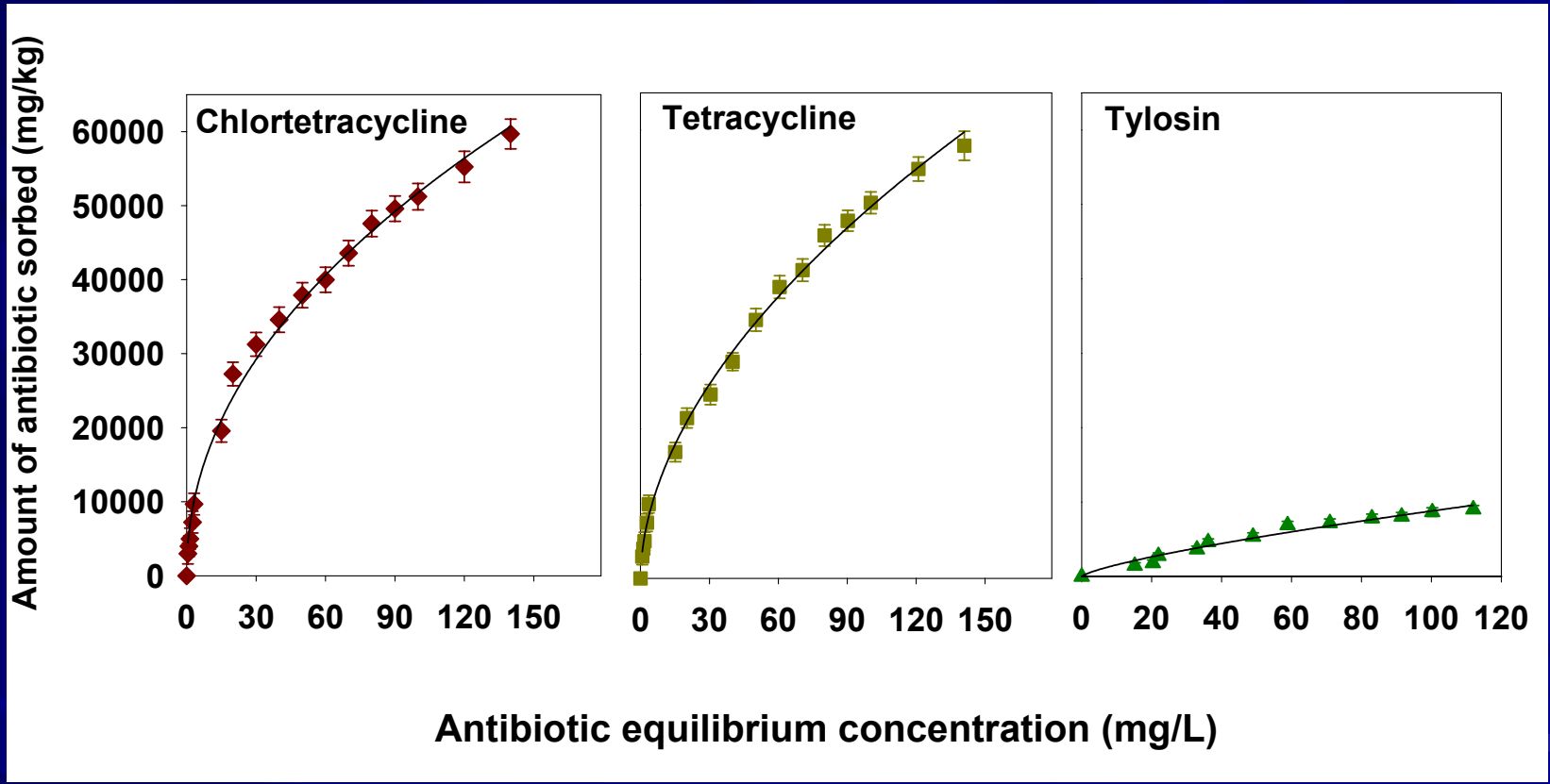
Dissolved Tylosin Losses via Surface Runoff

Event	Manure mg/ha
30 July	47
4 August	4
9 August	114
22 August	4
Total	169

0.07% of tylosin applied

Adsorption Isotherm- Batch Studies

Webster clay loam-34% clay



Kumar et al., 2003

Chlortetracycline (CTC) and Tylosin (TYL) Remaining in the Soil (Webster clay loam) after 1 Year

Treatment	0-15 cm g/ha	15-30 cm g/ha	Total (g/ha) (% of applied)
TYL -MP-M	76	41	117 (45%)
TYL -CP-M	91	56	147 (57%)
CTC -MP-M	84	16	100 (43%)
CTC -CH-M	117	26	142 (62%)

antibiotics not detected below 30 cm depth.

Antibiotic Half-life (Days) During Composting of Turkey Manure

Treatment	CHLOR-TETRACYCLINE	MONENSIN	TYLOSIN
Low Management	1	22	23
High Management	0.9	19	16
Vessel	0.8	11	19

Holly Swanson and Kuldip Kumar, 2008

Cowazaky
Another Energy Solution

Summary

- Land application of manure is a major pathway of spread of antibiotics in the terrestrial environment.
- Composting may reduce residual antibiotic concentrations in manure.
- The overall contribution of biosolids may be relatively small.

Land application of manure and biosolids may result in antibiotics entering the food chain ?

What is the Concern?

- Residues entering the food chain
- **Potential** adverse effects †
  - Development and spread of antibiotic resistance
  - Acute effects from allergic/ toxic reactions
  - Chronic effects from prolonged exposure
  - Disruption of digestive system functioning
- Not regulated (unlike animal residues)

† Kumar, K., S.C. Gupta, S.K. Baidoo, Y. Chander, and C.J. Rosen. 2005. Antibiotic uptake by plants from soil fertilized with animal manure. J. Environ. Qual. 34:2082-2085.

Help

Organic farming

US veg: not so organic?

By Jennifer Rohn

Reports that US growers of organ aic vegetables may be contaminating their produce with antibiotic-laden manure raises questions over the quality of the more than $40m (€34m) of 'organic' produce imported into the UK from the US every year.

Certified organic farmers in the US can use untreated manure from livestock treated with antibiotics and other drugs. But researchers from the University of Minnesota have shown that urine. Many farmers, conventional and organic, routinely recycle this waste as fertiliser.

Although it is known that these substances can leach into the environment, no one had checked whether they are incorporated into vegetables. Kuldip Kumar and colleagues at the University of Minnesota planted corn, cabbage and green onions in soil treated with manure from pigs fed antibiotics, and several weeks later were able to measure chlortetracycline in the edible plant tops human microbial diseases ineffective. Kumar believes that hormones may also be taken up by vegetables grown in raw manure.

According to Holly Givens of the Organic Trade Association of America, nearly 60% of organic farmers use raw manure 'frequently or regularly'. Other organic growers compost their manure first, and there is a mandatory time lag between manure spreading and harvest. But as little is known about how composting and time limits affect

Plants

Corn

Lettuce

Potato

Discussion

- Antibiotic uptake†
  - No uptake of tylosin (Bigger molecule)
  - Sulfamethazine: 0.008-0.100 mg kg^{-1} (ppm) *fresh weight*
  - Chlortetracycline: 0.002-0.017 mg kg^{-1} (ppm) *fresh weight*
- Overall recovery of sulfamethazine and chlortetracycline in plant tissues was **<0.1%** applied in manure
  - >70% in soil (i.e. not fully degraded)
- Differences due to:
  - Antibiotic structure/ chemistry
  - Biomass & concentration
  - Physiology
  - Crop stage

† Kumar, K., S.C. Gupta, S.K. Baidoo, Y. Chander, and C.J. Rosen. 2005. Antibiotic uptake by plants from soil fertilized with animal manure. J. Environ. Qual. 34:2082-2085.
Swanson, H., Kumar, K and Gupta, S.C. 2007. J. Environ. Qual., 36, 1224-1230

Discussion

U.S. Food and Drug Administration Regulations †

- **Animal residues: <0.1 mg kg^{-1} (ppm)**
- **Plant residues: NO REGULATION**
  - **Current study**
    - **<0.1 mg kg^{-1} (ppm) fresh weight**
    - **>0.1 mg kg^{-1} (ppm) dry weight**

- **Potential** for food supply contamination (low levels)
- Organic farming implications

Regulatory Purposes – Maximum Residue Levels (MRLs)

MRLs (antibiotics) in animal tissues < 1 mg kg^{-1} fresh weight.

Sulfamethazine MRL = 0.1 mg kg^{-1} fresh weight of animal based products.

Acceptable Daily Intake (ADI) for Veterinary Pharmaceuticals (JECFA, 2006)

ADI value indicates the level of chemical that can be ingested daily over a lifetime without health risk.

Antibiotics ADI = 50 μg kg^{-1} body weight

Effect of Cooking on Antibiotics in Plant/Animal Based Foods

- Sulfamethazine was stable for 6 h in boiling water but not in hot oil ($t_{1/2}$ = 120 min at 180 ^{o}C and 5 min at 260 ^{o}C).
- Sulfamethazine spiked into raw pork was also found to be stable during a variety of common cooking processes (casseroling, roasting, grilling, pressure cooking, microwaving, and frying).
- Oxytetracycline was not stable in water, oil, and cooking processes.

Summary

Manure

- Chances of antibiotics getting into plant based foods from manure applied soils are low
  - Very low concentrations
  - Actual health impact not known (low risk)

Biosolids

- Concentrations of antibiotics are way lower compared to manure to begin with.
- Not applied for use in human food crops in IL.

Bacterial Resistance to Antimicrobials

Life Magazine (Aug. 14, 1944)

- "…the greatest news event of World War II may well be the discovery and development…of penicillin."

- "miracle drugs"
- "wonder drugs"
- "magic bullets"

⇨ **The Golden Age**

The Golden Age

- 1969, Surgeon General of United States: "It is time to close the book on infectious diseases"
- Smallpox - global eradication, last case in 1977
- 1990, TB and pneumonia caused less than 4% of deaths
- Measles - record low level in 1995

Worldwide *Streptococcus pneumoniae* resistance (2003)

Country	Azithromycin %	Penicillin %
Ireland	18.9	18.9
France	54.2	35.4
USA	35.4	28.7
Hong Kong	82.9	64.3
Australia	16.8	13.6

Antibiotic Resistance

- **Susceptible = sensitive**
  - MIC is at a concentration attainable in blood or other appropriate body fluid using usually recommended dosages
- **Resistant**
  - MIC is higher than normally attainable levels in body fluids
- **Intermediate (moderately sensitive, moderately resistant)**
  - MIC is between sensitive and resistant levels, may be able to treat with increased dosage

The Golden Age has ended

Factors Associated with the Spread of Antibiotic-Resistant Bacteria

- Inappropriate use of antibiotics
  - Worldwide overuse
    - Extensive use in upper respiratory infections
  - Incomplete or incorrect therapeutic regimes
  - Availability of antibiotics without prescriptions
- Failure of hospital infection control policies
- Widespread use of antibiotics as a “growth enhances” in animal agriculture
- Increased opportunities for clonal dissemination of antibiotic-resistant bacteria both within and outside the hospital setting
  - Global dissemination of particular strains

Consequences of Antibiotic-Resistant Bacteria

- Change in the approach to the administration of "empiric antibiotic therapy"
- Increased number of hospitalizations
- Increased length of hospitalizations
- Increased morbidity and mortality
  - Emergence of strains totally resistant to all available antibiotics
- Choice of more expensive or more toxic therapeutic alternatives
- Increased costs by ~ 5 billion dollars

How did we get here?

Timeline of antibiotic resistance

- 1942 - penicillin available
- 1942 - penicillin resistant *S. aureus*
- 1940's-1950's - chlorampenicol, tetracycline, erythromycin resistance
- Early '60s - β-lactamase resistant penicillins available
- Late '70s - MRSA arose (methicillin resistant *S. aureus*)
- 1997 - first vancomycin resistant Enterococcus reported
- July 2002 - CDC reported first case of vancomycin-resistant *S. aureus* in US

It Can Happen to Anybody!

March 11, 2002

Oakland Tribune

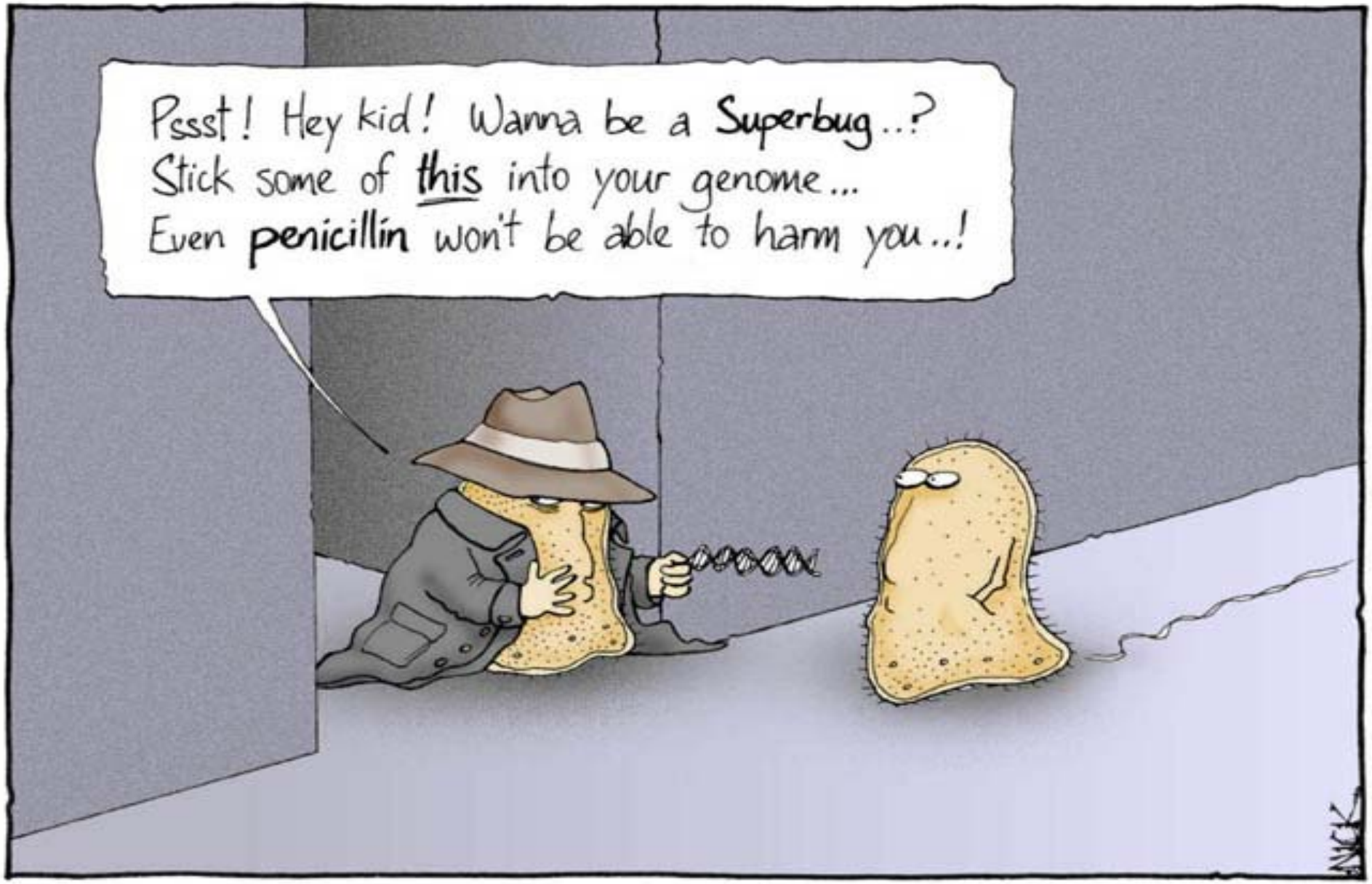
Drug-resistant bacteria turns cut into life threatening ordeal

Critics: Drugs overused in people, animals

By Matt Carter

BOBBI MCKEON, a nurse practitioner who lives in Pleasanton, shows the finger that landed her in the hospital after drug-resistant bacteria infected a paper cut.

How do they do it?

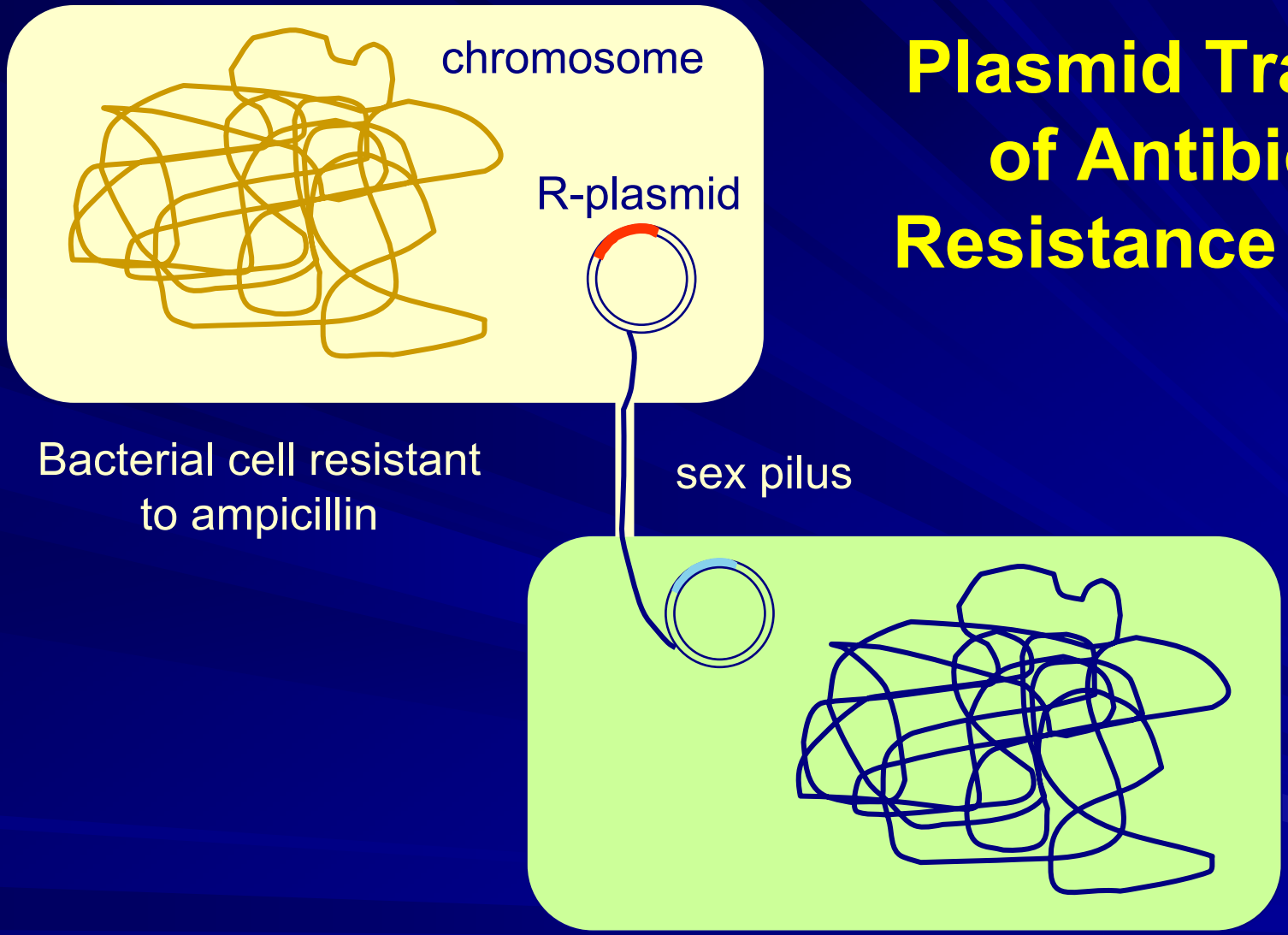


It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

Genetics of Resistance

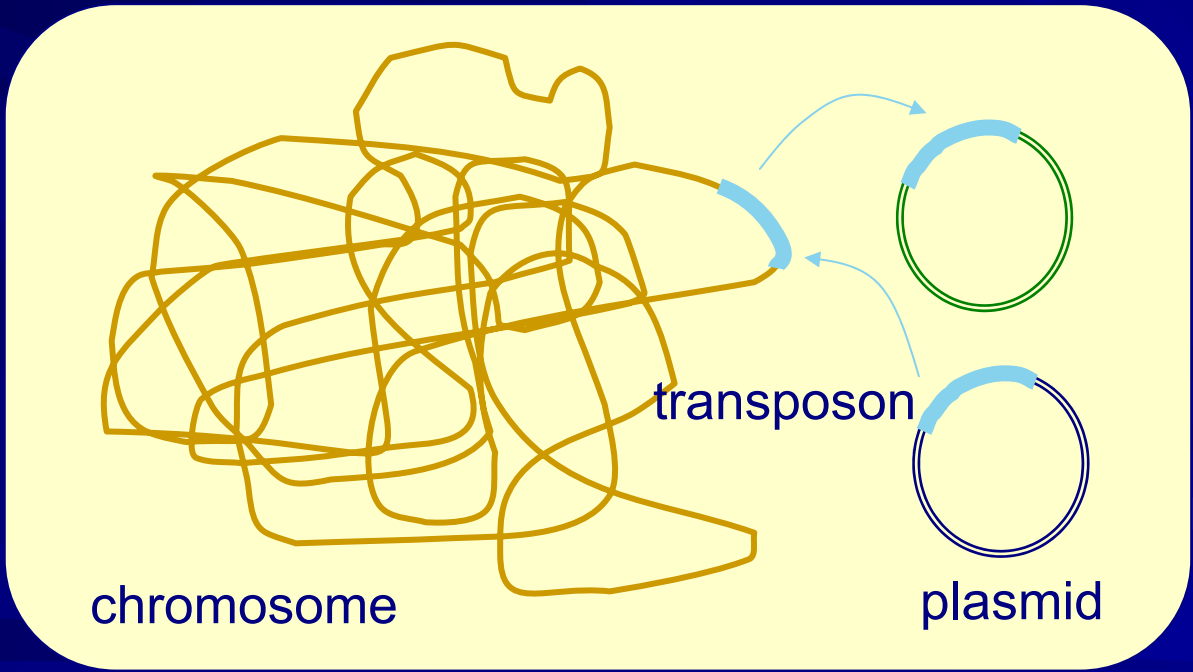
- Intrinsic
  - Proteins or impenetrable
- Acquired
  - Chromosomal mutation and selection
  - Plasmid-borne resistance
  - Transposition (Transposons)
  - Integrons

Plasmid Transfer of Antibiotic Resistance genes



How do plasmids acquire new genes?

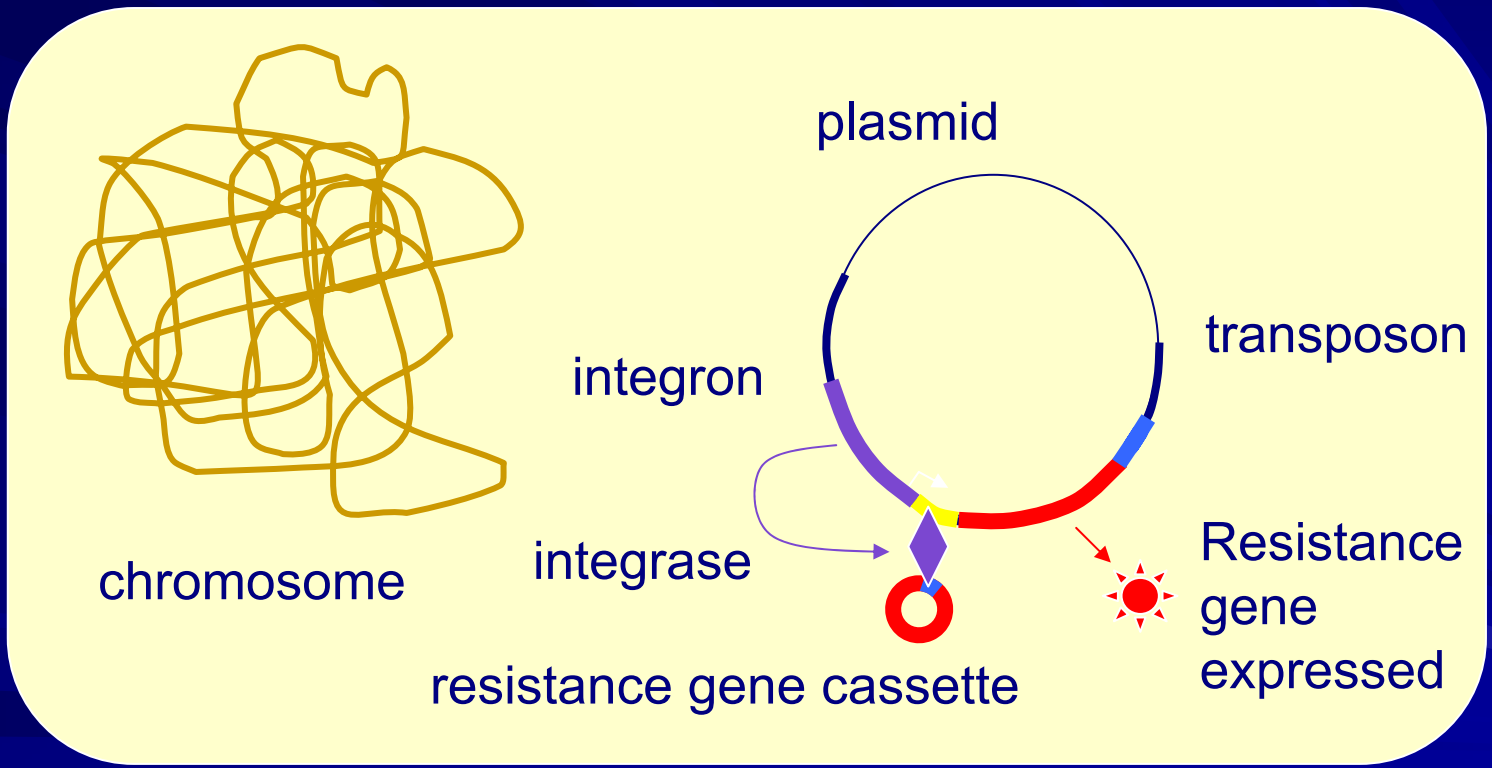
TRANSPOSITION - “jumping genes”



How do transposons acquire new genes?

INTEGRONS - gene capture and expression systems

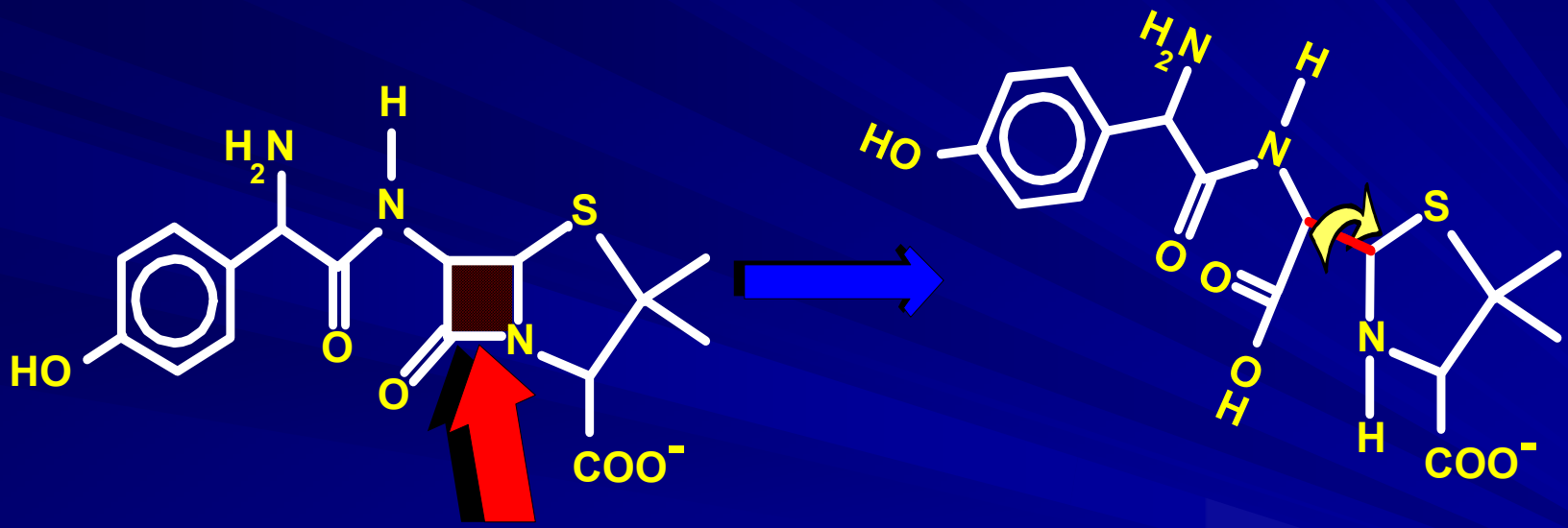
"natural" genetic engineering



Mechanisms of Chromosomal Resistance

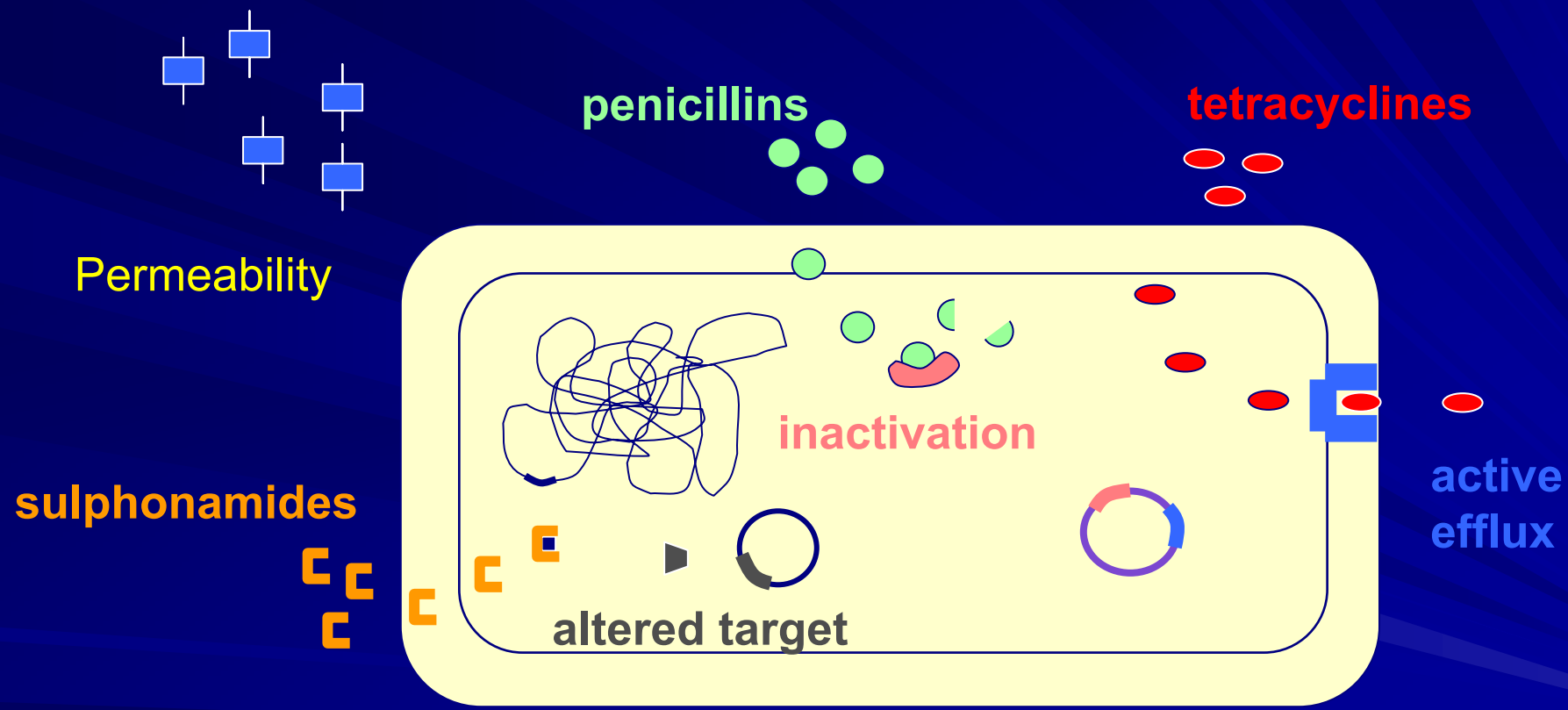
Impermeability	Tetracycline Most antibiotics with Pseudomonas
Efflux	Tetracycline Fluoroquinolones
Inactivation	β-lactam (β-lactamases) Aminoglycosides (modifying enzymes)
Hyperproduction	Trimethoprim
Altered Target	Trimethoprim Sulphonamides Fluoroquinolones Aminoglycosides

β-lactamase Action on Amoxycillin



β-lactamase

How do bacteria resist the action of antibiotics?



Question?

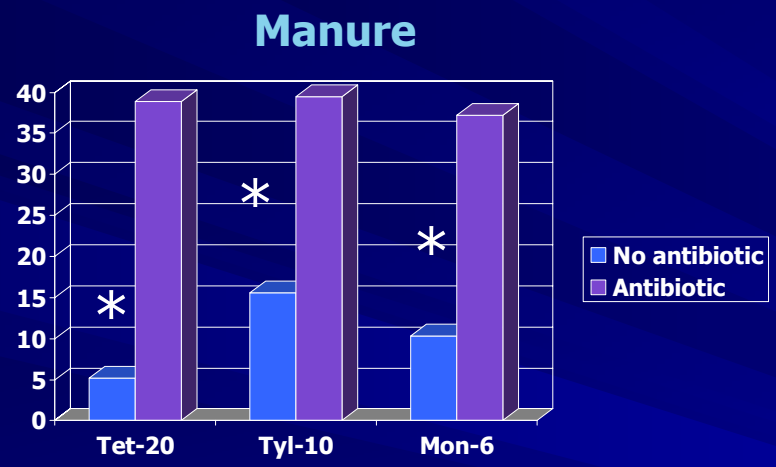
What is the role of antibiotic feeding on development of antimicrobial resistance on the farm?

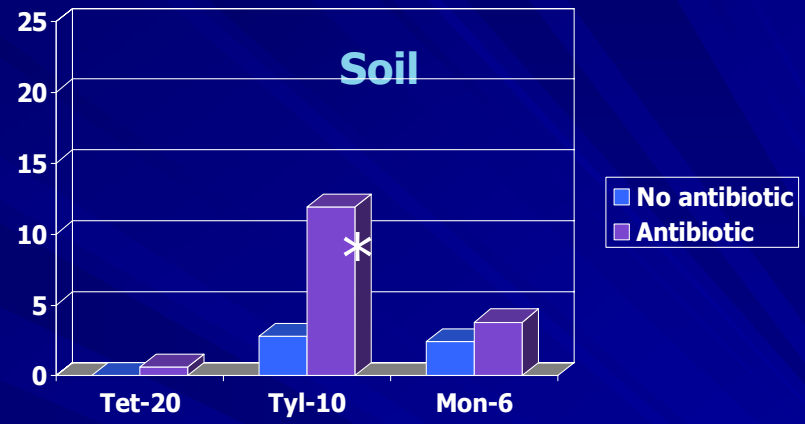
Pictures of Animal Farms

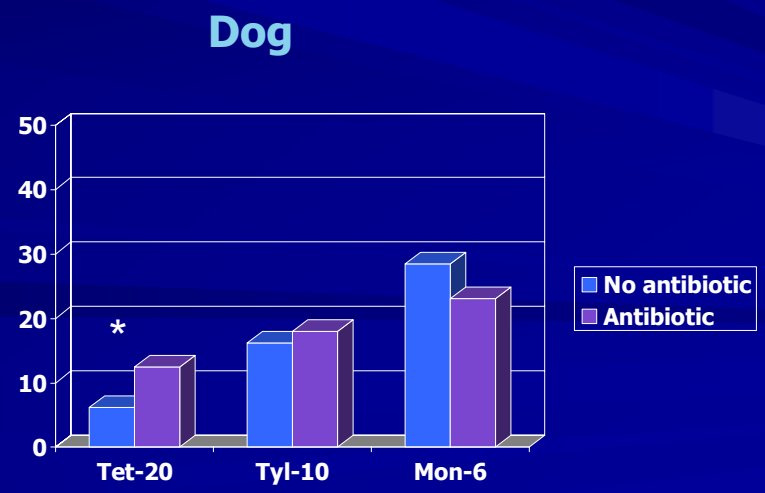
With antibiotic feeding

Without antibiotic feeding

Percent Antibiotic Resistance Bacteria – Swine Farms







Tet-Tetracycline
Tyl-Tylosin
Mon-Monensin

Summary

- Feeding antibiotics may lead to increased resistance in manure and soil and may be transferred to dogs.

Laughter is the best medicine – I guess entertain them

Evolution of Antimicrobial Therapy in a Nutshell

- Yr 2000 B.C. — "Here eat this root"
- Yr A.D. 1000 — "That root is heathen. Here, Say this prayer"
- Yr 1850 — "That prayer is superstitious. Here drink this potion"
- Yr 1920 — "That potion is snake oil. Here swallow this pill"
- Yr 1945 — "That pill is ineffective. Here take this penicillin"
- Yr 1955 — "OOPS, Bugs mutated. Here take this Tetracycline"
- Yrs 1960-07 more — "Forty seven more OOPS's Here, take this powerful antibiotic"

- Yr 2010… "The Bugs have won! Here eat this root"

What do we do now?

Patient Guidelines

- Don’t insist on antibiotics when your doctor says they are not needed
- If you are prescribed drugs, take the full course
- Never hang on to unfinished prescriptions with the intention of using them for new ailments
- Never share antibiotics with others
- Keep a diary of antibiotic use

Physician Guidelines

- Reduce inappropriate use of antibiotics
- Meticulous infection control, especially in hospitals and long term care facilities
- Reduce use of broad spectrum antibiotics, use narrow spectrum antibiotics when possible
- Urge patient compliance
- Increase surveillance

Federal Intervention

- FDA proposes ban of two poultry drugs (10/27/00)
  - Fluoroquinolones
  - Abbott has pulled drug, Bayer has not
- New antibiotics
  - Zyvox (linezolid) - active against MRSA, VRE
    - FDA approved 4/00
  - Synercid - active against MRSA
    - FDA approved 9/99
    - Turkeys fed virginiamycin have Synercid-resistant bacteria

Roadblocks

- Research and development of new antibacterial can take 15-20 years and cost over $500 million.
- Pharmaceutical companies want largest usage from products
- Farmers and ranchers resist bans on agricultural use

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Perspective

Antibiotics: Has the magic gone?

Chander… Kuldip Kumar

Not Over Yet

But there are serious concerns about the decreasing effectiveness of antibiotics because of increased antibiotic prevalence and emergence of antibiotic resistance in the environment


2000. 11. 2

Which bacteria are of greatest concern for antibiotic resistance?

Streptococcus pneumoniae

- Most common cause of bacterial pneumonia, also causes meningitis, bacteremia, >7 million ear infections per year,
  - 10-40% are caused by DRSP (drug-resistant *S. pneumoniae*)
- Until late 1970's, readily killed with penicillin
- Now, up to 30% are penicillin resistant

Enterococcus

- 1987 - Van-R Enterococcus - England and France
- 1989 - NYC
- 1991 - 38 US hospitals
- 1992 - lab transfer to *Staphylococcus*
- 1993 - 14% patients in ICU with VRE

Staphylococcus aureus

- Methicillin resistance common
- Vancomycin susceptibility decreased (VISA - vancomycin-intermediate *S. aureus*)
- VRSA - vancomycin resistant *S. aureus*

Neisseria gonorrhoeae

- More than 50% are resistant to penicillin or tetracycline or both
  - in SE Asia, ~98% are penicillin resistant
- Resistance to ciprofloxin increasing
- Gonorrhoea increases shedding of HIV, may also increase susceptibility

Mycobacterium tuberculosis

- 1/7 new TB cases is resistant to isoniazid and rifampin (5% die)
- Cost of treating one person with multidrug-resistant TB is 100 times greater than the cost of treating non-resistant cases.
  - NYC spent $1 billion to control outbreak of multidrug-resistant TB in early 1990s
- All known resistance due to mutation
  - Therefore, multiple drugs beneficial

Escherichia coli

- Resistance to fluoroquinolones
  - 1983-1990, all were susceptible (92 strains)
  - 1991-1993, 11/40 were highly resistant to 5 different quinolones