Fermentation – An Old Profession

Koji from rice by *Aspergillus oryzae* = 5,000 years

Cheese by *Penicillium roqueforti* = 4,000 years

Soy sauce in Asia = 3,000 years

Bread in Egypt = 3,000 years

(Hoelker *et al.,* 2004)

Microbes: Masters of the Biosphere

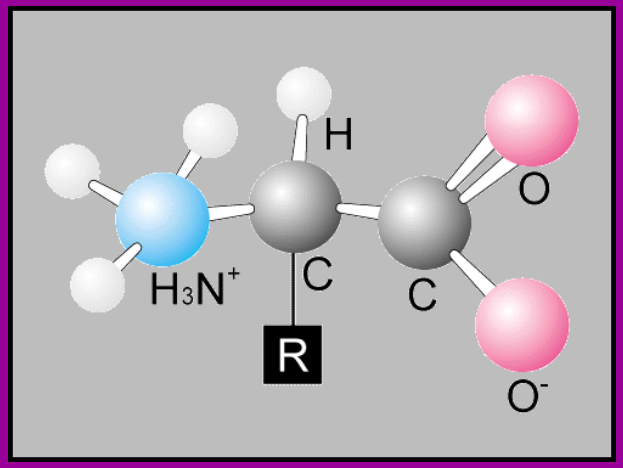
- **Life on earth is not possible without microbes**
- **They are the progenitors of all life on earth**
- **Characteristics:**
  - Rapid generation times
  - Genetic flexibility
  - Unequaled experimental scale
  - Manageable study systems
- **Estimate: $5x10^{31}$ microbial cells exist = 50 quadrillion metric tons**
- **Carry out more photosynthesis than green plants**
- **Over 90% of the cells in our bodies are microbial**
- **Sterile animals are less healthy then those colonized by microbes**

PRIMARY METABOLITES

- Integral part of normal growth processes
  - Building blocks for macromolecules
    - Amino Acids
    - Nucleotides
  - Precursors of coenzymes
    - Vitamins
  - Precursors of lipids
    - Fatty Acids
    - Glycerol
  - Precursors of polysaccharides
    - Sugars
  - Catabolic products
    - Organic acids
    - Ethanol
    - Acetone
    - Butanol

TITERS OF AMINO ACID PROCESSES

L-lysine HCl	170 g/L
L-glutamate	130
L-alanine	114
L-valine	105
L-threonine	100
L-proline	100
L-arginine	96
L-serine	65
L-tryptophan	60
L-tyrosine	55
L-phenylalanine	51
L-glutamine	49
L-histidine	42
L-hydroxyproline	41
L-isoleucine	40
L-leucine	34



Organic Acids

- Pyruvic: 80 g/L at 2 g/Lh by recombinant *Escherichia coli* – fed-batch
- Gluconic: 240 g/L with 99.4% yield by *Penicillium variable*; 50,000-60,000 tons, mainly by *Aspergillus niger*
- Fumaric: 107 g/L by *Rhizopus arrhizus*
- D-Lactic: 120 g/L by recombinant *Corynebacterium glutamicum*
- L(+) Lactic: 136g/L by *Rhizopus oryzae*
- Succinic: 146 g/L in 46h by recombinant *C. glutamicum*
- Malic: 113 g/L by *Aspergillus flavus*

(Crognale et al., 2008; Engel et al., 2008, Okino et al., 2008; Zelle et al., 2008;Skory, 2004; Ge et al., 2004; Ding and Tan, 2006; Zhu et al., 2008)

SECONDARY METABOLITES

- ANTIBIOTICS
  - ANTIBACTERIAL
  - ANTIFUNGAL
- NON-ANTIBIOTIC
  - INSECTICIDES
  - ANTITUMOR AGENTS
  - HERBICIDES
  - ANTI-PARASITIC AGENTS
  - PLANT-GROWTH REGULATORS
  - PHARMACOLOGICAL AGENTS
  - ENZYME INHIBITORS
  - IMMUNOSUPPRESSANTS

NATURAL PRODUCTS

- 1 million total
- - 500,000-600,000 by plants
- - 50,000 by microbes
- 200,000-250,000 biologically active
- - 22,500 biologically active from microbes
- * 10,100 (45%) by actinomycetes
- * 8,600 (38%) by fungi
- * 3,800 (17%) by unicellular bacteria

Berdy, 2005

ANTI-INFECTIVE MARKET IN 2000

- **Cephalosporins = $9.9 billion.**
- **Penicillins = $8.2 billion.**
- **Other β-lactams = $1.5 billion.**
- **Antivirals excluding vaccines = $10.2 billion.**
- **Quinolones = $6.4 billion.**
- **Antifungals and antiparasitics = $4.2 billion.**
- **Aminoglycosides = $1.8 billion.**
- **Tetracyclines = $1.4 billion.**
- **Other antibacterials = $6.1 billion.**
- **Total = $55 billion.**
- (M.S. Barber, 2001)

BENEFITS OF SECONDARY METABOLITES

- Average life expectancy in the USA increased from 47 years in 1900 to 74 years (males) and 80 years (females) in 2000.
- Reduced pain and suffering.
- Revolutionized medicine by facilitating organ transplantation.

(Verdine, 1996; Lederberg, 2000)

ANTI-CANCER AGENTS SINCE 1940

- >60%: Natural products, derivatives, or mimics
- Approved products
  - Actinomycin D
  - Anthracyclines (daunorubicin, doxorubicin, epirubicin, pirirubicin, valrubicin
  - Glycopeptolides (bleomycin)
  - Mitosanes (mitomycin C)
  - Anthracenones (mithramycin, streptozotocin, pentostatin)
  - Endiynes (calcheamycin)
  - Taxol

(Newman and Cragg, 2005)

METASTATIC TESTICULAR CANCER

- Uncommon (1% of male malignancies in USA; 80,000 in USA in 2000).
- Most common carcinoma in men aged 15-35.
- Cure rates:

  5% in 1974

  90% in 2001
- Combination chemotherapy:

  Bleomycin + etopside + cisplatin.

(L.H. Einhorn, 2002)

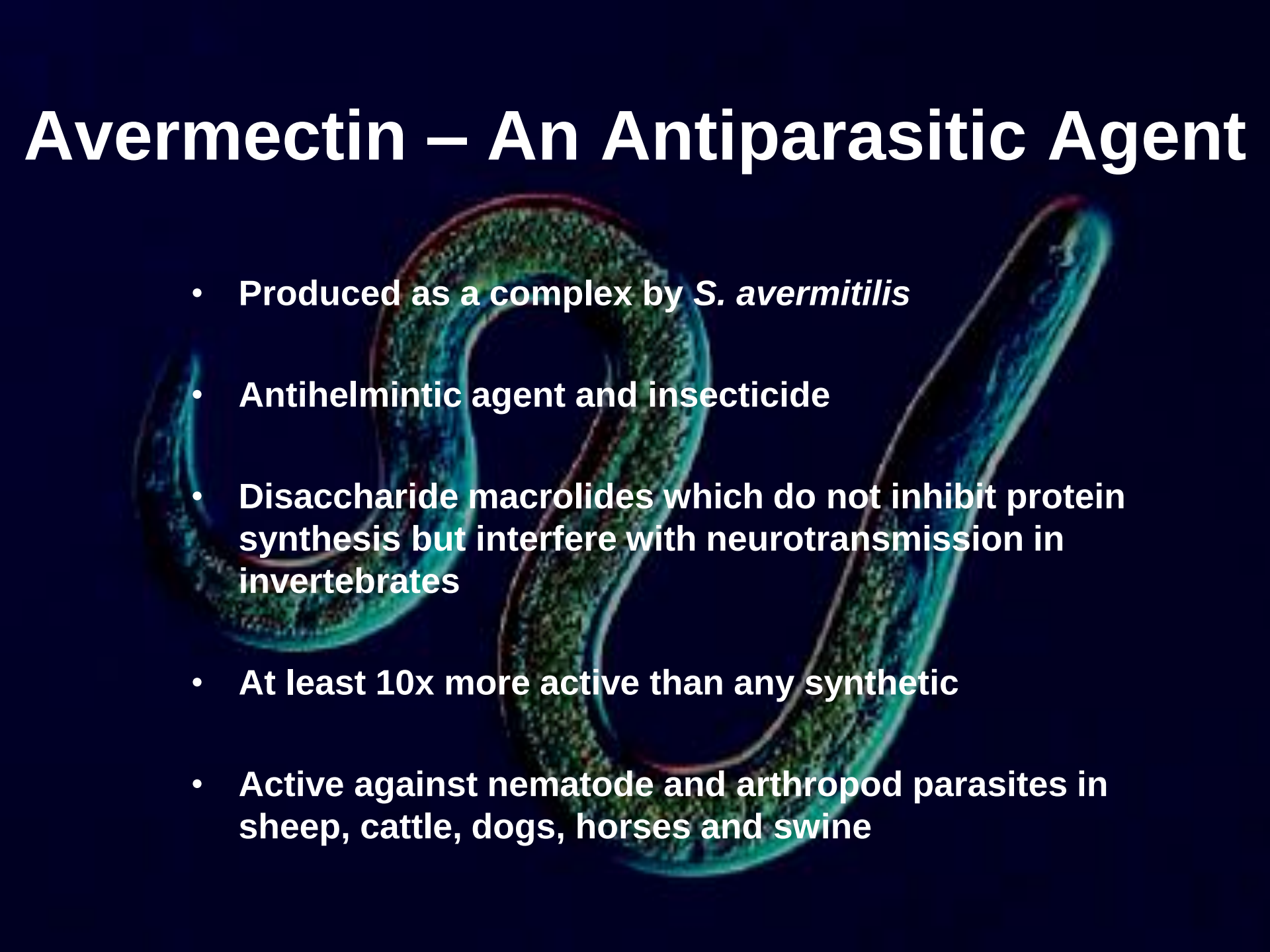
Rapamycin

- Discovered as antifungal agent.
- Produced by *Streptomyces hygroscopicus*.
- Unusual nitrogen-containing triene macrolide (polyketide) with very large 31-membered lactone ring.
- Has antitumor activity.
- Immunosuppressive potency somewhat greater than FK-506 and 150X cyclosporin A.
- Toxicity less than cyclosporin A.
- Precursors: acetate, propionate, methionine, pipecolate, shikimate.

STATINS

- Produced by *Aspergillus, Monascus, Penicillium, Doratomyces, Eupenicillium, Gymnoascus, Hypomyces, Paecilomyces, Phoma, Trichoderma,* and *Pleurotis.*
- Uses
  - Reduce risk of cardiovascular disease
  - Prevent stroke
  - Reduce development of peripheral vascular disease
  - Antithrombotic
  - Anti-inflammatory
- Lovastatin production by *A. terreus* = 7-8 g/L.
- Compactin production by *P. citrinum* = 5 g/L.
- Pravastatin can be made directly by certain strains of *Aspergillus* and *Monascus.*
-
- (Manzoni et al., 1998, 1999; Manzoni & Rollini, 2002)

Avermectin – An Antiparasitic Agent



- Produced as a complex by *S. avermitilis*
- Antihelmintic agent and insecticide
- Disaccharide macrolides which do not inhibit protein synthesis but interfere with neurotransmission in invertebrates
- At least 10x more active than any synthetic
- Active against nematode and arthropod parasites in sheep, cattle, dogs, horses and swine

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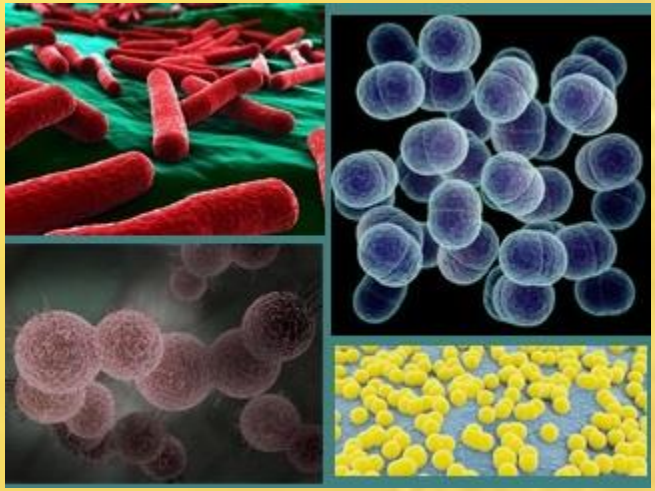

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