MID-ATLANTIC NUTRITION CONFERENCE 2017

NUTRITIONAL ALTERNATIVES TO ANTIBIOTICS: MODULATING GUT IMMUNITY WITHOUT COMPROMISING PRODUCTION

Kimberly Livingston, PhD
Prestage Department of Poultry Science
ANTIBIOTICS

• Greek means “life killing”

• A drug used to treat bacterial infections

• A substance that is capable of destroying microorganisms

• A substance produced by one organism that inhibits the growth of another
HISTORY OF ANTIBIOTICS

• Traces of tetracycline found in Sudanese Nubia skeletal remains

Tetracycline-labeled human bone from ancient Sudanese Nubia (A.D. 350)

EJ Bassett, MS Keith, GJ Armelagos, DL Martin, AR Villanueva
See all authors and affiliations

Science 26 Sep 1980:
Vol. 209, Issue 4464, pp. 1532-1534
DOI: 10.1126/science.7001623

• Traditional Chinese Medicine

Research Paper
Antimicrobial activity of Chinese medicine herbs against common bacteria in oral biofilm. A pilot study

Show more

http://dx.doi.org.proxy.lib.ncsu.edu/10.1016/j.ijom.2010.02.024
HISTORY OF ANTIBIOTICS

• Modern Antibiotic Era

Paul Ehrlich
• Discovered Salvarsan to treat syphilis

Alexander Fleming
• Antibacterial action of penicillium in 1929

Howard Florey and Ernst Chain
• Purification of penicillin in 1940
ANTIBIOTICS IN LIVESTOCK

• Moore et al. 1946 showed chickens given antibiotics had increased growth

USE OF SULFASUXIDINE, STREPTOTHRICIN, AND STREPTOMYCIN IN NUTRITIONAL STUDIES WITH THE CHICK*

By P. R. Moore, A. Evenson, T. D. Luckey, E. McCoy, C. A. Elvehjem, and E. B. Hart

(From the Departments of Biochemistry and Agricultural Bacteriology, College of Agriculture, University of Wisconsin, Madison)

(Received for publication, June 27, 1946)

• 1948-1952 numerous papers demonstrated similar responses with other antibiotics
Antibiotics employ different modes of action (Ferket, 2004)
GUT HISTOLOGY WITH ANTIBIOTICS

- Decreased
  - villi height
  - Crypt depth
  - VH:CD ratio

- Thinner muscle

- Still do not know molecular mechanism
Coats et al. 1952

• First to try explaining the improved growth of chicks with antibiotics
  Penicillin prevented ‘infection’ of gut

Antibiotics as Growth Promotants

1. **DIRECT**
   - Reduced competition with host for nutrients

2. **INDIRECT**
   - Decreased production of growth-depressing metabolites
     - Aromatic phenols
     - Ammonia
     - Bile degradation products
     - Reduced intestinal inflammation

- Reduced turnover of gut mucosa
  - Mature mucin
  - Digestive enzymes
  - Gut morphology

**Figure 3.** Diagram of the proposed effects of antibiotics mediated through their effects on small intestinal microflora.[6]
ANTIBIOTIC CONCERNS

• Starr and Reynolds (1951)
  – First report of bacterial resistance in poulets

• British Parliament (1969)
  – discussed banning subtherapeutic AGP

• United States
  – Institute of Medicine (1980, 1989)
  – Committee on Drug use in Food Animals (1998)

• World Health Organization
  – Publish report linking AGP with resistance (1997)
ANTIBIOTIC BANS

• Sweden bans AGP – 1986
• Denmark bans Avoparcin in 1995
  – 1997 bans virginiamycin
  – 1998 voluntary halt of all AGP
• European Union ban of AGP
  – bans the use of all AGP for livestock January 1, 2006
• South Korea
  – Bans AGP for livestock July 1, 2011
• United States
  – Veterinary Feed Directive effective January 1, 2017
ALTERNATIVES TO ANTIBIOTICS

• Probiotics
• Prebiotics
  – MOS and FOS
• Herbal extracts
• Organic acids
• Vitamin Supplements
• Oral vaccines

• Similar growth as antibiotics
• Changes in GI morphology
• Salmonella shedding
ALTERNATIVES TO ANTIBIOTICS

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Do they increase natural antibiotics?
HOST DEFENSE PEPTIDES

• Small cationic peptides
• Originally call antimicrobial peptides
  – Ability to kill bacteria
  – Can kill enveloped viruses, fungi, cancer cells
• Found in all classes of life
• Part of innate immune system
HOST DEFENSE PEPTIDES

Modulate the immune response
- Differentiation
- Chemotaxis
- Enhance phagocytosis
AVIAN HOST DEFENSE PEPTIDES

• 3 classes
  1. B-defensin
  2. Cathelicidins
  3. Liver-expressed antimicrobial peptide 2 (LEAP-2)
DEFENSINS

• Cysteine-rich, cationic peptide
  – 3 disulfide bridges
  – β-pleated sheet
• 14 avian defensins
  – 13 expressed as early as ED 3
• Expressed in wide range of tissue
DEFENSINS

- Active against fungi and bacteria
- Positively charge components interact with negatively charge membrane disrupting the pathogen
- Immunomodulation
  - Bind chemokine receptors
CATHELICIDINS

• Short peptides (<40 AA)
• α-helical
• Amphipathic structure
  – Reacts with negatively charged molecules
• Expressed on wide range of tissues
CATHELICIDINS

• Mainly bacteria killing
• Expression first detected at ED 3
• Mechanism of killing still unknown
• Immunomodulation
  – Inhibit IL-1β transcription
  – Cell differentiation and activation
  – Leukocyte migration
LEAP-2

- 40 AA cationic peptide
- 2 disulfide bridges
- 60% homology to mammalian LEAP-2
- Expressed in Liver, intestine, gall bladder, kidney, reproductive tract
NUTRITIONAL MODULATION OF HOST DEFENSE PEPTIDES

Probiotics
Probiotic lactobacilli and VSL#3 induce enterocyte β-defensin 2

Expression is time dependent and concentration dependent
HOST DEFENSE PEPTIDES & PROBIOTICS

A. **AvBD1**

B. **AvBD2**

C. **AvBD6**

E. **Cathelicidin**

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PROBIOTICS AND HDP

The effect of microbial-nutrient interaction on the immune system of young chicks after early probiotic and organic acid administration¹

J. C. Rodríguez-Lecomte,*² A. Yitbarek,* J. Brady,* S. Sharif,† M. D. Cavanagh,* G. Crow,* W. Guenter,* J. D. House,‡ and G. Cameloa-Jaimès§

*Department of Animal Science, University of Manitoba, Winnipeg R3T 2N2, Canada; †Department of Pathobiology, University of Guelph, Guelph, Ontario N1G 2W1, Canada; ‡Department of Human Nutritional Science, University of Manitoba, Winnipeg R3T 2N2, Canada; and §VH Biotechnology, Inc., West Palm Beach, FL 33401

Combination of probiotics and organic acids decreased AvBD-3 in bursa
NUTRITIONAL MODULATION OF HOST DEFENSE PEPTIDES

Butyrate
Butyrate-induced expression of the AvBD9 gene in different chicken cell types.

A

Fold Increase

0 3h 6h 12h 24h 48h

0 1000 2000 3000 4000 5000 6000

B

Fold Increase

0 0.5 1 2 4 8

Butyrate (mM)

0 100 200 300 400 500 600 700 800

C

Fold Increase

0 0.5 1 2 4 8

Butyrate (mM)

0 0.5 1 2 4

D

doi:10.1371/journal.pone.0027225
Up-regulation of HDPs in chicken jejunum (A) and ceca (B)

Reduction of the S. enteritidis titer in the cecal contents of chickens following oral supplementation of butyrate.

NUTRITIONAL MODULATION OF HOST DEFENSE PEPTIDES

Vitamin D
VITAMIN D & HOST DEFENSE PEPTIDES (HDP)

• Controls gene transcription
• Enhances HDP expression in humans
  – Cathelicidin (LL-37)
• Feeding vitamin D increased expression of some HDP
1,25D3 EFFECTS ON AVBD EXPRESSION IN PBMCS

1,25D3 & LPS EFFECTS ON AVBD EXPRESSION IN PBMCS

VITAMIN D HDP

(Zhang, Li et al. 2011)
CONCLUSIONS
CONCLUSIONS
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CONCLUSIONS

• Need to determine how antibiotics work
  – Mechanisms not theories

• Alternatives will not work exactly as antibiotics do
QUESTIONS?
Mid-Atlantic Nutrition Conference
April 6, 2017
We live in historical times.

The NRC is no more.
Long live the NRC!
Once upon a Civil War, 1863 – Lincoln signs a Congressional charter establishing the National Academy of Sciences as an independent scientific advisor.
Independent, Neutral, Non-governmental, Not-for-profit Leading (World) Scientific Authority having Credibility with Congress*
Independent, Neutral, Non-governmental, Not-for-profit
Leading (World) Scientific Authority having
Credibility with Congress*

Because when asked, the best scientists in the US and abroad
voluntarily serve on Academy panels that synthesize scientific information and data.
1863 – National Academy of Sciences was established.
1916 – (WWI) **National Research Council** was born as the operational arm of the NAS.
1964 – National Academy of Engineering established.
1970 – Institute of Medicine was established.
1863 – National Academy of Sciences was established.
1916 – National Research Council was born.
1964 – National Academy of Engineering established.
1970 – Institute of Medicine was established.
2015 – Institute of Medicine became National Academy of Medicine.
Three National Academies
NAS, NAE, NAS
2016-Operational Arm Renamed
NRC became NASEM
The National Academies of Sciences, Engineering, Medicine
Independent, Neutral, Non-governmental,
Not-for-profit*
Leading (World) Scientific Authority
Credibility with Congress
*Funded by contracts and grants from federal agencies, states, foundations, associations, industry
RECOMMENDED NUTRIENT ALLOWANCES FOR DOMESTIC ANIMALS

NUMBER I
RECOMMENDED NUTRIENT ALLOWANCES FOR POULTRY

A Report of the Committee on Animal Nutrition
Prepared by Sub-committee on Poultry Nutrition
W. W. Cravens, Chairman
H. J. Almquist, L. C. Norris
R. M. Betheke, H. W. Titus

NATIONAL RESEARCH COUNCIL
2101 Constitution Avenue N. W.
Washington 25, D. C.
June 1944

The National Academies of Sciences • Engineering • Medicine
First Species Reports
Second wave of species reports
REPORTS OF THE COMMITTEE ON ANIMAL NUTRITION

Report Number 1—Suggestions for Meeting the War-time Poultry Feed Situation. Issued April, 1942. Mimeographed.


Report Number 3—Nutrition and Reproduction of Farm Animals. Issued May, 1942. $0.25.


Report Number 7—The Effect of Storage of Grains on Their Nutritive Value. Issued March, 1943. $0.25.

Report Number 8—Suggestions for Meeting the Poultry Feed Situation during 1943. Issued April, 1943. $0.10. Mimeographed.


Report Number 10—The Use of Phosphorus-Containing Substitutes for Bone Meal in Livestock Feeding with Particular Reference to the Fluorine Hazard. Issued June, 1943. $0.10. Mimeographed.
Species reports are evolving
Trends in the evolution of reports

- New feed ingredients
- Feed processing effects
- Non-nutritive feed additives
- Feed contaminants
- Environmental concerns
- Conditional requirements
- Use of (models)
- Human nutrition
- Research needs
Academy Study Process

Study Initiation:
- Explore Issues
- Need for the Study

Secure Funding

Call for Nominations

Establish Study Committee

Preparation of Draft Report
- Committee Meetings
- Sponsor input
- Workshops
- Information-Gathering
- Writing

Committee Deliberations on final Recommendations
- Finalization of model
- Penultimate report draft

Committee Response to Review and Report Revision

External Anonymous Peer Review of Draft Report

Report Release
- Manuscript Publication
- Impacts Monitored

Board on Agriculture and Natural Resources

The National Academies of
Sciences • Engineering • Medicine
Proposal to Update the NRC Poultry

• Following a review of the literature, make new recommendations with consideration for the increased performance of different types of poultry, including broilers, turkeys, laying hens, and ducks. Update information on additional species, as appropriate, such as ostriches, pets, backyard birds.
Proposal to Update the NRC Poultry

• Reflect new information on energy, amino acids, lipids, minerals, vitamins, lipids, and water needed by poultry;
• Summarize the composition of feed ingredients, mineral supplements, and feed additives routinely fed to poultry;
Proposal to Update the NRC Poultry

• Include information about variability in feed ingredients sourced from different regions;

• Include information about feed ingredients from the biofuels industry and other new ingredients (e.g., novel soybean products).
Proposal to Update the NRC Poultry

• Provide information about variability in feed ingredients sourced from different regions; bioavailability of nutrients, and, information about feed ingredients from the biofuels industry and other new ingredients (e.g., novel soybean products).
Proposal to Update Poultry report

• The report will examine requirements for digestible phosphorus and amino acids and update concentrations of digestible phosphorus and amino acids in feed ingredients, examine new information about nutrient metabolism and utilization and provide a review of nutritional and feeding strategies to minimize nutrient excretion.
Proposal to Update Poultry report

• Discuss the effect of feeding on the nutritional quality of poultry meat and eggs.
• Address effects of the environment, feed management, and other production aspects on nutrient requirements, including antibiotics and their alternatives.
Proposal to Update Poultry report

• Include mathematical equations that reflect the biologic basis for predicting requirements and performance based on nutrient input-production response relationships. ill be identified.

• Identify future areas of needed research.
Academy Study Process

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Committee Deliberations on final Recommendations, finalization of model, Penultimate report draft
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BOARD ON AGRICULTURE AND NATURAL RESOURCES

The National Academies of
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<td>Adisseo</td>
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<td>PA Poultry Research Committee</td>
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<td>NRSP/NANP (Experiment Station Directors)</td>
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<tr>
<td>National Academy of Sciences (internal from reports sales)</td>
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<td>IFEEDER</td>
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<tr>
<td>Illinois Corn Marketing Assoc.</td>
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<td>Cost of study $480K</td>
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UPDATING THE REPORT: Next Steps

- Appoint Committee (May 2017)
- Hold 1st Committee Meeting (July 2017, PSA)
Science Breakthroughs

A year long effort to gather ideas from the scientific community that cross disciplinary boundaries and suggest compelling research directions for food and agriculture.

Call for ideas, white papers and discussion coming in April 2017. Town Hall in July 2017.
• Thank you!
For more information, contact:
Robin Schoen
rschoen@nas.edu
202-334-2236

Sign up for the quarterly newsletter:
http://dels.nas.edu/banr
Fed 100 percent certified organic feed, except for trace minerals and vitamins used to meet the animal’s nutritional requirements.

Managed without antibiotics, added growth hormones, mammalian or avian byproducts, or other prohibited feed ingredients (e.g., urea, manure, or arsenic compounds).
The History of Methionine

- Passed for use in poultry rations on 1/1994 as long as it is on the nation list of allowed synthetics
- Tap review done in 2001
- First put on allowed list on 10/01 with a sunset of 10/05
- Addressed in 2/1/2005 for 2009 sunset by Livestock Committee and put back on list for only three years.
Because Industry did not show up and we did nothing for first five years.

NOSB wanted to send a message that we needed to start looking for options.

Methionine Task Force formed in 2007 in Anaheim California.

Became a fully active board with officers and By laws 2017.
Presented to NOSB as an allied industry group looking for options to a common problem.

Members consisted of broilers and layers farmers.

Industry funded to support research, trials and literature search.

Provided information to NOSB and gave timeline for projects.
Given a two year extension to 2010

- No cap.
- NOSB wanted to see results.
- NOSB felt we needed more time.
- The board of 2010 wanted to make final decision on Methionine and wanted the issue closed once and for all. Now all of them are off the board and still no long standing decision!
2010 The year of confusion

- NOSB passed methionine with a cap based on species (layer/broiler/turkey).
- Cap was cut in half by the board in 2012 with no reason given.
- Passed to NOP for rule making.
- NOP requested reason for cut down, none was provided and NOSB would not reconsider.
NOSB did not schedule our petition on Methionine for Fall 2011 or all of 2012.

Without NOP action, effective 10/1/12 methionine not allowed.

NOP put the cap through to help our Industry. Without this Methionine would not have been allowed after 10/1/12.
Methionine is WAS the 2013 Spring agenda but moved by the NOSB to Fall 2013.

- Best time
- MTF presenting
- Industry asked for an average, not a hard cap
- Best methods of calculation?
- Study by North Carolina University paid for by M.T.F.
- Need support from entire industry to combat growing public push back
  - Written
  - Public comment
Spring 2015- Methionine petition from 2012 that was tabled in San Antonio was finally voted on. Passed 10-4 with the following:

- Changed the hard cap to an average over the life of the flock at the following levels:
  - Layers: 2.0 pounds
  - Broilers: 2.5 pounds
  - Turkeys/Ducks: 3.0 pounds
Future work/Meeting take away

- We need to advance the work on insects as a possible methionine source.
- We need to continue the work on high protein corn.
- We need to explore any and all natural sources of methionine.
- We need to look once again at breeds of layers to satisfy current members.
- Pasture as a source of methionine.
Thank you!