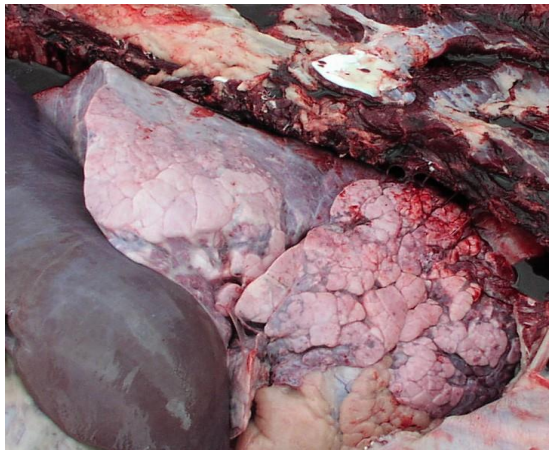
Feedlot AIP: What the Heck Causes It?



Amelia Woolums, DVM MVSc PhD DACVIM DACVM

Department of Pathobiology and Population Medicine

Mississippi State University

amelia.woolums@msstate.edu

Acknowledgements

Larry Hawkins
Gary Mason
Corrie Brown
Guy Loneragan
Susan Sanchez

Shamita Williams
Paula Bartlett
Sharon Chitwood

Bob Smith
Dan Gould

Jared Gould
Florence Duggan
Jenny Anderson
Jocelyn Fox
Scott Sturgeon

Participating feedyards and consultants

Funding:
USDA and UGA

AIP: Acute Interstitial Pneumonia

- Severe respiratory distress, usually fatal
- In feedlots, typically occurs > 60 d. on feed
- Treatment often unsuccessful
- Recognized for decades, although cause unknown


Courtesy Dr. Guy Loneragan

AIP in U.S. Feedlots

- NAHMS 2011: AIP was the third most commonly reported disease, behind shipping fever and lameness
- 72% of feedlots had cattle with AIP
  - 97% had cattle shipping fever
- 2.8% of cattle placed developed AIP
  - 16.2% developed shipping fever

Outline

- How AIP was discovered (the early years)
- Summary of evidence for causes of AIP
- Questions that remain

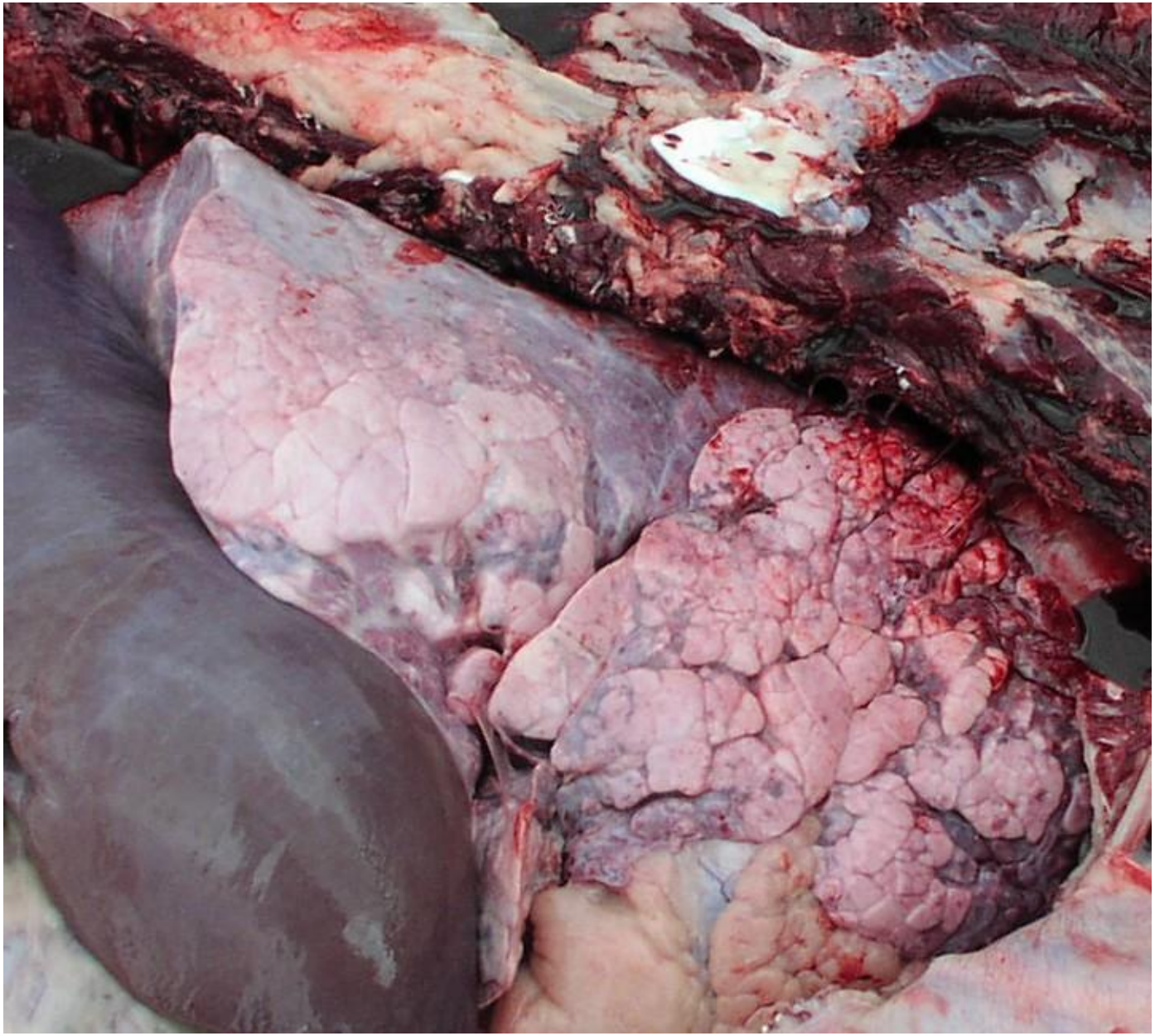
AIP: The Early Years

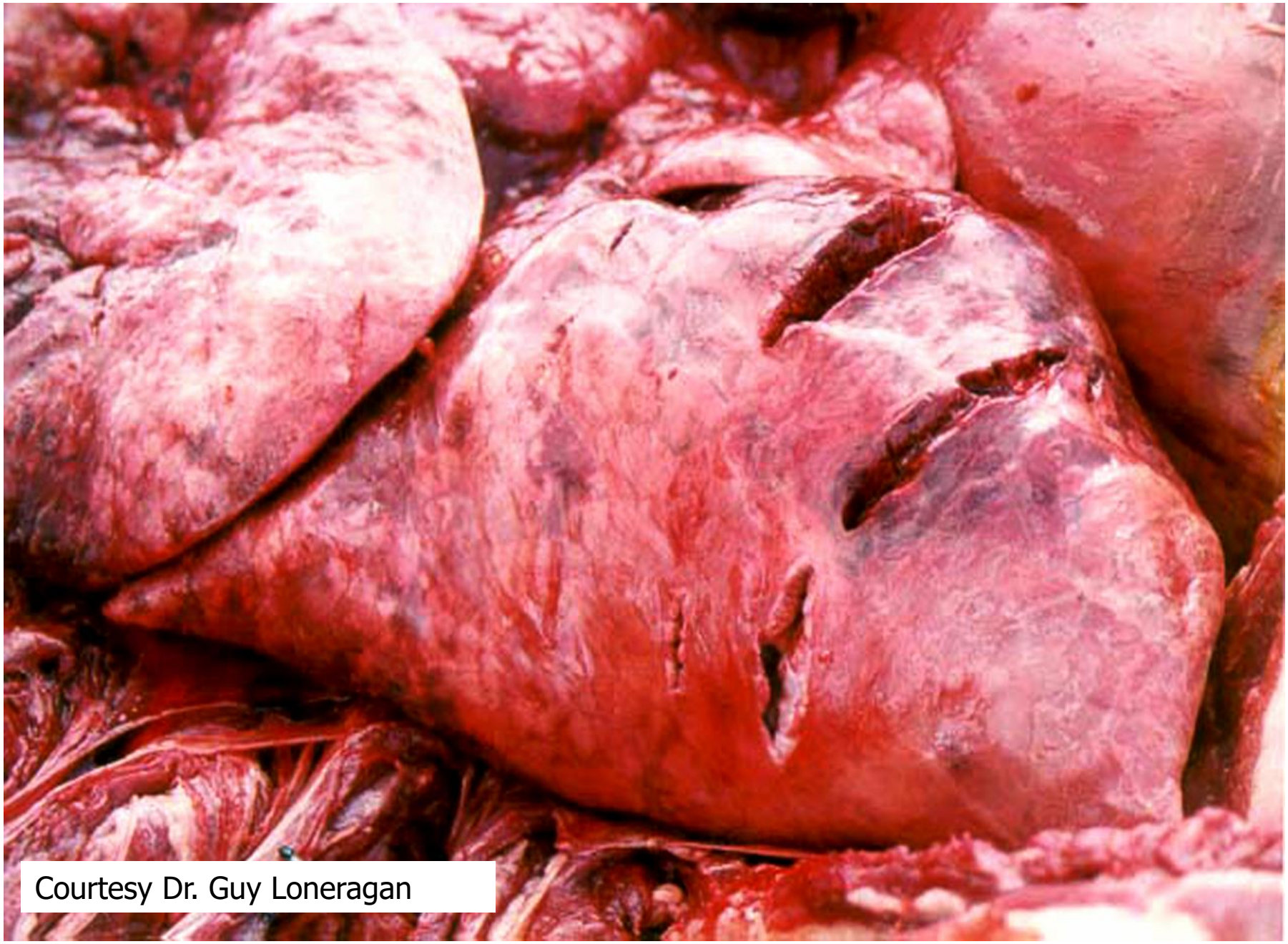
1940's – 1950's

- Episodes of severe respiratory disease unresponsive to traditional therapy
- Cattle of all ages affected
- Often linked to feed change
  - Moldy corn stalks, moldy sweet potatoes

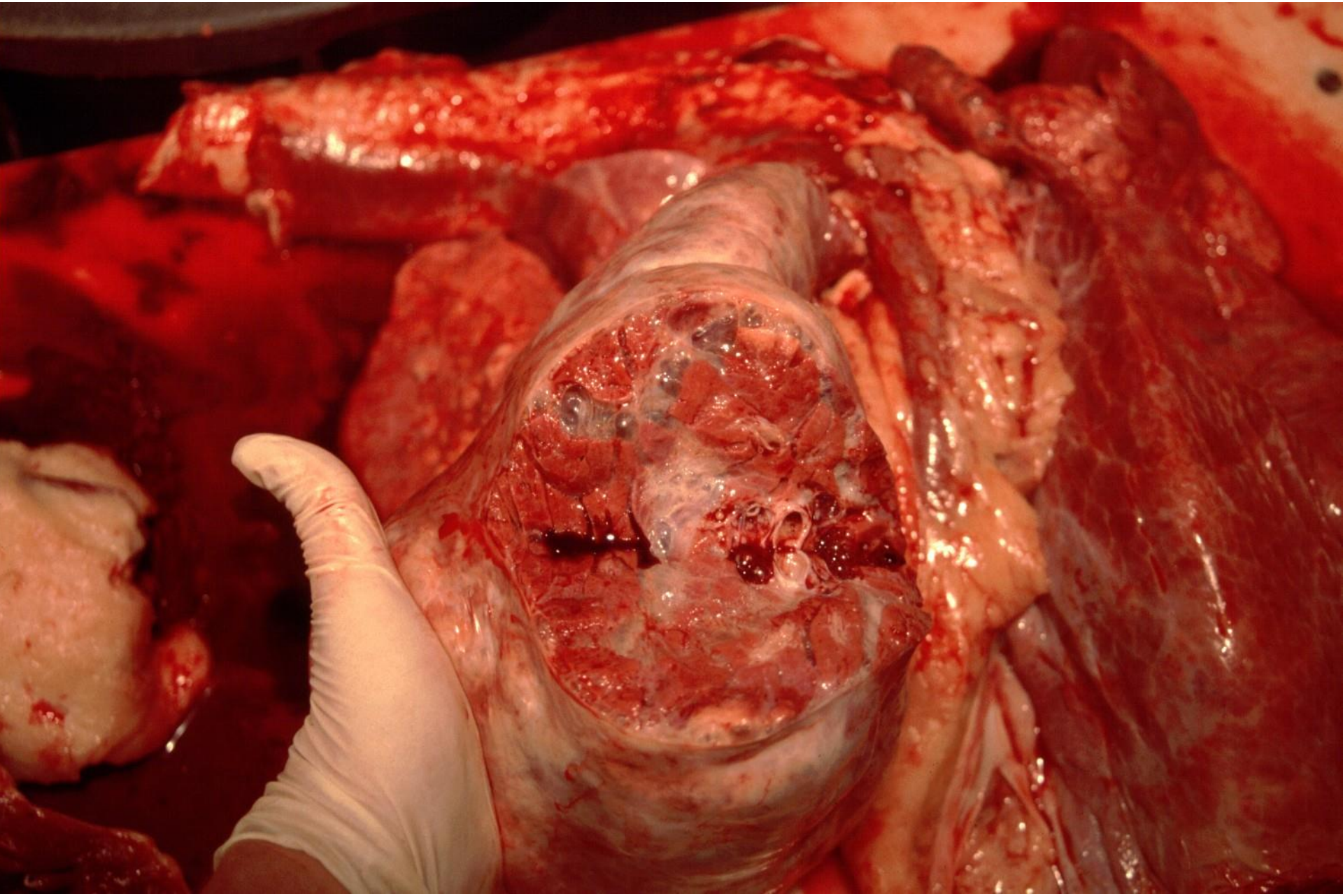
AIP: The Early Years

- Unusual (atypical) pathology noted
- Grossly: lungs expanded, “checkerboard” appearance
- Severe edema and emphysema



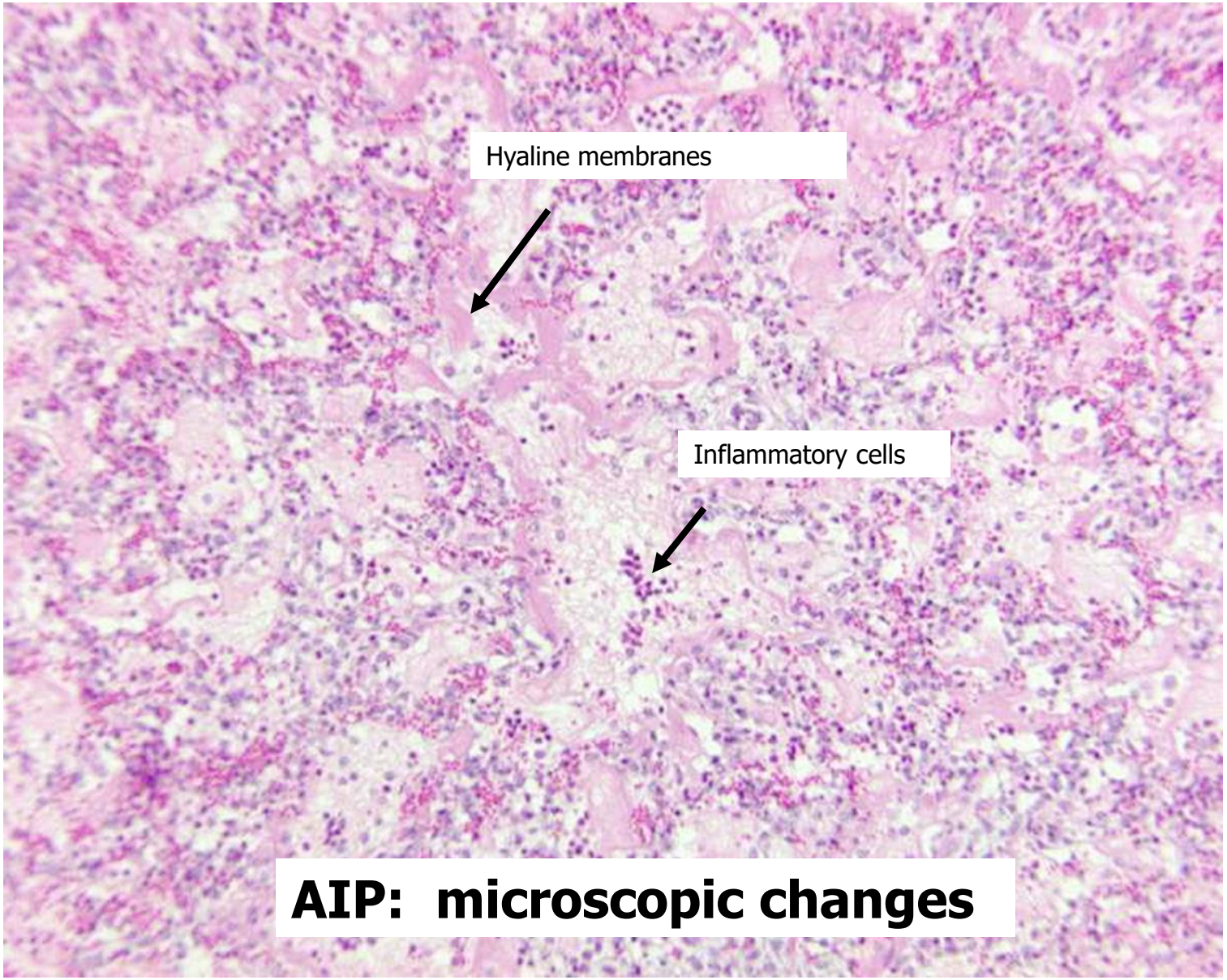


Courtesy Dr. Guy Loneragan



AIP: histopathology

- Microscopically: “hyaline membranes” lining alveoli
- Cuboidal cells lining alveoli
  - Type 2 pneumocyte proliferation
- Interstitial edema and hemorrhage
- Inflammatory cell infiltrate, possibly fibrosis
  - Alveolar and interstitial



AIP: microscopic changes

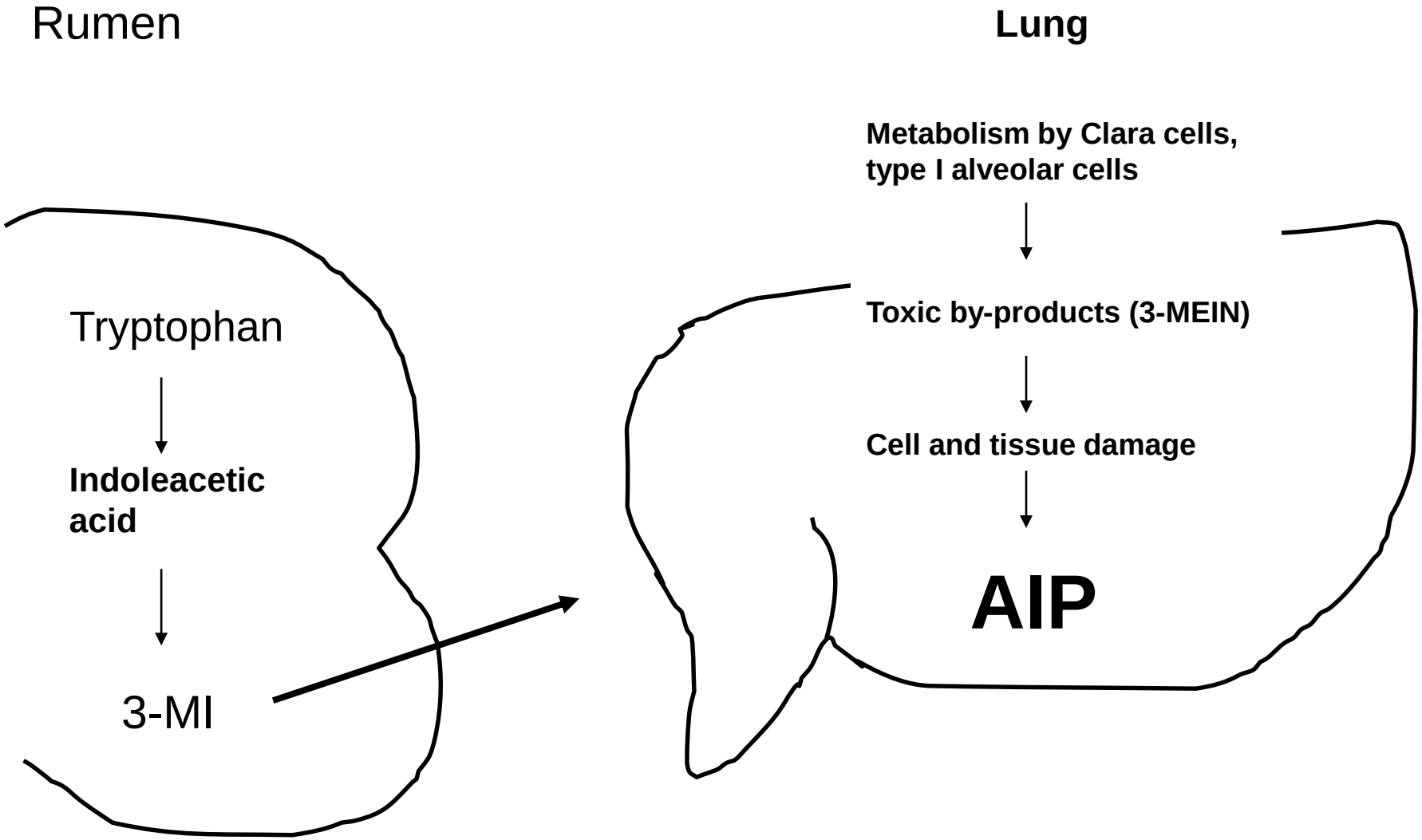
Courtesy Dr. Guy Loneragan

AIP: Descriptions

- Unusual clinical picture and pathology: “atypical interstitial pneumonia”
- Lesion actually “typical” of acute lung injury
  - Toxins, inflammatory mediators, severe infection
- Many other names: pulmonary adenomatosis, ABPE, “fog fever”

AIP: The Early Years

- 1970's – 1980's
  - Important breakthrough: 3-methylindole (3-MI) could cause AIP in cattle
  - Metabolism of dietary tryptophan to 3-MI in rumen led to damage in lung


Rumen
Lung
Tryptophan
Indoleacetic acid
3-MI
Metabolism by Clara cells, type I alveolar cells
Toxic by-products (3-MEIN)
Cell and tissue damage
AIP

AIP: The Early Years

- Other pneumotoxins found in moldy sweet potatoes, perilla (purple) mint
- Led to understanding that feed-related pneumotoxins could cause AIP
- Specific cause of pasture-associated AIP had been determined

The Early Years: AIP and BRSV

1960's – 1970's

- Discovery of virus that could cause AIP-like lesion in cattle: BRSV
- Microscopically, syncytial cell formation also characteristic

- Weaned calves especially affected
- Feeding silage anecdotally associated with outbreaks
- Virus difficult to isolate
- Confusion over relative role of feed-related pneumotoxins vs. BRSV

The Early Years:
AIP and anaphylaxis

- Hypersensitivity often discussed as a possible cause of AIP
  - Experimentally induced anaphylaxis caused acute but not subacute lesion of AIP Ladiges et al., 1974
- AIP apparently not due to classic anaphylaxis

AIP: The Early Years

- Summary of early reports (up to 1985)
  - Dietary pneumotoxins
    - Toxic metabolites of 3-MI
  - BRSV

…most likely to cause AIP

Reports of Feedlot AIP

1976, Jensen et al

- Characterized disease in 4 Colorado feedlots
- AIP mortality 0.03% of inventory
- 75% of animals affected on feed > 45 days
- Most cases occurred in summer and fall

Reports of Feedlot AIP

1983, Hjerpe

- AIP cases in one feedlot
- Most (144/149) had concurrent lesions of bronchopneumonia
- Over 4 years, mortality 0.5% of calves, 0.12% of yearlings
- No obvious seasonal occurrence

Reports of Feedlot AIP

Summary

- AIP could be important cause of mortality in feedyards
- Time of occurrence later than shipping fever
- Seasonal occurrence?
- Role of bronchopneumonia?

AIP: Role of BRSV

- Collins et al, 1988: role of BRSV
  - Naturally occurring feedlot cases
  - BRSV isolated from 11/15 AIP cases (73%)
    - 5/18 with other respiratory disease (27%)
  - BRSV concluded to be an important cause

3-MI and BRSV

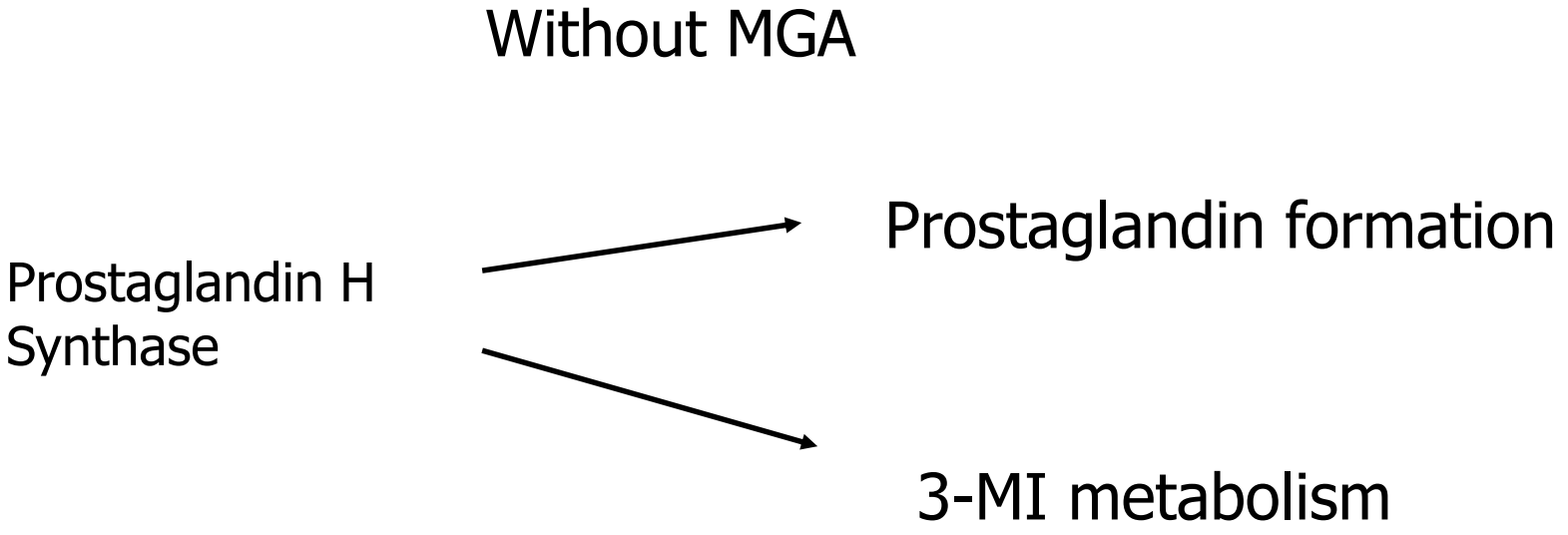
- Combined effect of BRSV and 3-MI
  - Castleman, 1990: disease not more severe
  - Bingham et al, 1998: disease was more severe
    - Difference of virulence of BRSV isolates used for challenge important

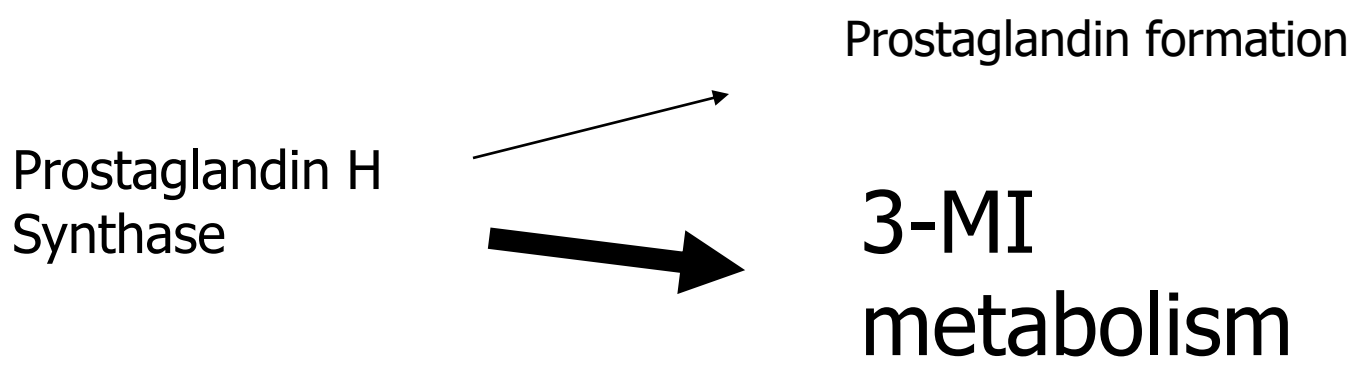
MGA and AIP

- Popp, McAllister, et al (1998-2000)
  - Heifers in Alberta feedyards more often developed AIP
  - Melengestrol acetate (MGA) withdrawal seemed to decrease disease

MGA and AIP

- How could MGA be involved?
  - 3-MI is metabolized by prostaglandin H synthase, mixed function oxidases
  - Metabolism leads to toxic products (3-MEIN, others)
  - MGA may change balance of 3-MI metabolism


Without MGA
Prostaglandin H Synthase
Prostaglandin formation
3-MI metabolism

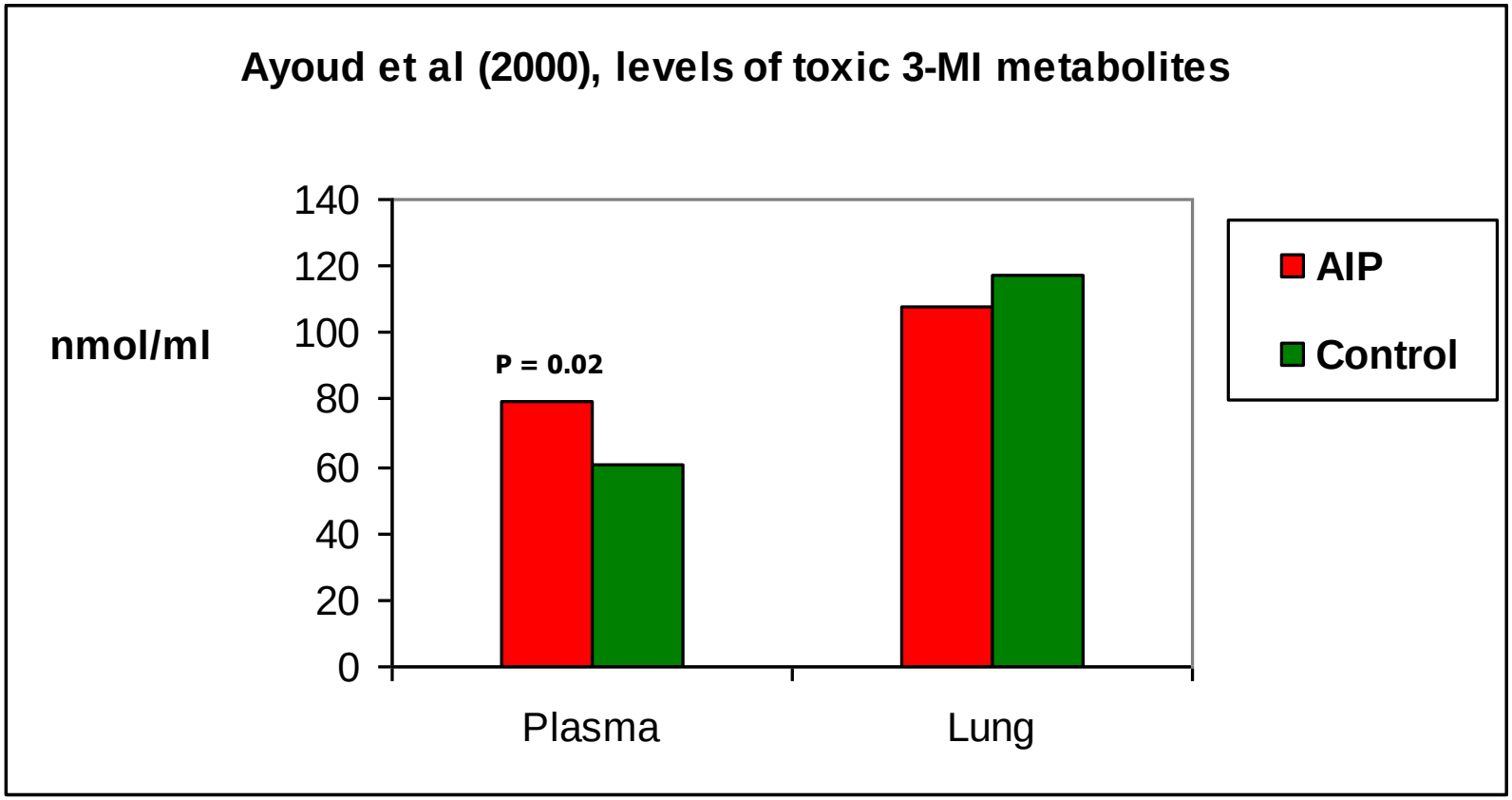

With MGA
Prostaglandin H Synthase
Prostaglandin formation
3-MI metabolism

MGA, 3-MI and AIP

- Popp et al, 1998
  - Sheep fed MGA for one month
  - Higher levels of 3-MI metabolite in plasma on d. 30 *before* 3-MI challenge
  - After 3-MI challenge: more rapid onset of respiratory distress in MGA group
    - Higher levels of lung 3-MI metabolites after challenge
- MGA appears to modify 3-MI generation and/or metabolism

3-MI and AIP

- Ayoud et al, 2000
  - Measured 3-MI metabolites in 31 fatal AIP cases and 7 controls
  - All AIP cases were heifers (MGA fed)


Ayoud et al (2000), levels of toxic 3-MI metabolites
nmol/ml
140
120
100
80
60
40
20
0
P = 0.02
Plasma
Lung
AIP
Control

- However, feeding heifers MGA didn’t lead to increased concentration of 3-MI metabolite in plasma, as was seen in sheep

Ayoud et al., 2000

3-MI and AIP

- Summary:
  - Sheep fed MGA developed respiratory disease more rapidly when challenged with 3-MI
  - MGA feeding increased baseline serum levels of 3-MI metabolites in sheep but not heifers
  - 3-MI metabolites higher in serum but not lung of heifers with feedlot AIP

3-MI and AIP

- Questions:
  - What if heifers fed MGA were challenged with 3-MI?
  - Why are plasma but not lung levels of toxic 3-MI metabolites higher in AIP cases?
  - What causes elevation of plasma levels of toxic 3-MI metabolites?

More on 3-MI

- AIP cases in 14 feedyards
- Tissues collected from
  - 108 AIP
  - 50 bronchopneumonia (BRD)
  - 25 controls
- 3-MI metabolites in lung and blood
- Also identified bacterial and viral pathogens

Loneragan et al., 2001

3-MI and AIP

- 3-MI metabolite in lung higher in AIP and BRD vs controls
  - But no difference AIP vs BP
- In (small number of) blood samples, 3-MI metabolite higher in AIP vs BP and control
  - 13 AIP
  - 3 BP
  - 41 controls

Loneragan et al., 2001

3-MI and AIP

- Loneragan et al, summary
  - 3-MI involvement with AIP indicated by levels of toxic metabolite in lung
  - 3-MI metabolite also increased in BRD cases: significance?

3-MI and AIP

- Questions:
  - What dietary factors influence levels of 3-MI in feedlot cattle?
  - If 3-MI metabolites are elevated in lung of BP as well as AIP, is an additional factor necessary for development of AIP?
    - If so, what is it that factor?

Bacterial infection and AIP

- In humans, AIP also occurs
  - Acute respiratory distress syndrome (ARDS)
- Sepsis often precedes ARDS in humans
- Could bacterial infection in the lung predispose cattle to ARDS?

Respiratory pathogens and AIP

- In 28 fatal AIP cases from 5 feedlots over 1 year
  - Histologic and microbiologic findings compared to normal slaughterhouse controls
- Concurrent bronchopneumonia in 75% of AIP cases
- Evidence of bronchiolar injury (b. obliterans) in 89%
  - Rare in controls
- BRSV found in only 2/28
- Most cases submitted in *winter*

Sorden et al., 2000

- In Loneragan 3-MI study (2001):
  - Bacterial pathogens isolated more often from BRD than AIP or controls
  - No difference AIP vs controls
- No difference respiratory viruses between BRD, AIP, controls
  - BRSV *less* likely to be isolated from AIP than controls
- No association with bacteria and AIP
  - Impact of prior antimicrobial treatment?

Back to BRSV

- Remember Collins et al, 1988:
  - BRSV isolated from 11/15 feedlot AIP cases (73%)
    - 5/18 with other respiratory disease (27%)
  - BRSV concluded to be an important cause of AIP
- Later studies did not support a role for BRSV
  - Ayoud et al, 2000
  - Sorden et al, 2000
  - Loneragan et al, 2001

What about BRSV and bacterial co-infection?

- Our hypothesis:
  - Low-grade elevation of proinflammatory cytokines leads to “hyperinflammatory” state of lung
    - Due to subclinical bacterial infection: pneumonia or liver abscesses
  - Superimposed acute inflammation induces AIP
    - Like maybe BRSV

Proinflammatory cytokines and acute lung injury

- TNF-α and IL-1β linked to AIP-like disease (ARDS) in humans
- Could bacterial pathogens induce feedlot AIP through proinflammatory cytokine upregulation?
  - *M. haemolytica* infection induces TNF-α and IL-1β in bovine lung

Bacterial co-infection and BRSV

- Study design:
  - Bacterial culture from AIP cases not treated with antimicrobials compared to normal penmates
    - Lung and liver sampled
  - Immunohistochemistry for BRSV from cases and controls
  - Histopathologic evaluation of lung and liver

Woolums et al., 2004

Methods

- 2 feedlots in western Kansas, 1 feedlot in eastern Colorado
    - Approximately 40,000 cattle on feed at each
- Data collected over 2 summers
- Cattle with signs of AIP selected by feedlot staff
  - Only cases with no history of antimicrobial therapy
  - Immediate euthanasia or emergency slaughter

Methods

- Rectal temperature (antemortem)
- Rumen pH (postmortem)
- Lung: aerobic and mycoplasma culture

  BRSV immunohistochemistry
- Liver: aerobic and anaerobic culture
- Histopathologic evaluation of lung and liver

Methods

- Control penmate selected by staff within one week
  - No history of treatment for any disease
- Slaughter and sampling as for AIP cases
  - Bacteriology, BRSV IHC, histopathology

Results

- 39 animals selected as AIP suspects
- 26 confirmed AIP (67%)
  - Based on histopathological findings
- 32 Control animals sampled

Results, AIP cases

- 17 female, 8 male
- Mean (+/- S.D.) days on feed: 136 +/- 56 days

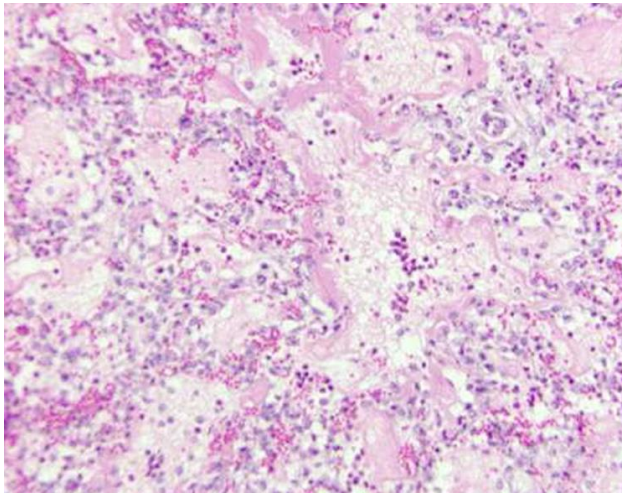
  Range: 75 – 243 days
- Mean rectal temperature: 104.0 +/- 1.3° F

  Range: 101.8 – 106.6
- Mean rumen pH: 6.3 +/- 0.5

  Range: 5.6 – 7.2

	Feedlot		
	1	2	3
Number of cattle suspected of having AIP	21	14	4
Number of confirmed AIP cases	15	7	4
AIP cases with bacterial lung pathogens	8/15	1/7	2/4
AIP cases with liver abscesses	3/14	0/7	1/4
AIP cases IHC positive for BRSV	6/15	2/7	1/4

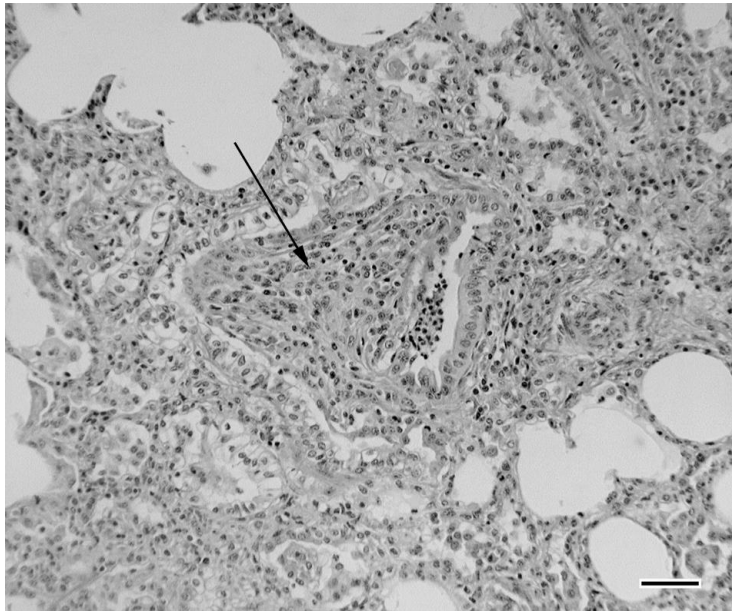
Histopathology



- In 26 confirmed AIP cases
  - 13 had lesions of AIP in cranial lungs
  - 26 had lesions of AIP in caudal lungs
- 9 of 26 had only acute alveolar damage with exudation
- 17 of 26 also had type II pneumocyte proliferation
- No AIP lesions in 32 controls

Bronchiolitis fibrosa obliterans

- Present in 11 of 26 AIP cases (42%)
- In 22 matched case-control pairs, BFO more often present in cases ($P = 0.02$)
- This was unexpected
  - Affected cattle more often infected by bacteria or BRSV



Results, lung bacteriology

- AIP cases:
  - *Pasteurella multocida* or *Mycoplasma* sp. isolated from 11 of 26 (42%)

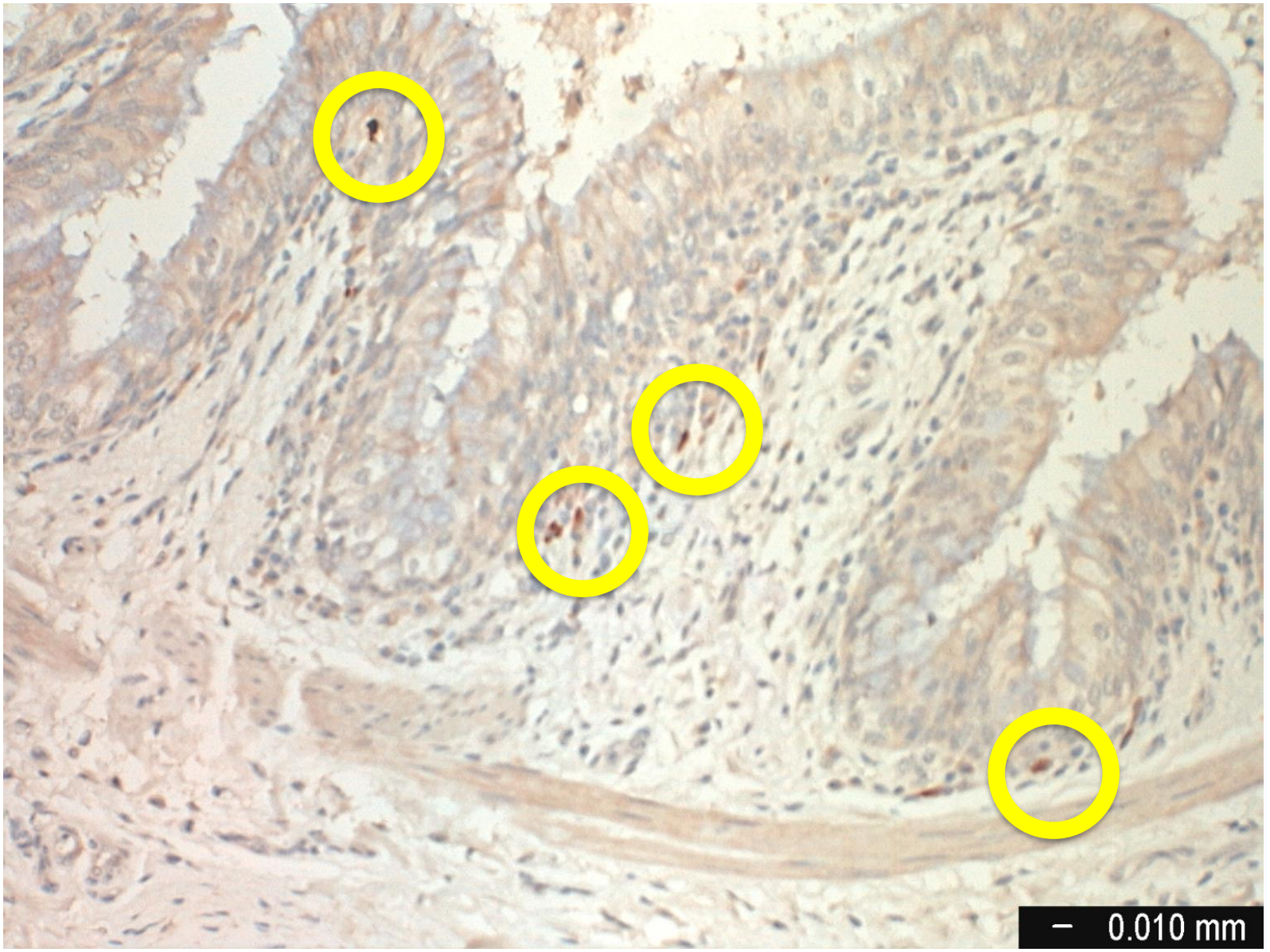
- Controls:
  - No respiratory pathogens isolated ($P = 0.04$)

Liver abscesses

- AIP cases: liver abscess in 4 of 25
- Controls: liver abscess in 2 of 32 ($P = 0.50$)

BRSV IHC

- AIP cases: 9 of 26 positive (35%)
- Controls: 0 of 32 positive ($P = 0.07$)
- Staining in peribronchiolar macrophages
  - Not in airway epithelial cells
  - Recent infection being cleared?



IHC for BRSV, in case 023-03296-2, demonstrating infrequent cells in bronchial submucosa positive for viral protein

Conclusions

- Bacterial respiratory pathogens were more likely to be isolated from feedlot AIP cases than matched controls
  - Cause or effect? Or coincidence?
- Gross and histopathologic evidence of chronic pneumonia present in some cases
  - Bacterial pneumonia may predispose to some cases of AIP

Conclusions

- Some AIP cases negative for bacterial respiratory pathogens even in absence of antibiotic therapy
  - Other non-infectious causes of these cases?
- Bacterial respiratory pathogens not isolated from normal cattle
- Role of BRSV: murky

Conclusions

- Chronic airway injury occurs in cattle that develop AIP
  - Past BRSV infection?
  - Bacterial infection?
    - *Pasteurella, Mannheimia, Mycoplasma*
  - Other insults?
    - Dust, irritant gases?

Conclusions

- Control of bacterial pneumonia late in feeding period may impact incidence of feedlot AIP in some feedlots

- Uncharacterized pneumotoxins may cause AIP in cases with no evidence of infection

Cause of feedlot AIP: current evidence

- Summary of research to date:
  - Toxic 3-MI metabolites likely important
    - Significance of metabolites in lung v blood unclear
    - May also impact other BRD
    - Unclear what about feed would impact 3-MI

Cause of feedlot AIP: current evidence

- Rumen abnormalities identified associated with AIP
  - Increased pH
  - Increased ammonia
  - Decreased cellulolytic populations
    - No difference lactobacilli, protozoa
  - Significance?

Cause of feedlot AIP: current evidence

- Hormonal influences
  - Heifers usually shown to be more at risk for AIP
  - Not clear if increasing or decreasing MGA would help
  - Need for more research

Cause of feedlot AIP: current evidence

- Bacterial or viral pathogens
  - Role for BRSV inconsistent
  - Chronic bronchiolar lesion consistent in many reports
    - Role for Mycoplasma, BRSV or other viruses, irritants?
  - **Chronic bacterial lung infection likely plays a role in a subset of feedlot AIP cases**

What the Heck Causes Feedlot AIP?

- Important to remember that lesion of AIP is not specific to a single etiology
  - Indicates **acute lung injury**
    - Focused at the **alveolar epitheilum and/or capillary endothelium**
  - Specific cause can vary
  - May be superimposed on chronic disease
  - Multiple causes may combine to cause some cases

What the Heck Causes Feedlot AIP?

- Research provides evidence for
  - Involvement of 3-MI
    - Dietary factors, rumen physiology linked?
  - Involvement of bacterial infection
    - Some but not all cases
  - Involvement of hormonal factors

What the Heck Causes Feedlot AIP?

- More research needed to evaluate
  - Involvement of environmental factors
    - heat, dust
  - Involvement of airway irritants
    - *B. obliterans*: mycoplasma, viruses, irritants?
  - **Dietary factors**
    - Unidentified pneumotoxins?