DR. ARONSON: Our next speaker is Dr. Wally Brandt. Dr. Brandt is a graduate of the University of Illinois, having received his D.V.M. degree in 1955. From 1955-1975, he was in private practice with a specialty in food animal medicine. In 1975 he joined the Hoffmann-LaRoche Company as a clinical veterinarian. Presently, Dr. Brandt is the Assistant Director of Animal Science Research for Hoffmann-LaRoche with responsibility for clinical research. It is my pleasure now to introduce Dr. Brandt.

DR. BRANDT: Thank you very much. It's certainly a distinct pleasure for me to be here and to have this opportunity to present what I think is the middle ground between the extreme of the mastitis and the otitis; I do agree with the previous two speakers, and for those that know me well, to say that Wally Brandt is a moderate is some degree of exaggeration -- but you know marvels never cease!

I think that my first exposure to statistics was when my father said that 90% more corn is grown in a crooked row than in a straight row, which didn't really make sense until he told me that 9 out of 10 people couldn't drive a straight row. That really tells you something about the work ethic I was raised under. In other words, hard work is good, straight rows are good, and weeds are bad. My first experience with regulatory medicine occurred in veterinary practice when I was a working veterinarian in a sale barn for 10 years. I survived that experience, but I also had what was probably one of the first GLP inspections of a sale barn that ever occurred in Illinois. One evening, 6 veterinarians, 3 federal and 3 state, descended upon this sale barn one hour prior to sale. These people lived with me throughout the night and proceeded to tell me in detail the minute things that I did not or did observe and did nothing about; as I said, I survived that experience but not without a letter from me back and forth to the state of Illinois. However, today we're talking about trying to evaluate oral drugs for antibacterial function...

Use of Clinical Trials for Dose Determination of Oral Drugs

Wallace E. Brandt, D. V. M.

The advent of a strict dose titration concept which is statistically valid, introduced the concept of the animal model. In many bacterial and viral diseases, the animal model is quite useful when a simple inoculation in susceptible animals will cause the disease condition expected. However, in several disease conditions the etiologic agent is ubiquitous in nature and disease is dependent on concommitant viral infection and/or a physical stress. The normal animal has an ability to clear the pathogenic bacteria and thus prevents disease. However, when concomitant viral and/or stress are applied, the disease created with compounded etiology in an animal model may be so unusual or abnormal that the observed parameters have no relationship to that seen in natural disease outbreaks.

Accordingly, a clinical trial situation with natural infections can, where feasible, by virtue of animal numbers, animal value and management be a most desirable alternative. Roche conducted such a trial. A clinical study was conducted to evaluate potentiated Albon and Albon® in calves with bacterial pneumonia. This clinical study was conducted in a calf-raising facility with a capacity of 1500 calves. All animals were purchased from local dairy farms at 1-2 days of age. All animals were Holstein, male calves. On arrival at the farm, all animals were vaccinated for IBR and BVD, injected with a vitamin E and selenium solution and a vitamin ADE solution. Calves were maintained in individual hutches for 60 days. Animals were started on a diet of 1/2 whole milk and 1/2 milk replacer and offered grain at 14 days of age. Animals were hand fed daily and observed for signs of illness. Normally, animals on this farm that experience pneumonia do so at six weeks of age or older. Prior to initiating the study, five calves from the farm which died from pneumonia were necropsied and lung tissue was cultured for bacterial isolates.

The purpose of the study was to evaluate the efficacy of two levels of potentiated Albon and one level of Albon in calves with bacterial pneumonia. Calves exhibiting clinical signs of pneumonia (including temperature 103°F or above, partial or total anorexia, dull, listless or depressed attitude and rales or other pneumonic sounds) were assigned to four treatment groups based on a pre-determined randomization of 72 calves (18 per treatment). The following treatments were given for five consecutive days:

Treatment	Dose Level (X=Daily Dose)
Nonmedicated	0
Potentiated Albon	1/2 X
Potentiated Albon	X
Albon	X

Calves were monitored for 12 days, five days while receiving treatment and the following seven days for observation. Temperatures, feed consumption, attitude, physical condition and ascultation score were recorded daily for each animal. Scores for temperature, feed consumption, attitude, physical condition and ascultation were added together for a composite score The number of calves exhibiting chronic symptoms of pneumonia and the number of dead calves in each treatment group of Day 12 were also recorded.

Summary of dead and dead plus chronic animals on day 12:

Treatment	N	Dead	Dead + Chronic
Nonmedicated	18	6	14_b
Potentiated Albon (1/2)	18	3_+	10^b
Potentiated Albon	18	1_+	3^{**}
Albon	18	1^+	9^a

Statistical significance (Fisher Exact test) of medicated treatments to non-medicated control denoted:

$+ P < .10$; $*P < .05$; $**P < .01$

Statistical significance (Fisher Exact test) of comparison to larger dose of potentiated Albon denoted:

$^a P < .10$; $^b P < .05$;

Bacterial pneumonia was selected for the efficacy evaluation for the following reasons:

1. Test animals were of a uniform background and management practice.

2. Test animals were available in sufficient number to complete the study in a short period of time and pre-study necropsies verified the disease condition.

3. The disease condition had a common etiology.

4. Test animals were available for purchase so that non-medicated animals could be evaluated.

5. Qualified personnel were available to direct the study on a daily basis.

6. A state diagnostic laboratory was available for bacterial isolations and tissue pathology examination.

Final Comment:

It is the opinion of the investigator that the data obtained from this study are very relevant to the effective dose of the potentiated Albon. In four subsequent well-controlled studies with natural infections, this same dose level had significantly less deaths and faster recovery of sick animals than non-medicated controls.

The described study is one of the several where we have utilized a natural infection for determining a dose range of drug. Since a dose range must contain unmedicated or placebo animals, it is only possible to conduct these studies where the owner can be reimbursed for his livestock losses. In most situations, the primary concern of the owner is for animal performance, and secondary projects which may interfere with this objective are not tolerated. In this study, the uniformity of animals and management provided a unique situation so that observations on drug response by test animals actually represented the differences of the drug treatments given.