Discussion

Question: My name is Dr. Dreyfus Froe, Terre Haute, Indiana (Pfizer Laboratories). I have two questions: one for Dr. Clark and Dr. Hjerpe. Did you use higher concentrations of the drugs than are approved? Dr. Hjerpe, I don't know whether you mentioned 100 milligrams versus 200, and Dr. Clark, 50 versus 100–different serum levels.

Answer: We determine the serum concentrations resulting from, I think there is a total of about seven different oxytetracycline formulations on the market and I've got some slides with me that I could show. There are some differences. Erythromycin–we have only looked at Abbott's product. Abbott has two products; one is erythromycin, which is really designed for intravenous use in humans. Then they have their animal product and we've looked at those too. I guess I don't completely understand the question.

Question: We've seen some differences in just concentrations of the product, not necessarily differences in who makes it, between the 50 mg product and the 100. For instance, we never get as high a blood level with the 100 mg product as we do with the 50, but the 100 mg levels are sustained longer and I wondered if anything like that had been done?

The next question that I had was Dr. Hjerpe mentioned the serum levels withdrawal periods with higher concentration of the drugs we use and I wonder, you didn't mention anything about tissue residue levels, for instance kidney and liver. I wonder how you were determining that; by, for instance, adding extra days serum levels or urine disappearance level?

Answer by Dr. Hjerpe: That's why I call it a Kentucky withdrawal period. It's one that you would use at your own risk, but the fact any time you deviate from the approved route of administration, even if you give the same dose, even if you use the approved dose, it's at your own risk. We have used these withdrawal periods and have not been found in violation. But, until someone does put the money into actually analysing tissue then we just don't know for sure. . . .

Question: I suppose my question was just a little more of a cautious kind of thing, because we know for instance streptomycin and neomycin, even though the blood levels disappear, we can find the kidney levels for as long as three months or so. . . .

Answer: These were urine concentrations, not blood concentrations, that we are talking about.

Question: I mean even after urine samples disappear we can still find concentrations in the kidneys so we should be a little cautious.

Answer by Dr. Powers: I wanted to respond to Dr. Hjerpe in regard to that because he was making a point that he was using a little Kentucky windage to try to get some idea on some drugs, but I go right along with you. The aminoglycosides are a very dangerous group to try to use urine concentrations or blood concentrations with, as far withdrawal times. Drugs like neomycin may have, if they were looked at, withdrawals as much as 90 to 120 days or maybe even longer due to hold-up in the kidneys. I think it should be emphasized, and I'm certain you were trying to make that point at the time.

Question by Dr. Don Williams, Guymon, Oklahoma: Dr. Kerr, do you see any hope of developing a protocol where drugs can be taken off the new animal drug list and put on a "not new" animal drug list?

Answer: I've got a couple people here in the audience from Food & Drug–I ought to ask them that. Dave Scarr, from Rockville, Maryland, Bureau of Veterinary Medicine, maybe he can tell what the status is on that.

Dr. Scarr: There is a procedure they're using in human drugs. It isn't operative yet, but they can produce a monograph and if there are data in the literature which will satisfy experts that the drugs are safe and effective, they can publish a monograph with those specific concentrations for those specific uses, and this procedure is under study right now.

Question: This question is for Dr. Kerr. I'm from Kentucky, by the way. The AABP mastitis committee has been doing some study on milk residues. At the present time in the United States there are three tests being used: the Bacillus subtilis, the Dellbo test, and the Sarcyna lutea test detecting inhibitors in milk. Is the FDA recognizing all three of these tests as their sensitivity varies considerably?

Answer: They were using Sarcyna lutea, I know.

Question: It seems to me that if we keep developing more sensitive tests, that down the road somewhere we're going to be picking up antibiotics out of the air and everything is going to be contaminated. I believe we are going to have to have a cutoff point somewhere.

Answer (Dr. Powers): I heartily agree. It's getting to the ridiculous stage where we are detecting the fractions of parts per billion on many of these things.

There are some cutoff points, though, not necessarily always completely established. Nitrofurans compounds, for instance, have no good tests that detect them at a low enough parts per billion to permit them, probably, to be continued to be used in veterinary medicine because they are potentially tumorogenic. When you get the drugs that are tumorogenic or capable of producing cancer, then you need a test that is extremely sensitive to recognize them. Again, I am pulling from the back of my head, but tetracycline is approved in foods at a level that is higher than the sensitivity of the test is, if I'm not mistaken, like 0.04 ugm/gm and the test is sensitive to 0.025 ugm/gm. There are some of these, and I agree that you need to know what are high risk levels and low risk levels, this type of thing, and to have these levels well defined for each drug.

Question (Dr. Sippel, College Station, Texas): Dr. Powers mentioned the development of resistance by certain organisms and their restrictions of certain antibiotics because of this development and Dr. Hjerpe's work certainly shows that these organisms do develop. I wonder how real the danger is of the spread of these organisms to human beings? It would seem, if this were in fact the danger, that we wouldn't have any feedlot cowboys who work in hospital pens alive and there would be a lot fewer veterinarians than there are. Is there any good evidence that this actually is a danger?

Answer (Dr. Powers): This is a question, of course, that everybody a few years ago kept asking. Until you prove it I don't even want to worry about it. So, they did show some proof; I think it was first over in England, in this area. But back here there has also been some related to people that work in slaughter plants and this type of thing that has been traced back as possibly being of animal origin. I can't come up with specifics but I know there were at least two or three of this type of thing. Dr. Huber, when he was back earlier at Illinois, was working along this line as to the use of antibiotics and the pressure effect and the occurrence of resistant factors. As he went through the epidemiological studies, he found that where antibiotics had been used in the herds, there was a much greater incidence of it in these animals and the people in contact with them. Yes, as far as I know, there is some; the numbers and cases are very limited though.

Question: Dr. Hjerpe, you referred to the cytopenic animal earlier as being nonresponsive in many cases to antibiotic therapy. Would corticosteroids, when used in the normal animal, cause a decrease in granulous form production?

Answer (Dr. Hjerpe): No, actually it tends to cause an increase in production but at reduced rate of collection in the area of infection. As an example, granulous cytopenia, from the standpoint of feedlot diseases, is the animal with pneumonia that comes down with BVD and develops a leucopenia from this and then becomes untreatable from the standpoint of bacterial infection. I see this happen quite frequently.

Question: With the two things we've been talking about, the prospect of increasing pressure on finding these drugs and then their resistance, all of you being attuned to advances, is there anything waiting in the wings when we finally wear out our antibiotics? Do any of you have anything in mind that we're going to use after that?

Answer (Dr. Powers): Acquisition of R-factor resistance is a real

problem, but they do lose it, too. They can lose R-factor resistance. Treatment of bacteria with certain acridine dyes can cause loss of R factor. So there is this approach of either using something to cause them to lose it, or there is the natural loss of it. Dr. Hjerpe, you are back to using penicillin G, I noticed in your lectures, and back up to big high doses. Isn't that what you were using, penicillin G? As you start using one drug and you use it awhile then you get resistance (not always R-factor) and then you don't use the old drug for awhile and you recheck the old drug and find out it is starting to be effective or the bacteria are sensitive. I think in human medicine the best example of a resistance problem (other than R-factor) was with erythromycin. Many of the staphylococci all across the country were resistant to erythromycin except a small area down in Florida. There had not been a script written for erythromycin down there and all the staphylococci were sensitive. I think at the time we're using it, we're selecting for it, but as time goes on and we don't use them, we'll see a change in patterns.

Dr. Hjerpe: I guess I could make another comment. We see a few cases where the infecting organisms are totally resistant, particularly to all the proved antibiotics. Particularly with respect to these pasteurella lung infections. But the vast majority of the cases we treat would respond to usually a tetracycline, a sulpha or a penicillin if you knew which to give. We autopsy every animal that dies of pneumonia, isolate the organism and test for sensitivity. It is very infrequent that the organism is not sensitive to penicillin, sulphonamide or tetracycline. The only time that I've had any problems was when we were routinely feeding an antibiotic in a relatively low level for prevention to all the cattle coming into the feedlot. We just try to avoid the use of antibiotics prophylactically as much as possible and to reserve them for use in therapy, at least in the feedlot situation. I don't see it as being a great problem. Some of you may have mastitis situations something like this, where it is a problem in your practice, but I don't feel threatened, at least in my feedlot work, with a great advancing cloud of resistant bacteria.

Question: Do you think the low level antibiotic feeding, Dr. Powers, could develop R-resistance factors in animals which would create a problem on treatment rather than, like Dr. Sippel mentioned, creating a problem with people as far as response to treatment?

Answer (Dr. Powers): My answer to that is yes, definitely. I feel that low level use of antibiotics is definitely a problem, because, again, development of resistance is dependent upon some microorganism being exposed to that antibiotic and the more that you use antibiotics, whether it be in therapy or as low levels in the feed, you are going to expose more and more organisms. And one of the best ways to expose more organisms, of course, is through this low level feeding of antibiotics. This could lead to R-factor resistance and it could go on farther. We cannot neglect the possibility that R-factor resistance is in the animal population and then could be transmitted to humans. Yes, this is something we dearly need to look at. I'm not on the side of saying feed additives are all wrong. I think we're discussing a philosophy here. Maybe this is the right place to throw it in. It's high time we returned and helped the FDA, or whoever it is, to return to the fact that there is risk in using drugs, whether it's inducing R-factor or other resistances or whether it's in killing animals or whether it's in leaving residues in tissues. We need to accept this problem of risk again. We need to accept some level of risk on all these things as we use drugs.

Dr. Hjerpe: I've been involved in one major problem with antibiotic-resistant pasteurella pneumonia which went on for about 13 months in this feedlot where I work and which circumstantially was strongly linked to a practice that we initiated where we were feeding all incoming cattle a milligram per pound per day of chlortetracycline in the feed for the first 21 days after arrival. We medicated 5,000 calves or cattle, yearlings and calves, this way over a 2-1/2 month period and during that time we observed an increase in the rate of deaths from organisms that were associated with pasteurella organisms resistant to sulphonamides, tetracycline, and penicillin by about 10-fold. This problem hung around for about a year and cost us approximately $200,000, during which time about 20,000 animals went through the feedlot, so something like $10 loss per animal through the feedlot as a result of this problem over about a one-year period.

Question: If I remember correctly, though, in reading your data, these were different cattle, different time of year. In other words, I think you would agree with me as a scientist that it probably wasn't as well controlled a study as you would have liked in terms of a good comparison of same-origin cattle, split randomly and everything. In other words there were different cattle, different time of year and could have even been different organisms or different level of resistance of the cattle or pathogenicity of the organisms. Would you agree with that?

Answer (Dr. Hjerpe): It wasn't a study at all; it was a description of something that happened. We have sent organisms to Dr. Stanley Falco, who is a medical microbiologist at the University of Washington Medical School, and also to Dr. Silver at the FDA in Beltsville where they have been working with these organisms, and the resistance is due to an R-factor. They have been able to transfer it from one organism to another by conjugation like Dr. Powers talked about earlier. I may not ever convince anyone else, but I am totally convinced in my own mind that this resulted from this so-called prophylactic low level feeding of chlortetracycline.

Question: This may be in some cases. The reason I'm asking this, and it worries me a little bit, is this R-factor, I think, is overdone. I think that the comment Dr. Powers made–can you document that with a real good controlled study or with clinical cases? The reason I'm concerned is I have had a chance here just because of the association with Montfords with large numbers. For 20 years now, ever since the tetracyclines came out at low level, they fed 70 mgs per head per day. The number one treatment of choice has been tetracyclines for pneumonia, which makes up about 75% of the sick cattle. Twenty years ago they had a 1% death loss, today we've got a 1% death loss. We had the same incidence of liver abscesses 20 years ago that we have today. Now, if this was such a roaring problem, why are we not seeing a higher level of death loss in these cattle?

Dr. Powers: Well, you make a good question in why we're not seeing a higher death loss but I guess I'm going to evade the answer the same way that you evaded previously. I'm not certain if that's a real good study to show whether R-factor is there or not. It is true, until you look as Charlie's group did, and he found that there were R-factors there that were transmissible. Then you're not certain.

Question: I would concur with you from the standpoint of a controlled study. It is circumstantial evidence at best, but I'd have to think that with those numbers after 20 years, if this R-factor truly clinically creates this problem, where is it?

Answer (Dr. Hjerpe): I could add one idea there and that is that the dosage that you're talking about is about 1/10 the dose that we use in our feedlot. In other words, we were using 500 mg per 10 pounds of starting ration and this would be like 1/2 gram to a calf; to a big yearling it might be a gram, you see, and you are talking about 70 mg per head per day.

Question: Why should you be more likely to have a problem?

Answer: Not necessarily, you see, because you probably don't even get a blood level with that low a dose. At least it is nowhere near one that you could measure. There may be no selective pressure on your bacterial population because you are not getting anything even close to anything that might inhibit a bacteria.

Question: It has reduced the liver abscesses in half, so we've got to be reaching a level high enough to effect microorganisms.

Dr. Bechtol: Can I interrupt here for just a minute. I think your problem is a definition of what "low level" is, rather than improper use of an antibiotic. Feeding 1 gram of antibiotic for 21 days is improper use, not low level, and I think that this is what we need to define because we can prove that every time we feed a 1 gram level for over 14 to 18 days, we're going to produce what you are talking about. So, that is improper use of antibiotics rather than a low level feeding and this is the problem we are having with our food and drug subcommittee on sub-therapeutic feeding. I think we need to do some definitions here. Seventy mg level is low level feeding and this is a good program.

Dr. Powers: I think you've hit on a good point. I know I'm talking too much, but I also talk too little sometimes. I left a little bit ago a statement–I said we've got to define what risks we want to take and that's what you are alluding-to now, which is another whole con-

ference in itself–of how much effect does one get out of controlling liver abscesses, how much does one get out of increased utilization of feed, and so forth, as defined by the risks one is taking. I say it's time we faced this problem. I was a little flippant but that's what I was referring to–is just what you're saying there. I still say that there is a real risk. There is definitely an R-factor being defined, and it can be induced by the low levels in feed. But, how big of a problem is it compared to the benefits derived? That's all.

Dr. Hjerpe: The minimum inhibitory concentrations for your organisms like *spherophorus necrophorous* with tetracyclines are a lot lower than they are with pasteurellas so you could get–for one thing you've got a local effector. You see, the tetracycline comes in and you dump 70 mg in the rumen and so it's in direct contact with the organisms in the rumen that may be starting to localize in an infection in the ruminal wall. You are dealing with organisms like *spherophorus necrophorous* for which the inhibitory concentration of tetracyclines may be 0.01 or 0.05 micrograms per ml. In the case of pasteurella, tetracycline gets absorbed very inefficiently from the rumen. We have to give 40 mg per pound per day in order to get an inhibitory concentration of either chlortetracycline or oxytetracycline in the blood–the same concentration that we get with 5 mg per pound when we inject it. The little bit that is absorbed then gets diluted out into the blood and body tissue and so forth, so that when it gets to the site where pasteurella may be, in the pharynx and possibly in the lung, and so forth, it may not have any effect in the lower doses, if you can see what I am driving at. In other words, we probably can identify ways of using these antibiotics in a low level in which the risk is acceptable. Now, the level that we are using is the same level in which Aureo 700 is used, about a milligram per pound per day, and I would say, yes, that is an improper use. At least I proved to myself that that is an improper use of a tetracycline.

Dr. Don Williams: The other thing I think we can add to Dr. Powers' remarks is that the antibiotics did not create R-factor. It was here long before we had antibiotics. Just the very presence of an R-factor in the environment does not necessarily mean that the antibiotics created it. Looking back to the first use of tetracyclines in 1950-51, we found animals at that time that were resistant to tetracycline.

Dr. Powers: I'll puncuate that. That is very well documented. There are islands where commercial antibiotics have never been, *but* there are microorganisms elaborating these antibiotics all over the world. I'm not certain that there was not a little bug there that might have been producing the antibiotic that helped select the R-factor out long before we knew what antibiotics were.