General Session

The Response of The Food and Drug Administration To The Antibiotic Resistance Problem in Animals

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Introduction of antibiotics in the early 1940's brought a dramatic decrease in the case fatality rates of certain formerly lethal diseases, such as pneumococcal pneumonia, meningococcal meningitis, subacute bacterial endocarditis, rheumatic fever, and syphilis. This has represented one of the great triumphs of modern medicine.

Since the introduction of antibiotics, however, there has been a serious increase in bacterial resistance to these drugs.

Failure of antibiotics to act effectively against bacteria has serious consequences. Antibiotics are used for disease prevention, in treating acute infections in animals and humans, and also for growth promotion and feed efficiency in animals at subtherapeutic levels.

In addition to the problems caused by treatment faiures for previously recognized pathogens, a new and major hazard has developed as a result of antibiotic usage.

There has been a shifting ecology of bacterial infections seen in hospital practice in the United States. Infections caused by certain gram-negative bacteria resistant to antibiotics have been rising. The case fatality rates among all bacteremic patients showed a dramatic decline after the introduction of sulfonomides and antibiotics. More recently, the mortality (35%) has risen to near the levels existent in 1941 before penicillins first became available.

The FDA has the responsibility for regulating usage of this class of drugs. In order to formulate regulations, advise on drug labeling and policy for the rational use of antibiotics, both in humans and in animals, there must be information collected regarding the nature, extent and distribution of bacterial resistance to the antimicrobials. There is a lack of information on certain aspects of bacterial resistance. Had there been adequate progress in developing the needed data, the FDA would not be required to exend the present level of effort in antibiotic resistance research.

Proposal To Restrict

The Food and Drug Administration has proposed to severely restrict the subtherapeutic uses of penicillin and the tetracyclines for animal health purposes as a result of the theoretical possibility that these uses could conceivably lead to human health problems caused by antibiotic-resistant bacteria. This proposal may have economic ramifications to consumers. The Congressional Office of Technology Assessment estimated recently that the banning of tetracyclines and penicillin in feed would increase the cost of meat to consumers by about $1,200,000,000 a year. OTA also reported that their calculations did not take into account the effect of substitutes for the banned antibiotics, although they note that the available substitute drugs are not as effective in hog, cattle and sheep production.

National Academy Of Sciences Contract

In the appropriation bill for FY 1979, the House Appropriations Committee mandated that FDA withhold any restriction on the use of penicillin and the tetracyclines (chlortetracycline and oxytetracycline) used in animal feeds until the National Academy of Sciences studied the matter. The Congress appropriated $250,000 for this activity.

The objective of the National Academy of Sciences research is to compare the health of humans **with extensive exposure** to animals (and/or their products) receiving antibiotics at the subtherapeutic level with the health of comparable individuals **not so exposed.** A contract was signed with the National Academy of Sciences on March 23, 1979. The scope of work to be performed by the National Academy of Sciences is as follows:

1. Review and critique existing literature — published and unpublished — which reports epidemiological studies that have been conducted or are being conducted. Summarize the results of such studies, noting any deficiencies. The review should include data from animal studies, to the extent that such studies are considered to be predictive of human health consequences.

2. Recommend action that should be taken in the future, if any.

3. Identify any useful epidemiological study or studies that can be conducted within the financial and time constraints of the current appropriations, and recommend the mechanism(s) for the conduct of any such study or studies.

Final report is due March 18, 1980.

Current Bureau Research

In addition to the National Academy of Sciences study described in 3 above, the Bureau has several other active research contracts addressing the antibiotics in animal feeds issue. (See Appendix.) None of these directly compare the health of exposed humans vs. the health of non-exposed humans.

Planned Course Of Action

To generate new epidemiological information by comparing the health of humans with extensive exposure to animals, and/or their products, receiving antibiotics at the subtherapeutic level with the health of comparable individuals not so exposed.

It is envisioned that the initial work in drafting the protocol (scope of work) will be done by representatives from the Bureau of Veterinary Medicine, Office of the Associate Commissioner for Health Affairs and the Center for Disease Control, taking into consideration the results of the National Academy of Sciences study to the extent possible.

The protocol that is drafted will then be submitted for comment to:

Bureau of Drugs

Occupational Safety & Health Administration

Office of Technology Assessment

U. S. Department of Agriculture

BVM, under the direction of a project officer, will then develop a mon in accordance with the protocol. The goal will be to have a contract let by the fourth quarter of FY 1980.

BVM will be further guided by the National Academy of Sciences report which is due next March. Pursuant to that report we will make the appropriate decisions on when and if evidentiary hearings will be held, and whether or not the presently proposed orders on penicillin and tetracycline should be continued, modified, put in abeyance or canceled.

APPENDIX

CURRENT BUREAU RESEARCH

Contractor	*Title*	*Objective*	*FY 78*	*FY 79*	*FY 80*	*FY 81*
Colorado State University	Data Base for Drug Resistant Bacteria for Animals	To develop a data base on occurrence & characteristics of bacterial drug resistance	$1,106,513	→	→	→
Public Health Research Institute of the City of NY	Compare R-Plasmids in Gram Positive Bacteria from Human & Animals Given Anitbiotics in Feed	To compare information about the molecular & genetic relationship between R-plasmids in Gram Positive bacteria — (Human and Animal)		$260,614	→	→
University of Missouri	Occurrence of Drug Resistance & the Spectrum of Drug Resistance in Pathogenic Bacteria	To collect data over past 5 years from Vet. diagnostic labs on bacterial resistance in animal pathogens — determine any change & if therapy compromised		$148,870.23	→	
Peter Bent Brigham Hosp.	National & Regional Surveillance of Bacterial Resistance to Veterinary Antimicrobials	To establish a data base of institutions which will regularly report on a cooperative basis the current levels of bacterial resistance		$260,368	$276,074	→
Univ. of Alabama	Bacterial Plasmids Mediating Drug Resistance in Pathogenic & Nonpathogenic Enterobacteria	To characterize the R-plasmids associated with the resistance patterns observed in various animal species receiving antibiotics thru feed		$155,563	→	→
Not Yet Awarded	The incidence & comparison of R-plasmids in anaerobes from animal and human popualitons	To assess & compare the incidence of anaerobic resistance in animal populations fed low level antibiotics and a control group (non-antibiotic fed) with incidence of resistance in farm workers who came in contact with the animal populations.			$ 70,000	→

Dr. Crawford's background - I graduated from Auburn in 1963 then I practiced for a time before joining American Cyanamid Research and Development and I was on leave from them for a short time to get a Ph.D. at the University of Georgia in Pharmacology. At the end of that time I decided to stay in Georgia. I went into administration at the veterinary school and served as Associate Dean for seven years or so and then I joined the FDA on a sabbatical basis in 1975. At the end of a year I came back to Georgia for a couple of years and then I became Director in 1978.

Moderator: Thank you for that information.

Now I would like to close this formal part of my presentation and attempt to answer any questions that might come up.

Q. Why were Louisiana, Mississippi, and Alabama not included in the liver fluke states?

A. We are working on that now. We have had input from Louisiana and Mississippi. We have not had any requests from Alabama but we have from about eight other states and I suspect that they will be declared about the same time that this is approved. We have to satisfy the fact that it is truely a liver fluke emergency. We will make contact with Alabama but they have not made contact with us.

Q. Are you at liberty to state what the compound is?

A. I cannot say what the compound is at this point. That has to come from the firm. Lately we have approved a couple of drugs for use in the United States and the firm has decided not to market it after going all the way through approval. In one of those cases we announced approval of that drug and so it is up to the company to say when they are going to ship it. I cannot say that myself until they do.

Q. What is motivation, where is the driving force that precipitated early action to restrict low level use of antibiotics? At one time the long range plan was to eliminate the use of low levels in all animal, all

antibiotics and sulfonamides that are used for therapy in man. As you stated there is no crisis, there is no other physician telling you that we have a real problem, other veterinarians saying that we have got to do something. I submit that is not the case because in our feedlot meeting yesterday, the drug of choice of the panel members for pneumonia conditions in cattle was almost exclusively tetracycline, so that indicates that resistance is not an overwhelming problem. What is the motivation, is it hysteria, is it political, what is it?

A. The question is where is the motivation for restricting penicillin, tetracycline coming from. It is a difficult question for me to answer because it was put into place before I was associated with the FDA. I think I can answer it though, because I know where it is coming from now. It began when FDA formed three panels in the late 60's and early 70's to look at this problem. Those panels consisted of mostly veterinarians, mostly people named from organizations such as this one, and they concluded that certain restrictions needed to take place and that more studies needed to be done. The more they looked at the problem, the more they turned up incriminating evidence that maybe something should be done in terms of restrictions. I would have to say in all candour, that when these inquiries were put into effect, starting about 1972, they had been like a roller coaster that no one can get off and the reason you cannot get off it is because the scientific evidence slaps you in the face every time you are about ready to put them in abeyance, or what ever. But those of us who are currently at the Bureau have about run out of patience. We would like to either take some steps or we would like to get off it. I believe we will go a long ways toward one or the other in the next six months because it can become self defeating for the industry, because they have to do defensive research for us because we have to take time off from approving new drugs in order to look at this old problem and it also hurts in the area of prestige and confidence of us, the livestock industry, the pharmacentical industry and perhaps the veterinary profession to continue to wallow this around in the news media. My pledge has been since I inherited the problem to bring it to a head as soon as possible. I must admit we are not quite there yet.

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