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Antibiotics in Food Preservation

Public Health and Regulatory Aspects

Henry Welch

The extension of the uses of antibiotics to fields other than prophylaxis and therapy of human disease has magnified the problems of the U.S. Food and Drug Administration from the standpoint of side reactions and possible significance to public health. Antibiotics are used in animal nutrition for promotion of growth in swine, chicks, and poults. Therapeutic and prophylactic use of large quantities of antibiotics is made for animals such as cows, beef cattle, swine, chicks, and mink. These drugs are now being used as crop sprays to prevent blight in apples, pears, walnuts, and beans and bacterial diseases of tobacco, tomatoes, peppers, and cherries. Studies have been made to show the value of antibiotics in the preservation of vegetables, fish, beef, ham, chickens, and other perishables.

The actual or potential introduction of antibiotics into the food supply poses the same problem as does the use of any other chemical, and this growing use of chemicals in food is one of the most serious problems facing the Food and Drug Administration. It should be emphasized, however, that the problem of contamination of foods with antibiotics is a small one compared with our other problems of food safety. There is virtually no limit to the expanding list of chemicals that may find their way into our food supply. Chemicals are promoted as stabilizers, preservatives, disinfectants, antioxidants, extenders, tenderizers, emulsifiers, growth promoters, fumigants, herbicides, defoliants, fungicides, miticides, bleaches, sweeteners, conditioners, colors, and flavors. In addition, food packages which incorporate new plastics, enamels, films, plasticizers, catalysts, and coatings are further potential sources of food adulteration.

In 1942 when penicillin was first introduced into this country, it is questionable whether anyone realized that this event was the beginning of a new billion-dollar industry. During the first year of commercial production, about 29 pounds of penicillin were made available. In this past year, over 960,000 pounds were produced. Total antibiotic production was 2.5 million pounds in 1956. It need not be emphasized here that these drugs have had very wide and, in some cases, indiscriminate use. Their remarkable curative powers, more pronounced perhaps in the early days than now, resulted in their being injected, insufflated, given by mouth, spread on every part of the body, and sprayed intra-abdominally, intracisternally, intrapleurally, and intravaginally; no surface or cavity of the body has remained inviolate. There are over 400 preparations of antibiotics available for clinical use today, and they run the gamut of injectables, ointments, powders, sprays, capsules, syrups, ear and eye drops, suppositories, troches, tablets, and vaginal bougies. Antibiotics have saved tens of thousands of lives in the past 14 years, and the reduction in mortality, morbidity, and complications of diseases has affected the lives of millions.

Side Reactions

Nevertheless, with such major advances in therapy we unfortunately have to face the accompanying untoward side reactions. These invariably follow. In the case of penicillin, a relatively atoxic drug, the "side reaction" is its potentiality for sensitizing certain unfortunate individuals. Although the other antibiotics are, in general, poor sensitizers, other side reactions may occur following their administration.

It is estimated that about 10 percent of our population has a tendency to become sensitive, in the course of a lifetime, to some food, drug, cosmetic, or other substance, while the great majority of individuals are resistant. Within this 10 percent there is a great variation in susceptibility to sensitization. Some acquire it easily, while others are more resistant. Some may be sensitive on first contact (the atopic group), while others require one contact, and still others may require several contacts, before exhibiting a reaction. The reactions, too, vary in degree from mild, transient rashes to prolonged urticaria and from a brief asthmatic attack to fatal anaphylactoid shock. Allergic manifestations occur less frequently in children.

Antibiotics are probably our most important and most widely used therapeutic agents. It is unlikely that any one of us will go through life without having antibiotics administered to us by our physician for sound medical reasons. Thus, with a population for this country of over 170 million, according to the most recent figures, we are concerned primarily with perhaps 17 million people who may react to a contact with antibiotics, be it through its therapeutic use for some disease condition or, inadvertently, through eating or drinking foods containing them. In the first case the physician and patient have a choice, but in the latter instance there is none.

Antibiotics in Animal Feed

Antibiotics used for stimulation of growth are usually present in feed in small amounts (5 to 20 parts per million). When antibiotics are used in these quantities, antibiotic residues are not found in the blood or tissue of the animal. When 50 to 200 parts per million are used for prophylactic or therapeutic purposes in feed for chicks or poults, it may be demonstrated that there are residues in the tissues during the period in which the animal is being fed these higher concentrations. However, the anti-

Dr. Welch is director of the Division of Antibiotics of the U.S. Food and Drug Administration.

biotics are rapidly excreted within a few days after the drug is withdrawn. The use of antibiotics as described above, under present normal marketing conditions, does not, in our opinion, constitute a public health hazard. Antibiotics used as crop sprays are dissipated before the edible portion of the plant is formed, and since they do not reach the consumer, no public health problem is involved.

Food Preservation

Extensive experiments have been conducted to explore the potentialities of antibiotics as food preservatives. In November 1955 the Food and Drug Administration approved the use of chlortetracycline for the preservation of raw poultry, and about one year later similar approval was given for oxytetracycline. Tolerance levels for these drugs were established under the provisions of the Miller Pesticide Chemicals amendment to the Food, Drug, and Cosmetic Act, passed by the 83rd Congress in 1954. These drugs act as preservatives and extend the "shelf life" of the fowl. Under the Miller amendment, the applicant must demonstrate "usefulness" to the satisfaction of the Department of Agriculture and "safety" to the Food and Drug Administration. The tolerance level for both chlortetracycline and oxytetracycline in the raw bird was established at 7 parts per million, in any part of the bird. Before approval of this tolerance level was granted, it had to be shown that no significant antibiotic residues could be found in the poultry after cooking by broiling, frying, boiling, or baking. A considerable number of investigations of the usefulness of antibiotics in the preservation of fish and meats have also been completed. However, approval of such uses by the establishment of tolerance levels under the Miller amendment can be obtained only when conclusive evidence is presented that such use is not detrimental to the health of the general public.

Indirect Adulteration

In addition to being directly introduced in these ways into the food supply, antibiotics may also find their way into foods indirectly. In 1948 it was first noted that when milk from cows that had been treated for mastitis by intramammary infusion was mixed with antibiotic-free milk for the purpose of making cheese, failure to produce a satisfactory cheese product often resulted. This was due to the inhibition of the starter culture used in cheese manufacture by the antibiotic present in the milk. Realizing that antibiotics might also reach the consumer by way of milk, the Food and Drug Administration, by regulation, required that mastitis preparations carry a warning in their labeling to the effect that "milk from treated segments of udders should be discarded or used for purposes other than human consumption for at least 72 hours after the last treatment." In further recognition of the possibility that antibiotics might get into the food supply, a statement of policy was issued in February 1953 by the Secretary of the Department of Health, Education, and Welfare concerning the direct or indirect addition of antibiotic drugs to foods for human consumption. In effect, the policy statement was as follows: "The presence of antibiotic drugs in foods intended for human consumption, or the direct or indirect addition of such drugs to such foods, may be deemed an adulteration within the meaning of section 402 of the Federal Food, Drug, and Cosmetic Act."

Very large amounts of antibiotics are used in the treatment of milk-producing cows infected with mastitis. It is estimated that more than 75 tons of these drugs are used yearly in the treatment of this widespread infection. The great bulk of infected cows are treated by udder infusion, and a variety of products are available for this purpose. Penicillin is perhaps used in the greatest volume, since this drug is quite effective in those cases caused by streptococci, particularly *Streptococcus agalactiae*, the organisms responsible for most cases of mastitis. However, the disease is also caused by other organisms, such as the corynebacteria and the *coli-aerogenes* group of organisms, and, as a result, other antibiotics, such as dihydrostreptomycin, streptomycin, the tetracyclines, neomycin, and bacitracin, and the sulfonamides are used for treatment and prophylaxis.

Treatment usually consists of application of a single tube or injection of a syringe full of the preparation for each infected quarter of the udder, but as many as four treatments, at 12-hour intervals, may be necessary per quarter. Thus, in a single treatment, an animal that is being treated with a combination preparation may be given 500,000 units of penicillin, 500 milligrams of dihydrostreptomycin, 50 milligrams of neomycin, and 750 milligrams each of sulfanilamide and sulfathiazole. If the infection is severe, the animal may receive as much as four times these amounts within a 48-hour period.

When the antibiotic preparation used is effective, the clinical result is quite dramatic, and a marked change in the appearance of the teat and udder takes place within 24 hours. However, the disappearance of the signs of infection and the consequent reduction of inflammation are no guarantee that the infection is eliminated. This can only be determined by bacteriologic examination of the milk. Certainly, a favorable change in appearance of the infected udder is no guarantee that the drugs infused have been completely absorbed or eliminated. As a matter of fact, experimental evidence points to the opposite conclusion. It is necessary to milk infected cows twice daily for a period of at least three days to be sure that the great bulk of the drugs has been milked out. Experience has shown that practically the entire amount of infused antibiotic is eliminated by regular milking over a period of three days. It appears that failure to observe the warning given in the labeling of mastitis preparations concerning the discarding of milk from treated cows is largely responsible for the presence of antibiotic residues in the milk supply.

Surveys and Solutions

During the last three years (1954, 1955, and 1956), three surveys have been made of fluid market milk to determine its antibiotic content. In these surveys a total of 2274 samples were examined, and samples from all states were included. An average of 6.9 percent of the samples examined contained penicillin, in concentrations varying from 0.003 to 0.550 units per milliliter. Other dairy products tested, including powdered milk, evaporated milk, ice cream, butter, cheese, shell eggs, and broken eggs were found to be free from antibiotic residues.

The relatively large number of positive samples noted in the year that separated the first and second surveys caused some concern, and it seemed advisable to obtain some opinion on the possible public health significance of the presence of penicillin in these quantities in market milk. Accordingly, some 30 experts in the fields of antibiotic therapy, allergy, and pediatrics were asked to express their views on this matter. The majority of these experts believed that penicillin in these amounts is unlikely to modify the oral or intestinal flora, cause the emergence of resistant strains, or provoke sensitization of an insensitive person. However, the majority felt that such concentrations might possibly cause a reaction in a highly sensitive individual. Recently the Food and Drug Administration has taken three steps to alleviate the public health problem involved:

1) Through cooperation with the U.S. Department of Agriculture, an intensive program has been initiated to educate the farmer concerning the importance of discarding, or using for purposes other than human consumption, milk from cows treated for mastitis with antibiotic

drugs for a period of three days following the last treatment. In addition, the National Milk Producers Federation, which reaches some 500,000 farmers, is assisting in this education program through their state agents.

2) On 23 Jan. 1957 we published in the *Federal Register* notice of a proposal concerning the warning statement regarding disposition of milk from treated cows which is required in the labeling of antibiotic drugs intended for intramammary infusion. It was proposed that this warning be placed on the immediate container of the drug rather than in the literature accompanying it. This is now in effect.

3) On 9 Feb. 1957 a "Notice of Proposed Rule Making" was published in the *Federal Register,* limiting the penicillin content of mastitis preparations to 100,000 units per dose. This became effective on 12 August.

It is hoped that these three steps will alleviate the problem of antibiotics, particularly penicillin, being present in our milk supply. However, if these procedures are unsuccessful, it may be necessary to ban the use of penicillin in mastitis preparations in the United States.

Complex Problem

The control of antibiotics in our food supply becomes more complex daily. We now have before us for consideration the use of chlortetracycline and oxytetracycline in fish as a means of extending "shelf life." Unfortunately, in contrast to demonstrations with poultry, we have been unable to demonstrate that ordinary methods of cooking treated fish (broiling, frying, boiling, or baking) eliminate the residual antibiotic. Furthermore, some fish are eaten raw, smoked, or pickled, and in all these cases the consumer would ingest antibiotic residues. Before tolerance levels can be established for these antibiotics in fish it will be necessary for those requesting them to demonstrate that the residues found are not dangerous to public health.

As we attempt to feed more and more people better and better, and as more and more uses are found for antibiotics in foods, those charged with the responsibility of seeing to it that such foods are safe will find themselves in an increasingly difficult position. In the United States we plan to move slowly and cautiously in response to each new proposal concerning antibiotics in foods, keeping in mind the fact that if the public, or any unfortunate segment of it, has reservations concerning the safety of our food, it must at the same time question the effectiveness of our operations.

AAAS Meeting in Indianapolis

Raymond L. Taylor

Since the appearance of the preliminary announcement of the fourth Indianapolis meeting, which will be held from 26 to 30 December, inclusive [*Science* **125**, 1047 (24 May 1957)], the symposia and other programs listed there have been developed and augmented. From such program details as the names and addresses of the authors of the hundreds of papers, and from such data as the advance registrations and applications for housing accommodations, which have been received in increasing volume since July, it is quite apparent that this year's AAAS meeting—the 124th—will enjoy an excellent attendance and that all sections of the United States and many foreign countries will be represented.

The Annual Exposition of Science and Industry, as the alphabetical directory of exhibitors and the descriptions of their exhibits makes evident, will fill the large Egyptian Room of the Murat Temple and would in itself be worth a trip to Indianapolis.

As the outline of symposia shows, virtually no principal field of science will be neglected, and the number and variety of special events, characteristic of AAAS meetings, are greater than usual. A conspectus of these follows.

Conferences and Special Programs

In recent years, in addition to the Academy Conference, several conferences have become recurrent events at AAAS meetings. Also, not infrequently, interest in special subjects may develop to the point where a special program is arranged. These conferences and special programs are open to all who are interested.

Academy Conference; 28 Dec., morning, afternoon, evening.

Conference on Scientific Editorial Problems; 26 to 29 Dec., mornings and afternoons (five sessions).

Conference on Scientific Manpower; 30 Dec., morning and afternoon.

Mathematics Instruction; a program of AAAS Section A–Mathematics, cosponsored by the National Council of Teachers of Mathematics and the AAAS Cooperative Committee on the Teaching of Science and Mathematics; arranged by John R. Mayor, educational director, AAAS; 27 Dec., morning.

Social Aspects of Science as Illustrated by the Radiation Problem; a general session sponsored by the AAAS Committee on Social Aspects of Science, arranged by Chauncey D. Leake, chairman; 29 Dec., afternoon.

AAAS Special Sessions

One of the characteristic and most important features of the annual meetings of the Association is the series of outstanding general addresses by distinguished experts, sponsored by organizations that meet regularly with the AAAS. These special events are joint sessions with the Association and are open to the general public of the city in which the meeting is held.

Special Address of the Biometric Society, Eastern North American Region; 27 Dec., morning; Boyd Harshbarger, department of statistics, Virginia Polytechnic Institute, and president, Biometric Society, Eastern North American Region, presiding. "Smoking and Lung Cancer: An Example of the Interpretation of Statistical Data in the Observational Sciences," by Sir Ronald A. Fisher, Arthur Balfour professor of genetics, Cambridge University, England.

Joint Annual Address of the Society of the Sigma Xi and the Scientific Research Society of America; 27 Dec., evening; George H. Boyd, dean of the Graduate School, University of Georgia, and president, Society of the Sigma Xi, presiding. "The Fickle Fashions of Science," by Crawford H. Greenewalt, president, E. I. duPont de Nemours and Company.