Problems of Antibiotics in Food as the Food and Drug Administration Sees Them

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Though this paper is chiefly concerned with the possibility of harm from the presence of penicillin in milk, there is much else in it of direct interest to many of us, in addition to those to whom it was addressed.

In 1942 when penicillin was first introduced into this country few 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 440 tons were produced. It need not be emphasized here that this drug, which has been proved a highly antigenic substance, has had a wide and in some cases indiscriminate use. Its remarkable curative powers, more pronounced perhaps in the early days than now, resulted in its being injected, insufflated, given by mouth, spread on every part of the body, and sprayed intraabdominally, intracisternally, intrapleurally, and intravaginally—no surface or cavity of the body remaining inviolate.

There are 150 preparations of penicillin available for clinical use today and they run the gamut of injectibles, ointments, powders, sprays, tablets, troches, and vaginal bougies. Penicillin has saved tens of thousands of lives in the past 14 years and the reduction in morbidity, and complications of diseases has affected the lives of millions. Nevertheless, with advances in therapy, we unfortunately have to face the accompanying untoward side-reactions that invariably follow. In the case of penicillin, a relatively atoxic drug, its "side reaction" is its potentiality for sensitizing certain unfortunate individuals.

It is estimated that about 10 per cent of our population have a "proneness" to become sensitive during their lifetime to some food, drug, cosmetic, or other substances while the great majority of individuals are resistant. Within this 10 per cent there is a large variation in susceptibility to sensitization: some acquire it easily while others are most resistant. Some may be sensitive on first contact (the atopic group), others require one contact, while 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.

Penicillin is still one of our most important and most widely used therapeutic agents. It is unlikely that any one of us will go from "cradle to grave" without its being administered to us by our physician for sound medical reasons. Thus, with the most recent population figures for this country of 170 million, we are concerned primarily

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with perhaps 17 million people who may react to a contact with penicillin, be it through its therapeutic use for some disease condition or inadvertently through eating or drinking foods containing it. In the first case the physician and patient have a choice, but in the latter instance there is none.

As early as 1948 it was reported that milk from cows treated for mastitis by intramammary infusion contained enough drug to inhibit cheese-starter cultures. Recognizing that in a similar manner antibiotics in milk might reach the consumer, the Food and Drug Administration required producers of antibiotic preparations for mastitis to insert a statement in the circular accompanying each package that milk from treated cows be discarded if intended for human use for at least three days following medication. During the past three years three surveys have been made of fluid market milk to determine its content of antibiotics. The data obtained have been published.

To summarize these results briefly, in the first survey 3.2 per cent of 94 samples were found to contain penicillin. In this preliminary study a number of other dairy products, such as cheese, butter, dried milk, and evaporated milk, were tested. No antibiotic activity was demonstrated in these products. In the second survey 474 samples of market milk were tested and 11.6 per cent were found to contain penicillin. The concentrations in the milk varied from 0.003 unit per ml to 0.08 unit per ml (highest amount 80 units per quart).

In the third survey, completed in January of this year, 1,706 samples were examined and these were collected from all the 48 states and the District of Columbia. This extensive survey showed penicillin in concentrations of 0.003–0.550 unit per ml in 5.9 per cent of the samples examined (highest amount 550 units per quart). In addition, one of the penicillin positive samples apparently contained streptomycin, and 17 additional samples (approximately 1 per cent) appeared to contain bacitracin, one of the tetracyclines, or a combination of these drugs. Penicillin was confirmed by the penicillinase identity test, while the other antibiotics could not be specifically identified.

The Food and Drug Administration has had a number of letters from consumers, those interested in the dairy industry, and state officials, indicating their concern and asking for information about steps being taken to solve the problem. Further, we have had letters from one or two doctors indicating that either they or one of their patients are highly sensitive to penicillin, and in two instances these physicians believed they had evidence of serious reactions following ingestion of milk presumed to be adulterated with penicillin. It should be stated here, however, that at this time we do not have a single proved case of a reaction following the ingestion of fluid milk known to contain penicillin.

Following our second survey of the milk supply, opinions were obtained from some 30 authorities in the fields of antibiotic therapy, allergy, and pediatrics, concerning their views on the significance of these quantities of penicillin in market milk from a public health standpoint. The majority of these experts were of the opinion that these concentrations were unlikely to modify the oral or intestinal flora, cause the emergence of resistant strains, or provoke sensitization of an insensitive consumer. However, the majority felt that these concentrations might possibly cause a reaction in an exquisitely sensitive individual. The antibiotics used in mastitis preparations are mainly penicillin, streptomycin, bacitracin, neomycin, polymyxin, oxytetracycline, and chlortetracycline. The evidence seems to be that the broad-spectrum antibiotics are poor sensitizers, as are neomycin and

streptomycin by mouth. Both bacitracin and polymyxin, being polypeptides, are poor sensitizers also. Our major concern is with penicillin.

Although it is possible that penicillin has been added to milk illegally to lower bacterial counts, we have felt from the beginning that the presence of penicillin in milk is caused mainly by the producer sending milk to the dairy sooner than 72 hours after treatment of the mastitic cow with the antibiotic preparation. Although the very great bulk of the antibiotic is eliminated in the first few milkings following treatment, small increments of antibiotic may be demonstrated for relatively long periods of time. The finding of antibiotics in milk and the possible unauthorized use of antibiotics as food preservatives provoked the publication by the Secretary of the Department of Health, Education, and Welfare on February 25, 1953, of a statement of policy which, in essence, stated that the addition of antibiotics to foods either directly or indirectly constituted adulteration.

For the past several years certain antibiotics, penicillin, chlortetracycline, bacitracin, and oxytetracycline, have been used to stimulate the growth of chicks, poults, and swine. These drugs are used in feed in concentrations of from 5 to 20 ppm. Carefully controlled studies in our own and in other laboratories demonstrate conclusively the absence of antibiotic residues in these farm animals fed in this manner. In some cases higher concentrations of antibiotics are utilized (50–200 ppm) for prophylactic or therapeutic purposes in chickens and poults. Residues may be demonstrated in the blood and tissues of these animals while being fed these higher concentrations. However, the drugs are rapidly excreted, disappearing from both blood and tissue within a few days after the animals are placed on nonmedicated feed. The use of antibiotics as just described under normal marketing conditions does not, in our opinion, constitute a public health problem.

In November, 1955, the Food and Drug Administration under the Miller Amendment approved the use of chlortetracycline in the processing of poultry. This drug acts as a preservative extending the shelf-life of such processed birds. Under this amendment the applicant must demonstrate "utility" to the satisfaction of the Department of Agriculture and "safety" to the Food and Drug Administration. In the process the clean dressed bird is immersed in a tank of ice water containing 10 ppm of chlortetracycline, usually for a period of two hours. The tolerance established was 7 ppm in any part of the bird, the "part" consisting of its normal complement of skin, fat, muscle, and other tissue. The application for this use of chlortetracycline was under consideration and study for over three years before final approval. It was not until conclusive scientific evidence was presented that the drug could not be found in the "cooked" bird—be it by broiling, frying, boiling, or baking—that a final tolerance was established. Recently, the same tolerance was established for oxytetracycline for similar uses.

Antibiotics are in use in the treatment of prophylaxis of plant diseases. Both streptomycin alone and streptomycin and oxytetracycline combined are marketed for apple, pear, and walnut blight. Successful studies have been reported in the control of halo blight of beans and bacterial diseases of tobacco, tomatoes, peppers, cherries, and potatoes. Here, too, there seems to be no public health problem involved, since none of the drugs used reach the final consumer, all being dissipated before the fruit or vegetables are eaten.

A considerable number of investigative studies of the usefulness of antibiotics in the preservation of fish and meats have been completed. The evi-

dence is quite substantial that these drugs will extend the shelf-life of these important food products. However, approval of such use by the establishment of tolerances under the Miller Amendment can be obtained only when conclusive evidence is presented that such use will not endanger the public health.

On September 10 of last year a Medical Advisory Panel accepted the invitation of the Commissioner of the Food and Drug Administration to consider the public health problems involved by the presence of antibiotics in market milk.* In addition to the panel, representatives of the American Drug Manufacturers Association, Associated Veterinary Laboratories, Animal Health Institute, Department of Agriculture, Food Protection Committee of the National Research Council, Milk Industry Foundation, American Medical Association, Public Health Service, American Veterinary Medical Association, California Creamery Operators Association, and the Food and Drug Administration were present.

Following the all-day session, during which the problems involved were discussed thoroughly, it was apparent that our main health problem is concerned with penicillin to the exclusion of the other antibiotics that are used in mastitis preparations. It was the consensus of the panel that antibiotics, such as the tetracyclines, bacitracin, polymyxin, and neomycin, all of which may be found in mastitis preparations, do not pose a public health problem, even though they may find their way into market milk.

It was agreed that penicillin is a highly active antigenic substance and, even in the very small concentrations found in milk, might well cause reactions in highly sensitive individuals. It was apparent that the latter individuals are most concerned with this public health problem and that they constitute something less than 10 per cent of the population. It seemed certain that reactions could occur in these individuals of varying intensity from mild transient ones to possibly serious ones, the serious reactions occurring in those individuals "exquisitely" sensitive. Because scientific proof is essential, it was the consensus of the panel that further studies were necessary with highly sensitive human volunteers to determine whether or not the ingestion of milk containing those concentrations of penicillin now found in market milk would cause allergic manifestations. Two of the panel members, Drs. Feinberg and Siegel, in collaboration with the Food and Drug Administration, will carry out such studies.

Although it was recognized by the conference members that penicillin could be added illegally to milk as a means of lowering bacterial counts, it seemed obvious from the discussion that penicillin was reaching the milk supply primarily through the improper use of mastitis preparations for the treatment of infected dairy animals. Although, as noted previously, the labeling of mastitic preparations carries a warning to the farmer that milk from treated cows should not be sold for human use for three days after the last treatment, it is his failure to follow these instructions in some cases that causes the major adulteration of the milk supply. Furthermore, this warning appears in the labeling but not on the label of each preparation. It seems advisable, in order to carry the warning more directly to the user, that it be placed prominently on the label of each mastitis preparation

* On the advisory panel were: Wesley W. Spink, M.D., Chairman, University of Minnesota; Harry F. Dowling, M.D., University of Illinois; Samuel M. Feinberg, M.D., Northwestern University; Chester S. Keefer, M.D., Evans Memorial Hospital; Perrin H. Long, M.D., State University of New York; Walsh McDermott, M.D., Cornell University Medical College; Robert Popper, M.D., Veterans Administration; and Bernard B. Siegel, M.D., Jewish Hospital of Brooklyn.

container. Steps are now being taken to make the necessary amendments to the antibiotic regulations.

During the past few years the Department of Agriculture has been concerned with the problem of antibiotics in milk because of the interference of these drugs with cheese-starter cultures. In their studies they have been able to demonstrate that certain dyes incorporated in mastitis preparations will color the milk from such animals so that it is readily recognized as being from an infected animal. Considerably more work has to be done in this area. If a satisfactory dye is found, it may be quite advisable to require by regulation that it be added to all mastitis preparations so that for several milkings after treatment the milk will be distinctly colored and therefore unfit for use as market milk.

It is quite likely that milk producers do not recognize the possible danger to the public health that is associated with the adulteration of market milk with antibiotics. It is likely also that the warning, which now appears in the labeling of these preparations, has not been brought forcibly home to milk producers. Actually, milk from infected cattle is adulterated, per se, because of its content of pus and bacteria, and the milk shipped to the market too early after treatment of the cows with an antibiotic preparation is doubly damned because of the presence of both antibiotic and evidences of infection. It is quite possible that the public health problem involved here may be considerably reduced by a strong educational program directed to those who are responsible for the production of market milk. It was the consensus of the Medical Advisory Panel that an educational program of considerable magnitude may be helpful in at least partially alleviating the situation.

In closing, it should be emphasized that the problem of contamination with antibiotics in our foods and particularly in milk is a small one compared to our other current food safety problems which have arisen in large part as a result of technologic progress in food production, processing, and distribution. In the processing of food, preservatives, antioxidants, colors, bleaches, flavors, coatings, drying agents, moistening agents, thickening agents, sequestering agents, "aging" agents, stabilizers, emulsifiers, neutralizers, acidifiers, and sweeteners are utilized. In production and processing of food, new equipment cleaners, sanitizers, lubricants, surfacing materials, and alloys composing the equipment itself may all contaminate the food processed. In distribution, food packages which incorporate new plastics, enamels, films, plasticizers, antioxidants, catalysts, and coatings are further potential sources of food adulteration.

These agents utilized in processing, production, and distribution of foods may be inherently toxic and may have an accumulative effect, and combinations of them may have synergistic toxic effects—in short, the problems involved with such agents are enormous. As noted above, the case of penicillin in milk is a minor problem by comparison. Penicillin is a relatively atoxic substance and may be taken by nonsensitive individuals in enormous concentrations. Our problem with penicillin, it should be repeated, is related to a relatively small proportion of our population, namely, those unfortunate individuals who have become sensitized to the drug. Nevertheless, milk is consumed by the strong and the weak, the old and the young, the well and the sick, and the allergic and the nonallergic individual. Even though the adulteration of milk with penicillin may affect only a small percentage of the population, this percentage can represent several million people all of whom must and will be fully protected from adulterated food under the Food, Drug, and Cosmetic Act.