Nonpharmaceutical Uses of Antibiotics

Nonpharmaceutical uses of antibiotics have been the base of an outstanding scientific development in agricultural and food chemistry during the past few years. In September, the Fermentation Subdivision of the Division of Agricultural and Food Chemistry of the AMERICAN CHEMICAL SOCIETY sponsored a symposium on the subject under the chairmanship of Nestor Bohohos, Lederle Laboratories. With that material as a base, rounded out by information gathered from many other sources, AG & FOOD has surveyed applications and theory. High lights and trends suggest an increasingly important future for antibiotics

IN THE PERIOD following Sir Alexander Fleming's discovery of the antibiotic powers of penicillin, the implications of the availability of this new class of "wonder drugs" for human therapy became staggering. Yet within only a few years, research work stemming from that finding began to reveal another great area—the stimulation of growth through the inclusion of antibiotics in animal rations. Today the market for antibiotic growth stimulants is approaching a position of such importance that it must be recognized beside the human therapeutic uses as an important economic outlet for industry. In 1952 antibiotic sales amounted to about $267 million. Of this approximately 13% of the total, by weight, was fed to farm animals. There has been an impressive increase in feed supplements during 1953. A year ago the capital invested in antibiotics production was estimated in the neighborhood of $200 million.

The growth in use of antibiotics outside pharmacy is not stopping there. Animal feed supplements are commercial and already important business. But research now under way, some already at the point of field testing, is carrying these products of fermentation into other fields. Sterilization and preservation of food was, of course, a likely area, and studies have been under way there for some time. But where direct consumption of a product having strong physiological effects is involved outside direct medical supervision, there are many complex factors involved. Because of this, the use of antibiotics in preservation of foods is not ready for the public. The Food and Drug Administration has come out in open opposition to the use of antibiotics in foods, at least until more detailed and exact knowledge of all possible effects on public health have been clarified more satisfactorily.

Plant disease is one of the areas in which great strides are being made. Striking discoveries have been announced at scientific meetings during the past year and even research workers in the field admit surprise at the speed of development in this area. Already, at least one product is being marketed, while field tests, which may lead to commercial development of others, are under way. Some of the more optimistic predictions go so far as to suggest that this may make possible revival of apple and pear orchard cultivation in the Southeast, from whence it virtually disappeared years ago because of blight.

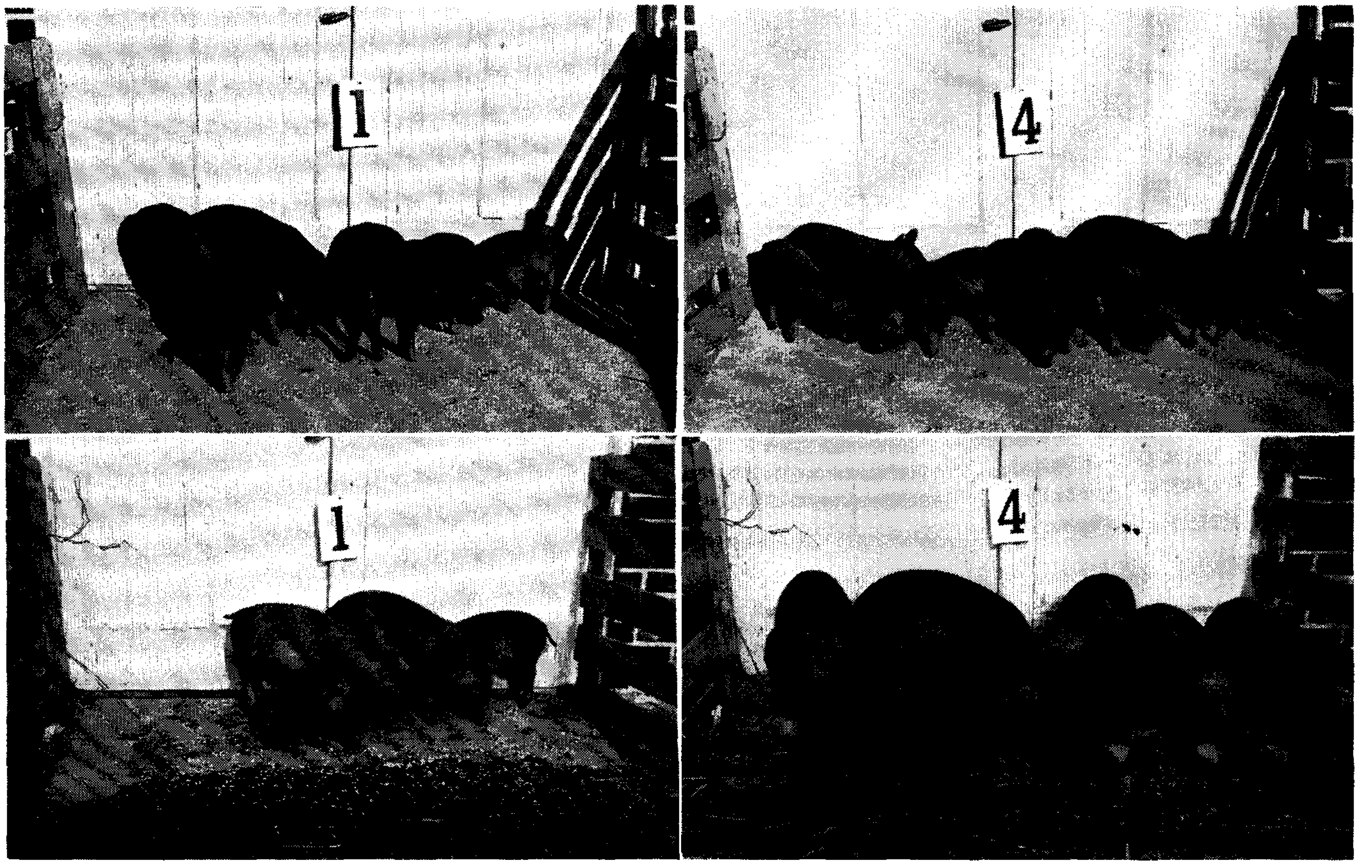
Animal Growth Stimulation

It was not until 1950 that reports began to appear indicating that antibiotics could exert a stimulating effect on the growth of animals. In the relatively short time since then, the addition of these materials to feeds has become commercial and progressed to the point where a high percentage of feeds for young pigs and chicks contain some antibiotic material and calf feeds now are beginning to make use of these supplements.

Although the growth stimulation has not been explained to the complete satisfaction of the scientists, the farmers of the nation have been rapidly persuaded by the dollars and cents factors of their practical experiments and the results furnished them by their state agricultural colleges and experimental stations, as well as big companies producing antibiotics. The "pig-omics" of the situation has been summarized by a publication from the Iowa Agricultural Experiment Station (Table I) based on experimental work carried out there.

In raising hogs, the addition of antibiotics to feed increases the feed efficiency and gets the hogs ready for market in a shorter period of time and with less feed than can be done with the basal ration alone. Also, the supplements seem to reduce the incidence of subclinical diseases of livestock, swine enteritis, calf scours, and chronic respiratory diseases in chickens. Where the diseases have developed, increased levels of antibiotics have proved effective in arresting them.

In 1953, R. Braude *et al.* published a review paper which cited 111 scientific papers dealing with the use of antibiotics in swine rations alone. Even this amount of work has not clarified all as-



Practical demonstration carried out at Iowa State Agricultural Experiment Station showing the effects of antibiotic growth supplements. Two groups of 8 "runt" pigs each were started on a balanced basal ration. Ten mg. of Aureomycin per pound of ration was added to the feed of group 4. The lower pictures were taken two months later. Group 1, on the basal ration, suffered a 50% mortality and showed an average daily weight gain of 0.86 pound. Group 4, receiving the added antibiotic, showed a 59% faster weight gain on 14% less feed and suffered no mortality

pects of the action and effects of antibiotics in the stimulation of growth. Recently, Damon Catron, of Iowa State College, one of the leaders in research on antibiotics in swine nutrition, prepared for the Fourth Nutrition School fos Feed Men, University of Wisconsin, summaries of the fairly well established facts and the possibilities not yet definitely proved about the subject (page 1098). His summary was based on experiments involving more than 3000 animals at the Iowa Agricultural Experiment Station, as well as results reported from other sources and was presented with the statement that present status of knowledge leaves several gaps which demand considerable research.

Agents and Their Use

The growth stimulating effect is common, to varying degrees, to several antibiotics. The most widely used and effective of these seem to be: chlorotetracycline (Aureomycin), oxytetracycline (Terramycin), diamine penicillin, and procaine penicillin and Bacitracin.

Because of the dual action of these materials as both growth stimulants and therapeutic agents, a distinction is made between the two use levels: 5 to 20 parts per million is generally accepted as growth stimulant level, while 100 to 200 p.p.m. is considered therapeutic.

As indicated elsewhere, the control of nonspecific diseases seems to be accepted as a factor in growth stimulation. The extent of growth stimulation is often related to the subclinical disease level among animals which have a high incidence of such infections. The stimulatory action may be produced by any one or a combination of the following: suppression of microorganisms which compete with the animal for food supply or tax the normal metabolism through subclinical disease; an increase of organisms which produce growth factors; or suppression of organisms which interfere with the absorption of nutrients through the gut.

Table I. APPLIED "PIG-OMICS"

Value of Feeding Antibiotics Based on a 20-Sow Herd

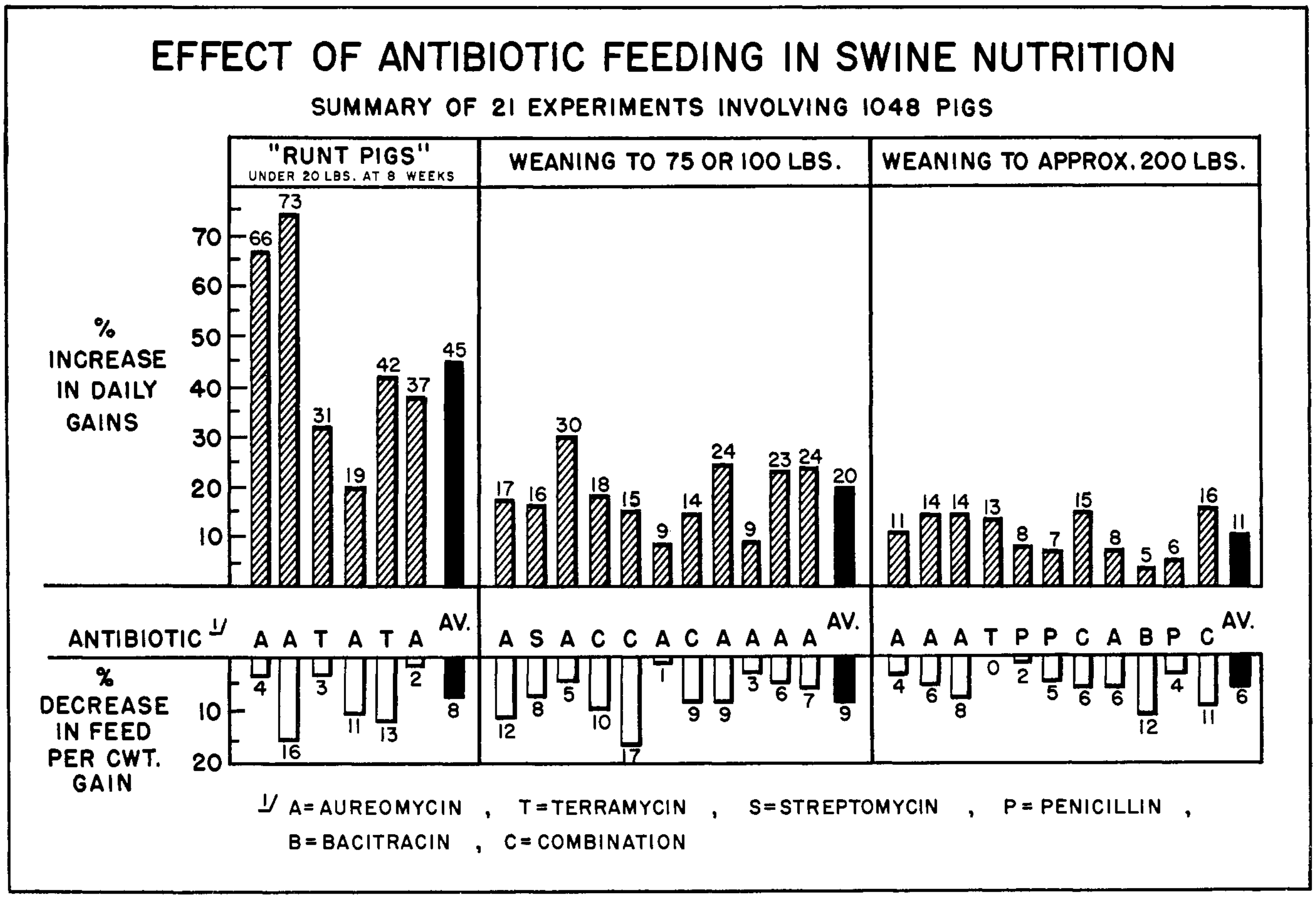
I. **Manpower Saving**
   - 20 Sows × 6.5 Pigs/Litter = 130 Pigs
   - 130 Pigs × 240 pounds (Av. Market Wt.) = 31,000 pounds Pork
   - 312 (Cwt. Pork) × 1.53 Manpower Hours/Cwt. =
   - 477 mph × 10% Faster Gains with Antibiotics =
   - 47.7 Manpower Hours or 6–8 hour days saved

II. **Feed Saving**
   - 312 (Cwt. Pork) × 20 pounds Feed Saved/Cwt. =
   - 6240 pounds Feed Saved × 4¢/pound = $249 –
   - $93 (Cost of antibiotics) = $156 Net Saving
   - or
   - $156 ÷ 130 Pigs = $1.20 more profit per pig

Source: Iowa Agr. Exp. Station
Based on 31 Experiments with 1814 Pigs

Speer and coworkers reported in the *Archives of Biochemistry*, December 1950, evidence to support the idea that the "disease level" theory might explain observed failure of antibiotics to improve gains or feed efficiency in germ-free animals. Healthy, previously well-fed pigs, managed under relatively disease-free conditions might not respond as would unthrifty animals fed in unsanitary surroundings. The idea became generally accepted among workers in swine nutrition. The relationship of disease conditions and nutritional adequacy of ration as factors in the response to growth stimulants is presented in graphic form by Dr. Catron (page 1100).

S. K. Kon and his coworkers, in England, have demonstrated that the stimulation of growth in chicks is absent when the



Source: Damon Catron, Iowa State College

birds are raised in rooms not previously used for chicks, suggesting the importance of suppression of subclinical disease which is prevalent under normal growing conditions.

Recent Theories

In the recent AMERICAN CHEMICAL SOCIETY Symposium on Nontherapeutic Uses of Antibiotics, B. Connor Johnson, University of Illinois, reported work which leads his group to the belief that nature of growth response can be explained by intestinal flora stimulation. Using radioactive thiamine as a tracer and deriving an index of nutrient synthesis and absorption, they found indications that the feeding of antibiotics resulted in greater synthesis of vitamin B_1 in the intestinal tract. Explanation of the basic mechanism for this phenomenon has not yet been elucidated.

A very recent report, by L. A. Quinn, Iowa State College, before a symposium in Washington, D. C., sponsored by the Food and Drug Administration and the Journal of *Antibiotics and Chemotherapy* suggested stimulation was effected by production of a growth factor by the intestinal flora in pigs. Experiments indicated Aureomycin did not stimulate growth in pigs raised on wire screen so as to prevent eating of feces. The inference was that the growth stimulating principle resulting from the feeding of the antibiotic was synthesized in the lower intestine of the pig and was effective only when food contaminated by the feces was consumed. Bacteriological examination of the feces of swine fed the antibiotic supplement showed an increase, over the control, of the population of the fungus *Apergillus flavus*. Feed containing cultures of that fungus produced a growth response in swine. There was no inference, however, that this fungus suppressed subclinical disease and thus no suggestion that it could replace antibiotics in all growth stimulation.

Special Factors with Ruminants

The use of antibiotics in rations fed to ruminants has not progressed so far as it has with swine and poultry, but is increasing rapidly. Some research work, almost all *in vitro*, has indicated that antibiotics hinder utilization of cellulose and of nonprotein nitrogen. Other researchers have found no detectable effects. Bartley, for example, found no consistent difference in microflora of control and Aureomycin-fed calves. At Iowa State, Jacobson and his group have found a general growth increase of 20 to 25% in dairy calves during the first four months. Animals have been fed from birth to the age of three years without finding detrimental effects on reproduction or milk production. The greatest growth stimulation comes in the early months and control animals eventually attain similar size. But the high morbidity and mortality among calves in the first few months is appreciably reduced. This appears to be the principal benefit visible at present and is particularly important for the production of veal calves. Results of work by Knodt and his group at Penn State are in agreement.

Research on young beef cattle, reported by Beeson, at Purdue, has shown a striking growth stimulation by addition of antibiotics to six-months-old calves not previously fed these supplements. Growth stimulation is, however, transitory; the effect lasts about six weeks to two months and thereafter falls off sharply. Similar results were observed at Iowa State with dairy calves.

Louis Russoff, Louisiana State University, postulated before the ACS symposium that the action of antibiotics in stimulating growth in calves may be concerned with more rapid absorption of nutrients through the gut, or perhaps biosynthetic reactions are influenced, resulting in an increased synthesis of essential nutrients without modification of the intestinal bacteria. Dr. Russoff administered antibiotics by injection into the blood stream, bypassing the rumen, and found that growth was stimulated.

Antibiotic carryover, or transfer from feed into animal products later to be used for human food has been a problem causing considerable concern. The sensitivity of assay for the various antibiotics adds some complicating factors here, as they vary. Aureomycin, for example, can be detected in concentrations as low as 1 to 5 parts per 100 million, while some of the others can be detected only at appreciably higher levels.

In animal feeding experiments using normal growth stimulating levels of Aureomycin—5 to 10 parts per million—no residual antibiotics were detectable in the meat. At higher levels, such as 50 parts per million in the feed, Aureomycin was detectable in the flesh of chickens. The lowest level producing detectable carryover in pigs has been 200 parts per million. At a feeding level of 1000 parts per million, carryover is detectable in most animal tissues. But even at this level, the antibiotic usually is undetectable in tissues two or three days after the material is withdrawn from the diet. Lederle Laboratories researchers have pointed out that aureomycin present in meat at detectable levels is destroyed by cooking.

While the situation appears to be satisfactory with respect to meat, the Food and Drug Administration has not yet agreed that all is well in the cases of eggs and milk, which are not always cooked before eating.

Food Preservation

In discussing antibiotics in food preservation, emphasis should be placed first of all on the fact that the U. S. Food and Drug Administration has taken a definite stand against the addition of antibiotics to foods which are to be consumed by humans. This stand will undoubtedly continue, until more satisfactory evidence is presented to the FDA to support contentions of harmlessness to food consumers of antibiotic preservatives. A similar stand is taken by the USDA's Meat Inspection Service.

Thus any discussions here refer only to research studies and it must be clearly understood that these techniques are *not commercial* practices and are *not approved* by the FDA by USDA for use in foods sold to the public.

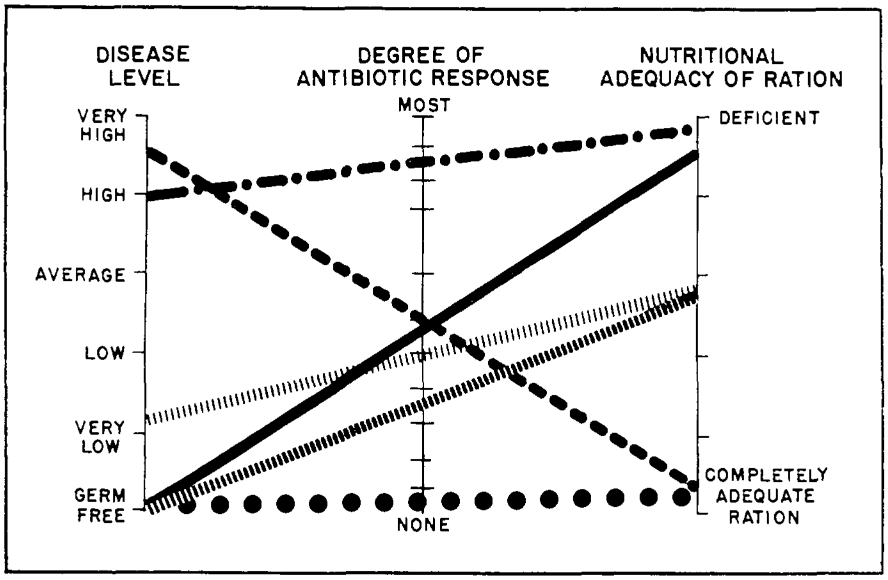
For purposes of considering antibiotic application, food preservation may be divided into two general types, interim preservation and permanent preservation. Interim processes are intended to protect the food from spoilage for a relatively brief period, as in the care of fresh fish between catch and consumption, or the handling of fresh vegetables. Permanent, or long-term, preservation is designed to maintain the food free from spoilage for an indefinite period of time, as in the canning of fruits and vegetables.

Short-Term Preservation

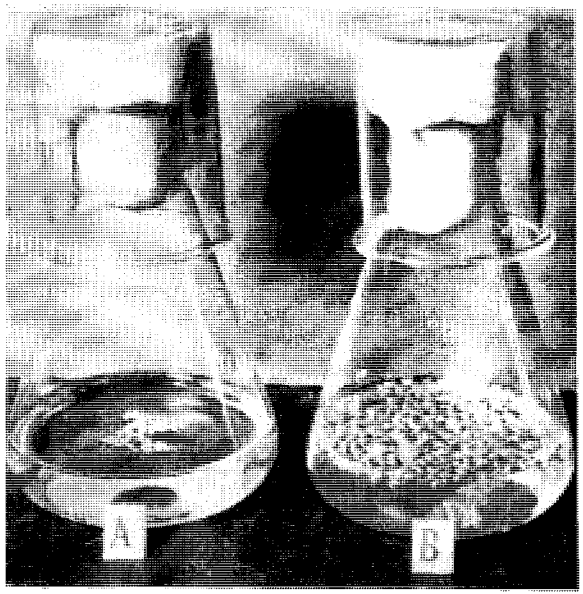
Internal spoilage, known as "sours" often develops in freshly-killed meat if not promptly chilled after slaughter. The origin of this internal spoilage is found in the vascular lymphatic system.

F. E. Deatherage, Ohio State University, has developed an antibiotic infusion technique, which, in experimental use, has inhibited the deep spoilage of meat for at least 48 hours. Such a technique could make possible dressing and cutting animals immediately after killing, bypassing the present deep-chilling interim. It has been emphasized that this is considered useful only as a possible step in meat processing; long-term preservation would continue to depend on refrigeration.

The degree of growth response to antibiotic feed supplements is affected by the subclinical disease level and the nutritional adequacy of the ration. Greatest response is obtained by addition to deficient ration of animals with a moderately high subclinical disease level



Source: Damon Catron, Iowa State College



Effects of Terramycin on growth of duckweed studied by L. G. Nickell, Chas. Pfizer & Sons. Both flasks contain a basal medium and have been cultured aseptically for 8 weeks, 5 parts per million of Terramycin were added to flask B

Deatherage infused a saline solution of antibiotic through the circulatory system of the animal immediately after killing. Bacterial counts made 120 hours after killing were only slightly higher on meat which had been infused and kept from refrigeration 48 hours than those on meat normally processed.

H. L. A. Tarr, of the Pacific Fisheries Experiment Station, in British Columbia, reported to the ACS symposium on methods showing potential promise for extending the storage life of chilled fish, a factor which now limits the cruise length of fishing boats. Flaked ice containing 1 to 4 micrograms of Aureomycin per gram was used as a preservative with good effect in retarding bacterial spoilage action. Dipping the fish in a solution containing 5 to 10 parts per million of Aureomycin before storage on ordinary ice was also found to be effective. Similar results have been reported with experiments on shrimp boats in the Gulf of Mexico. Tarr says that about 90% of the Aureomycin present on the fish would be destroyed by exposure to 100° C. for 30 minutes.

The brown rot decay of packaged green vegetables exposed to room temperature is an important economic problem which has attracted attention of antibiotics researchers. The decay of packaged spinach, for example, is so rapid that 1 to 2 days at room temperature can render it a commercial loss. W. L. Smith of the USDA station at

An Appraisal of Results of Feeding Antibiotics to Swine

DAMON CATRON, Iowa State College

Results which seem fairly well established:

1. Antibiotics are not nutrients—they are classified as drugs.
2. Antibiotics of choice for stimulating growth in swine are Aureomycin, Terramycin, and procaine penicillin. Bacitracin in combination with penicillin has also increased growth rate in some experiments.
3. The optimum practical feeding level of these antibiotics is approximately 5 milligrams per pound of total ration. Therapeutic levels commonly used in treating diseases are 30 to 100 times recommended feeding levels.
4. They are effective in either dry-lot or pasture feeding; however, greater growth increments are usually obtained under dry-lot feeding conditions.
5. Antibiotics of choice increase growth rate 5 to 20% from weaning to 200 pounds under average feed-lot conditions.
6. They produce a maximum growth response when fed to young pigs—less increase in gains in pigs from 100 to 200 pounds.
7. When antibiotic feeding is discontinued after pigs reach 75 to 125 pounds, cessation of accelerated growth rate occurs and the growth rate tends to follow that of the controls. However, the pigs previously fed antibiotics maintain their early growth advantage for some time.
8. Increased appetite is indicated by 10 to 20% greater daily feed consumption when an antibiotic is fed. Inasmuch as water consumption is positively related to feed consumption, antibiotic-fed pigs usually drink more water.
9. Improvement in feed efficiency from antibiotic feeding varies from 0 to 12%; however, on an average it saves about 5% of the feed required (20 pounds per 100 pounds gain) by growing-fattening pigs under average feed-lot conditions.
10. Antibiotic feeding reduces the number of runts and makes pigs within litters grow with much greater uniformity in size. Slow-growing, runt pigs show a dramatic response to antibiotic feeding—19 to 73% (average 45%) faster gains on from 2 to 16% (average 8%) less feed than similar pigs fed balanced rations with no antibiotics.
11. One of the most important values of antibiotics in swine rations is their ability to control a high percentage of the nonspecific enteritis in swine. This has been observed in both experimental and practical farm conditions. This has been confirmed by challenge experiments.
12. The response of pigs to antibiotic feeding appears to be in proportion to the disease level. Apparently healthy pigs, pigs reared on wire floors, and pigs raised on disease-free units have failed to respond to antibiotic feeding in well controlled experiments. This has been confirmed by poultry research and by disease-free animal research.
13. Antibiotic of choice feeding alleviates the deficiency of certain nutrients in an otherwise well-balanced ration. Antibiotic feeding spares certain water-soluble vitamins, e.g., vitamin B_{12}, riboflavin, pantothenic acid, and niacin and protein. Apparently the composition of the ration and degree of deficiency of the nutrient in question affects the degree of sparing action that can be exhibited by any antibiotic "of choice." Antibiotics show a definite specificity for "sparing" certain vitamins which are present in quantities thought to be suboptimal for maximum growth.
14. Antibiotic feeding does not interfere with the conception rate in sows.
15. Sows fed Aureomycin transfer it into their milk, detectable by present assay methods if fed at 20 milligrams, or higher, per pound of ration. From 2 to 4 times normal feeding levels must be fed to sows if they are to be transferred into the milk for the nursing pigs.
16. Antibiotics do not replace the necessity of practicing careful swine sanitation. However, they do make possible the successful profitable production of pigs under high disease level conditions where such was not possible before.

Indications drawn from research but not definitely proved:

1. There is insufficient research evidence as to the value of antibiotic feeding to sows during gestation and/or lactation. However, there is enough evidence to indicate that antibiotic feeding does not interfere with gestation and lactation performance.
2. There is insufficient research evidence as to whether or not combinations of antibiotics are more effective than a single antibiotic "of choice" when fed at equal levels to swine. However, Bacitracin seems to be ineffective when fed alone, yet when it is combined with penicillin a significant growth increase has been obtained.
3. Although two groups of investigators have reported that antibiotic feeding increases the depth of back fat and in general lowers carcass quality. Results of extensive research at the Iowa, Wisconsin, Ohio, and other experiment stations have shown that antibiotic feeding does not interfere with carcass quantity when fed in a properly balanced ration.
4. Antibiotics do not appear to lose their effectiveness when fed continuously. However, as animals reach maturity the nonantibiotic fed groups tend to catch up with the antibiotic fed animals.
5. Aureomycin, Terramycin, and procaine penicillin seem to be fairly stable in dry mixed feeds when stored under good conditions for a practical length of time.
6. Bacteriological studies of feces and intestinal tract contents indicate that the feeding of an antibiotic of choice modifies the intestinal flora, inhibiting certain classes of microorganisms and stimulating other types. Contrary to early opinion, antibiotic feeding actually increases the total count following an initial transitory decrease in numbers of organisms. (The most recent report of work supporting this idea was that of Quinn, before a symposium in Washington, D. C., sponsored jointly by the Food and Drug Administration and the Journal of *Antibiotics and Chemotherapy* from which proceedings will be published in December 1953.)
7. Although the multiple mode of action of antibiotics is not yet entirely known, evidence to date indicates that their activity is confined to modifying the intestinal flora, thereby (1) permitting the synthesis of and/or sparing critical nutrients needed by the host (nutritional effect), and/or (2) inhibiting pathogenic, semipathogenic, and/or toxin forming microorganisms injurious to the host (disease control effect).

Based on 53 growing-fattening experiments involving more than 3000 pigs and 9 gestation-lactation experiments involving 311 sows at Iowa Agricultural Experiment Station as well as on the results reported from other stations and laboratories.

From Proceedings of Fourth Nutrition School for Feed Men, 1953, University of Wisconsin.

Beltsville, Md., studied the use of streptomycin against the soft rot bacteria causing spinach loss. Both preharvest sprays and postharvest dips were tested on different batches of spinach which were contaminated with cultures of soft rot bacteria. The treatment extended the shelf life of the spinach at 70° F. by at least a day. The postharvest dip appeared to offer advantages over the preharvest spray. Terramycin was comparable in this use with streptomycin and Aureomycin gave some control.

Dr. Smith has recently been investigating antibiotics for control of postharvest decay in peaches.

The two opened packages of spinach have been stored at room temperature for 3 days. Spinach on left has almost completely deteriorated due to brown rot, spinach on right was sprayed with water solution containing 1 part of streptomycin per 1000 before harvest. Experiments reported by L. W. Smith, USDA

Long-Term Preservation

For permanent or long-term preservation, requirements are much more stringent. Here the emphasis is placed on the total eradication of the *Clostridia*, a genus of anaerobic bacteria which produces extremely dangerous toxins. Perhaps the best known species of this genus is *C. botulinum*, the causative agent of botulism. These anaerobic bacteria can grow only in the absence of air. Hermetically sealed tin cans provide ideal environment for their development. In addition to their great toxicity, these bacteria form inactive spores which are among the most heat-resistant of the organisms normally considered in food processing schemes. The high temperature cycles of food processing are required for the eradication of *Clostridia*.

A survey of the possible applications of antibiotics in normal permanent food preservation techniques has been prepared by J. C. Lewis. This survey presents a discussion of the use of various antibiotics to lower the heat threshold of the resistant spore form of the botulinus organism. Lewis believes that if an antibiotic could be found which would bring about an appreciable increase in the heat sensitivity of these spores, it could be of commercial value in food processing.

If an antibiotic cannot be found which will bring about a reduction in the heat necessary for eradication of these spores, then perhaps one can be found which will fill either of two other conditions:

A highly stable antibiotic might be used to maintain a bacteriostatic condition within the canned food for the shelf life of the product. Although this seems extremely unlikely, such an antibiotic would be lethal when the *Clostridia* changed from the resistant inactive spore form to the active more sensitive bacterial form.

Another possible application would be an additive which would stimulate the complete germination of all the vegetative spores of *Clostridia* which might be present within the can. Such an additive coupled with a stable antibiotic might bring about an eradication of the organisms within a relatively short period of time.

The previous reports of success and failure using the antibiotic subtilin in conjunction with heat treatment for the eradication of *Clostridia* are explained by Lewis as due to the presence of resistant spore forms of the bacteria within the food being processed. These spore forms are perhaps resistant to subtilin and germinated after the subtilin has deteriorated.

As yet no antibiotic has been found which will completely satisfy any or all of these basic conditions. Although of experimental interest, the application of antibiotics for permanent food preservation does not now seem imminent.

Fermentation Control

Another application recently reported for antibiotics is in the control of "wild bacteria" for industrial fermentation processes. This is an example of the application of short term processing techniques for adaptation to an existing processing cycle.

The control of souring microorganisms in grain fermentation processes is complicated by the fact that presterilization of the fermentation medium is impractical; heat would destroy the enzymes responsible for the saccharification of grain starch. Barley malt, the source of many of these enzymes, is heavily laden with bacteria, from one to ten million organisms per gram.

W. H. Day has reported a survey of a number of antibiotics to control the contaminants in alcohol fermentation. All of the antibiotics seemed to inhibit the contaminants and in addition some beneficial effects were noted: increasing yeast counts, control of bacteria without destruction of the amylase enzyme system.

Similar studies were reported by Strandskov. The effectiveness of a number of antibiotics for control of mixed cultures of the bacteria commonly found as contaminants in beer fermentation was evaluated (Table III).

Table III. Effective Concentrations of Antibiotics for Control of Fermentation Contaminants

	Micrograms/ml.
Streptomycin	125
Bacitracin	125
Terramycin	50
Penicillin	125
Aureomycin	50

Plant Growth

Various research workers have reported a stimulation of plant growth for antibiotics. However, there is no evidence which indicates any relation between the stimulation in plants and animals.

L. G. Nickell of Chas. Pfizer and Son, in studies with duckweed, has found evidence to indicate certain antibiotics stimulate growth. The duckweed is the largest flowering plant that can be sterilized and grown under aseptic conditions on a chemically defined liquid medium. Several antibiotics have been tested for plant growth stimulation, as shown in Table IV.

Johnstone, at the University of Southern California, some time ago reported growth increases as great as 75% with bean seedlings grown in garden soil containing a few parts per million of Terramycin. Penicillin and Aureomycin also showed some effect.

Hypotheses for the mechanism of

growth stimulation in plants vary widely at present: degradation products of the antibiotic may be the stimulators; properties other than antibacterial characteristics may be the cause, as for example, a chelation ion may be formed; detoxification of metabolic products rather than direct growth stimulation; sparing action on essential nutrients.

Plant Disease

Another significant area in which research findings rapidly are pointing the way toward new and potentially important uses for antibiotics is plant disease. Applications in which the antibiotic is absorbed into the plant system and transported therein are showing promise.

In a review before the ACS symposium, Curt Leben and G. W. Keitt, University of Wisconsin, considered the possible applications of antibiotics for plant disease control. Antibiotics with their high bacteriostatic activity seem to offer certain advantages compared with chemical treatments now in use.

Table IV. Effects of Antibiotics on Growth of Duckweed

Antibiotic	*% Wt. Change, Compared with Control (Wet Wt. Basis)* 1 p.p.m.	20 p.p.m.
Actidione	−85	−90
Bacitracin	0	+130
Chloromycetin	+40	−75
Neomycin	−20	−90
Rimocidin	−10	−50
Penicillin G	+40	+330
Streptomycin	+50	−10

Source: L. G. Nickell, Chas. Pfizer & Son.

Chemical treatment usually is of a preventative nature. The chemical compound is sprayed onto the plant to prevent the development or spread of the infection on the plant's surface. This form of treatment is often referred to as nonsystemic, the chemical is not introduced into the plant tissue. There has, however, been extensive research directed toward the development of systemic treatments for plant disease; thus far there has been little success with chemical compounds in this attack.

The systemic theory of treatment is aimed at the application of some material which will be absorbed and transported within the plant system. To be an effective systemic, a material must be nontoxic to the plant and highly effective against the disease organism. The effective concentration of any systemic material within a plant would, of necessity, be low.

Streptomycin has also been reported to be effective for protection of seeds against attack by pathogenic bacteria. Generally streptomycin seems to have been ineffective for the protection of seeds against fungi.

Of the research which has been reported on the use of antibiotics for the control of plant disease, Actidione and streptomycin seem to have received the greatest amount of attention. These two diverse antibiotics seem to offer the greatest promise for application at present. However, in the reports on these materials, the major drawback has been that in some cases the amounts necessary for the control of disease are harmful to the infected plants.

Fireblight Treatment Promising

Fireblight, a damaging disease of fruit trees, which was the major cause of eradication of pear and apple orchards in southeastern U. S., is the disease against which most dramatic results recently have been reported. R. N. Goodman, University of Missouri, recently reported effective treatment of this malady with a streptomycin-Terramycin spray on apple trees. One group of Johnathan apple trees naturally infected and another innoculated showed very promising results. Dunegan, USDA, and Ark, in California, also have reported control of fireblight under field conditions with antibiotic sprays.

In 1952, Mitchell, Zaumeyer, and Anderson reported on greenhouse tests in which the primary leaves of bean seedlings were protected from a bacterial disease, halo blight, by application of small amounts of streptomycin sulfate to the stem before inoculation with the blight organisms on the leaf. A significant discovery which had to be taken into consideration here was the finding that the antibiotic only moved upward through the plant system. Zaumeyer now has reported on field tests using streptomycin sprays. Two varieties of beans susceptible to halo blight were sprayed with a preparation containing 0.1% streptomycin. Control plants were treated with a dithiocarbamate fungicide. Three days later the plants were sprayed with blight organisms. Final observations after 40 days showed 41% of the plants receiving one application of streptomycin infected. In the group receiving two applications 10% were infected, and the group receiving 3 or 4 sprays showed no infection. Untreated controls showed 93% infections while those treated with fungicides were 88 to 91% infected.

Zaumeyer and his group believe that streptomycin sprays offer practical possibilities for control of halo blight on young bean plants.

As a result of these and similar reports Chas. Pfizer and Sons recently announced plans to conduct extensive field tests with a Terramycin-streptomycin mixture next year. Sufficient quantities of the mixture will be distributed to test its efficacy against fireblight on 100,000 pear and apple trees. It also is being tested for control of halo blight of beans, bacterial spot of tomatoes, and other plant diseases.

Actidione (cycloheximide) seems to be the only antibiotic developed commercially for use exclusively in plant disease control. It is a nonsystemic fungistatic product currently used for the control of various fungal smuts and rusts. It is being marketed to treat fungus diseases of grass and fruit trees. However, Actidione has been shown to be phytotoxic to many plants.

Seed treatment is yet another approach to antibiotic use and Actidione is being used in that way to prevent attacks by pathogens already on the seed or in the soil. Encouraging results have been reported with cereal grains.

Phytotoxicity and effective concentrations for disease control appear to be the limiting factors in the use of antibiotics against plant disease, according to Dr. Leben. Present indications are that within these limits, new antibiotics may be developed for use exclusively in that area.

Future

With large quantities of antibiotics already being used commercially in animal feeds, research is constantly proceeding toward the elucidation of factors and mechanisms involved in the growth stimulation effect. Problems still exist to hamper some applications in this area, but they are being cleared little by little. On the basis of experience in the past few years it seems likely that this area of application will continue to grow.

Use in food preservation has especially firm barriers to overcome in providing thoroughly adequate evidence that no undesirable effects will occur in the consumer of food so treated. Research is continuing and the situation, at best in some areas, is more promising than it was a year ago. Experimental results which will gain the approval of the Food and Drug Administration is a goal needed here before commercial development can come about.

Application to plants is a relatively new field of use. Plant growth stimulation is still a research question and further elucidation of present findings must be awaited before a view of the possibilities can be gained. Plant disease treatment, on the other hand, has developed through research at a very rapid rate. Actidione is already in commercial use. Large scale field tests to assess the possibilities of an antibiotic spray against fruit blights are being planned for next year. Optimism seems to prevail on that score, but final conclusions must await further study.

The developments of the past few years make the accuracy of predictions very doubtful. But it seems certain that the future of nonpharmaceutical uses of antibiotics is one of expanded use through research and development.