

GROWTH CHANGES IN THE GUINEA PIG AS A RESULT OF ORAL
ADMINISTRATION OF Aureomycin AND Penicillin

By

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INTRODUCTION

Numerous studies have been made of the effect of small amounts of antibiotic supplements in the diet of certain animals. In general, increased growth, better food utilization, and fewer digestive disturbances have been reported. The mode of action of the drugs in producing growth has not been definitely established. Although the body weight provides some idea of growth, it may to a great extent represent fat deposition rather than true growth. Histological studies on the effects of antibiotic administration have been neglected. In a review of the literature it was found that an investigation had not been made of the effects of administration of low levels of antibiotics in the guinea pig. It is the purpose of this investigation, therefore, to determine if daily oral administration of low levels of aureomycin and penicillin stimulates growth and initiates certain anatomical, histological, physiological, and immunological changes in the guinea pig. The study was approached from the standpoint of: changes in organ and body weights, skeletal growth, and organ and bone structure; determinations of hematocrit and concentrations of the antibiotics in the blood; presence or absence of antibodies; and effects on reproduction.

Drug makers a few years ago measured antibiotics as grains of costly substance. Now, they sell crude extracts of the drugs by the carload. These extracts are mostly

derived from broths that used to be discarded. As small an amount as \$1.60 worth of antibiotic mixed with \$100.00 worth of feed will hasten the growth of many different animals by as much as 10% to 30%. Antibiotics have been found to stimulate runt animals to grow to normal size. The drugs, however, have been found not to cause abnormal growth at maturity.

Antibiotics are defined by Bechtel (1951) as drugs that prevent, injure, or destroy life, but those which promote growth and vigor are considered as probiotic. Briggs (1950) likens antibiotics, which produce increased growth, to "promotants." He defines a "promotant" as any substance or agent, which produces a desirable effect; such as, faster growth, better feed efficiency, or improved reproduction, by its action on the intestinal flora, when added to the diet of a non-ruminating animal—it may be a drug, a vitamin, or any other type of compound. Promotants include phenylarsonic acid derivatives (which are used as coccidiostatic agents) and several of the sulfa drugs as well as some antibiotics, Blight, King, and Ellis (1952).

Antibiotics Which Stimulate Growth. Many investigators have classified aureomycin, bacitracin, chloromycetin, penicillin, streptomycin, and terramycin as antibiotics, which stimulate growth in animals.

Aureomycin: Aureomycin is elaborated by Streptomyces aureofaciens and was first described by Duggar (1948). It is bacteriostatic in low concentrations, and in high concentrations it has bactericidal properties. As a growth

promotant, this drug has been found to be an aid to chicks when added to their basal rations by Stokstad (1950), Jukes and Stokstad (1951), Couch and Reed (1950), Bird (1950a), Whitehill, Oleson, and Hutchings (1950), Cunha (1950), March and Biely (1952), and Scott and Glista (1950). Some of these investigators recommend such amounts of aureomycin per quantity of feed as: 12 mg. per pound, 7 to 10 mg. per pound, 25 mg. per kilogram, and 20 g. per ton. A 22% increase in the weight of chicks at 10 weeks of age was noted by Couch and Reed (1950), when aureomycin was added as a supplement to a basal ration. Another investigator, Stokstad (1950) reported improved feathering, pigmentation, and appearance in chicks fed this antibiotic. Berg et al (1950) found that removal of supplemental aureomycin from the ration of four-week-old chicks resulted in immediate cessation of accelerated growth, which had existed during the 0 to 4-week period. Gravens (1952) reported good stimulation of growth in chicks and turkey poults with aureomycin added to a complete ration.

That aureomycin stimulated increased growth in turkeys and turkey poults, was proved by Jukes and Stokstad (1950), (1951). At 12 mg. per pound of ration, growth was stimulated in turkeys and turkey poults by Atkinson and Couch (1952) and Stokstad and Jukes (1950).

According to Rusoff (1951) calves were found to increase in weight and have stimulated appetites by feeding aureomycin. Loosli and Wallace (1950) obtained the same results by using 15 mg. of the drug per 100 pounds of body weight.

Pigs or weanling pigs have been reported to increase in growth when fed aureomycin by Cuff et al (1951), Stokstad (1950), Jukes and Stokstad (1951), Cunha (1950), Blight, King, and Ellis (1952), Briggs and Beeson (1952), Sheffy et al (1952), Powick et al (1951), and Carpenter (1951). These investigators used such amounts of aureomycin per quantity of feed as: 22 mg. per pound, 12 mg. per pound, 20-25 g. per ton, 9.1 grams per 100 pounds, 1.8 mg. per pound, and 8.5 mg. per pound. An increase in weight of 40% in pigs, when aureomycin was added to their feed at 20 to 25 grams per ton, was noted by Stokstad (1950). Cunha (1950) fed 9.1 g. of aureomycin per 100 pounds of ration to pigs and noted that they doubled their body weight and showed a smoother hair coat. Bird (1950a) and Briggs (1950) independently, fed aureomycin with feed and obtained good growth in unthrifty weanling pigs. Additions of aureomycin above the optimum level for increased growth, had no beneficial effects on pigs, Edwards (1950).

Rats and weanling rats, also, show increased growth as a result of feeding aureomycin, Meites (1951), Oleson (1950) and Bentley (1952). Sauberlich (1952) found similar results by feeding 0.01% aureomycin. Rats react to the stimulatory effect of antibiotics incorporated at low levels in a complete ration, Oleson, Hutchings, and Whitehill (1950). Vijayaraghavan, Murphy, and Dunn (1952) state that 50 mg. of aureomycin per kilogram of basal ration stimulates growth in mice.

Aureomycin Fed in Combination with Vitamins:

Certain vitamins included with aureomycin stimulate growth in some animals. Rats fed limiting amounts of Vitamins B-1 and B-2 plus aureomycin increased in growth equal to those fed a diet containing double the amount of vitamins without the antibiotic, Lih and Baumann (1951) and Lih (1951). The combination of aureomycin and Vitamin B-12 was found to be most effective in rat growth, Meites (1951). Similar results were obtained in both weaning and post-weaning weights of rats, according to Stern and McGinnis (1949), (1951).

Oleson, Hutchings, and Whitehill (1950) reported that a combination of aureomycin and Vitamin B-12, when fed to chicks, caused increased growth—the minimal amount of the drug needed being less than 5 mg. per kilogram of feed. Oleson (1950) stimulated growth in chicks, when they were fed 25 mg. of aureomycin per kilogram of diet with graded levels of Vitamin B-12.

Working with poultry up to 8 weeks of age, Branion and Hill (1951) fed 25 mg. of aureomycin per kilogram of an all-vegetable protein ration plus Vitamin B-12 and reported a definite growth increase. A 20% to 25% weight increase in turkey poults was obtained in the first 8 weeks by feeding aureomycin and Vitamin B-12, according to Couch and Atkinson (1950). Similar results were obtained with turkey poults by Stokstad and Jukes (1950).

Pigs fed all the required vitamins plus aureomycin, were stimulated in growth twice the amount found in normal pigs, Cunha (1950). Growth was reported in pigs and weanling

pigs by Jukes et al (1950) and Briggs and Beeson (1952), when fed aureomycin and Vitamin B-12. Terrill et al (1952) noted an increase in weight of 25% above normal in weaning pigs up to 100 pounds, which were fed Vitamin B-12 and 5 mg. of aureomycin per pound of feed. In the opinion of Sewell et al (1952), Vitamin B-12 is needed as a supplement in a basal diet with aureomycin.

Penicillin: Penicillin is derived from Penicillium notatum and was first investigated as an antibacterial agent in 1928 by Fleming. It is bacteriostatic in threshold concentrations and bacteriocidal in higher concentrations, but neither effect is observed unless bacterial cells are in growth stages. Certain strains of the notatum microorganisms are able to produce penicillinase, an enzyme which is capable of destroying the drug.

Stimulation of growth in chicks by feeding penicillin as a diet supplement was reported by Elam, Gee, and Couch (1951a) and Bird (1950b). Penicillin in the amount of 7 to 10 mg. per pound of feed has been found to be required by chicks for growth increase. In a basal ration which included all required vitamins plus penicillin, good growth stimulation was noted by Cunha (1950) in chicks, Cravens (1952) in chicks and turkey poults, and Sieburth et al (1951) in turkey poults.

Penicillin is especially effective in turkey poults, because it stimulates earlier growth than other antibiotics, Stern et al (1952) and McGinnis and Stern (1952) have found in their investigations that turkey poults respond in growth

to penicillin when fed at 5 p.p.m. Turkeys were noticeably promoted in growth when grass juice concentrate and penicillin as feed supplements were used by Slinger, Pepper, and Hill (1952).

Investigations reveal that pigs respond with favorable weight gains when fed penicillin as a feed supplement, according to Cuff et al (1951), Beeson (1951), and Carpenter (1951). Some of these investigators found the following amounts of penicillin per quantity of feed to be effective: 22 mg. per pound and 20 grams per ton. Weanling rats, also, show growth increases with penicillin added in the amount of 0.01% to the diet, Sauberlich (1952).

Penicillin Fed in Combination with Vitamins:

Greater growth stimulation has been achieved in some animals by the addition of B vitamins to penicillin as feed supplements. Sauberlich (1952) reported increased growth in rats by the use of penicillin with Vitamins B-1, B-2, and B-6. Working with rats, also, Lih and Baumann (1951) found that a diet, which included supplements of penicillin and Vitamin B-1 or B-2, provided growth stimulation equivalent to doubling the vitamin content of the diet in the absence of the antibiotic.

By feeding penicillin and Vitamin B-12 to turkey poults, Couch and Atkinson (1950) noted good growth stimulation. Branion and Hill (1951) reported that penicillin, when added at 25 mg. per kilogram of basal diet plus Vitamin B-12, caused increased growth in poultry up to 8 weeks of age.

Bacitracin: Bacitracin, another antibiotic which promotes growth, is derived from an aerobic strain of *Bacillus subtilis*. It was first obtained from the bacterium, which had been isolated from the tissue cleaned from a compound fracture of the tibia. Johnson, Anker, and Meleney described the preparation and some of its properties in 1945.

Terrill (1952) found that pigs, when fed 5 mg. of bacitracin per pound of feed, showed a 16% increase in gain rate from weaning up to 100 pounds, and a greater gain when fed the same level of antibiotic from weaning up to 200 pounds in weight. In disagreement with these results is the report of Cuff et al (1951), which states that no growth increase over normal hogs resulted by feeding bacitracin. Chicks and turkey poults were found to be stimulated in growth when bacitracin was added to their ration, Cravens (1952) and McGinnis and Stern (1952).

Chloromycetin: Chloromycetin (chloramphenicol) is derived from cultures of *Streptomyces venezuelae*, which Burkholder was the first to isolate and identify. This antibiotic seems less active than others in promoting growth. According to Branion and Hill (1951), poultry, when fed 25 mg. of chloromycetin per kilogram of basal ration, did not improve in growth or feed efficiency up to eight weeks of age. Briggs (1950) apparently agrees with these results, for he reports that chloromycetin is generally inactive in growth production. In other experiments when turkey poults were fed 5 and 10 p.p.m. of the drug, they increased in

growth, but showed no greater growth when given 50 p.p.m. of the antibiotic.

Streptomycin: Waksman, in 1939, pioneered a search for an antibacterial substance, which would act on gram negative bacteria. As a result of many investigations streptomycin was discovered. This antibiotic is derived from Streptomyces griseus. By hydrogenation, the drug can be changed to dihydrostreptomycin. Streptomycin and dihydrostreptomycin have been found to be beneficial to the growth of some animals when fed in certain concentrations.

Cunha (1950) and Stokstad (1950) state that growth promotion is stimulated by feeding streptomycin to chicks. According to Bird (1950b) chicks require 7 to 10 mg. of streptomycin per pound of feed to promote any growth increase, while 20 to 40 mg. per kilogram of feed were progressively stimulative, and 200 mg. per kilogram of feed gave the greatest stimulation. Conversely, after 5 weeks, withdrawal of 20 mg. of the drug per kilogram of feed caused no change in the growth rate; withdrawal of 40 mg. per kilogram caused a sharp decrease in weight, and withdrawal of 200 mg. per kilogram caused a depression. He found, also, that chicks showed no growth response when fed at the lower level of 10 mg. of streptomycin per kilogram of feed.

Additions of streptomycin to complete rations caused good growth results in turkey poults, Atkinson and Couch (1952), and in weanling pigs, Briggs and Beeson (1952). A ration including all the required vitamins plus streptomycin, resulted in increased gain in pigs, according to

Gunha (1950). Nesheim and Johnson (1950) obtained similar results with two-day-old pigs, when fed for 49 days. To some of the pigs, they gave an additional 500 mg. of the drug per kilogram of feed. Those receiving the larger amount showed a greater increase in average weight gain and efficiency of feed utilization. By parenteral or oral administration of the drug, Carpenter (1951) noted good growth increases in weaned pigs. No growth stimulation was obtained in hogs, which were fed streptomycin, Guff et al (1951).

Streptomycin Fed in Combination with Vitamins:

Streptomycin and Vitamin B-12, when added to a basal ration, resulted in increased growth in turkey poults, Couch and Atkinson (1950). Branion and Hill (1951) obtained similar results in poultry up to 8 weeks of age, but they implied that growth stimulation was greater from 4 to 8 weeks than from 0 to 4 weeks.

Pigs, which were fed streptomycin and Vitamin B-12, showed better growth response than when they were fed streptomycin alone, Sheffy et al (1952), Luecke, McMillen, and Thorp (1950), Miller et al (1951), and Briggs and Beeson (1952). Some of these workers noted increases in growth of pigs of 22% and 40%. Carpenter (1951) found that oral and parenteral administration of streptomycin and Vitamin B-12 produced no added stimulation in growth of weaned pigs above those which were fed the antibiotic or vitamin alone.

Terramycin: Terramycin was discovered and isolated in the Biochemical Research Laboratories of the Charles Pfizer and Company, Incorporated. It was obtained as the

result of a collection of thousands of soil samples from various parts of the world. This drug is derived from elaboration products of Streptomyces rimosus. It is bacteriostatic in low concentrations, and has bactericidal properties in high concentrations. Terramycin is another antibiotic which has a stimulative effect on growth of some animals.

Growth response to this drug was noted in poultry by Bird (1950b) and McGinnis and Stern (1952). To stimulate growth, chicks are said to require 7 to 10 mg. of the drug per pound of feed, whereas turkey poults show better response when fed 50 p.p.m. of terramycin as a feed supplement than when fed no antibiotic feed supplement. Growth stimulation of turkey poults was obtained by Sieburth et al (1951) by adding terramycin to a basal ration.

Weaned pigs were found to be stimulated in growth when fed terramycin as a feed supplement, Carpenter (1951). Cuff et al (1951) noted the same results with growing pigs, which were fed 22 mg. of the drug per pound of basal ration.

Lawrence and McGinnis (1952) noted no significant difference in rate of weight gain in 6 weeks when weanling rabbits were fed dosages of 1, 3, 10, and 50 p.p.m. of terramycin.

Terramycin Fed in Combination with Vitamins: It was found that Vitamins B-1, B-2, and B-12, in addition to terramycin, are needed as feed supplements to promote growth in rats, Bentley (1952) and Stern and McGinnis (1951).

Branion and Hill (1951) obtained growth increases in poultry up to 8 weeks of age by feeding Vitamin B-12 and

25 mg. of terramycin per kilogram either of a basal ration or of an all-vegetable protein diet. They imply that growth increases were greater from the 4- to 8-week period than from 0 to 4 weeks.

Animals Used in Antibiotic Feeding Experimentation:

Antibiotics have been found to hasten growth in white rats, to produce sturdier and healthier pups (dogs), and to give good results in fish hatcheries. Poultry, rabbits, and swine have, also, shown growth increases. Antibiotics may or may not promote growth in ruminants. These animals have pouchlike rumens, or stomachs, in which bacteria act on foods to produce essential vitamins, and antibiotics might kill off these necessary bacteria and do more harm than good. Aureomycin was not beneficial to ruminants, according to Stokstad (1950), but it may be beneficial to calves where the rumen has not started to function.

Berg (1951) and Sewell and Glasscock (1951) point out that growth-promoting effects of antibiotics vary with the species of animal, providing the basal diet is complete.

Antibiotic Administration: Antibiotics are commonly fed in low levels mixed with the ration intended for the respective animal. Briggs (1950) emphasizes this fact by stating that antibiotics must be fed and not injected to stimulate growth. However, Elam, Gee, and Couch (1951b) found that parenteral administration of either penicillin or autoclaved penicillin increased the growth rate of chicks. Oral administration of aureomycin, terramycin, penicillin, streptomycin, and chloromycetin has been found by Carpenter

(1951) to stimulate the growth of weaned pigs. Rusoff (1951) was successful in stimulating appetite and increased weight in weaned calves by means of daily oral administration of capsules containing 15 mg. of aureomycin per 100 pounds of body weight. Carpenter (1951) found that streptomycin and Vitamin B-12 given alone either orally or parenterally stimulated growth in weaned pigs.

Ages of Animals at Which Antibiotics Stimulate Growth. Antibiotics apparently stimulate greater growth at different ages in different animals. Supplementary aureomycin was removed from the ration of four-week-old chicks by Berg et al (1950) and immediate cessation of the accelerated growth rate, which existed from the 0- to 4-week period, resulted. Scott and Glista (1950) report that aureomycin, when added to a basal ration for chicks, caused no improved growth at 8 weeks of age but caused slight growth response during the first 4 weeks. When aureomycin was added to the feed of chicks by Couch and Reed (1950), a 22% growth increase in 10 weeks was obtained. Antibiotics were found by Henser (1952) to increase the early growth rate (from 2 to 4 weeks) as much as 25% in turkeys and 10% to 15% in chicks. Cravens (1952) reports that antibiotics are not effective after 12 weeks of age in turkey poults and chicks. When aureomycin and Vitamin B-12 were fed to turkey poults as feed supplements, Couch and Atkinson (1950) found a 20% to 25% increase in weight in the first 8 weeks. Branion and Hill (1951) used aureomycin and Vitamin B-12 in an all-vegetable protein diet and noted growth increases in poultry

up to 8 weeks of age. Crystalline aureomycin added to milk or milk substitutes for calves by Loosli and Wallace (1950) resulted in an increased weight gain up to 8 weeks.

The Effect of Antibiotic Administration on Tissues and Organs. Aureomycin, chloromycetin (chloramphenicol), and terramycin have been found to be readily absorbed by the human into the general circulation after oral administration by Collins et al (1948) and Werner, Knight, and McDermott (1950).

Large amounts of penicillin are destroyed in the alimentary tract after oral administration, according to Pedersen-Bjergaard and Tonnesen (1950). McDermott et al (1946) traced orally administered penicillin to find why it is less efficient than penicillin administered by other routes. They found that absorption of ingested penicillin occurs chiefly in the duodenum, the stomach absorbing little. Penicillin is inactivated to a small extent by the acid gastric content. This inactivation is limited by a number of conditioning variables. According to these investigators the absorption of penicillin is rapid--maximum concentrations are obtained in the blood within 30 to 60 minutes after ingestion. The persistence of penicillin in the blood is due to the height of a maximum concentration originally obtained, and not a result of continued absorption from the alimentary tract. McDermott et al (1946) explain that the absorption of ingested penicillin is incomplete--two-thirds or more of the orally administered dose is not absorbed. Only insignificant amounts of penicillin are absorbed once the peni-

cillin has passed through the small intestine. They further state that unabsorbed penicillin in the intestine is inactivated by bacteria in the colon, or if an excess of the drug is present, it is excreted in the feces. They add that larger amounts of penicillin are required by oral administration than by the intramuscular route, because of incomplete absorption and not because of destruction by acid or bacterial action. Pedersen-Bjergaard and Tonnesen (1950) agree with McDermott et al (1946) that there is small stomach absorption of penicillin by rats. Maximum concentrations of the antibiotic were found in the blood of rats in 30 to 60 minutes after oral administration by Pedersen-Bjergaard and Tonnesen (1950). According to the same authors dihydrostreptomycin, also, is partially unabsorbed and excreted in the feces.

Maximum serum concentrations of antibiotics in humans after oral doses of 50 mg. of the drugs per kilogram of body weight, were 25 to 50 mcg. per milliliter of chloromycetin, 12 to 16 mcg. per milliliter of terramycin, and 3.3 to 12.5 mcg. per milliliter of aureomycin. High serum concentrations of all three drugs were maintained by oral administration of 50 to 100 mg. per kilogram of body weight, according to Werner, Knight, and McDermott (1950). The normal rat needs 12.5 times more penicillin G, $7\frac{1}{2}$ times more penicillin K and 25 times more dihydrostreptomycin, when administered orally than when given subcutaneously, to obtain the same concentration in the blood, Pedersen-Bjergaard and Tonnesen (1950). These writers also state that blood

concentration of 3.5 to 4.5 mcg. of penicillin G per milliliter is obtained from 2 mg. of penicillin G given subcutaneously or 25 mg. administered orally.

Oral administration of penicillin modified with aluminum hydroxide or magnesium hydroxide allows prolonged absorption of the drug, Welch, Price, and Chandler (1945). This modification provides the maintenance of higher blood levels of the antibiotic over a period of time than the administration of the drug alone.

Measurable concentrations of the antibiotics in the cerebrospinal fluid and other body fluids were found when large doses of the drugs were administered, Dowling et al (1949) and Werner, Knight, and McDermott (1950). High levels of penicillin in all sections of bone were obtained by intra-arterial injection of penicillin, Piskorz and Kuhnberg (1952). Sutherland et al (1951) found no demonstrable increase in liver function when aureomycin was administered.

Story (1950) found that oil occurred in cysts surrounded by eosinophils when procaine penicillin in oil was injected. Some muscle degeneration was present and fat-bearing phagocytes were plentiful around the oil and in the adjacent lymph nodes. Aureomycin passes the blood-brain barrier in dogs, according to Harned et al (1948). Aureomycin accumulates in other fluids of the human body when the antibiotic is administered orally. Herrell and Heilman (1949) found concentrations of aureomycin in the spinal fluid, liver, kidney, placenta, spleen, and lung after oral

administration. Pedersen-Bjergaard and Tonnesen (1950) state that penicillin K is partially destroyed after absorption by passage through the liver.

Streptomycin affects the semicircular canal reflexes of the rabbit. These reflexes were eliminated first and later the otolith reflexes were affected in the experiments conducted by Kleyn and van Deirse (1950). They state that development of dissociations in the semicircular canal reflexes justify the conclusion that streptomycin exercises a paralyzing influence upon the central vestibular nuclear region.

Chemotherapeutic effectiveness of penicillin is not believed to parallel blood level curves, Schwartz, Lewis, and Ercoli (1950). They believe that the effectiveness depends on the method of therapy. This may be due to accumulation and distribution of penicillin in the organs. This view is substantiated by urinary elimination of penicillin and the presence of penicillin in the lymph at negative blood levels. This theory is presented as an analysis of the relation between the fate of the antibiotic in the host and the therapeutic effectiveness of the antibiotic.

No consistent differences in hemoglobin levels were apparent in various lots of pigs, according to Sheffy et al (1952), after feeding streptomycin as a supplement to the ration. Sasaki and Ichihashi (1950), in studies on the action mechanism of penicillin in therapy, found that the filtering action of the spleen and other reticulo-endothelial systems have no relation to maintaining penicillin levels in

the body. The action of penicillin cannot be explained by concentration in the organs, according to these investigators. The last statement appears to be in disagreement with the views of Schwartz, Lewis, and Ercoli (1950), who suggest that the therapeutic effect may be due to the accumulation and distribution of penicillin in the organs.

In the early investigations of penicillin therapy Fleming et al (1944) were not sure whether it was better to maintain a constant low level of penicillin in the blood, or to have a very high level for a short time after injection. Clinically, both of these methods have worked excellently. According to Paolantonio and Sulli (1948) penicillin has no effect on the urinary excretion of Vitamins B-1 and P. Glazko, Dill, and Wolf (1952) report that the routes of excretion of chloromycetin (chloramphenicol) are in the urine and the bile.

Meads et al (1945) determined that plasma penicillin levels in vivo should be at least as high as those required for in vitro inhibition of bacteria. Baggs et al (1946) and Chandler, Price, and Randall (1945) believe that blood specimens contain natural inhibitors of Bacillus subtilis even when penicillin is not present.

Mesonyi, Palos, and Komaromy (1949) found that penicillin's ability to coagulate blood depends on the phase in which the substance is added to the system. (This statement brings into harmony the many controversial observations by various authors.) These investigators report that when penicillin is administered into the circulation, the drug

inhibits the inactivation of thrombin and diminishes the clotting time, which gives rise to thrombus formation. When penicillin is applied to wound surfaces or added to in vitro systems in high concentrations, it acts on fibrinogen in a manner inhibiting its precipitation. This view supports the old Palos concept of correlation between coagulation and oxido-reduction processes.

Shapse and Wright (1950) found that aureomycin produced slight changes in the clotting time of human blood. At 6, 12, 24, and 48 hours, variations in coagulation were not sufficient to be clinically significant. But Galt and Hunter (1950) have reported that the clotting time of blood containing aureomycin is prolonged in four out of five cases.

Macht and Farkas (1949) mention that Moldavsky, Hasselbrook and Cateno were the first investigators to report that the blood of patients receiving penicillin injections clotted more quickly than normal. Macht and Farkas (1949) state that streptomycin also coagulates blood more rapidly than normal. They report that aureomycin, when administered orally, causes a decrease in the coagulation time of blood in both humans and animals. The decrease is greatest at the height of antibiotic therapy. However, they find that there is no difference in the prothrombin time between aureomycin-fed and normal animals, thus indicating that shortened clotting time must be due to other factors.

One reference was found regarding the importance of hematocrit values. According to Von Dieter (1950) hematocrit percentage is a valuable diagnostic aid in a

number of infections.

Information on the effects of administered antibiotics on the formation of antibodies is scant. Buccellata (1946) mentions the effect of penicillin therapy on the opsonic index in various diseases. One of the purposes in this investigation is to determine whether or not antibodies are formed in response to antibiotic feeding.

The Effect of Antibiotic Feeding on Progeny.

Reports from investigators indicate that the feeding of certain antibiotics has a definite effect on the growth of the progeny of some kinds of animals. Elam, Gee, and Couch (1951a) found that pullets fed penicillin and injected with Vitamin B-12 had higher egg production than control pullets. However, antibiotics are not believed to improve egg production in hens, according to Cravens (1952) and Mariakulandai, Myint, and McGinnis (1952). Halick and Couch (1951) found that hatchability of eggs from hens fed a basal diet unsupplemented with antibiotics decreased to 0 after the fourth week, but injections of Vitamin B-12 improved hatchability somewhat. Peterson et al (1952) found that neither aureomycin nor streptomycin, when fed to hens at 50 mg. per kilogram of ration improved hatchability. Elam, Gee, and Couch (1951a) have reported that a 39% hatch was obtained from the eggs of pullets fed penicillin continuously. Lillie and Bird (1952) published the fact that Vitamin B-12 with aureomycin supplement fed to hens was less effective than crystalline Vitamin B-12 in hatchability. Mariakulandai, Myint, and McGinnis (1952) state that in the absence of

Vitamin B-12, terramycin improved the hatching of fertile eggs, and that the combination of terramycin and Vitamin B-12 further improved hatchability.

According to Bird (1950a) feeding antibiotics to breeding chickens caused no benefit to progeny. Stokstad (1950) mentions that Vitamin B-12 was carried over from hen to chick, but antibiotics do not appear to be. But Slinger, Ferguson, and McConachie (1952) found that chicks from hens fed a regular diet and penicillin grew more rapidly than those from hens fed the same diet and no antibiotic. Chicks, also, were fed penicillin and the maternal influence was apparent at 10 weeks of age. Penicillin evidently stimulates the synthesis of an unknown component of the animal protein factor complex in the intestinal tract of the hen, and this is deposited in the egg and utilized by the developing chick.

Vitamin B-12 and aureomycin in the maternal diet seem to give excellent chick performance, according to Lillie and Bird (1952). However, the greatest growth of chicks is achieved on a basal diet plus Vitamin B-12 and aureomycin, irrespective of the maternal diet. Chicks from hens fed Vitamin B-12 and/or aureomycin were found to grow better on a basal diet than chicks from hens fed no supplement. Turkey poults from hens fed no animal protein increased in growth more on antibiotics and Vitamin B-12 than on Vitamin B-12 alone, Kratzer (1952). Progeny of hens, which were fed Vitamin B-12 plus aureomycin were found to have no advantage over progeny from hens fed Vitamin B-12 alone. Beeson (1951) points out that antibiotics have no effect on young pigs

when fed to gilts in gestation. Jaffe (1951) concludes that in the reproduction of rats and mice, which were fed a basal ration for 5 generations, with or without 100 mg. of aureomycin per kilogram of feed, no significant difference was apparent with or without aureomycin. Fusillo et al (1952) studied the effects of chloromycetin (chloramphenicol) and streptomycin on a 9-day-old chick embryo heart. Growth was inhibited by concentrations of 90,000 micrograms per milliliter of streptomycin and high concentrations of chloromycetin. Growth increase, however, was apparent with 240 micrograms per milliliter of chloromycetin.

The Effect of Antibiotic Feeding on Intestinal Microflora. It was not the purpose of this investigation to determine the genera or species of microflora, which were present in the intestines of the guinea pigs, but other investigators have made such studies on several kinds of animals. Jukes (1952) found that small amounts of antibiotics in rations act on micro-organisms in the intestines of animals. Microbial counts of intestinal contents of chicks receiving a diet of 100 mg. of aureomycin per kilogram of feed were compared with controls by Williams et al (1951). The numbers of coliform-type bacteria and lactic acid bacteria were not appreciably changed. The total number of anaerobes were reduced 150 to 200 fold by aureomycin. Clostridia-type anaerobes, about 1% of the total number of anaerobes, were decreased 10 to 150 fold. Hemolytic Clostridia were eliminated almost completely from the intestinal contents and feces of the chicks by feeding aureomycin.

March and Biely (1952) state that high levels of aureomycin depressed the numbers of total aerobic, lactic acid, and coliform bacteria in chicks. Low levels of aureomycin seemed to lower the numbers of lactic acid bacteria with no effect on the total aerobic coliform count. Cunha (1952) mentions that in pigs, aureomycin may have killed some harmful micro-organisms and stimulated some beneficial organisms.

Elam, Gee, and Couch (1951b) state that feeding penicillin to pullets increased penicillin- and aureomycin-resistant micro-organisms as well as the total number of intestinal micro-organisms. Penicillin caused an increase in the number of enterococci of the intestine during the first 14 weeks of their experiment. Administration of penicillin by intravenous injection also resulted in a marked increase in the number of penicillin-resistant micro-organisms in the intestinal tract. Parenteral administration of penicillin had no effect on fecal microflora, according to these investigators. The effect of penicillin on the intestinal microflora of turkey poults is not equalled by those substances which failed to stimulate growth, Stern et al (1952).

Sieburth et al (1951) stated that at 2 and at 3 weeks, no consistent differences were observed in turkey poults between the control groups and groups receiving antibiotics with respect to total aerobes, total anaerobes, lactose negative rods and enterococci in the cecal contents. The genus Proteus was found in the birds fed the antibiotics, but not in the birds fed the basal diet. The count of an

organism having characteristics of Clostridium perfringens, which was noted in the cecal contents of birds on the basal diet, was greatly reduced by the antibiotics in all cases. The organism was observed in large numbers in the feces of young pigs, which were fed a purified diet. Addition of terramycin greatly reduced the count of this organism and stimulated the growth of the pigs.

According to Beeson (1951) in his work on pigs, the total number of micro-organisms in the digestive tract are not changed by antibiotics, but the types are changed. Bacitracin administered orally or parenterally failed to have any effect on fecal microflora in pullets, but parenteral administration of bacitracin and autoclaved penicillin increased the growth rate with little effect on the fecal aerobic microflora count, Elam, Gee, and Couch (1951b). Roine and Elvehjem (1950) state that there are more coliform and anaerobic bacteria in the cecal flora of guinea pigs when the animals are fed on more complete diets. These authors believe that there is a well balanced symbiosis between the host animal and the different bacteria, and that the bacterial flora have important functions in the physiology of the animals. They, also, state that certain diets can easily disturb this balance and thus produce nutritional disturbances in the animal. In humans Bierman and Jawetz (1951) found that aureomycin and/or chloromycetin, when given for 29 to 96 days, caused suppression of fecal flora for long periods. Penicillin and dihydrostreptomycin in combination, when administered parenterally, were unable

materially to influence the fecal flora, Aureomycin caused the prompt disappearance of coliform organisms from the stool with marked reduction in the usual associated flora. Resistant staphylococci, Pseudomonas, and yeasts were cultured from the stool during aureomycin therapy. Resistant organisms appeared as the effective antibiotics suppressed the normal coliform bacteria and enterococci, but the normal flora returned within 24 to 48 hours after the drugs were discontinued. Permanent alteration of the fecal flora was not observed in any patient after therapy ceased.

In studies of the intestinal flora of the dog, Jacob et al (1951) noted that coliform, clostridia, and enterococci were moderately reduced, but did not disappear as a result of intravenous aureomycin. They, also, report that aureomycin administered intravenously has a definite antibacterial action on the normal fecal flora of the dog, but its suppressive effect was inferior to that of the preparation administered orally. In studies of the intestinal flora of man, they mention that intravenous aureomycin is more effective in man than in dogs in the suppression of the normal intestinal flora. Coliform organisms, clostridia, and enterococci were neither completely nor partially suppressed. These investigators believe the excretion of the drug into the gastro-intestinal tract in man is by way of the bile and salivary glands. They mention that intravenous aureomycin has been shown to be excreted in the bile in high concentration, and the oral lesions following intravenous administration suggest excretion in the saliva. They state

that following oral therapy, the effect of aureomycin on the intestinal flora is identical in both man and dog.

Krantz and Carr (1951) report that investigators have suggested that the antibiotic toxicity to bacterial cells and to animal tissue may be in some way related to the ability of aureomycin to inhibit aerobic phosphorylation. They state that in general the most characteristic property of an antibiotic with respect to its antibacterial action is the inhibition of metabolic functions vital to the cell.

Mode of Action of Antibiotics in Stimulation of Growth. Theories persist as to how the antibiotics achieve their outstanding stimulation of growth. Growth effects by antibiotics in rations were found by Bechtel (1951) to be associated with the influence of the antibiotic on the intestinal tract. He states that more facts from many sources are needed to better understand and use antibiotics in rations. Bird (1950a) postulates the theory that with chicks, antibiotics probably do not accumulate in the tissues, but may stimulate growth by: (1) modifying the population of the digestive tract, changing the microflora from undesirable to desirable types, which synthesize unknown growth factors, or (2) removing undesirable toxin-producing organisms. Davis and Chow (1951) believe that the growth enhancement effect of aureomycin might be due to the increase in the production of Vitamin B-12 and perhaps other accessory factors by the bacterial organisms in the intestinal flora.

A notation by Ingram and Edgar (1951) indicates that antibiotics do not act on growth through inhibition of

cecal coccidiosis in chicks. Williams et al (1951) state that the growth-promoting action of aureomycin and other antibiotics, when added to the diet of certain animals, including chicks, is thought to be the result of the effect on the intestinal flora. They, also, mention that the combined antitoxins of certain clostridia were without effect on the growth of either control or aureomycin-fed chicks. Slinger, Pepper, and Hill (1952) working with turkeys, found that penicillin may influence a factor or factors present in grass juice concentrate that may be synthesized in the intestinal tract or made more readily available to poultry. Sieburth et al (1951) suggest the possibility that the growth-stimulating action of antibiotics in pigs could be due to the inhibition of the toxin-producing organism, Clostridium perfringens. Monson, Dietrich, and Elvehjem (1952) noted a synergistic effect of combinations of antibiotics in enhancing the growth of chicks.

Aureomycin killed intestinal micro-organisms in pigs and rendered their accessory factors more available to the host, as noted by Powick et al (1951). Guff et al (1951) relate that antibiotics producing the fastest weight gains also controlled an enteritis, which was present and probably enabled pigs to grow faster. Total anaerobic counts were made on the feces collected near the end of the experiment, but they did not correlate with the average daily gains nor the amount of scouring. Sieburth et al (1951) found that the addition of terramycin greatly reduced the count of Clostridium perfringens and stimulated the growth of pigs.

A postulation was made by Linkswiler, Baumann, and Snell (1951) that aureomycin may act to prevent utilization or destruction of the growth-limiting nutrient, Vitamin B-6, by intestinal microflora, thus increasing the amount available to the rat. This may be the cause of the growth-promoting effects of antibiotics. That aureomycin may decrease the number of Escherichia coli in the intestinal tract of the rat is thought by Cravioto-Munoz (1951) to allow an increase of other bacteria; such as, Bacillus megatherium, which can produce adequate quantities of Vitamin B-12 for rat growth.

Stern and McGinnis (1949) believe that the increase in the growth rate in the rat is due to alterations in the intestinal flora, and that antibiotics may change the bacterial population of the digestive tract. Beeson (1951) states that the exact way antibiotics function in growth is not known. There is a presumption by Roine and Elvehjem (1950) that the growth rate of guinea pigs, when fed a complete diet, but not including antibiotics, depends on the formation and maintenance of proper intestinal flora. Antibiotics may stimulate growth, according to Elam, Gee, and Couch (1951b) by some other mechanism than intestinal microflora. The antibiotic molecule or fragment of it might act as a metabolite within the body of chicks.

Hypersensitivities Produced by Antibiotics. The usual level of 10 to 20 mg. of antibiotics per kilogram of feed is not toxic to most animals, Bird (1950a). Two hundred mg. of streptomycin or 250 mg. of aureomycin per kilogram of

feed caused no toxic effects in several different kinds of animals. Vanderhaeghe (1950) noted that toxic doses of streptomycin were fatal to rabbits. Stokstad and Jukes (1951) have reported that aureomycin reduces mortalities in chicks. Allergic hypersensitivity of a generalized nature or local sensitivity reactions are the common toxic reactions to penicillin, when the drug is given parenterally. The drug is relatively non-toxic. Symptoms of hypersensitivity in humans are: urticaria, contact dermatitis, periorbital or labial edema, drug fever, gastrointestinal reactions, headache, eosinophilia, edema of the hands, faintness, skin flushing or pruritis, generalized arthralgia, myalgia, malaise, and serum sickness. According to Stuart and Slavin (1951) intramuscular doses of 20,000 units of penicillin daily for 10 days caused the deaths of 13 of 20 guinea pigs in 3 to 10 days. No deaths resulted in the control undosed animals over the period of the observation. They report that there is no "piling up" effect of intramuscularly injected penicillin in animals treated with penicillin for 3 weeks over the administration of the drug to animals not previously dosed. According to Bell et al (1951) steers, which were fed 0.2 grams of aureomycin daily, showed a marked reduction in digestibility of crude fiber and had digestive disturbances. With 0.6 grams of aureomycin fed to steers daily, a marked anorexia and diarrhea developed within 48 to 72 hours and persisted for several days.

Antibiotic Feeding in Overcoming Pathologic Conditions. Therapeutic effects often result from the

feeding of antibiotics to animals. Rusoff, Davis, and Alford (1951) report that Loosli and Wallace (1950) fed calves 500 mg. of aureomycin per 100 pounds of feed and incidence and severity of scours were prevented. Crystalline aureomycin and supplements of all known B vitamins, including Vitamin B-12, were without significant effect in the prolonged survival of hyperthyroid rats, Ersheff (1950). With immature male albino rats on a Vitamin B-12 deficient diet, Meites (1951) injected cortisone for 30 days. Depressions of body, hair, and thymus growth resulted and were overcome by incorporating Vitamin B-12 or 0.005% of aureomycin in the ration. Vitamin B-12 was more effective than aureomycin, and a combination of the two substances was more effective than either alone. How the protection of the thymus by Vitamin B-12 and aureomycin against cortisone action occurs, is not known. Cunha (1950) and Sewell, Cunha, and Shawver (1952) found that aureomycin prevented periodic diarrhea in pigs. All antibiotics, except orally administered chloromycetin, according to Carpenter (1951), controlled an enteritis-type of diarrhea in pigs. Also, streptomycin, administered orally or parenterally, controlled diarrhea. In addition to causing increased growth, the drugs have measurably decreased many animal diseases that usually resulted in high mortality rates.

Bacterial Resistance to Antibiotics. In studies on the development of resistance to streptomycin by Staphylococcus pyogenes, no differences were found by Barbour (1950) between strains of bacteria, which were made resistant in

vitro and those which had become resistant in vivo. It seems plausible that such resistance could be similar in most antibiotics. Haight, Wilcox, and Finland (1952) found that organisms transferred in antibiotic-free media did not develop resistance, but micro-organisms grown in streptomycin or neomycin media developed resistance to the respective antibiotic in most, but not all, instances. Some micro-organisms developed neomycin resistance as a result of repeated exposures to streptomycin and vice-versa. None of the strains made streptomycin- or neomycin-resistant became more resistant to penicillin, aureomycin, terramycin, chloromycetin, or bacitracin, and some even appeared to become more sensitive. Stokstad (1950) found no evidence of strains of bacteria, which were resistant to aureomycin, but Abraham et al (1941) found an adaptation of Staphylococcus aureus to high concentrations of penicillin.

Kaipainen (1951) reports that as resistance of bacteria of species E. coli, A. aerogenes, Sal. typhi, P. vulgaris, and Ps. aeruginosa increases to one of the following antibiotics: aureomycin, chloromycetin, or terramycin, a simultaneous increase in resistance to the other two antibiotics occurs. He believes that when resistance increases to streptomycin, sensitivity to aureomycin, chloromycetin, and terramycin shows a simultaneous increase.

According to Chandler et al (1951) 16% of 25 respiratory strains of staphylococcus studied were resistant to more than one microgram of penicillin. They state that all but one of the resistant strains produce penicillinase,

but none of the sensitive strains produce it. These investigators have found that aureomycin tends to inhibit the production of this enzyme.

METHODS AND MATERIALS

The studies made in this investigation were arranged in two separate experiments. In both experiments weanling male and female guinea pigs of the English breed were employed. Oral administration of aqueous solutions of aureomycin* and penicillin** was continued throughout each experimental period.

EXPERIMENT I

Part I. The animals used in this experiment were given oral administration of aqueous solutions of aureomycin and penicillin to determine whether or not growth changes would occur. Aureomycin in the form of crystalline aureomycin hydrochloride and penicillin in the form of crystalline penicillin G sodium were used. After the animals had reached the age of 15 weeks, the experiment was concluded. Some animals were used for breeding purposes to provide first litters for further studies of the effects of the antibiotics.

Weanling guinea pigs, the age of which was 5 weeks plus or minus 5 days, were used in the experiment. All animals were housed in the animal room in cages of the raised screen floor type, which were cleaned daily and disinfected

* Aureomycin was generously supplied by Dr. Stanton M. Hardy of the Lederle Laboratories, Pearl River, New York.

** Penicillin was supplied through the kindness of Dr. Lyon P. Streaan of Merck and Company, Rahway, New Jersey.

once a week. The temperature of the animal room ranged between 26° C. and 29° C.

The animals were fed rabbit chow checkers, which is a complete ration, except for Vitamin C, Table 1, page 40. This vitamin was supplied by adding ascorbic acid to the drinking water in the proportion of 500 mg. per liter. Daily provision was made of ample food and fresh water.

Thirty-six male guinea pigs were divided at random into 3 equal groups. In addition to the regular diet one group was fed aureomycin, another group was fed penicillin, and a third group was used as a normal control group. Thirty-six female guinea pigs were also divided into 3 equal groups and fed the same as the male groups. The animals of each group were identified by individual ear markings.

After the animals had been housed in their new quarters for four days, oral administration of the drugs was begun. The animals at this time had reached an average age of 5.5 weeks. The weight of each animal was recorded, and the plan of weighing twice a week thereafter was followed throughout the experimental period. The antibiotics were administered daily by means of a 0.5 ml. calibrated pipette similar in appearance to an ordinary medicine dropper. Aureomycin and penicillin solutions were prepared by dissolving the crystalline drugs in distilled water so that the concentration of each was 1.1 mg. per milliliter. Each animal of the aureomycin-fed and penicillin-fed groups was given 0.5 ml. of the respective aqueous solution, which contained 0.55 mg. of the drug. This dosage was continued for

one week, and upon the loss of 2 animals in the aureomycin-fed groups and 11 in the penicillin-fed groups, it was decided to change the dosage. Consequently, 0.5 ml. of each aqueous solution containing 0.6 mg. of the antibiotic, was given orally on alternate days throughout the remainder of the first part of the experiment. The average age of the animals was 15 weeks at the end of the experimental period.

The control groups were fed only the normal diet of rabbit chow checkers. Their drinking water contained ascorbic acid in the same concentration as was given to all the experimental animals.

At the end of the experimental period, seven female animals of each of the aureomycin-fed, penicillin-fed, and normal control groups were placed in separate breeding cages. Two females were placed in one cage, two in the second, and three in the third cage. Three boars from each of the groups were placed in these cages—one boar to a cage. With this arrangement three or four animals were housed in one cage, and one boar was used for two or three sows.

Male guinea pigs reach sexual maturity at approximately 60 days of age, but the females are sexually mature when 35 to 40 days of age. Young sows are not bred until they are about three or four months of age, or when their individual weight is 454 grams—approximately one pound. The weight of the guinea pigs, which were used for breeding purposes in this experiment, averaged more than 454 grams.

At the end of the experimental period, the male controls, which had not been used for breeding, were

sacrificed for histological studies. The purpose was to compare the structure and weights of the normal tissues with the tissues of the experimental animals in Experiment II. The liver, kidney, heart, and spleen were removed, freed of fat, weighed, and placed in 10% formalin. The left inferior extremity was removed as a unit by disarticulation of the femur from the acetabulum and detachment of the muscles of the thigh from their attachments on the pelvic girdle. The foot was disarticulated at the ankle joint. The thigh and leg were freed of fat and weighed. The muscles were detached from the femur, tibia, and fibula, and the bones were cleaned and weighed. Measurements of the lengths of the tibial bones were recorded. All tissues were placed in 10% formalin.

Part II. This portion of the experiment was conducted to determine: (a) if aureomycin and penicillin, when administered to the parent guinea pigs, resulted in weight increases in the F-1 generation at birth as compared with normal F-1 controls; (b) whether or not the antibiotics, when fed at low levels to the offspring of the experimental animals, stimulate their growth; (c) what concentrations of the antibiotic occur in the blood; (d) the relative effect of the administered antibiotics on hematocrit and (e) if formation of antibodies results in response to antibiotic feeding.

Within 24 hours after the breeding sows gave birth to their first litters, the weight of each offspring was recorded. All litters were kept in the cages with their parents for 3 weeks. At the end of 3 weeks, the young in

each breeding cage were weaned by placing them in separate cages, the males being separated from the females. Not more than 7 nor less than 5 animals occupied a cage. The average was 6. The young animals were kept in the animal room under the same conditions as the parents.

Within 48 hours after the birth of each experimental animal, 0.1 mg. of each specified drug, designated to be fed to the respective group to which the animal belonged, was administered orally in a quantity of 0.5 ml. of distilled water. All experimental animals were given this dosage daily for six weeks. The normal control animals were fed only the usual diet of rabbit chow checkers. At the age of 6 weeks, the young female experimental animals were changed to a 0.6 mg. dosage of the respective antibiotic per day. This was administered in 0.5 ml. of distilled water and continued on a daily basis until the females had reached the age of 15 weeks. The young male animals were continued on the initial dosage of 0.1 mg. until the age of 15 weeks.

The first-litter animals were weighed weekly and the weights recorded. The range of their ages was plus or minus 5 days. At the end of the 15-week experimental period, these animals were used in determining the following: drug concentration in the blood, hematocrit, and antibody formation.

Assays of the pooled blood of the animals in each experimental group were made to determine the concentration of aureomycin or penicillin in the blood. In this experiment the most suitable method of assay for the determination of

the drug concentrations in the blood was that devised by Herrell and Heilman (1949) for aureomycin. A modification of this method was used for penicillin.

Hematocrit, or the volume of erythrocytes per 100 ml. of blood of an animal, was determined in both experimental and normal control animals. This was done to find whether or not differences in percentage occur. This determination was made by using the calibrated conical centrifuge tube and citrated (anticoagulated) guinea pig blood. The blood was centrifuged at 3,000 r.p.m. for 20 minutes, Fowler (1949).

Precipitin and opsonocytophagic tests were made of the pooled blood of the animals in each experimental group to determine whether or not antibodies were formed as a result of oral administration of the antibiotics. The methods used were those described by Shay (1947), (1949).

EXPERIMENT II

The animals in this experiment were fed varied low levels of aureomycin and penicillin to determine which level resulted in the greatest weight gain. Forty-eight male weanling guinea pigs were used. The average age of the animals was 5 weeks plus or minus 5 days. They were evenly divided into two groups—one to receive aureomycin and the other penicillin. To determine the optimum of the low feeding levels, it was necessary to subdivide each experimental group into 4 groups of 6 animals each. In order that each group of 6 would weigh approximately the same, certain

animals were shifted from one cage to another. One week was allotted for the animals to become acclimated to their new quarters. Each of the groups for aureomycin feeding was designated as AA, AB, AC, and AD, and each of the groups for penicillin feeding PA, PB, PC, and PD. Each animal in Group AA was given 0.2 mg. of aureomycin per day, each in Group AB 0.3 mg., each in Group AC 0.4 mg., and each in Group AD 0.5 mg. Each animal in Group PA was given 0.2 mg. of penicillin per day, each in Group PB 0.3 mg., each in Group PC 0.4 mg., and each in Group PD 0.5 mg. These dosages in 0.5 ml. of distilled water were given by oral administration. The drugs were administered for a period of 9 weeks, at the end of which time the animals were 15 weeks of age.

At the end of the experiment, it was noted that Groups AB and AD of the aureomycin experimental animals showed the greatest gain in weight as compared to the male normal controls of Experiment I. To compare the tissues of these animals with those of the male normal controls, each animal in these two aureomycin groups was sacrificed, and the same procedure was followed in the removal of tissues as in Experiment I. The animals remaining in the aureomycin experimental groups and all of the penicillin experimental animals were kept for the determination of drug concentrations in the blood and for hematocrit and antibody tests as were the F-1 generation animals in Experiment I.

Table 1

Chemical Composition of Rabbit Chow Checkers
(Complete)

Moisture Percent	9.16
Protein Percent	21.60
Fat Percent	2.48
Fiber Percent	16.21
Ash Percent	8.04
Non-Fibrous Element Percent	42.51
Calcium Percent	1.12
Phosphorus Percent	0.65
Magnesium Percent	0.19
Iron Parts per Million	161.00
Manganese Parts per Million	55.00
Copper Parts per Million	7.40
Cobalt Parts per Million	0.13
Potassium Percent	1.03
Carotene Parts per Million	23.00
Thiamin Parts per Million	3.70
Riboflavin Parts per Million	7.40
Niacin Parts per Million	38.80
Vitamin D U.S.P. Units/gram	2.20

RESULTS

Throughout the determinations, which appear in the tables and figures, the numbers represent averages of groups of guinea pigs.

The average weights of the male and female experimental and normal control animals of Experiment I during the experimental period are shown in Figures 1 and 2. The average weight gain of groups of aureomycin-fed, penicillin-fed, and normal control male and female guinea pigs from 5.5 weeks to 15 weeks of age are compared in Table 2. A comparison is made in Table 3 between the average weight gain of groups of aureomycin-fed, penicillin-fed, and normal control male and female guinea pigs between 6 and 15 weeks of age.

The average weights of male and female F-1 experimental and F-1 normal control animals are charted in Figures 3 and 4, respectively. The relationships between the average weights of male and female F-1 guinea pigs fed aureomycin and the average weights of male and female F-1 normal control animals are shown in Figure 5. A comparison is made in Figure 6 of average weights of male and female F-1 guinea pigs fed penicillin and male and female F-1 normal controls.

Tables 4, 5, and 6 contain a comparison of average weight gains of male and female F-1 aureomycin-fed, F-1 penicillin-fed, and F-1 normal control guinea pigs during the experimental period.

The relation between average weights of male and female F-1 experimental animals and the average weights of male and female normal controls is found in Figures 7 and 8.

A comparison is made in Figure 9 between the average weights of male and female F-1 normal control guinea pigs and male and female normal controls.

Figure 10 expresses the comparison between average weights of groups of male guinea pigs fed 0.2 mg. and 0.3 mg. of aureomycin, and a third group of male normal controls, which were fed a basal ration with no antibiotic supplement.

A comparison is shown in Figure 11 between the average weights of one group of male animals fed 0.4 mg. of aureomycin, another group fed 0.5 mg. of aureomycin, and a third group of male normal controls fed a basic diet.

In Table 7 is a comparison of average weight gains between groups of male guinea pigs, which were fed 0.2 mg., 0.3 mg., 0.4 mg., and 0.5 mg. of aureomycin.

Relationships are illustrated in Figure 12 between groups of male animals fed 0.2 mg., 0.3 mg., 0.4 mg., and 0.5 mg. of penicillin, and a group of male normal controls, which were fed no antibiotic.

Average weight gains are compared in Table 8 between groups of male guinea pigs, which were fed 0.2 mg., 0.3 mg., 0.4 mg., and 0.5 mg. of penicillin.

The average weights of groups of male guinea pigs, which were fed 0.2 mg. of aureomycin, 0.2 mg. of penicillin, 0.3 mg. of aureomycin, and 0.3 mg. of penicillin, respectively, are compared in Figure 13. A relationship is

expressed in Figure 14 between the average weights of groups of male guinea pigs, which were fed 0.4 mg. of aureomycin, 0.4 mg. of penicillin, 0.5 mg. of aureomycin, and 0.5 mg. of penicillin, respectively.

The average organ and tissue weights in aureomycin-fed and normal control male animals are summarized in Table 9.

The average birth weights of males and females of first litters of aureomycin-fed, penicillin-fed, and normal control animals are listed as follows:

<u>Group</u>	<u>Average Birth Weight of F-1 Aureomycin-fed Animals</u>	<u>Average Birth Weight of F-1 Penicillin-fed Animals</u>	<u>Average Birth Weight of F-1 Normal Control Animals</u>
Males	97.4 g.	93.8 g.	94.2 g.
Females	97.5 g.	94.3 g.	89.8 g.

Changes in bone growth of groups of male experimental and normal control animals are indicated by tibia lengths and weights as listed below:

<u>Group</u>	<u>Length of Tibia</u>	<u>Weight of Tibia</u>
Fed 0.3 mg. aureomycin	45.9 mm.	1.40 mg.
Fed 0.5 mg. aureomycin	46.1 mm.	1.50 mg.
Normal control	44.2 mm.	1.10 mg.

Pooled blood from experimental animals in Experiments I and II was used in the determination of blood levels of aureomycin and penicillin. The concentration of aureomycin was 2 micrograms per milliliter of blood of guinea pigs, which had received an oral dosage of an aqueous solution of 0.6 mg. of aureomycin 3 to 4 hours previous to the determination. The concentration of penicillin in the

blood was not successfully determined.

Hematocrit, or the volume of erythrocytes per 100 ml. of blood, was determined in male and female experimental and normal control animals. The average hematocrit values are listed below:

<u>Group</u>	<u>Hematocrit (%)</u>
Aureomycin-fed	49.1
Penicillin-fed	49.0
Normal control	45.4

The antibody studies reveal that specific antibodies are not formed in response to feeding low levels of aureomycin and penicillin in sufficient quantities to be detected by the precipitation method. However, opsonins (antibodies that are normally present) tend to increase in activity in animals, which are fed low levels of aureomycin and penicillin. The opsonic indices (ratio of the phagocytic index of experimental animal serum to that of normal animal serum) of the blood of the experimental animals are listed in the following:

<u>Group</u>	<u>Opsonic Index</u>
Aureomycin-fed	2.50
Penicillin-fed	2.25
Normal control	1.00

The phagocytic indices (average number of Staphylococcus aureus per leucocyte) of the blood of the experimental animals and the normal control animals were determined and are listed below:

<u>Group</u>	<u>Phagocytic Index</u>
Aureomycin-fed	100
Penicillin-fed	90
Normal control	40

Abscesses were observed toward the end of the experimental period in the neck and shoulder region of 8 penicillin-fed, 4 aureomycin-fed, and 2 normal control male and female animals. A predominance of this condition occurred in the groups of animals of Experiment II, which were fed varied low levels of the antibiotics.

In the first part of Experiment I the mortality of penicillin-fed animals was greater than that of the aureomycin-fed animals. Thirteen animals (9 males and 4 females) of the penicillin-fed animals died of toxic effects of the drug within 8 days. Among the aureomycin-fed animals of the first part of Experiment I, 4 animals (1 male and 3 females) died of toxicity within 10 days. No mortalities occurred in any of the groups of the F-1 experimental animals, but one F-1 female normal control died of pneumonia.

In Experiment II the penicillin-fed animals showed a high mortality rate. Of 24 animals 14 died of hypersensitivity to the antibiotic. The mortalities did not follow a specific pattern among the groups, which were fed low levels of penicillin. The mortality rate among the groups is as follows: 3 in the group fed 0.2 mg., 1 in the group fed 0.3 mg., 4 in the group fed 0.4 mg., and all of the total number of 6 in the group fed 0.5 mg. of the drug. No mortalities occurred in any of the groups of animals, which were fed varied low levels of aureomycin.

Table 2

Comparison of Average Weight Gain Between Aureomycin-fed, Penicillin-fed, and Normal Control Male and Female Guinea Pigs from 5.5 to 15 Weeks of Age

Group	Average Weight at		Average Weight Gain (grams)	Percent Gain
	5.5 Weeks (grams)	15 Weeks (grams)		
Aureomycin-fed Males	257.0	491.5	234.5	91.2
Penicillin-fed Males	262.1	496.2	234.1	89.3
Normal Control Males	251.0	537.8	286.8	114.3
Aureomycin-fed Females	254.8	467.0	212.2	83.3
Penicillin-fed Females	255.4	463.9	208.5	81.6
Normal Control Females	254.8	458.7	203.9	80.0

Table 3

Comparison of Average Weight Gain Between Aureomycin-fed, Penicillin-fed, and Normal Control Male and Female Guinea Pigs from 6 to 15 Weeks of Age

Group	Average Weight at		Average Weight Gain (grams)	Percent Gain
	6 Weeks (grams)	15 Weeks (grams)		
Aureomycin-fed Males	225.9	491.5	265.6	117.6
Penicillin-fed Males	223.3	496.2	272.9	122.2
Normal Control Males	259.1	537.8	278.7	107.6
Aureomycin-fed Females	222.0	467.0	245.0	110.4
Penicillin-fed Females	244.6	463.9	219.3	89.7
Normal Control Females	255.5	458.7	203.2	79.5

Table 4

Comparison of Average Weight Gain Between F-1 Aureomycin-fed, F-1 Penicillin-fed, and F-1 Normal Control Male and Female Guinea Pigs from 0 to 15 Weeks of Age

Group	Average Weight at		Average Weight Gain (grams)	Per- cent Gain
	0 Weeks (grams)	15 Weeks		
Aureomycin-fed F-1 Males	107.6	671.7	564.1	524.3
Penicillin-fed F-1 Males	100.2	620.2	520.0	519.0
Normal Control F-1 Males	110.4	638.7	528.3	478.5
Aureomycin-fed F-1 Females	113.2	535.8	422.6	373.2
Penicillin-fed F-1 Females	93.9	537.1	443.2	472.6
Normal Control F-1 Females	110.5	546.7	436.2	394.8

Table 5

Comparison of Average Weight Gain Between F-1 Aureomycin-fed, F-1 Penicillin-fed, and F-1 Normal Control Male and Female Guinea Pigs from 5.5 to 15 Weeks of Age

Group	Average Weight at		Average Weight Gain (grams)	Per- cent Gain
	5.5 Weeks (grams)	15 Weeks		
Aureomycin-fed F-1 Males	352.6	671.7	319.1	90.5
Penicillin-fed F-1 Males	300.5	620.2	319.7	106.4
Normal Control F-1 Males	345.1	638.7	293.6	85.1
Aureomycin-fed F-1 Females	314.9	535.8	220.9	70.1
Penicillin-fed F-1 Females	284.3	537.1	252.8	88.9
Normal Control F-1 Females	315.8	546.7	230.9	73.1

Table 6

Comparison of Average Weight Gain Between F-1 Aureomycin-fed, F-1 Penicillin-fed, and F-1 Normal Control Male and Female Guinea Pigs from 6 to 15 Weeks of Age

Group	Average Weight at		Average Weight Gain (grams)	Per- cent Gain
	6 Weeks (grams)	15 Weeks		
Aureomycin-fed F-1 Males	371.6	671.7	300.1	80.8
Penicillin-fed F-1 Males	323.8	620.2	296.4	91.5
Normal Control F-1 Males	369.3	638.7	269.4	72.9
Aureomycin-fed F-1 Females	333.2	535.8	202.6	60.8
Penicillin-fed F-1 Females	301.9	537.1	235.2	77.9
Normal Control F-1 Females	331.1	546.7	215.6	65.1

Table 7

Relation of Average Weight Gains of Groups of Male Guinea Pigs

Group AA - Fed 0.2 mg. Aureomycin
 Group AB - Fed 0.3 mg. Aureomycin
 Group AC - Fed 0.4 mg. Aureomycin
 Group AD - Fed 0.5 mg. Aureomycin

Group	Average Weight at		Average Weight Gain (grams)	Percent Gain
	6 Weeks (grams)	15 Weeks		
Fed 0.2 mg. Aureomycin	274.6	592.7	318.1	115.8
Fed 0.3 mg. Aureomycin	273.1	606.3	333.2	122.0
Fed 0.4 mg. Aureomycin	274.7	583.6	308.9	112.4
Fed 0.5 mg. Aureomycin	276.9	610.8	333.9	120.6

Table 8

Relation of Average Weight Gains of Groups of Male Guinea Pigs

Group PA - Fed 0.2 mg. Penicillin

Group PB - Fed 0.3 mg. Penicillin

Group PC - Fed 0.4 mg. Penicillin

Group PD - Fed 0.5 mg. Penicillin

Group	Average Weight at		Average Weight Gain (grams)	Percent Gain
	6 Weeks (grams)	15 Weeks (grams)		
Fed 0.2 mg. Penicillin	260.9	441.5	180.6	73.1
Fed 0.3 mg. Penicillin	260.2	476.5	216.3	83.1
Fed 0.4 mg. Penicillin	260.6	534.0	273.4	104.9
Fed 0.5 mg. Penicillin	258.5	—	—	—

Table 9

Comparison of Average Weights of Organs and Tissues of
Aureomycin-fed Male Guinea Pigs with Those of
Male Normal Controls
(Grams)

Tissue	Groups Fed Aureomycin		Normal Control Group
	0.3 mg.	0.5 mg.	
Liver	24.20	24.10	19.80
Kidney	4.30	4.30	4.40
Heart	1.50	1.50	1.90
Spleen	0.50	0.40	0.90
Thigh and Leg	23.50	23.60	20.80
Femur, Tibia, and Fibula	3.20	3.10	2.78
Tibia	1.40	1.50	1.10
Muscles (thigh and leg)	20.30	20.50	18.03

Comparison of Average Weights of Organs and Tissues of
Aureomycin-fed Male Guinea Pigs with Those of
Male Normal Controls
(Percentage Weights of Body Weight)

Liver	4.00	3.90	3.60
Kidney	0.70	0.70	0.80
Heart	0.25	0.24	0.30
Spleen	0.08	0.07	0.16
Thigh and Leg	3.90	3.90	3.80
Femur, Tibia, and Fibula	0.50	0.50	0.50
Tibia	0.20	0.20	0.20
Muscles (thigh and leg)	3.30	3.30	3.20

Figure 1

Comparison of Average Weights of Groups of Male Guinea Pigs

Group I - Fed Aureomycin

Group II - Fed Penicillin

Group III - Normal Control

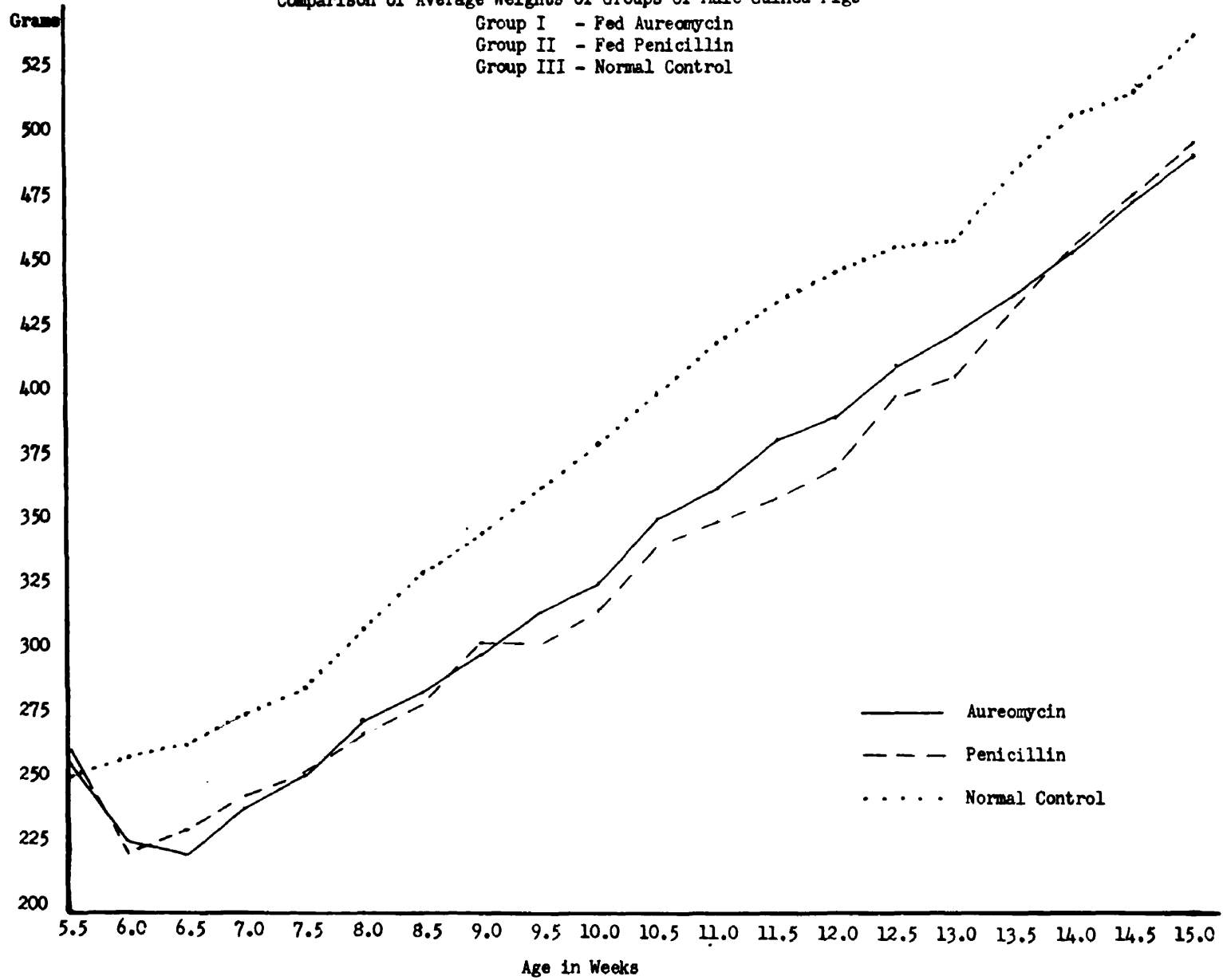


Figure 2

Comparison of Average Weights of Groups of Female Guinea Pigs

Group I - Fed Aureomycin

Group II - Fed Penicillin

Group III - Normal Control

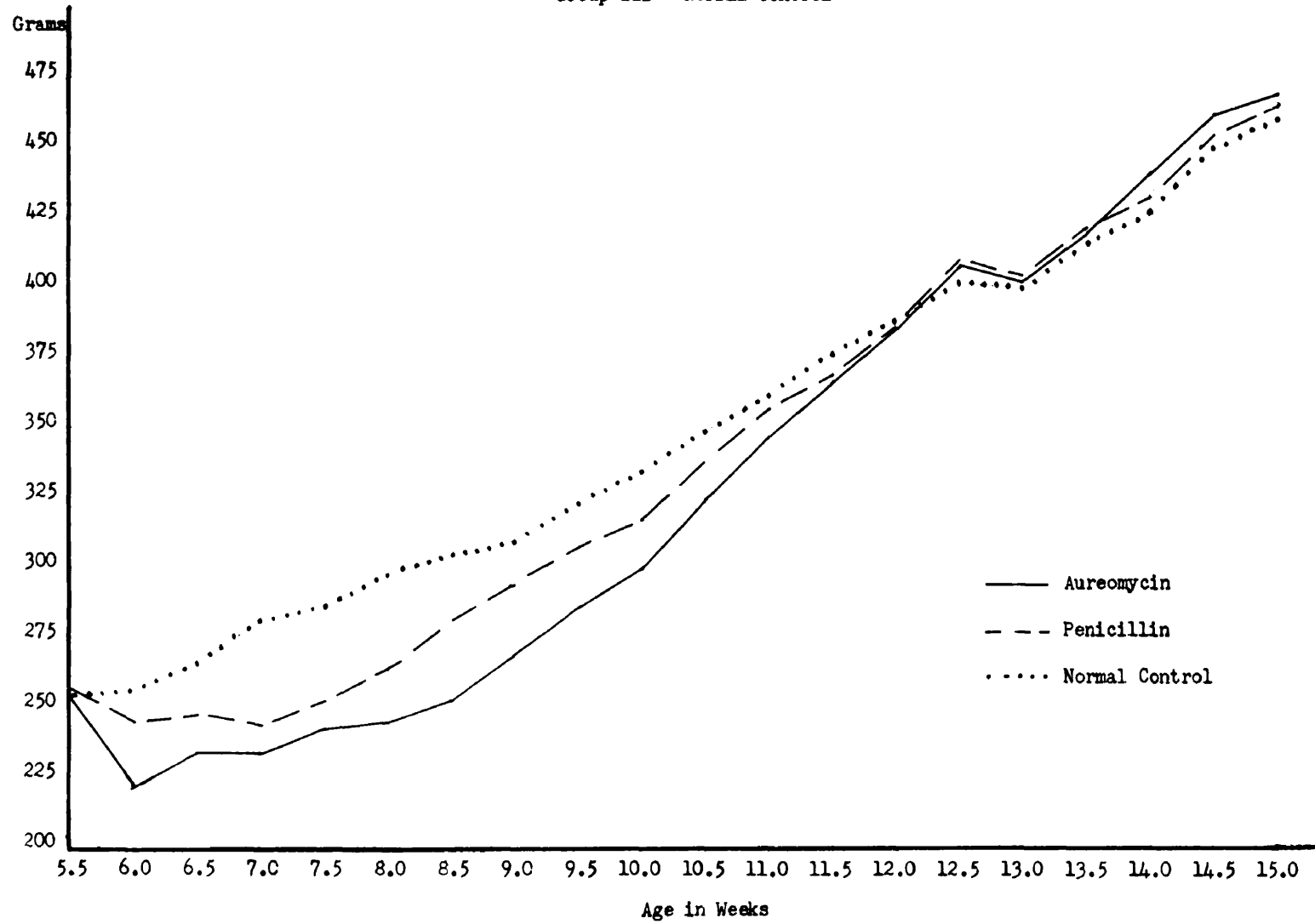


Figure 3

Comparison of Average Weights of Groups of Male F₁ Guinea Pigs

Group I - Fed Aureomycin
Group II - Fed Penicillin
Group III - Normal Control

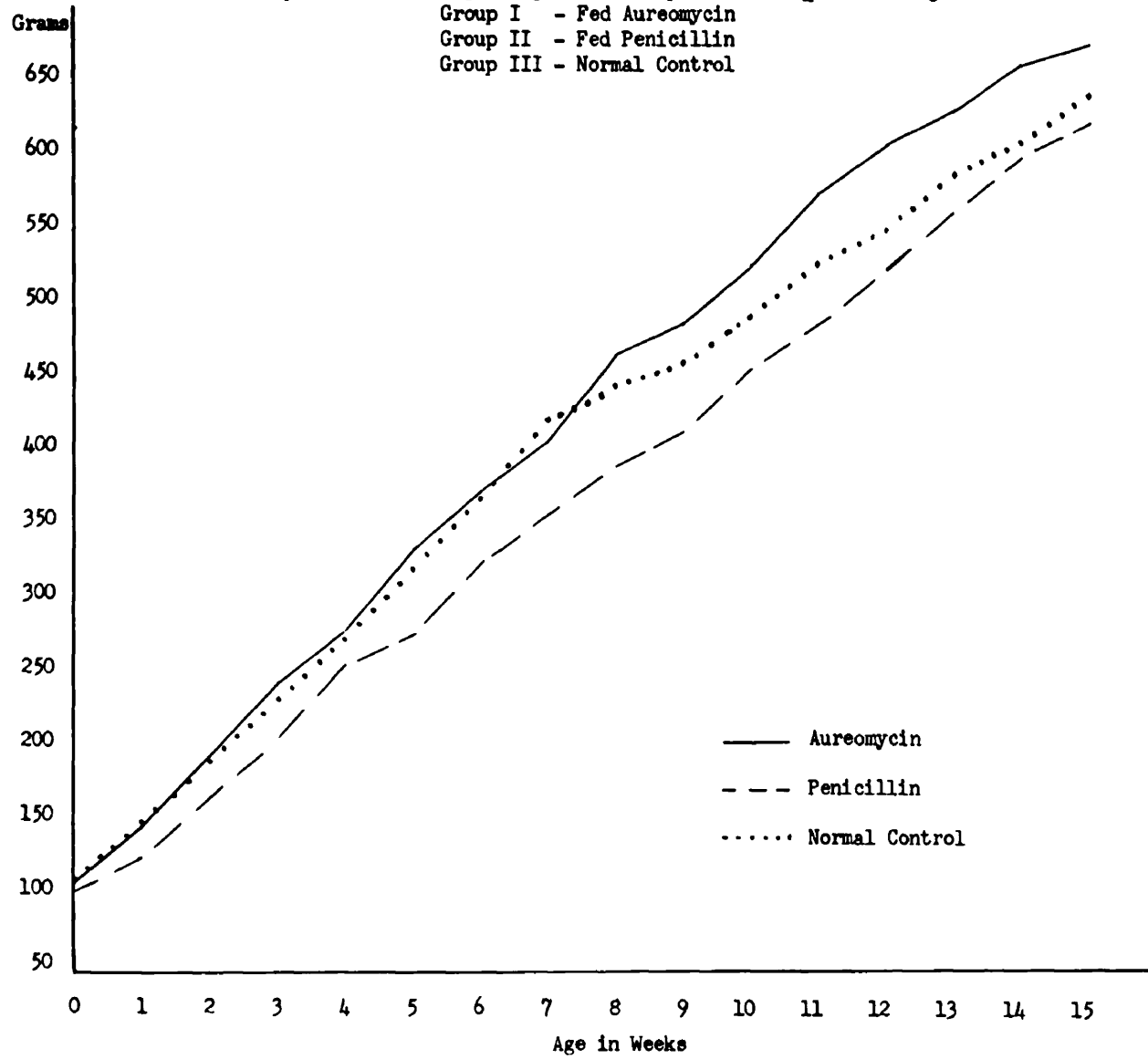


Figure 4

Comparison of Average Weights of Groups of Female F₁ Guinea Pigs

Group I - Fed Aureomycin

Group II - Fed Penicillin

Group III - Normal Control

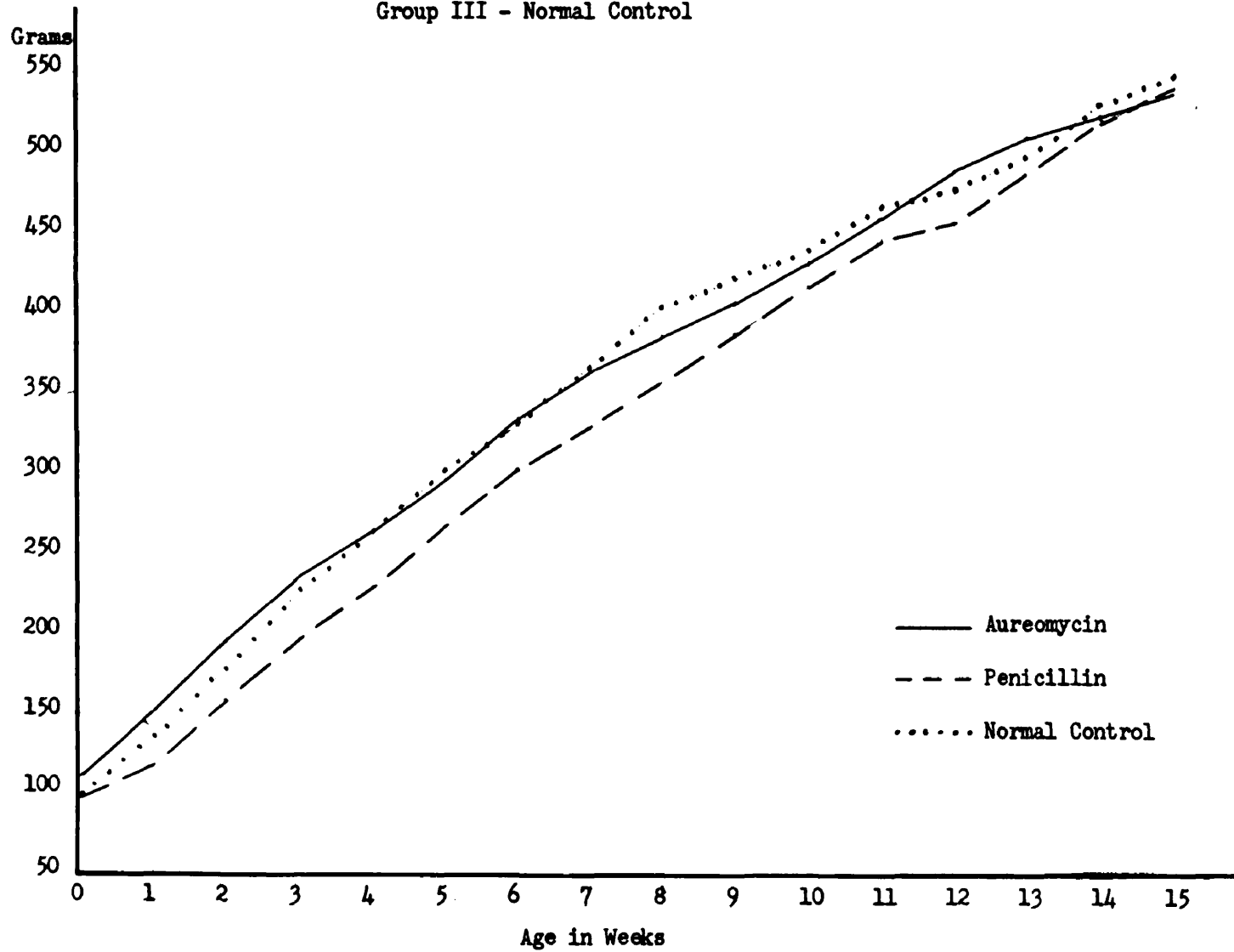


Figure 5
 Relation of Average Weights of Male and Female F₁ Guinea
 Pigs Fed Aureomycin to Average Weights of
 Male and Female F₁ Normal Controls

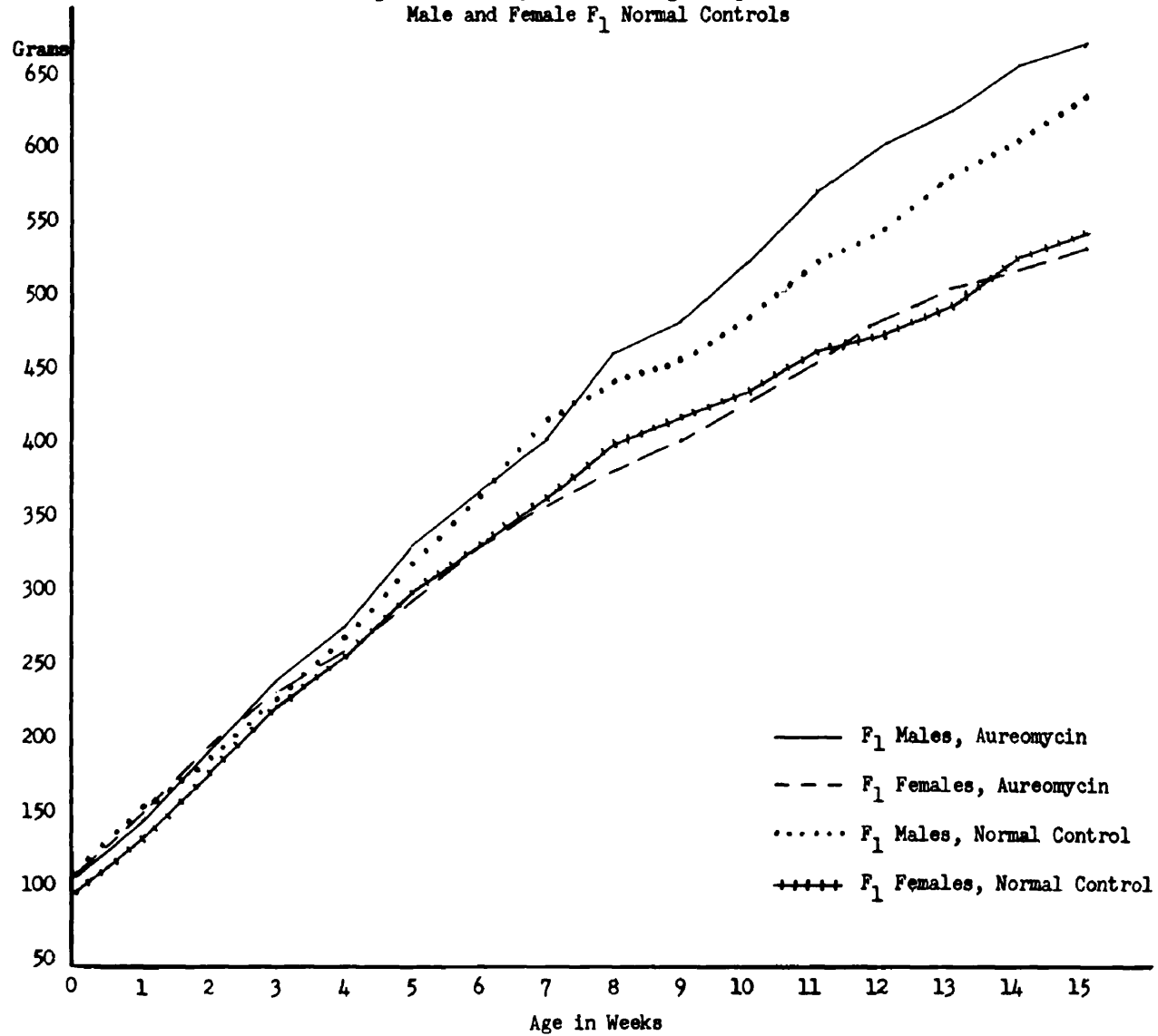


Figure 6
 Relation of Average Weights of Male and Female F_1 Guinea
 Pigs Fed Penicillin to Average Weights of
 Male and Female F_1 Normal Controls

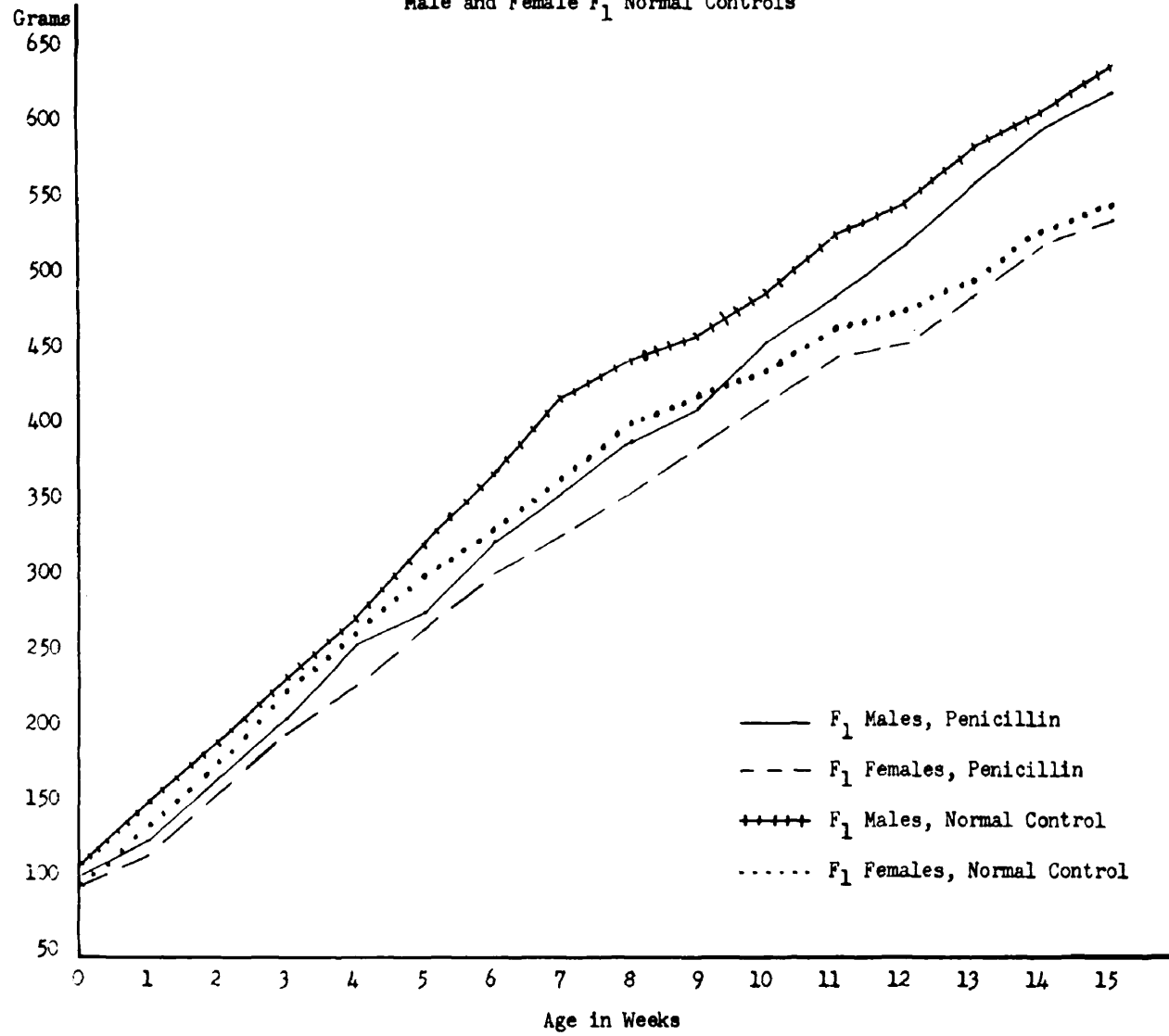


Figure 7

Relation of Average Weights of Male and Female F_1 Guinea Pigs Fed Aureomycin to Average Weights of Male and Female Normal Controls

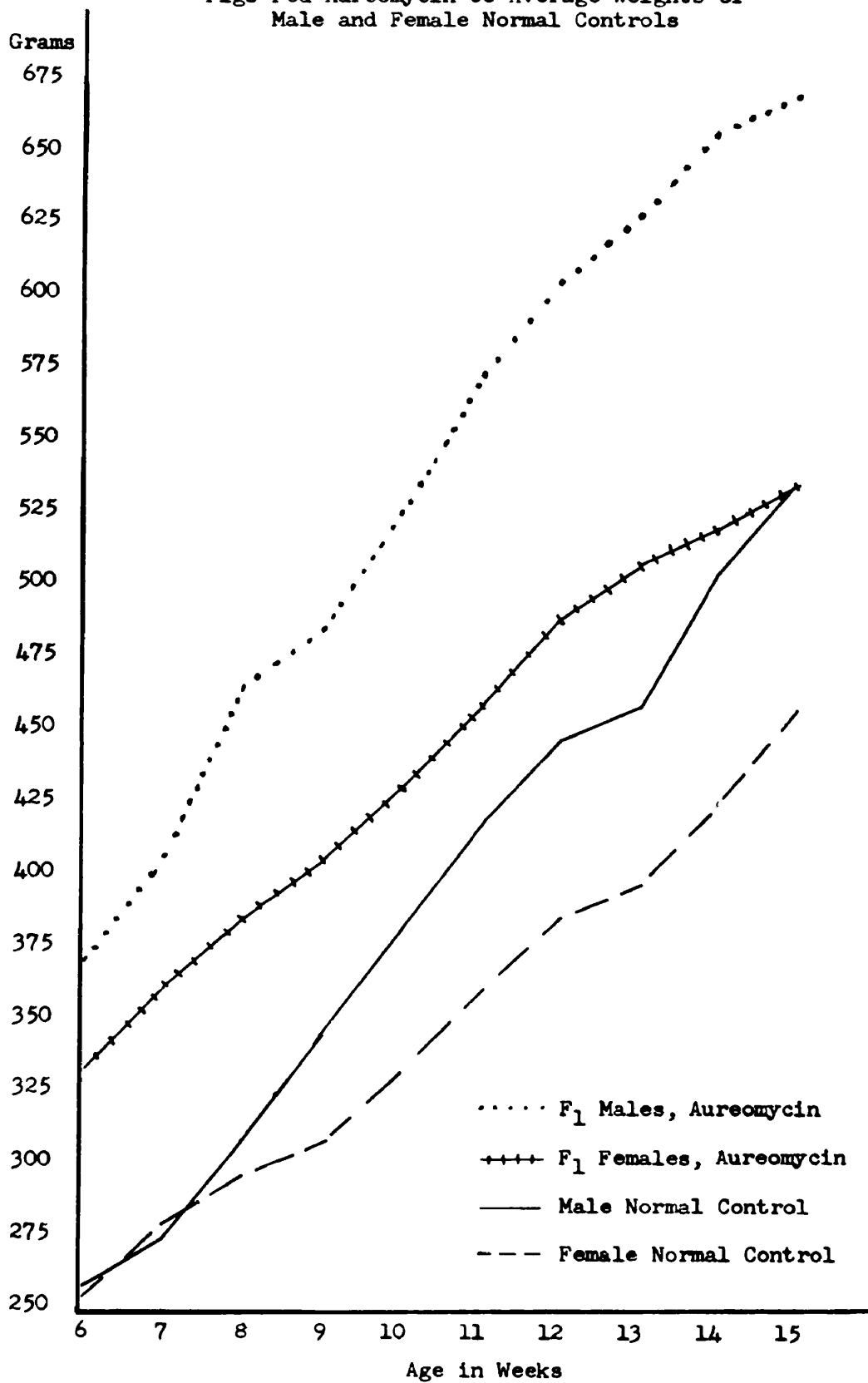


Figure 8

Relation of Average Weights of Male and Female F_1 Guinea Pigs Fed Penicillin to Average Weights of Male and Female Normal Controls

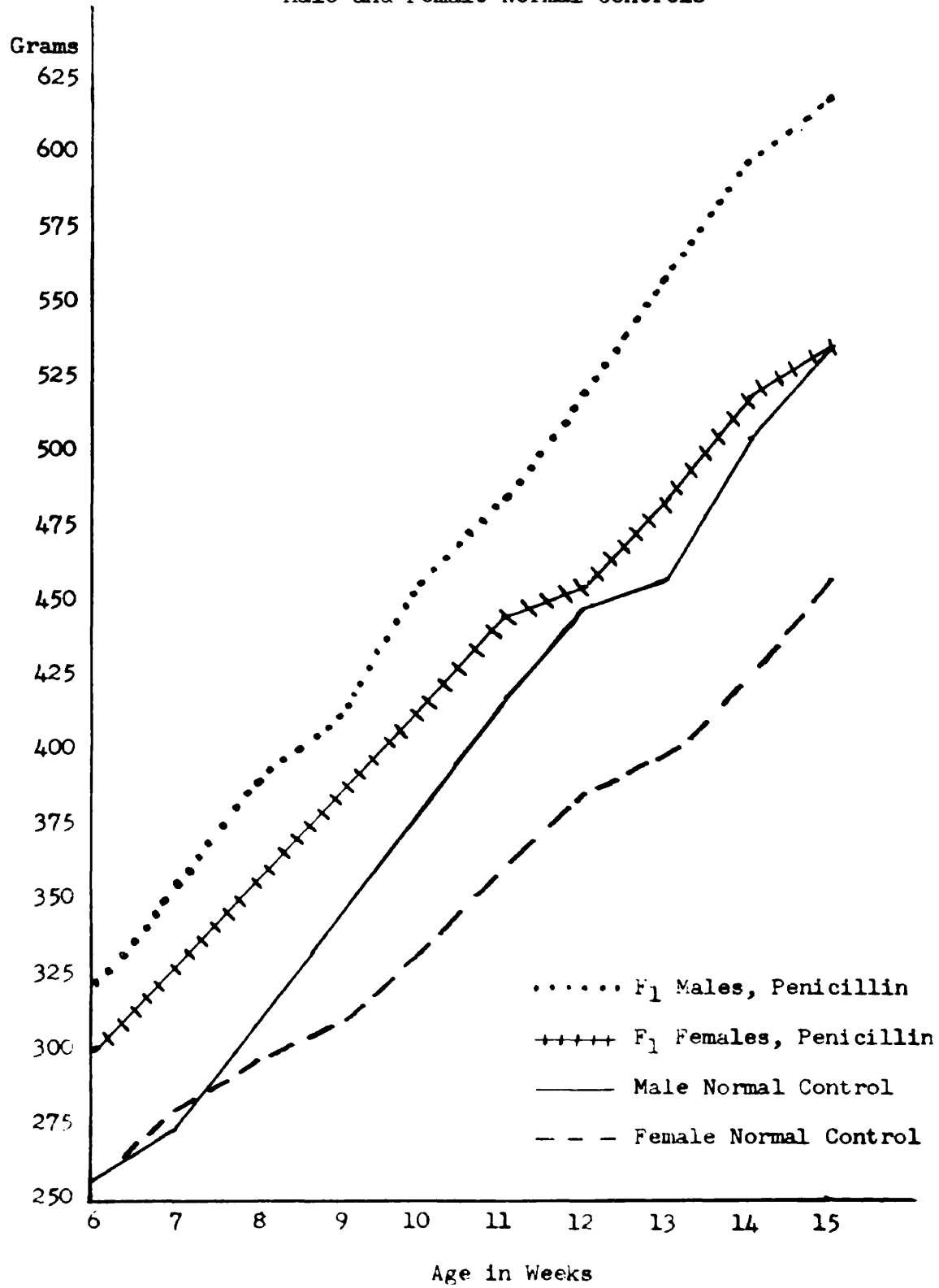


Figure 9

Relation of Average Weights of Male and Female F_1 Normal Control Guinea Pigs to Average Weights of Male and Female Normal Controls

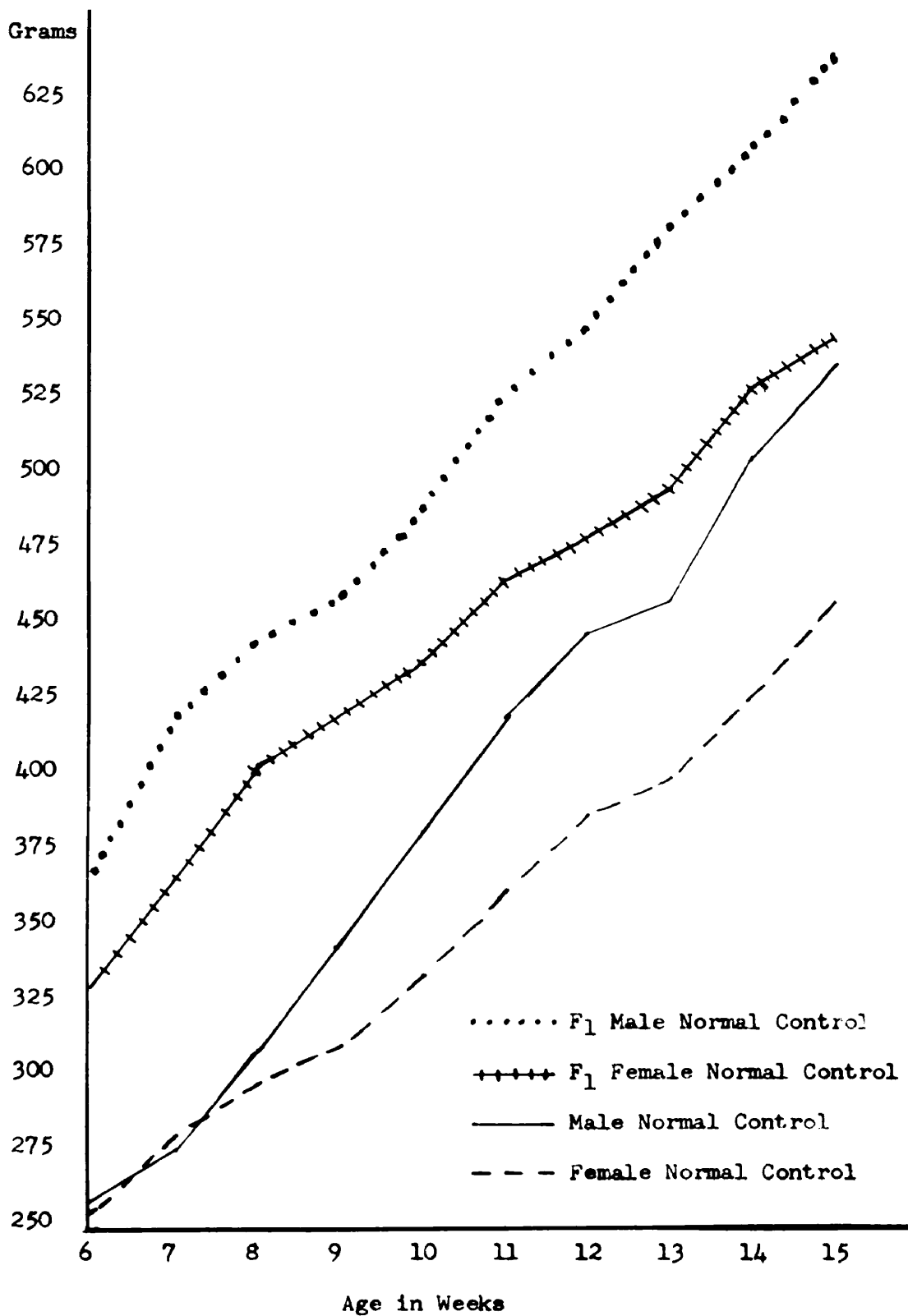


Figure 10

Comparison of Average Weights of Groups of Male Guinea Pigs

Group AA - Fed .2 mg. Aureomycin

Group AB - Fed .3 mg. Aureomycin

Group III - Normal Control

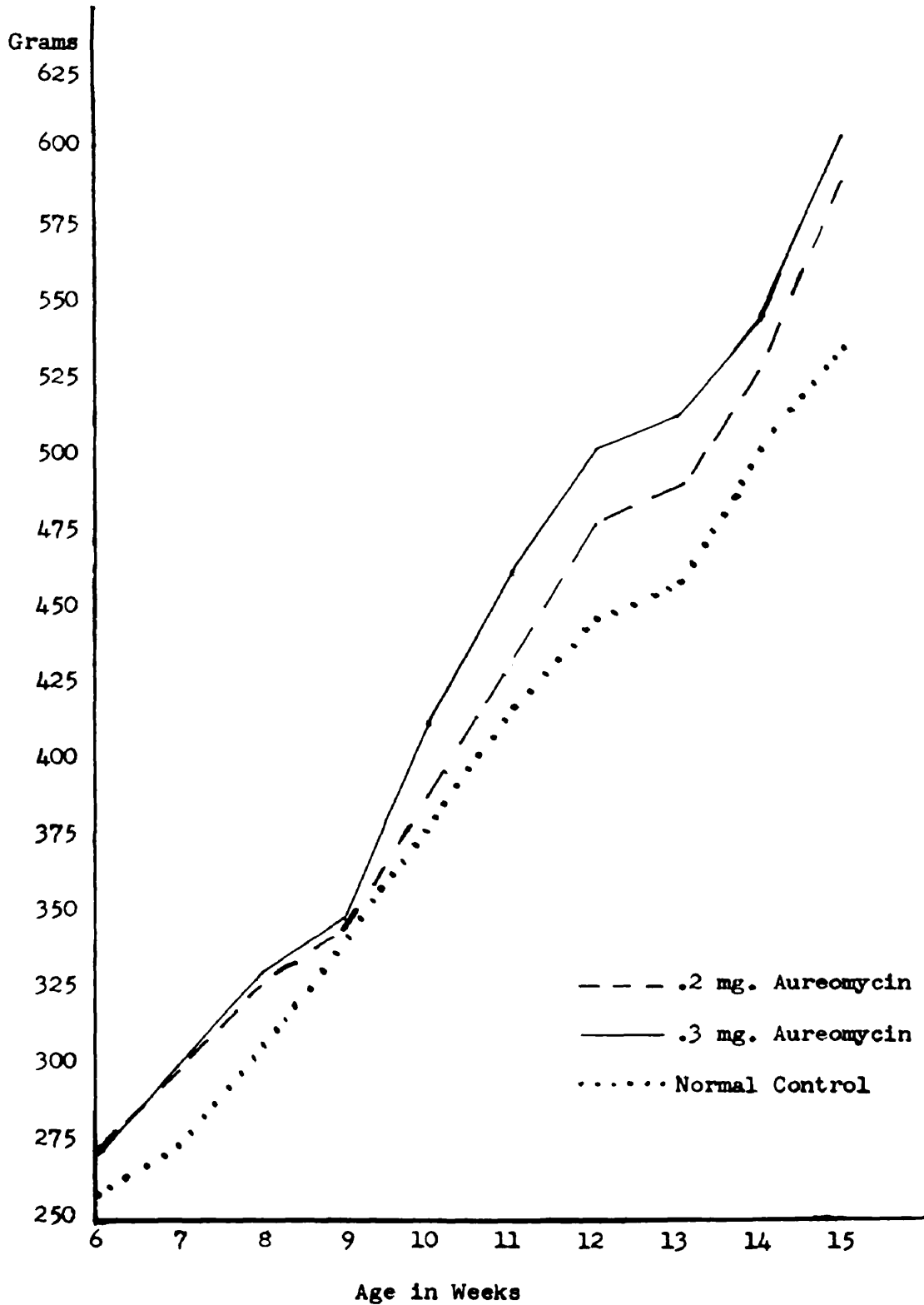


Figure 11

Comparison of Average Weights of Groups of Male Guinea Pigs

Group AC - Fed .4 mg. Aureomycin

Group AD - Fed .5 mg. Aureomycin

Group III - Normal Control

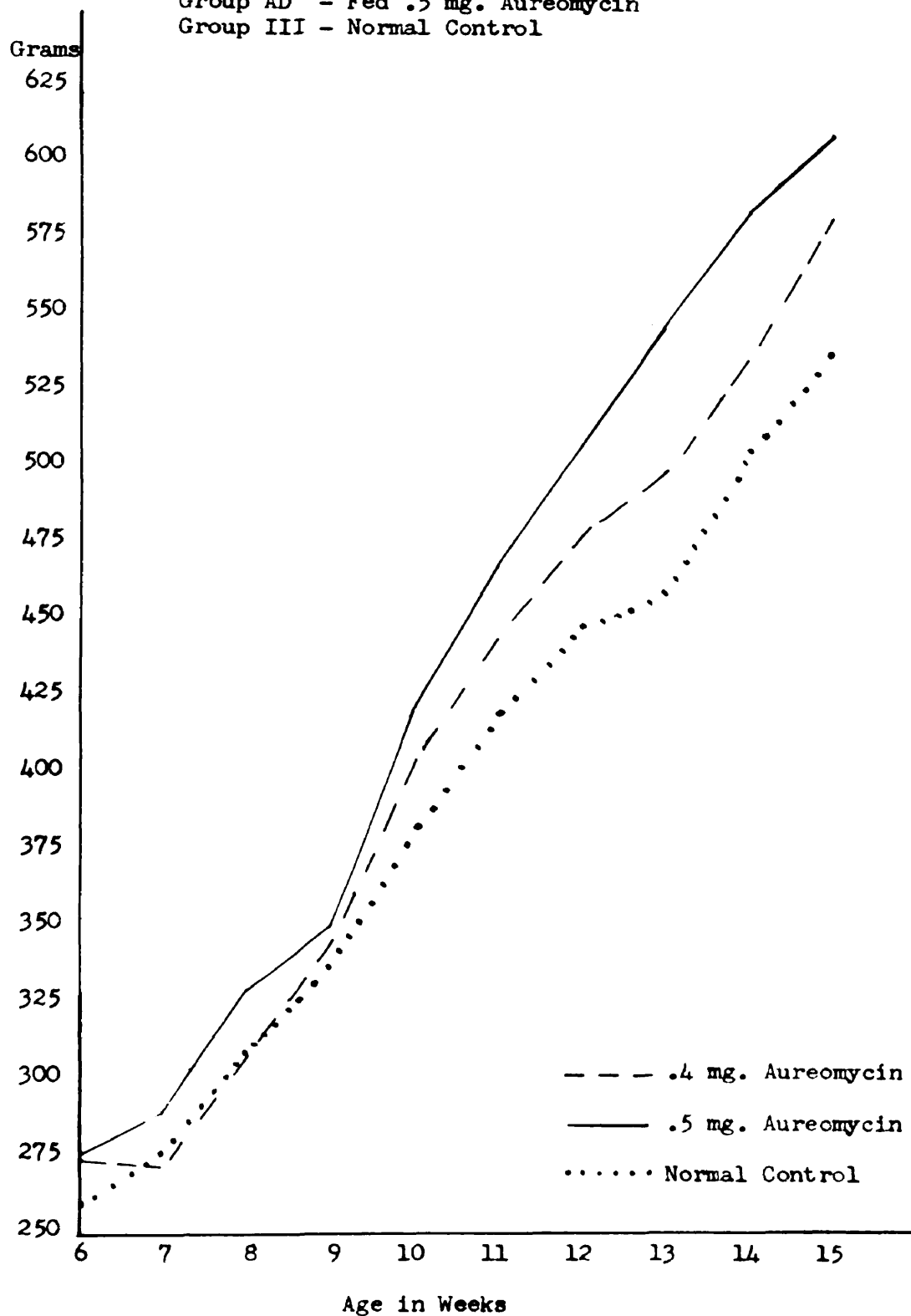


Figure 12

Comparison of Average Weights of Groups of Male Guinea Pigs

Group PA - Fed .2 mg. Penicillin
 Group PB - Fed .3 mg. Penicillin
 Group PC - Fed .4 mg. Penicillin
 Group PD - Fed .5 mg. Penicillin
 Group III - Normal Control

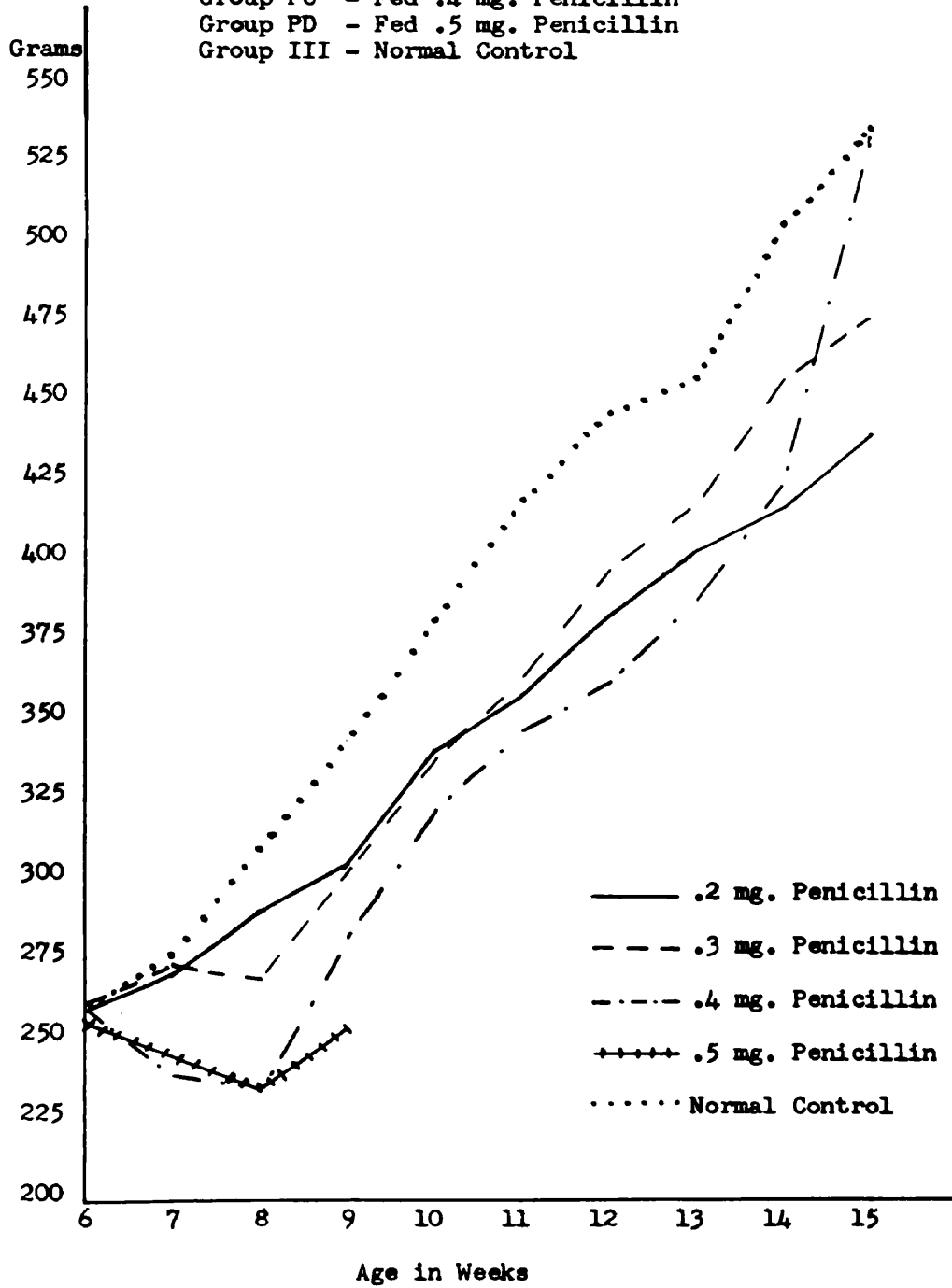


Figure 13

Comparison of Average Weights of Groups of Male Guinea Pigs

Group AA - Fed .2 mg. Aureomycin

Group PA - Fed .2 mg. Penicillin

Group AB - Fed .3 mg. Aureomycin

Group PB - Fed .3 mg. Penicillin

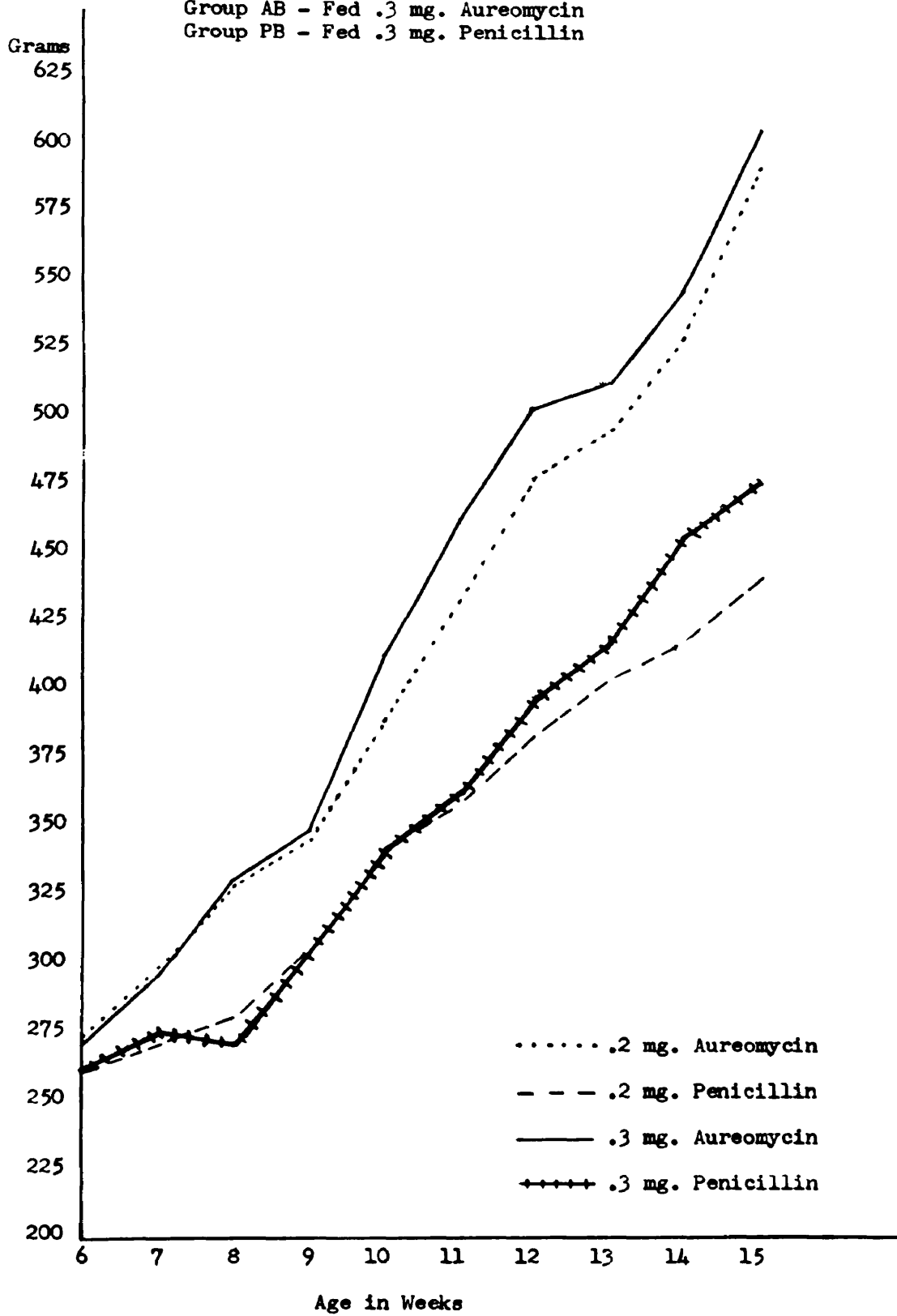
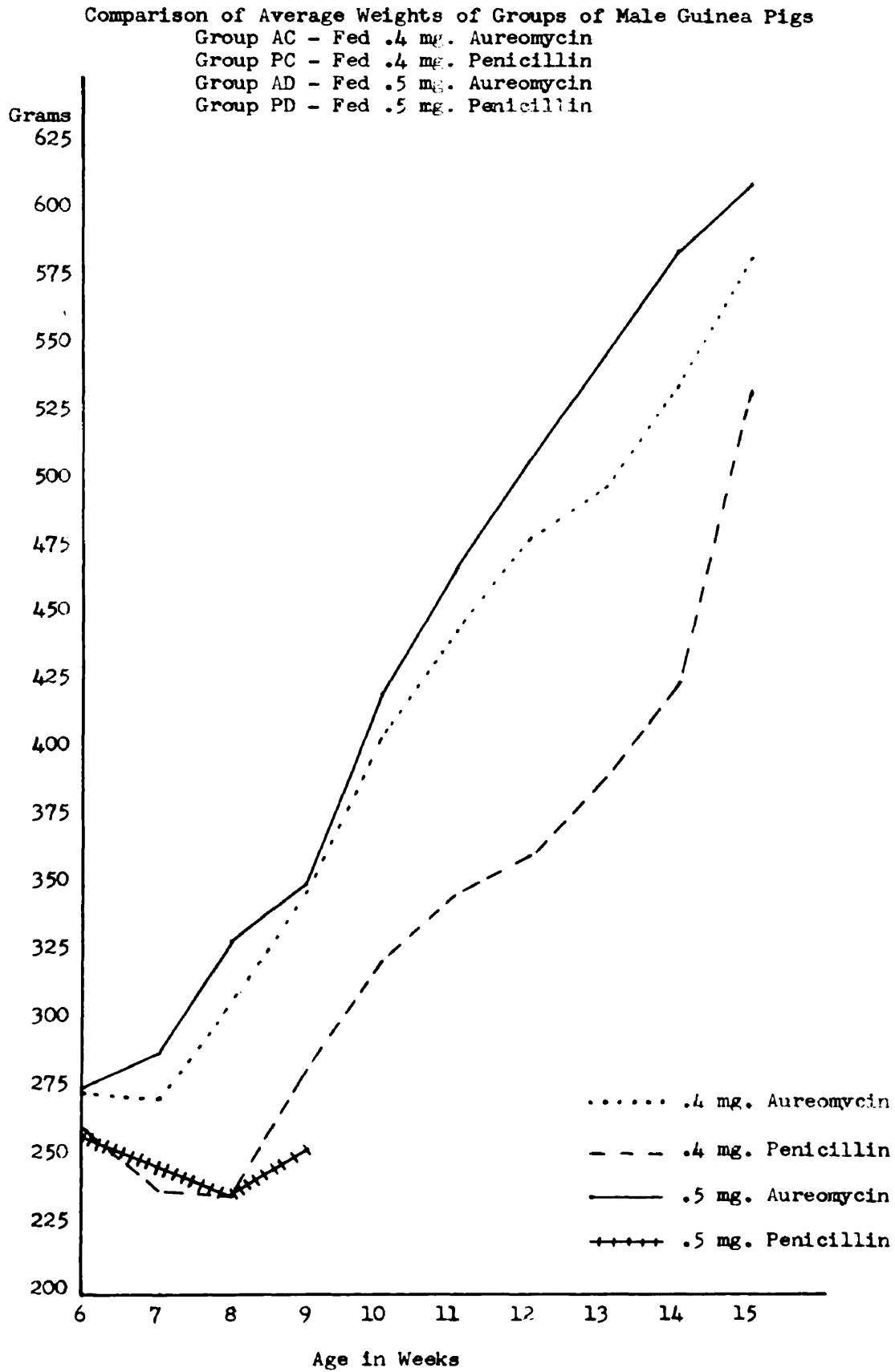


Figure 14



DISCUSSION

The antibiotics, which have been found to promote growth increases in certain animals, are: aureomycin, penicillin, bacitracin, chloromycetin, streptomycin, and terramycin. In this investigation aureomycin and penicillin were chosen as representatives of these drugs. Since the feed for this experiment consisted of a ration including all of the essential vitamins, except Vitamin C, no additions of any substance to the feed were made. However, ascorbic acid was dissolved in the drinking water to provide a sufficient quantity of Vitamin C.

A number of different animals have been used in growth experiments to determine the effects of feeding certain antibiotics. In a review of the literature no information was available as to the effects of feeding antibiotics on the growth of guinea pigs.

Antibiotics are administered to animals in a number of ways. The usual method of administration is by mixing the proper level of the drug with the feed. Since animals waste much of their feed in the process of eating, it is difficult to determine the exact amount of the drug that an animal actually consumes each day. Only by collecting and weighing this waste feed is it possibly to ascertain how much the animals have eaten. Injections of antibiotics have been carried on in some growth experiments, but there is always the possibility of infection, besides the difficulty

of making proper injections. Oral administration of the drugs by pipette is a suggested method, which permits administration of an exact quantity of a drug. This method enables the operator to administer the antibiotic in aqueous form with little difficulty. Because of these advantages, aureomycin and penicillin were administered by this method in the present experiment to the respective groups of guinea pigs.

Since a number of different kinds of animals have been stimulated in growth by the addition of the small average quantity of 20 to 25 mg. of antibiotic per kilogram of feed, it was decided to use this amount as a guide in determining the quantity to administer to the experimental animals. Guinea pigs consume an average of 25 grams of feed each day. On this basis, if the crystalline drugs were mixed with their feed, they would receive an approximate average of 0.5 to 0.6 mg. per day. By oral administration with a calibrated pipette, an aqueous solution made from the crystalline drugs, would give the same results. Therefore, it was decided to use 0.55 mg. of the antibiotics daily in the oral administration of the drugs to the guinea pigs.

Experiments with different kinds of animals indicate that increased growth due to feeding antibiotics, is obtained up to 8 and 10 weeks of age in chicks by Couch and Reed (1950) and Branion and Hill (1951); in turkey poults by Couch and Atkinson (1950); and in calves by Loosli and Wallace (1950). Another investigator, Cravens (1952), reports that feeding antibiotics to turkey poults and chicks

is not effective after the age of 12 weeks. In the present investigation some groups of guinea pigs were fed aureomycin and some penicillin between the ages of 5.5 and 15 weeks and 6 and 15 weeks, while other groups were fed the drugs from the day following birth up until they had attained the age of 15 weeks. No apparent plateau in the growth curve was found in the graphing of the average weights of the various groups in the experiment during the periods of antibiotic administration. It appears that certain groups of guinea pigs are stimulated in growth by the drugs up to the age of 15 weeks, at least.

The Effect of Antibiotic Feeding on Body Weight.

Throughout Experiment I it was noted that the male guinea pigs weighed more on the average than the females. It was apparent, also, that the average weight of the F-1 generation animals was considerably greater than the average weight of the animals from which the parents were selected. Greater increases in average weights were obtained, also, between the ages of 5.5 and 15 weeks in the F-1 animals than in the groups of animals which included their parents.

Higher average body weights and increased average weight gains were found in the aureomycin-fed and penicillin-fed females when compared with those of the normal control females between the ages of 5.5 and 15 weeks (Table 2). In spite of the toxic effects at the beginning of the experiment, the surviving aureomycin-fed and penicillin-fed females showed growth gains, when compared with the normal control females. However, the aureomycin-fed and penicillin-fed males, which survived the toxic effects of the drugs, were

inferior in average body weight and had lower average weight gains, when compared with the normal control males.

In the second part of Experiment I in which no toxic effects occurred, a higher average body weight and a greater average weight increase in aureomycin-fed F-1 males between the ages of 0 and 15 weeks were maintained than in the normal control F-1 males. A greater average weight gain was noted in the penicillin-fed F-1 females than in the normal control F-1 female animals between the ages of 0 and 15 weeks (Table 4). Aureomycin-fed and penicillin-fed females weighed more and showed higher weight gains between 6 and 15 weeks of age than the normal control females. Greater average body weights and increased average weight gains in the aureomycin-fed F-1 males over those of the normal control F-1 males were obtained between the ages of 6 and 15 weeks of age. Both penicillin-fed F-1 males and females showed greater average weight increases than those of the normal control F-1 males and females between the ages of 6 and 15 weeks of age (Table 6).

It was noted from the tabulations of the average body weights of the F-1 guinea pigs that the male and female progeny of aureomycin-fed parents weighed more at birth than the offspring of the penicillin-fed or normal control animals. However, the only apparent carry-over effect of antibiotic stimulated growth from dam to progeny at the end of the 15-week experimental period was in the aureomycin-fed F-1 male animals.

The daily dosage of aureomycin and penicillin

administered to the F-1 female experimental groups was changed from 0.1 mg. to 0.6 mg. when the animals became 6 weeks of age, but no apparent effects were evident in average body weight during the following 9 weeks of the experimental period.

In Experiment II higher average body weights and greater average weight increases were evident in the groups fed various low levels of aureomycin than in the groups fed various low levels of penicillin during the 9-week period of drug administration.

Higher average weights and greater average weight gains were found between the ages of 6 and 15 weeks in the groups of males of Experiment II, which were fed low levels of aureomycin, than in the aureomycin-fed males or the normal control males of Experiment I. The average weights of the normal control males of Experiment I between the ages of 6 and 15 weeks were much greater than those of the groups of males of Experiment II, which were fed low levels of penicillin. Normal control males showed higher average weight gains between 6 and 15 weeks of age than the male animals which were fed low levels of penicillin. Only the group of male animals in Experiment II which were fed 0.4 mg. of penicillin showed a higher weight and a slightly greater weight increase during the experimental period than the penicillin-fed male group of Experiment I.

The average weights of aureomycin-fed F-1 males and normal control F-1 males of Experiment I were greater when compared with those of the various groups of males of

Experiment II, which were fed low levels of aureomycin, but their average weight gains during the 9-week experimental period were less. Between the ages of 6 and 15 weeks the penicillin-fed F-1 males of Experiment I maintained a greater average body weight and a higher average weight gain than the groups of males of Experiment II, which were fed low levels of penicillin. It was noted, also, that the group of normal control F-1 males weighed on the average more than any of the male groups of Experiment II, which were fed various low levels of penicillin.

In comparing the results of the daily administration of 0.1 mg. of aureomycin to F-1 male guinea pigs with those of the daily administration of 0.3 mg. and 0.5 mg. of the drug to male guinea pigs between the ages of 6 and 15 weeks, it was concluded that a 0.1 mg. dosage of aureomycin stimulates greater body weight, whereas the 0.3 mg. and 0.5 mg. doses of aureomycin tend to promote greater weight gains. In contrast to this, the daily administration of 0.1 mg. of penicillin to F-1 male guinea pigs stimulated both greater body weight and higher weight gains than did the administration of 0.2 mg., 0.3 mg. or 0.4 mg. of the drug.

It is not known what effect B vitamins fed in combination with aureomycin or penicillin will have on the growth of guinea pigs.

The Effect of Antibiotic Feeding on Skeletal Growth.

The bone growth of the guinea pigs in this investigation is somewhat proportional to the body weight. Both groups of sacrificed male experimental animals showed a definite

increase in tibial length over that of the male normal controls. This was in relative proportion to the body weight. Quimby (1947) states that other investigators have kept animals on a low calorie diet at constant body weights without cessation of skeletal growth. This would indicate that skeletal growth is not necessarily dependent upon gain in body weight.

The Effect of Antibiotic Feeding on Birth Weights of First Litters. The male offspring of the aureomycin-fed animals of Experiment I weighed on the average more than the male offspring of either the penicillin-fed animals or the normal controls. The male offspring of the penicillin-fed animals, however, weighed less than the male offspring of the normal controls.

The female offspring of the aureomycin-fed animals of Experiment I weighed more than the female offspring of either the penicillin-fed animals or the normal controls. On the other hand, the female offspring of the penicillin-fed animals weighed more than the female offspring of the normal controls.

These interesting results with guinea pigs agree with the report of Slinger, Ferguson, and McConachie (1952) that chicks from hens, which were fed a regular diet plus penicillin, showed unexpectedly the maternal influence in their growth up to 10 weeks of age. Jaffe (1951) disagrees with these results in his recent investigations with rats and mice; finding that reproduction in these rodents for 5 generations is not noticeably affected by the addition to the feed

of aureomycin at 100 mg. per kilogram of ration. These varied results may be due to differences between animal classes.

The Effect of Antibiotic Feeding on Organs and Tissues and Their Weights. With the exception of the heart, kidney, and spleen the organs and tissues, which were removed from the sacrificed experimental animals weighed more than those of the normal controls. This result coincides well with the increase in body weights of the sacrificed experimental animals over that of the sacrificed normal control animals. Also apparent was the slight increase in average tissue weights of the animals fed 0.5 mg. of aureomycin over those of the animals fed 0.3 mg. of the drug. The average weights of the kidney, heart, and spleen of the normal control animals was slightly greater than those of the experimental animals. There was a uniformity of average weights of these organs, however, in the experimental groups regardless of whether or not they were fed 0.3 mg. or 0.5 mg. of aureomycin.

Sections of the liver, spleen, kidney, bone and bone marrow revealed no differentiation between the male experimental animals and the male normal controls. The literature did not contain information relative to the effect that antibiotics might have on the microscopic structure of organs or tissues in stimulated growth.

However, concentrations of aureomycin were found in the spinal fluid, liver, kidney, placenta, spleen and lung by Herrell and Heilman (1949). In dogs this drug has been

found to pass the blood-brain barrier, Harned et al (1948). Streptomycin in certain dosages exercises a paralyzing influence upon the central vestibular nuclear region, according to Kleyn and van Deirse (1950). The theory that antibiotics interfere with the reaction between pyruvate and oxalacetate, sometimes called the "Krebs condensation," has been introduced by Molitor and Graessle (1950). This reaction constitutes the system whereby a wide variety of substances enter the terminal respiration system. This reaction is important in animal tissues. In the animal a permeability barrier exists at the cell wall and also at the mitochondria, where this reaction is localized in the animal cell. This barrier prevents the antibiotic from penetrating to the site of the "Krebs condensation."

The Effect of Antibiotic Feeding on Blood. Antibiotics, which are administered orally, are absorbed into the general circulation of the body. Therapeutic levels of the drugs may be obtained by the proper dosage. Herrell and Heilman (1949) believe that repeated and prolonged administration of an antibiotic does not result in a "piling up" effect, nor does this occur following multiple doses, provided there is no impairment of renal function. Aureomycin is known, also, to be absorbed and distributed in many body fluids and tissues. After absorption it is diffused readily into the cerebrospinal fluid in amounts which might be considered therapeutically effective. Studies by Herrell and Heilman (1949) demonstrate that aureomycin diffuses through the placentas and is available in the fetal circulation. When

therapeutically effective amounts are present in the serum, diffusion into the pleural fluid occurs. This antibiotic appears to be concentrated in the normal hepatic system and excreted in the bile. Large amounts of aureomycin are constantly excreted in the urine of patients receiving this drug. The antibiotic has been found, also, in several organs and tissues of the body. Hawkins et al (1950) have reported that streptomycin is carried by the blood to the brain, where concentrations of the drug have been determined.

Investigators are in general agreement that oral dosage requirements of penicillin are four or five times the parenteral requirements in order to obtain comparable serum concentrations, Seeberg, Illg, and Brown (1946). Human sera has been found by Woznicka (1949) to inactivate penicillin G to a more pronounced extent than the sera of the guinea pig, rabbit, horse, beef, or hog. It is possible that this inactivation is partially responsible for the need of higher dosages in humans after previous illnesses to combat infection.

Numerous methods have been devised for the assay of antibiotics in body fluids. Many are impractical, obsolete, and uniformly unsatisfactory. For the determinations of blood concentrations of antibiotics in this experiment, it was considered advantageous to use the method of Herrell and Heilman (1949) for aureomycin and a modification of this method utilizing Staphylococcus aureus for the determination of penicillin. Other investigators have used different methods for the determination of penicillin, and a lack of uniformity in their results is evident. In the present

investigation the concentration of aureomycin in the pooled blood of the aureomycin-fed guinea pigs of Experiments I and II was 2 micrograms per milliliter. This blood level determination of the drug was made from blood, which was collected from the animals 3 to 4 hours after the oral administration of an aqueous solution of 0.6 mg. of aureomycin. The result of this assay was in harmony with the results obtained by Herrell and Heilman (1949). Considerable difficulty was encountered in attempting to determine the concentration of penicillin in the blood, which was collected from the animals of Experiments I and II. These animals had received oral administration of an aqueous solution of 0.6 mg. of penicillin 30 to 60 minutes prior to the collection of blood. Because of conflicting reports of blood levels of penicillin, it was decided not to continue with more attempts to determine the blood level of this drug.

It is known that the highest concentration of penicillin in the blood is present within one hour after oral administration of the drug, while aureomycin reaches its highest concentration within 3 to 6 hours after oral administration.

The blood of the guinea pig coagulates more readily than that of the human. Coagulation occurred in the blood of the antibiotic-fed guinea pigs in a shorter time than in the normal control animals. This result agrees with the report of Macht and Parkas (1949) that there is a decrease in coagulation time of either human or animal blood which contains aureomycin, and the report of Mosonyi, Palos, and

Komaromy (1949) that penicillin in blood diminishes the clotting time. Galt and Hunter (1950) disagree with these findings by stating that aureomycin prolongs clotting time. It is believed that coagulation of blood is hastened by the antibiotic inhibition of thrombin inactivation.

The hematocrit values of the aureomycin-fed animals were slightly higher than the values of the penicillin-fed animals, and excessively higher than those of the normal control animals. The hematocrit value of penicillin-fed animals was markedly higher, also, than that of the normal controls. Von Dieter (1950) has reported that variations of hematocrit values above and below normal are valuable diagnostic aids. It is known that the hematocrit values of human males, generally, exceeds that of human females by 3% to 4%. In this experiment the average hematocrit values of both male and female normal control guinea pigs were determined, and it was found that the average hematocrit values of these animals was slightly higher than the averages of human males and females, which were reported by Fowler (1949).

Malfunctions and Mortalities Resulting from Antibiotic Administration. Aureomycin and penicillin have a cumulative toxic effect on guinea pigs, whereas, they are relatively non-toxic for most other animals, Heilman (1948). He mentions that subcutaneous injections of aureomycin ranging between 1 mg. and 6 mg. per day for a number of days on several guinea pigs weighing between 260 and 300 grams, caused a large number of deaths between 7 and 14 days. Daily oral administration of aureomycin in the present

investigation was found to be toxic between the second and twelfth days to guinea pigs weighing on the average about 256 grams, when administered at the low dosage of 0.55 mg. per day. A few animals died, but those which survived went through a period of apathy, during which loss of weight and ruffled fur were evident. With another group of guinea pigs, which were fed 0.5 mg. of aureomycin daily, no toxic effects were evident. However, a group of animals fed 0.4 mg. of the drug daily, showed a slight loss in weight during the first week, but this was overcome in the second week. No other toxic symptoms were apparent.

The relative toxicity of aureomycin is low, according to Bryer et al (1948). The intravenous LD-50 in mice and rats is 134 mg. and 118 mg. per kilogram, respectively. Krantz and Carr (1951) report that large doses (50 to 100 mg. per kilogram of body weight) by intravenous injection to dogs produces hyperpnea, weakness, and anorexia. The daily oral administration to mice or dogs of 100 mg. per kilogram of body weight for 9 to 15 weeks caused no gross or microscopic pathologic changes in the viscera. No serious toxic effects have been observed in man following single or repeated oral doses of aureomycin. The most frequent symptoms of toxicity are: gastrointestinal distress, nausea, vomiting, and diarrhea. These side effects are believed to be caused by variations in commercial lots of the drug.

Heilman and Herrell (1944) noted that subcutaneous injections of 1,000 to 5,000 units (1,666.7 units are equivalent to 1 mg.) of penicillin daily in divided doses,

caused the deaths of guinea pigs weighing 200 grams. A day or two preceding death, the animals were lethargic and loss of weight, ruffled fur, and anorexia were apparent. These investigators noted that vasodilation was evident in the capillaries of sections of the brain, liver, and kidneys. It was noted in the present investigation that guinea pigs weighing between 255 grams and 265 grams lost weight, were apathetic, and had ruffled fur and anorexia when fed 0.3 mg., 0.4 mg., 0.5 mg., and 0.55 mg. of penicillin. Some of the animals survived and overcame their loss of weight to some extent during the following weeks, but approximately 50% died of the toxic effects of the drug. Other investigators believe that the susceptibility of individual animals of similar weights to the toxicity of penicillin vary greatly—the toxic effects varying with the dosage of the drug.

The relative toxicity of penicillin is low; the intravenous LD-50 of pure penicillin G in mice is 3,500,000 units (21 mg.) per kg. of body weight. Penicillin does not affect leucocytes, lymphocytes, fibroblasts, or macrophages. In experiments on toxicity of penicillin Cormia (1947) concluded that purified penicillin seems to be more toxic to guinea pigs than the commercial type. Hamre et al (1943) do not agree with this belief, but blame the cause of death on impurities. In Cormia's (1947) experiments with subcutaneous injections of penicillin, guinea pigs died of acute necrosis involving the cortex of the adrenal gland.

In experiments on mice, rats, guinea pigs, rabbits, and cats, which had been previously treated with penicillin,

Macht and Hoffmaster (1950) found no difference in the toxicity of the drug between the treated and the normal animals. Gernez-Rieux and Beerens (1949) noted that the death between 3 and 29 days of 38 of a total number of 59 guinea pigs, which were treated with sodium penicillin, was independent of the dose, dosage schedule, and source of the drug. They believe that the explanation for this response lies in the differences in the genetic makeup or in the nutritional state of the animals. The pathologic findings in the affected animals were: anorexia, rise in polymorphonuclear leucocytes, increased blood urea, and congestion of the liver, spleen, and kidneys.

The mortality rate among guinea pigs ran high in the present investigation when aureomycin and penicillin were administered orally in the quantity of 0.55 mg. per day. This factor was eliminated by administering 0.6 mg. of the drugs on alternate days. The F-1 female experimental animals were given daily oral doses of 0.1 mg. of the drugs up to 6 weeks of age to determine if this procedure would prevent toxic effects when a higher dosage was administered. Then, they were given 0.6 mg. of the drugs on a daily basis for the remaining 9 weeks of the experiment, and, as a result, there were no toxic effects or mortalities. This procedure apparently accustomed the animals to the drug, and the larger dosage had no deleterious effect on them.

There is no explanation for the peculiar hypersensitivity of guinea pigs to penicillin G, but it is known that guinea pigs are hypersensitive to many drugs including

other antibiotics, such as, aureomycin, and it appears that the low penicillin tolerance of this genus belongs to the group of allergic phenomena.

The formation of abscesses as a result of antibiotic administration is reported by Virenque et al (1951). The peculiar characteristic of these abscesses is the lack of an enveloping membrane. Four of the 24 aureomycin-fed and 8 of the 24 penicillin-fed animals of Experiment II, developed abscesses in the neck and shoulder region. Only 2 of the normal control animals developed this condition. From sections made of these abscesses, it was noted that an enveloping membrane was present. It is inferred that penicillin to a greater extent and aureomycin to a lesser extent, either allow or stimulate the growth of these abscesses. The type of abscess found in this experiment is unlike that reported by Virenque et al (1951).

Immunity of Antibiotic-fed Animals to Bacteria.

Immunity may be natural or acquired. Guinea pigs will develop antibodies in their blood in response to inoculations of small non-lethal doses of many types of bacteria. One phase of the present experiment was devoted to the determination of whether or not guinea pigs will form antibodies in response to the continued administration of low levels of aureomycin and penicillin. Since specific antibodies were not formed in detectable quantities, it was thought that the opsonocytaphagic index of the blood might reveal something of interest. It was found that blood from the experimental animals containing low concentrations of the antibiotics

showed increased phagocytic action over that of the normal controls. Staphylococcus aureus was used as the test organism in this study. Phagocytosis of Staphylococcus albus cells by polymorphonuclear leucocytes were reported by Munoz and Geister (1950). They found that high concentrations (1,000 micrograms per milliliter) of aureomycin inhibited this phagocytic action in vitro. It is believed that their results were due to the high concentration of this antibiotic in the blood. The average of the opsonic indices of the experimental animals ranged from 125% to 150% above that of the normal controls. Buccellato (1946) treated patients with penicillin and found that at therapeutic levels this drug, besides its bacteriostatic action, had no influence on the opsonic index. This disagreement with the present results may be due to the difference between low levels and therapeutic levels of the drug in the blood.

From the results of the present investigation, the thought is projected that it may be possible in the future to use low levels of the antibiotics with our foods. Crude residues from the manufacture of the pure crystalline antibiotics contain a small quantity of the antibiotic and some vitamins, which serve as feed supplements for a number of animals. Not only do the animals grow faster, but the incidence of a number of diseases is markedly reduced. It is possible that refined antibiotic residues would help young children grow to be sturdier and more healthy as a result of the incorporation of these residues in such food as cereals. A great deal more experimentation will be required before

such possibilities can be realized. Another factor that must be considered is that of increased resistance of certain bacteria to low levels of the antibiotics. Such a condition would necessitate larger dosages of specific antibiotics in case of a severe infection. On the other hand, minor illnesses might be readily overcome by having low concentrations of the antibiotics in our bodies as a result of their inclusion in our food. This factor might offset the disadvantages of larger dosages in major infections, which are usually infrequent in occurrence.

CONCLUSIONS

1. Daily oral administration of aqueous solutions of aureomycin and penicillin to guinea pigs by means of a calibrated pipette promotes growth in certain groups of animals up to the age of 15 weeks.
2. A plateau was not reached in the growth curve of any group of guinea pigs up to the age of 15 weeks.
3. Greater body weight and greater weight gain relationships are considered indicative.
4. Female guinea pigs treated with the antibiotics show greater body weights and increased weight gains.
5. Normal control males weigh more and have higher weight gains than male animals fed low levels of penicillin.
6. The progeny of animals treated with aureomycin and the female progeny of animals treated with penicillin weigh more at birth.
7. Only the male progeny, which were fed 0.1 mg. of aureomycin, showed a carry-over effect of antibiotic-stimulated growth from dam to progeny following birth.
8. When offspring from parents fed the antibiotics are in turn fed aureomycin and penicillin from birth to 15 weeks, their average weight is greater than that of their parents.
9. Male progeny, which were fed 0.1 mg. of aureomycin, maintained higher body weights and greater weight gains.

10. Male progeny from normal control animals show greater body weights than males fed low levels of aureomycin.

11. Male progeny fed 0.1 mg. of aureomycin weigh more than male animals, which are fed 0.2 mg., 0.3 mg., 0.4 mg., or 0.5 mg. of aureomycin. However, the latter show higher weight gains than the former.

12. Male offspring fed 0.1 mg. of penicillin maintain greater body weights and higher weight gains than males fed 0.2 mg., 0.3 mg., or 0.4 mg. of the drug.

13. Female progeny, which were fed 0.1 mg. of penicillin for 6 weeks followed by 0.6 mg. of the drug for 9 weeks, show greater weight increases.

14. Male animals fed 0.4 mg. of penicillin show greater body weights and weight gains than males at the same ages, which are daily fed 0.55 mg. of the drug for one week followed by 0.6 mg. of the drug given on alternate days.

15. Male guinea pigs fed 0.2 mg., 0.3 mg., 0.4 mg., or 0.5 mg. of aureomycin weigh more and show higher weight increases than males, which are fed the same levels of penicillin.

16. In body weight and weight increases male animals fed levels of 0.2 mg., 0.3 mg., 0.4 mg., or 0.5 mg. of aureomycin exceed the males and females, which are daily fed 0.55 mg. of the drug for one week followed by 0.6 mg. of the drug on alternate days, as well as the normal control males.

17. The skeletal growth of guinea pigs is relatively proportional to the body weight. Bone growth of aureomycin-fed animals shows a definite increase.

18. Average organ and tissue weights of aureomycin-fed animals, with the exception of the heart, kidney, and spleen, are greater. These organ and tissue weights are in relative proportion to the increased body weights.

19. Sections of liver, spleen, kidney, bone, and bone marrow show no differentiation in structure between the aureomycin-fed animals and the normal controls.

20. Antibiotics are readily absorbed into the general circulation of the body after oral administration. Two micrograms of aureomycin per milliliter of blood are present 3 to 4 hours after oral administration of an aqueous solution of 0.6 mg. of the drug.

21. The blood of the guinea pig coagulates more readily than that of the human. Coagulation time of the blood of aureomycin-fed and penicillin-fed animals is less than that of normal control animals.

22. Hematocrit values of the aureomycin-fed animals are slightly higher than the values of the penicillin-fed animals, and much higher than those of the normal controls.

23. Aureomycin and penicillin have a cumulative toxic effect on guinea pigs. Mortalities, due to toxicity following 0.55 mg. dosage, averaged 17% in aureomycin-fed animals and 55% in penicillin-fed animals. A small dosage of 0.1 mg. of the drugs administered to guinea pigs for 6 weeks, prevents toxic effects when this procedure is followed by a dosage of 0.6 mg.

24. Aside from the toxic effects of the drugs, there was one mortality caused by pneumonia.

25. Eight penicillin-fed and 4 aureomycin-fed guinea pigs developed abscesses during the period of antibiotic administration. These incidences are high for a small number of animals, since only two normal controls of a similar number of animals were afflicted.

26. Specific antibodies are not formed in guinea pigs in detectable quantities in response to feeding the drugs.

27. Opsonins are increased in activity as a result of the oral administration of both drugs. The opsonic index of the blood of aureomycin-fed animals is 2.50; of penicillin-fed animals, 2.25; and of normal control animals, 1.00. The phagocytic index of the blood of aureomycin-fed animals is 100; of penicillin-fed animals, 90; and of normal controls, 40.

SELECTED BIBLIOGRAPHY

- Abraham, E. P., E. Chain, C. M. Fletcher, H. W. Florey, A. D. Gardner, N. G. Heatley, and M. A. Jennings. "Further Observations on Penicillin." LANCET, 2: 177-188, 1941.
- Atkinson, R. L., and J. R. Couch. "Crystalline Antibiotics in the Nutrition of Poults Kept on Raised Screen Floors." POULTRY SCIENCE, 31 (1): 115-118, 1952.
- Baggs, C. W., B. Bronstein, J. W. Hirshfield, and M. A. Pilling. "The Presence in Normal Serum of Inhibiting Substances Against B. subtilis." SCIENCE, 103: 363, 1946.
- Barbour, R. G. H. "The Development of Resistance to Streptomycin by Staph. pyogenes." AUSTRALIAN JOURNAL OF EXPERIMENTAL BIOLOGY AND MEDICAL SCIENCE, 28 (4): 415-420, 1950.
- Bechtel, H. E. "How Far Can You Travel on Antibiotics?" FEEDSTUFFS, 23 (32): 18, 1951.
- Beeson, W. M. "Antibiotics in Nutrition of Swine." FEED BAG, 27 (12): 48-51, 1951.
- Bell, M. C., C. K. Whitehair, and W. D. Gallup. "The Effect of Aureomycin on Digestion in Steers." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 76 (2) 284-286, 1951.
- Bentley, O. G. "Some Factors that Influence the Response to Vitamin B-12 and Antibiotics." FEEDSTUFFS, 24 (3): 46-49, 1952.
- Berg, L. R., G. E. Bearse, J. McGinnis, and V. L. Miller. "The Effect of Removing Supplemental Aureomycin from the Ration on the Subsequent Growth of Chicks." ARCHIVES OF BIOCHEMISTRY, 29 (2): 404-407, 1950.
- Berg, L. R. "Antibiotics in Feed For Broilers." FEEDSTUFFS, 23 (20): 31-33, 1951.
- Bierman, H. R., and E. Jawetz. "The Effect of Prolonged Administration of Antibiotics on the Human Fecal Flora." JOURNAL OF LABORATORY AND CLINICAL MEDICINE, 37 (3): 394-401, 1951.
- Bird, H. R. (a) "Antibiotics in Feed." FEEDSTUFFS, 22 (40): 10, 15, 1950.

- _____. (b) "New Trends in Poultry Feeding." FEED BAG, 26, (7): 15, 59, 60, 1950.
- Blight, J. C., James X. King, and N. R. Ellis. "Effect of Vitamin B-12 and Aureomycin Concentrates on the Growth Rate of Unthrifty Weanling Pigs." JOURNAL OF ANIMAL SCIENCE, 11 (1): 92-96, 1952.
- Branion, H. D., and D. C. Hill. "Comparative Effect of Antibiotics on Growth of Poults." POULTRY SCIENCE, 30 (6): 793-798, 1951.
- Briggs, G. M. "Antibiotics in Poultry Rations." FEEDSTUFFS, 22 (32): 32-36, 1950.
- _____. "A Review of Recent Developments in Poultry Nutrition: Vitamin B-12, Antibiotics, and New Growth Factors." TRANSACTIONS OF THE AMERICAN ASSOCIATION OF CEREAL CHEMISTS, 10 (1): 31-50, 1952.
- Briggs, J. E., and W. M. Beeson. "The Effect of Vitamin B-12, Aureomycin and Streptomycin or Dried Whey Factor Supplements on the Growth of Weanling Pigs." JOURNAL OF ANIMAL SCIENCE, 11 (1): 103-111, 1952.
- Bryer, M. S., E. B. Schoenbach, C. A. Chandler, E. A. Bliss, and P. H. Long. "Aureomycin: Experimental and Clinical Investigations." AMERICAN MEDICAL ASSOCIATION JOURNAL, 138: 117-119, 1948.
- Buccellato, Gaetano. "Ricerche Sull'influenza della Cura Penicillinica Sull'indice Opsonico in Infermi con Malattie Varie." (Effects of Penicillin Therapy on the Opsonic Index in Various Diseases.) PEDIATRIA, 54: 612-615, 1946.
- Carpenter, Lawrence E. "The Effect of Antibiotics and Vitamin B-12 on the Growth of Swine." ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, 32 (1): 187-191, 1951.
- Chandler, C. A., V. Z. Davidson, and P. H. Long. "Studies on Resistance of Staphylococci to Penicillin: The Production of Penicillinase and its Inhibition by the Action of Aureomycin." BULLETIN OF THE JOHNS HOPKINS HOSPITAL, 89 (2): 81-89, 1951.
- Chandler, V. L., C. W. Price, and W. A. Randall. "Control and Evaluation of Blood Serum Assays for Penicillin." SCIENCE, 102: 355-356, 1945.
- Collins, H. S. "Urinary Excretion of Aureomycin." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 69: 174-175, 1948.

- Cormia, F. E., G. M. Lewis, and M. E. Hopper. "Toxicity of Penicillin for the Guinea Pig." JOURNAL OF INVESTIGATIVE DERMATOLOGY, 9: 261-267, 1947.
- Couch, J. R., and R. L. Atkinson. "Vitamin B-12, APF Concentrates, and Antibiotics in Turkey Rations." FEEDSTUFFS, 22 (30): 57, 1950.
- Couch, J. R., and J. R. Reed. "Vitamin B-12, APF Concentrates, and Antibiotics in Poultry Rations." FEEDSTUFFS, 22 (27): 16, 1950.
- Couch, J. R., J. F. Elam, and L. L. Gee. "Effect of Penicillin on Growth, Egg Production, and Hatchability." FEDERATION PROCEEDINGS, 10 (1): 379. 1951.
- Cravens, W. W. "Not All Feeds Need Antibiotics." FEED BAG, 28 (6): 50-53, 1952.
- Cravioto-Munoz, J., H. G. Poncher, and Harry A. Waisman. "Vitamin B-12 Sparing Action of Aureomycin in the Rat." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 77 (1): 18-19, 1951.
- Cuff, P. W., H. M. Maddock, V. C. Speer, and D. V. Catron. "Effect of Different Antibiotics on Growing-Fattening Swine." IOWA STATE COLLEGE JOURNAL OF SCIENCE, 25 (4): 575-580, 1951.
- Cunha, T. J. (a) "Effect of Aureomycin on the Pig." FEEDSTUFFS, 22 (17): 26, 1950.
- _____ (b) "Antibiotic Effect May Differ." FEEDSTUFFS, 22 (40): 12, 1950.
- Dowling, H. F., M. H. Lepper, E. R. Caldwell, Jr., R. L. Whelton, and R. L. Brickhouse. "The Concentration of Aureomycin in Urine and Cerebrospinal, Pleural, and Ascitic Fluids after Oral and Intravenous Administration." JOURNAL OF CLINICAL INVESTIGATION, 28: 983, 1949.
- Duggar, B. M. "Aureomycin: A Product of the Continuing Search for New Antibiotics." ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 51: 177-181, 1948.
- Edwards, H. M., T. J. Cunha, G. B. Meadows, R. F. Sewell, and C. B. Shawver. "Observations on Aureomycin and APF for the Pig." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 75 (2): 445-446, 1950.
- Elam, J. F., L. L. Gee, and J. R. Couch. "Effect of Feeding Penicillin on the Life Cycle of the Chick." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 77 (2): 209-213, 1951.

- . "Function and Metabolic Significance of Penicillin and Bacitracin in the Chick." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 78 (3): 832-836, 1951.
- Ershoff, Benjamin H. "Prolonged Survival of Hyperthyroid Rats Fed Penicillin and Aureomycin Residues." ARCHIVES OF BIOCHEMISTRY, 28 (3): 359-363, 1950.
- Fleming, Alexander. "Micro-methods of Estimating Penicillin in Blood Serum and Other Body Fluids." LANCET, 2: 620, 1944.
- Fleming, Alexander, M. Y. Young, and J. Suchet. "Penicillin Content of Blood Serum After Various Doses of Penicillin by Various Routes." LANCET, 2: 621, 1944.
- Fleming, Alexander, and Charles Smith. "Estimation of Penicillin in Serum." LANCET, 1: 401-402, 1947.
- Fowler, Willis M. HEMATOLOGY. New York: Harper and Brothers, 1949. 535 pp.
- Fusillo, Matthew H., and M. J. Romansky. "The Simultaneous Increase in Resistance of Bacteria to Aureomycin and Terramycin upon Exposure to either Antibiotic." ANTI-BIOTICS AND CHEMOTHERAPY, 1: 107-109, 1951.
- Fusillo, Matthew H., Joseph F. Metzger, and Dwight M. Kuhns. "Effect of Chloromycetin and Streptomycin on Embryonic Tissue Growth in In Vitro Tissue Culture." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 79 (3): 376-377, 1952.
- Galt, Jabez and Richard B. Hunter. "The Effect of Aureomycin on Certain Liver Function Tests and Blood Coagulation." AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 220: 508-510, 1950.
- Gernez-Rieux, C., and H. Beerens. "Toxicite de la Penicilline pour le Cobaye." (Toxicity of Penicillin for the Guinea Pig.) ANNALES DE L'INSTITUT PASTEUR DE LILLE, 2: 100-107, 1949.
- Glazko, Anthony J., Wesley A. Dill, and L. M. Wolf. "Observations on the Metabolic Disposition of Chloramphenicol (Chloromycetin) in the Rat." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, 104 (4): 452-458, 1952.
- Haight, Thomas H., Clare Wilcox, and Maxwell Finland. "Cross Resistance to Antibiotics." JOURNAL OF LABORATORY AND CLINICAL MEDICINE, 39 (4): 637-648, 1952.

- Halick, J. V., and J. R. Couch. "Antibiotics in Mature Fowl Nutrition." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 76 (1): 58-62, 1951.
- Hamre, D. M., G. Rake, C. M. McKee, and H. B. MacPhillamy. "The Toxicity of Penicillin as Prepared for Clinical Use." AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 206: 642-652, 1943.
- Harned, B. K., R. W. Cunningham, M. C. Clark, R. Cosgrove, C. H. Hine, W. J. McCauley, E. Stokey, R. E. Vessey, N. N. Yuda, and Y. Subbarow. "The Pharmacology of Duomycin." ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, 51: 182-210, 1948.
- Hawkins, Joseph E., Jr., George E. Boxer, and Viola C. Jelinek. "Concentration of Streptomycin in Brain and Other Tissues of Cats after Acute and Chronic Intoxication." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 75 (3): 759-761, 1950.
- Heilman, F. R., and W. E. Herrell. "Penicillin in the Treatment of Experimental Leptospirosis Icterohaemorrhagica (Weill's Disease)." PROCEEDINGS OF THE STAFF MEETINGS OF THE MAYO CLINIC, 19: 89-99, 1944.
- Heilman, F. R. "Aureomycin in the Treatment of Experimental Relapsing Fever and Leptospirosis Icterohaemorrhagica (Weill's Disease). PROCEEDINGS OF THE STAFF MEETINGS OF THE MAYO CLINIC, 23: 569-573, 1948.
- Henser, G. F. "Antibiotics for Poultry." FLOUR AND FEED, 52 (8): 38, 1952.
- Herrell, W. E., and F. R. Heilman. "Aureomycin: Studies on Absorption, Diffusion, and Excretion." PROCEEDINGS OF THE STAFF MEETINGS OF THE MAYO CLINIC, 24: 157-166, 1949.
- Ingram, G. R., and S. A. Edgar. "The Effect of Certain Antibiotics and Other Drugs on the Growth of Chicks Infected with Eimeria tenella." POULTRY SCIENCE, 30 (6): 918, 1951.
- Jacob, Stanley, Fritz B. Schweinburg, and A. M. Rutenburg. "Effect of Intravenous Aureomycin on the Intestinal Flora of Dog and Man." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 78 (1): 121-122, 1951.
- Jaffe, Werner G. "Efecto de la Aureomicina en Ratas y Ratones Deficientes en Vitamina B-12." (Effect of Aureomycin on Rats and Mice Deficient in Vitamin B-12). ARCHIVOS VENEZOLANOS DE NUTRICION, 2 (2): 381-390, 1951.
- Jukes, Thomas H., and E. L. R. Stokstad. "Vitamin B-12 and Animal Growth." FLOUR AND FEED, 51 (9): 27, 1951.

- Jukes, Thomas H. "Recent Studies of the Role of Antibiotics in Nutrition." MICHIGAN STATE COLLEGE VETERINARIAN, 12 (2): 90-95, 1952.
- Jukes, Thomas H., E. L. R. Stokstad, R. R. Taylor, T. J. Cunha, H. M. Edwards, and G. B. Meadows. "Growth-promoting Effect of Aureomycin on Pigs." ARCHIVES OF BIOCHEMISTRY, 26 (2): 324-325, 1950.
- Kaipainen, W. J. "Does Induced Resistance of Bacteria to One Antibiotic Result in Simultaneous Sensitivity Changes to Other Antibiotics?" ANNALES MEDICINAE EXPERIMENTALIS ET BIOLOGIAE FENNIAE, 29 (Suppl. 1): 1-96, 1951.
- Kleyn, A. P. H. A. de, and J. B. van Deinse. "The Influence of Streptomycin on the Vestibular System." ACTA OTOLARYNGOLOGICA, 38 (1): 3-7, 1950.
- Krantz, John C., and C. J. Carr. THE PHARMACOLOGIC PRINCIPLES OF MEDICAL PRACTICE. Baltimore, Md.: The Williams and Wilkens Company, 1951.
- Kratzer, F. H. "Vitamin B-12 and Antibiotics in the Diet of Turkey Poults from Hens Fed No Animal Protein." POULTRY SCIENCE, 31 (3): 519-523, 1952.
- Lawrence, John M., and James McGinnis. "The Effect of Terramycin on the Growth of Rabbits." ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, 37 (1): 164-166, 1952.
- Lih, Hwa, and C. A. Baumann. "Effects of Certain Antibiotics on the Growth of Rats Fed Diets Limiting in Thiamine, Riboflavin, or Pantothenic Acid." JOURNAL OF NUTRITION, 45 (1): 143-152, 1951.
- Lillie, Robert J., and H. R. Bird. "Effect of Antibiotic Supplements Upon Hatchability and Upon Growth and Viability of Progeny." POULTRY SCIENCE, 31 (3): 513-518, 1952.
- Linkswiler, Hellen M., C. A. Baumann, and E. E. Snell. "Effect of Aureomycin on Growth Response of Rats to Various Forms of Vitamin B-6." FEDERATION PROCEEDINGS, 10 (1): 387, 1951.
- Loosli, J. K., and H. D. Wallace. "Influence of APF and Aureomycin on the Growth of Dairy Calves." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 75 (2): 531-533, 1950.
- Luecke, R. W., W. N. McMillen, and F. Thorp, Jr. "The Effect of Vitamin B-12, Animal Protein Factor, and Streptomycin on the Growth of Young Pigs." ARCHIVES OF BIOCHEMISTRY, 26 (2): 326-327, 1950.
- Luecke, R. W., F. Thorp, Jr., H. W. Newland, and W. N. McMillen. "The Growth-promoting Effects of Various Antibiotics on Pigs." JOURNAL OF ANIMAL SCIENCE, 10 (2): 538-543, 1951.

- Macht, David I., and Robert Farkas. "Aureomycin and Blood Coagulation." *SCIENCE*, 110: 305-306, 1949.
- Macht, David I., and Thomas Hoffmaster. "Toxicity of Penicillin for Previously Treated Animals." *FEDERATION PROCEEDINGS*, 9 (1): 298, 1950.
- March, B., and Jacob Biely. "The Effect of Feeding Aureomycin on the Bacterial Content of Chick Feces." *POULTRY SCIENCE*, 31 (1): 177-178, 1952.
- Mariakulandai, A., Than Myint, and James McGinnis. "Effect of Terramycin and Vitamin B-12 on Hatchability." *PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE*, 79 (2): 242-244, 1952.
- McDermott, Walsh, P. A. Bunn, M. Benoit, R. DuBois, and M. E. Reynolds. "The Absorption, Excretion, and Destruction of Orally Administered Penicillin." *JOURNAL OF CLINICAL INVESTIGATION*, 25: 190-210, 1946.
- McGinnis, James, Joel R. Stern, R. A. Wilcox, and J. S. Carver. "The Effect of Different Antibiotics on Growth of Turkey Poults." *POULTRY SCIENCE*, 30 (4): 492-496, 1951.
- McGinnis, James, and Joel R. Stern. "Antibiotics in Turkey Nutrition." *FEEDSTUFFS*, 24 (10): 20-26, 48, 1952.
- Meads, Manson, E. M. Ory, Clare Wilcox, and Maxwell Finland. "Penicillin Sensitivity of Strains of Six Common Pathogens and of Hemophilus hemolyticus." *JOURNAL OF LABORATORY AND CLINICAL MEDICINE*, 30: 725-729, 1945.
- Meites, Joseph. "Counteraction of Cortisone Inhibition of Body, Hair, and Thymus Growth by Vitamin B-12 and Aureomycin." *PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE*, 78 (3): 692-695, 1951.
- Molitor, Hans, and Otto E. Graessle. "Pharmacology and Toxicology of Antibiotics." *JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS*, 98 (4 pt. 2): 1-60, 1950.
- Monson, W. J., L. S. Dietrich, and C. A. Elvehjem. "The Effect of Different Carbohydrates and Antibiotics on the Growth of Chicks and the Storage of Vitamins." *JOURNAL OF NUTRITION*, 46 (3): 411-423, 1952.
- Mosonyi, L., L. A. Palos, and J. Komaromy. "Penicillin and Blood Coagulation." *ACTA MEDICA SCANDINAVICA*, 135: 458-464, 1949.
- Munoz, J., and R. Geister. "Inhibition of Phagocytosis by Aureomycin." *PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE*, 75 (2): 367-370, 1950.

- Oleson, J. J., B. L. Hutchings and A. R. Whitehill. "The Effect of Feeding Aureomycin on the Vitamin B-12 Requirement of the Chick." ARCHIVES OF BIOCHEMISTRY, 29 (2): 334-338, 1950.
- Paolantonio, U., and G. Sulli. "Contributo Allo Studio dei Rapporti fra Sostanze Antibiotiche e Metabolismo Vitaminico. (1) Azione della Penicillina Sulla Eliminazione Urinaria dell'acido Nicotinic. (2) Azione della Penicillina sulla Vitamina B-1." (Relationships between Antibiotic Substances and Vitamin Metabolism. (1) Action of Penicillin on Urinary Excretion of Nicotinic Acid. (2) Action of Penicillin on Vitamin B-1.) FISILOGIA E MEDICINA (Roma), 16: 215-217, 219-220, 1948.
- Pedersen-Bjergaard, K., and M. Tonnesen. "Fates of Some Antibiotics in the Rat. 1. Penicillin and Streptomycin." ACTA PHARMACOLOGICA ET TOXICOLOGICA, 6: 250-262, 1950.
- Peterson, C. F., A. C. Wiese, R. V. Dahlstrom, and C. E. Lampman. "Influence of Vitamin B-12 and Antibiotics on Hatchability." POULTRY SCIENCE, 31 (1): 129-132, 1952.
- Piskorz, A., and W. Kuhnberg. "Experimental Investigations on the Action of Penicillin in the Bone." BULLETIN OF THE STATE INSTITUTE OF MARINE AND TROPICAL MEDICINE (Gdansk, Poland), 3 (1/2): 49-55, 1950.
- Powick, W. C., N. R. Ellis, C. N. Dale, and M. R. Zinober. "Effect of Nicotinic Acid, Vitamin B-12, and Aureomycin on Growth of Pigs and on Resistance to Artificial Infection with Salmonella chloraesus." JOURNAL OF ANIMAL SCIENCE, 10 (3): 617-623, 1951.
- Quimby, F. H. STUDIES ON CHRONIC INANITION AND RECOVERY IN YOUNG MALE ALBINO RATS. Thesis, University of Maryland, College Park, Md., 1947.
- Rammelkamp, C. H. "A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 51: 95-97, 1942.
- Rammelkamp, C. H., and J. D. Helm. "Studies on Absorption of Penicillin from the Stomach." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 54: 324, 1943.
- Rammelkamp, C. H., and C. S. Keefer. "Absorption, Excretion, and Distribution of Penicillin." JOURNAL OF CLINICAL INVESTIGATION, 22: 425, 1943.
- Roine, Paavo, and C. A. Elvehjem. "Significance of the Intestinal Flora in Nutrition of the Guinea Pig." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 73 (2): 308-310, 1950.

- Rusoff, L. L., A. V. Davis, and J. A. Alford. "Growth-promoting Effect of Aureomycin on Young Calves Weaned from Milk at an Early Age." JOURNAL OF NUTRITION, 45 (2): 289-300, 1951.
- Sasaki, Shogo, and Jasuo Ichihashi. "Studies on the Action Mechanism of Penicillin, Especially on its Distribution, Decrease, and Increase in Vivo." JOURNAL OF ANTIBIOTICS (Japan), 3 (6): 380-386, 1950.
- Sauberlich, H. E. "Effect of Aureomycin and Penicillin Upon the Vitamin Requirements of the Rat." JOURNAL OF NUTRITION, 46 (1): 99-108, 1952.
- Schwartz, B. S., M. N. Lewis, and N. Ercoli. "Distribution of Penicillin in the Body by Various Treatment Methods." AMERICAN JOURNAL OF THE MEDICAL SCIENCES, 219: 617-626, 1950.
- Scott, H. M., and W. A. Glista. "The Effect of Aureomycin and Arsonic Acid on Chick Growth." POULTRY SCIENCE, 29 (6): 921-923, 1950.
- Seeberg, V. P., P. L. Illg, and D. J. Brown. "The Intestinal Absorption of Penicillin G." SCIENCE, 104: 342-343, 1946.
- Sewell, A. M. P., and R. S. Glasscock. "A Comparison of Aureomycin, Streptomycin, Penicillin, and an Aureomycin-Vitamin B-12 Feed Supplement for the Pig." ARCHIVES OF BIOCHEMISTRY, 30 (2): 269-271, 1951.
- Sewell, R. F., T. J. Cunha, C. B. Shawver, W. A. Ney, and H. D. Wallace. "Effect of Aureomycin on Diarrhea and on the Vitamin B-12 and Methionine Needs of the Pig." AMERICAN JOURNAL OF VETERINARY RESEARCH, 13 (47): 186-187, 1952.
- Shapse, Joseph B., and Louis T. Wright. "Effect of Aureomycin on the Clotting Time of the Blood." ANGIOLOGY, 1 (4): 306-311, 1950.
- Sheffy, B. E., R. H. Grummer, P. H. Phillips, and G. Bohstedt. "Comparison of Growth Responses of Two-day-old Pigs to Streptomycin, Aureomycin, and Crude APF, Alone and in Combination with Vitamin B-12." JOURNAL OF ANIMAL SCIENCE, 11 (1): 97-102, 1952.
- Sieburth, J. McN., Jose Gutierrez, James McGinnis, Joel R. Stern, and B. H. Schneider. "Effect of Antibiotics on Intestinal Microflora and on Growth of Turkeys and Pigs." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 76 (1): 15-18, 1951.

- Slinger, S. J., A. E. Ferguson, and J. D. McConachie. "A Carry-over Effect of Penicillin from Dam to Progeny." *POULTRY SCIENCE*, 31 (1): 172-174, 1952.
- Slinger, S. J., W. F. Pepper, and D. C. Hill. "Interaction Between Penicillin and Grass Juice Concentrate in Turkeys." *POULTRY SCIENCE*, 31 (1): 187-188, 1952.
- Stern, Joel R., and James McGinnis. "Antibiotics and Early Growth of Rats Fed a Soybean Oil Meal Diet." *ARCHIVES OF BIOCHEMISTRY*, 28 (3): 364-370, 1950.
- Stern, Joel R., John McN. Sieburth, and James McGinnis. "Lack of Growth Response of Turkey Poults to Certain Antibiotics and Bacteriostatic Agents." *POULTRY SCIENCE*, 31 (1): 179-180, 1952.
- Stokstad, E. L. R. "Effect of Aureomycin on Animal Nutrition." *FEEDSTUFFS*, 22 (28): 17, 18, 46-48, 1950.
- Stokstad, E. L. R., and T. H. Jukes. "Growth-promoting Effect of Aureomycin on Turkey Poults." *POULTRY SCIENCE*, 29 (4): 611-612, 1950.
-
- . "Effect of Various Levels of Vitamin B-12 upon Growth Response Produced by Aureomycin in Chicks." *PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE*, 76 (1): 73-76, 1951.
- Story, Peter. "Histological Reactions to Injections of Procaine Penicillin in Oil." *BRITISH MEDICAL JOURNAL*, 1: 1467-1468, 1950.
- Stuart, P., and G. Slavin. "Toxicity of Penicillin to Guinea Pigs." *NATURE*, 167: 319-320, 1951.
- Terrill, S. W., D. E. Becker, C. R. Adams, and R. J. Meade. "Response of Growing-fattening Pigs to Bacitracin, Aureomycin, and Other Supplements." *JOURNAL OF ANIMAL SCIENCE*, 11 (1): 84-91, 1952.
- Vijayaraghavan, P. K., Edward A. Murphy, and Max S. Dunn. "The Effect of Aureomycin on the Growth of Mice." *ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS*, 36 (1): 127-131, 1952.
- Virenque, J., R. Olle, and J. Secail. "Drug Abscesses Caused by Antibiotics." *TOULOUSE MEDICAL*, 52 (4): 227-233, 1951.
- Von Dieter, Otto Schmid. "Das Hamatokrit und Seine Diagnostische Bedeutung." (Hematocrit and Its Diagnostic Significance.) *ACTA HAEMATOLOGICA*, 4: 22-32, 1950.

- Welch, Henry, C. W. Price, and V. L. Chandler. "Prolonged Blood Concentrations of Modified Penicillin." AMERICAN MEDICAL ASSOCIATION JOURNAL, 128: 845-847, 1945.
- Werner, Charles A., Vernon Knight, and Walsh McDermott. "Absorption and Excretion of Terramycin in Humans: Comparison with Aureomycin and Chloramphenicol." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 74 (2): 261-267, 1950.
- Whitehill, A. R., J. J. Oleson, and B. L. Hutchings. "Stimulatory Effect of Aureomycin on the Growth of Chicks." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 74 (1): 11-13, 1950.
- Williams, William L., Robert R. Taylor, E. L. R. Stokstad, and Thomas H. Jukes. "Mechanism of the Growth-promoting Effect of Aureomycin in Chicks." FEDERATION PROCEEDINGS, 10 (1): 270, 1951.
- Woznicka, W. "Inactivation of Penicillin by Blood Sera." MEDYCINA DOSWIADCZALNA I MIKROBIOLOGIA (Warsaw), 3 (1): 25-31, 1951.

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