Volume 18 | Issue 2 Article 1

1956

Dangers of Indiscriminate Antibiotic Use

J. G. Graca
Iowa State College

Dangers of—

Indiscriminate Antibiotic Use

J. G. Graca, B.S., Ph.D.

THE INTRODUCTION OF ANTIBIOTICS INTO THERAPY during the past ten years has provided a potent weapon against many diseases. The apparent innocuous nature and low toxicity of these drugs qualified them for the label of "miracle" drugs. The antibiotics have altered therapeutics to an amazing degree, and have done much in overcoming the dangers of some types of diseases. However, like high powered bullets, they can be dangerous if uncontrolled. Unlike most other drugs, antibiotics do not have a self-limiting cure-or-kill basis, but have ramifications of undesirable effects which may persist to provide health hazards to an alarming degree not only to animals but to persons working with them. In recent years an increasing number of articles have appeared in the scientific literature on hazards associated with indiscriminate widespread use of these potent drugs. While recognizing the undisputed role of antibiotics in present day therapy, the subject of this report is concerned with undesirable effects and an evaluation of what present indiscriminate use of antibiotics can lead to.

Von Oettingen (32) of the National Institute of Health summarized these dangers in the 1954-55 Antibiotics Annual with the following: "Antibiotics should not be used indiscriminately; they must be carefully selected for various types of infections and patients treated with antibiotics should be watched carefully for the appearance of side reactions. . . . Furthermore, it appears likely that their use for promoting the growth of young domestic animals may also result in the production of resistant bacterial strains of at least the bacteria harbored by these animals. Thus, it is apparent that antibiotic therapy is a powerful weapon in our fight against infectious diseases; but there is real danger that this weapon be dulled by indiscriminate use and by not restricting its use for curative purposes only and to those cases where it is really indicated."

Unfortunately it is difficult to accumulate information on the extent of damage produced by the widespread use of these drugs in home use of veterinary products. The disease treated is many times guessed at, dosage is uncertain and some of the consequences of irrational therapy, often more serious than the condition treated can be ascertained only by clinical and laboratory tests. The information presented here is drawn from a large number of clinical and laboratory findings in the fields of human and veterinary medicine. There is a serious gap in our knowledge of findings under field conditions. Although statements are made citing lack of evidence of toxic or resistance manifestations under field conditions, these are essentially negative

The Author is a Assistant Professor in the Department of Physiology and Pharmacology, Iowa State College.

arguments which really state that these factors were not tested.

It would be impossible to assay all the factors of residual damage through indiscriminate use of antibiotics in the short space alloted here because of the complex nature of the problem. However, an attempt will be made to elucidate some of the problems in the course of this discussion.

Complications of antibiotic therapy may be divided into two phases. First, the effects of the drug or microorganisms themselves, and secondly, the effects produced on the host, or the patient treated. Ideally, the drug should destroy the organism and not harm the patient. We do not have any ideal drugs.

Problems relating to the effects on the microorganism are primarily those of: 1. developing resistance to the drug; 2. the unbalancing of normal bacterial relationships in the host which can give rise to "superinfections" by organisms not susceptible to the antibiotic used, or; 3. the conversion of normally saprophytic parasites to pathogens. Inadequate dosage or continual exposure to small doses of antibiotics can produce resistance to that antibiotic, so that the progeny of the resistant strain are unaffected by the antibiotic but are as fully capable of producing a disease in another individual as is the sensitive strain.

The most striking increase in bacterial resistance is shown by the micrococcus. In 1945, when penicillin was first introduced, the incidence of resistance to penicillin by these organisms, sampled at random, was 14 percent. At the present time the incidence has increased to 75 percent or higher. Maxwell Finland (1) of Boston City Hospital in 1953 tested 500 strains of *Staphylococcus aureus* for sensitivity to nine antibiotics. He found that about three-fourths of the strains were resistant to penicillin, one-fourth were resistant to chlortetracycline (aureomycin®) and one-third were resistant to oxytetracycline (terramycin®). There was no close correlation between the source of the strains and their antibiotic resistance. The fecal strains, however, included a higher proportion of strains resistant to penicillin, chlortetracycline and oxytetracycline than did those from any other source. His data suggests that while previous antibiotic therapy of any given patient may be an important factor in the occurrence of strains resistant to that antibiotics, the widespread use of antibiotics may be of equal or greater importance in the increase of incidence of staphylococci that are resistant to those antibiotics. Such strains may become or remain pathogenic and retain their resistance when they are disseminated and acquired by patients who have themselves not received such antibiotics.

The increase in resistance of staphylococci to antibiotics with time is presented in Table I. This is based primarily on the work of Kirby and Ahern (2).

EMERGENCE OF ORGANISMS RESISTANT TO ANTIBIOTICS

Drug	Aug. '51-May '52	Jan.-Apr. '53
Penicillin	1946-14.1% 1947-38% 1948-59%	73%	68%
Chlortetracycline (Aureomycin)	42	61
Oxytetracycline (Terramycin)	42	61
Chloramphenicol (Chloromycetin)	20	6
Bacitracin	3	5
Erythromycin (Mayo Clinic)	—	2 Mar. 53—0. Mar. '54—7%

Table I. Note increase in resistant organisms since 1946.

The changes in resistance shown for penicillin from 1946 to 1948 are from other sources. The decrease in resistance of penicillin for 1953 may be attributed to the increased use of other antibiotics. The decrease in resistance to chloramphenicol for the same period may be attributed to the decrease in use of this drug following reports of development of agranulocytosis.

The serious consequences of infections with antibiotic resistant strains may be seen in Figure 1. Gagne (3) in 1955 reported on staphylococcal pneumonia in infancy, with a report of 40 autopsied cases. The interesting thing here is that although these 40 cases were reported between 1951 and 1954 the incidence

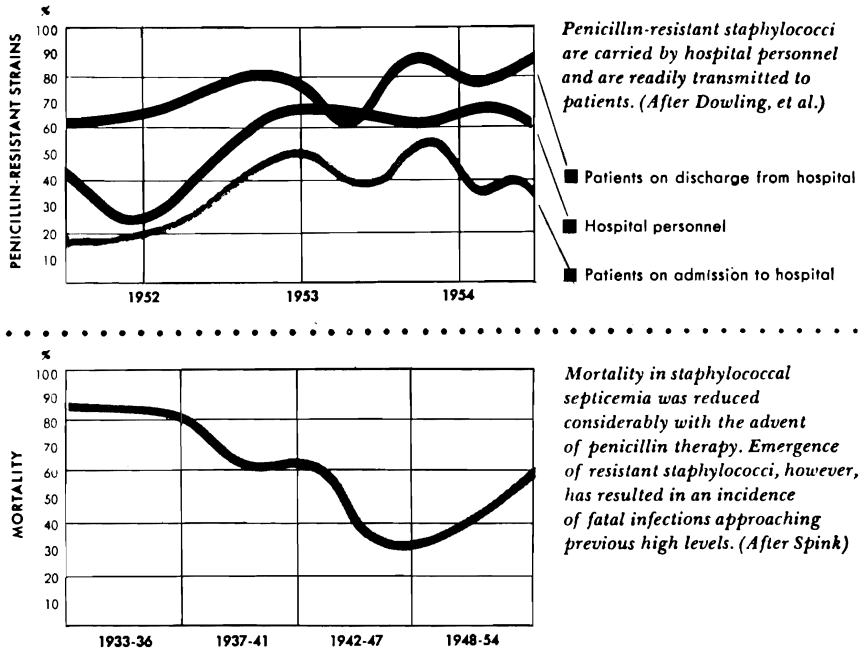


Fig. 1. Reproduced by courtesy of Parke, Davis & Company's Therapeutic Notes

showed a marked yearly increase; 5 cases 1951, 8 in 1952, 11 in 1953 and 16 in 1954. The tragedy in this situation may be seen in that 10 of the 40 children were hospitalized for conditions of a non-infectious nature (malnutrition, dematitis, icterus, harelip, pyloric stenosis and anemia. **Fatal pneumonia resulted from contamination in the hospital wards.** He concluded that this disease is apparently increasing in frequency in infants and that it seems to be due to a wide dissemination of highly virulent and antibiotic resistant strains of staphylococcus.

The effects of resistant staphylococci were summarized in a lead article in Lancet (4) November 1954 with the following: "Penicillin, now a plentiful drug, is no longer the drug of choice for treating staphylococcal infections arising in hospitals. Virtually all such staphylococci are resistant to penicillin and nearly three-fourths of them are also resistant to streptomycin, aureomycin and terramycin. Penicillin's usefulness outside the hospital is also questioned. Of staphylococci isolated from out-patients, 24 to 37 percent have proved to be penicillin resistant."

The carrier rate for penicillin-resistant staphylococci appears to be higher among hospital workers than control groups. Wilson (5) reported in 1952 that where 11 to 25 percent of a control group of dormitory residence girls were resistant carriers, that 74 percent were carried by the medical staff. This was an increase from 46 percent in 1947. Frequent exposure to resistant sources of infection, such as animal handlers using antibiotics or veterinarians must be kept in mind as possible sources of antibiotic resistant sources of infection not only for themselves but their families as well. The promiscuous use of these drugs is not without risk. Studies of changes in sensitivity to erythromycin at the Mayo Clinic (6) over a two-year period (1952-53) showed that 37 of one-thousand patients had infections with resistant strains. Admittedly this is not a high ratio, but is significant since there were two the first year and 35 the second. In 25 patients the resistant strains presumably originated in carriers.

Other types of organisms have also shown development of resistant strains. Wright (7) described in 1954 the sus-

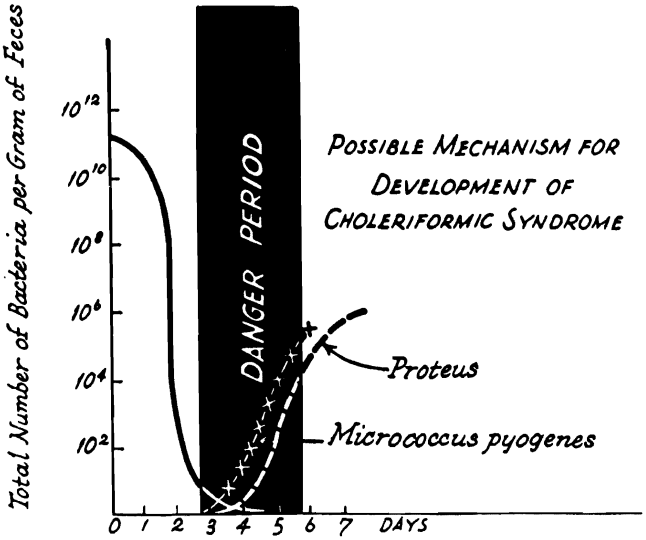
ceptibility of pseudomonas to 10 antibiotics and found, "A comparision of recently isolated strains with those isolated in 1949 showed a significant increase in the incidence of resistance to chlortetracycline, streptomycin, tetracycline and neomycin." The increase of resistance to tetracycline and neomycin is believed to be the result of cross-resistance with chlortetracycline and streptomycin, respectively. "The resistance of the strains to any of the antibiotics tested could not be correlated with a history of previous treatment of the patient with homologous or other antimicrobial agents."

In a report in 1953, Schalm and Woods (8) pointed out in a review of their work and of others that in the mastitis complex there has been a shift in dominance from *Streptococcus agalactiae* to *Micrococcus pyogenes* and an increasing number of other organisms incriminated as agents involved in the mastitis complex. This has been attributed to extensive use and the improper administration of intramammary therapy. In a study of over 15,000 milk samples submitted by practicing veterinarians over a 6 year period, Packer (33) found mastitis organisms in 36.6 percent of the samples. It is interesting to note that *Staphylococcus aureus* was present in 72.6 percent of samples yielding mastitis organisms, *Streptococcus agalactiae* in 7.78 percent, *Streptococcus pyogenes* in one sample, and *Pasteurella multocida* in 0.71 percent.

In addition to the selective elimination of antibiotic sensitive forms of many common pathogens and the emergence of resistant variants as the cause of disease, Rantz (9) has pointed out the increasingly frequent occurrence of infection by organisms which were virtually unknown a few years ago as causes of disease. This is the second type of effect, or what is called "superinfection." Speare (10) and others (11) have pointed out the increasing occurrence of pseudomembranous enterocolitis as a fatal postoperative complication. This complication appears to be related to the emergence of antibiotic-resistant strains of *Micrococcus pyogenes*. In almost all recent reports, pure cultures of this organism resistant to penicillin, streptomycin, chlortetracycline and oxytetracycline have been found in the stools and intestinal lesions of these patients. This problem has been related to the upset in balance of the normal flora of the intestinal tract. Tyson (12) reported that daily oral doses of 7.5 to 3 Gm. of terramycin® administered for one to two weeks in patients without gastrointestinal disease showed that the essential bacteriologic change was a replacement of *Escherichia coli* by entercococci, proteus and yeast. Terramycin given alone resulted in increased resistance of certain bacteria to auromycin® and chloramphenicol as well as to terramycin. Sieburth (13) reported that no members of the genus Proteus were detected in the intestinal contents of turkey poults not receiving antibiotics; after terramycin was added to the basal diet the number of coliforms were greatly reduced while strains of proteus became established. It was suggested that terramycin resistant proteus may become established in the intestinal tract of turkey poults receiving terramycin supplements as a result of elimination or reduction in numbers of the terramycin susceptible proteus antagonists. In experimental studies of terramycin in rats Scaletti (14) found that the effect of terramycin was independent of the ration and markedly increased the numbers of proteus species with all rations.

Poth (15) has described a possible mechanism by which proteus and staphylococcal organisms might emerge to produce the coliformic syndrome through suppression of the normal intestinal saprophytes by antibiotics. This is described in Figure 2. Possible sites of secondary infections arising from coliform organisms are shown in Figure 3.

In a summary of side effects of terramycin therapy, Hay (16) reported that side-effects other than mild gastrointestinal upsets were observed in 8 percent of 603 patients treated with terramycin in children the dose was 20 mg./kg./day x 5, in those 12 years of age or over the dose was 2 Gm. per day). Copious fluids



Representation of what may be the sequence of events when the so-called choleriformic syndrome develops following oral administration of chlortetracycline or oxytetracycline. When the bacterial flora is markedly suppressed on the third to fourth day, Proteus organisms grow out quite regularly and may cause diarrhea. Should a resistant Micrococcus pyogenes develop that produces a potent enterotoxin, then nausea, vomiting, bloody diarrhea, hyperpyrexia, collapse, and death may result. This simplified diagram cannot present all the possibilities.

Fig. 2. From the Journal of the American Medical Association.

and supplements of vitamin B were given. The following syndromes associated with staphylococcal infections were found:

2 cases of fulminating gastroenterocolitis
7 cases of sore throat with rash (staphylococcal scarlet fever syndrome)
8 cases of sore throats without rash
1 case af balanitis with scarletina
3 cases of urinary infection

Other syndromes:

24 cases of fever
3 urticarial lesions
4 cases of transient erythema

The report on superinfections might properly be included also as an effect on the host since the consequences of bacterial resistance are found there.

The problems relating to the host are many: effects on metabolism, interference with antibody formation, drug sensitivity which is of great importance and very serious, blood dyscrasias and masking of signs and symptoms in disease.

Calesnick (17) found in studies done with radioactive iodine that antibiotics produce an anti-thyroid effect in experimental rats. Stevens (18) demonstrated that penicillin, dihydrostreptomycin, aureomycin and terramycin are all capable of severely depressing the primary immune response to a soluble protein antigen in the rabbit. In laboratory studies in rats and mice Slanetz (19) found that feeding aureomycin, terramycin, chloramphenicol, antibiotic residues and other substances had a significant influence on antibody production. Feeding antibiotics for relatively short periods resulted in increased antibody production, but prolonged feeding of antibiotics and antibiotic residues appeared to interfere with the production of antibodies. The adverse effect of prolonged feeding of antibiotics could be counteracted in part by supplementing the stock diet with yeast, certain B factors, or lecithin.

Manheim (20) presented data on 300 patients who developed anorectal complications as a direct result of oral treatment with aureomycin, terramycin or chloramphenicol for a variety of conditions. The complications were far more annoying and in some instances were

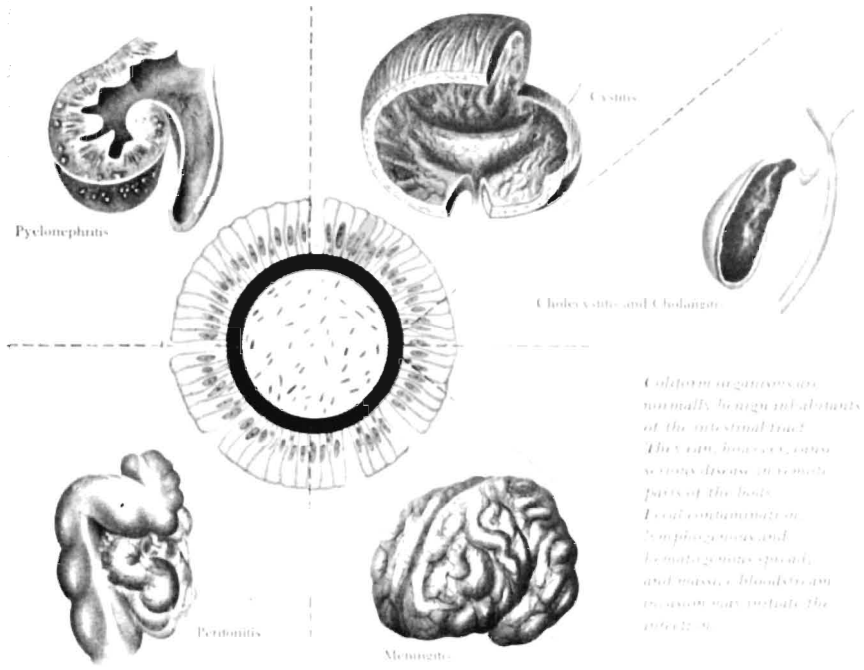


Fig. 3. Reproduced by courtesy of Parke, Davis & Company's Therapeutic Notes.

more serious than the original conditions for which the drugs were given. Fifteen patients required surgery because of the complications that had developed (crypt abscesses, fistulas and anal ulcers). Treatment had been difficult and more than two-thirds of the patients developed recurrences of the anorectal complications after apparent cure, although the drugs were not again administered. Some had recurrences for over 2 years. There seems to be no correlation between the total dose of the antibiotic and either the onset or severity of the complications. One patient took aureomycin lozenges for 1 day for a mild sore throat and had recurrent anorectal symptoms for over 2 years. Two-thirds of the patients never had previous anorectal disease.

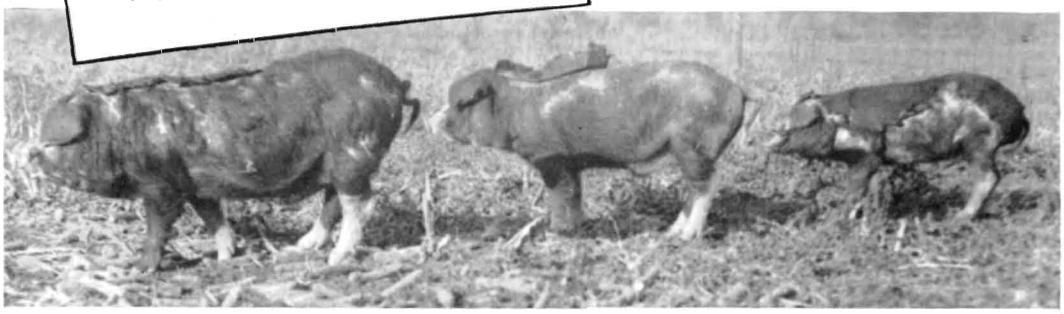
In a broad sense the acquisition of sensitivity to antibotics probaby presents the most serious problem as a health hazard. As more and more exposure to antibiotics is made, deliberately or inadvertently, the more we can expect the problem to recur. Rostenberg (21) stated the problem thus in regard to sensitization, "It is well to realize the ubiquity of use and the casualness of attitude toward the prescribing of the antibiotics, especially the newer, broad spectrum ones. Parenthetically, it appears that the medical profession is now beginning to reap its harvest from a population allergically sensitized to penicillin. It may, therefore, not be amiss to consider in some detail the various types of cutaneous reactions that have so far been reported developing after antibiotic therapy. We should also like to predict that as yet undescribed ones and increasingly severe ones will make their appearance as more and more of the population become exposed." In a report on penicillin sensitivity reactions Strauch (22) described 33 cases of penicillin reactions severe enough to warrant hospitalization. In many instances the reaction was more troublesome than the primary disease. Included was a fatal anaphylactoid reaction in a 6-week-old infant that had never received penicillin before, the mother had penicillin without reaction and there was no family history of allergy.

a Lysate

Therefore BETTER for ACTIVE Immunity Against Erysipelas

*rhusigen

Lysed—therefore releases its antigens speedily and readily, instead of locking them up in the unruptured cells, as do most erysipelas bacterins.



Avoids the need to use live culture, hence can not infect premises.

Uses a 2 cc. dose instead of the 5 cc's required by other bacterins.

Produces full immunity within two weeks.

This full immunity persists for at least eight months, possibly longer.

Immunizing capacity not affected by simultaneous use of anti-swine-erysipelas serum, if indicated for immediate *protection.*

20 cc. vial (10 doses) code: Baryp
100 cc. vial (50 doses) code: Balum

Pitman-Moore Co.
division
ALLIED LABORATORIES, INC.
Indianapolis

*Trade Mark name for Erysipelas Bacterin (Lysate) P.-M. Co. Bio. 914:
Produced under license from the Institut Merieux, Lyon, France. (Patent Pending)

Since an anaphylactic reaction requires previous sensitization, one might speculate on the insidious nature by which a reaction might arise in an individual not knowingly exposed to the sensitizing drug. It should lead to a consideration of whether free access to the antibiotics should be allowed to continue. In 1955 the Food and Drug Administration (23) tested 474 samples of fresh fluid milk (both raw and pasteurized) from 16 areas in the United States, for their antibiotic content. Concentrations of from 0.003 to 0.08 units per milliliter were found in 55 (11.6 percent) samples. The reckless use of the antibiotics can produce effects far removed from the animal treated. Barr (24) has shown that the uncontrolled use of broad spectrum antibiotics has produced an increase in antibiotic resistant calf scour producing organisms. As more and more organisms become resistant, the less valuable become the antibiotics.

Once sensitivity is acquired, severe reactions may follow with even relatively minute quantities of antibiotics. A severe anaphylactic reaction occurred following the ingestion of one tablet of penicillin for a sore throat (25).

That hypersensitivity to a drug can be serious may be seen in two other unusual cases reported: Coleman (26) reported production of severe reactions in hypersensitive individuals through unintentional administration of penicillin with contaminated syringes used for other drugs, or from boiling syringes in penicillin contaminated sterilizers. Another (27) was of an individual so sensitive that he experienced tightness of the chest in a drug store when the pharmacist was changing penicillin tablets from one bottle to another.

Weinstein (28) reported on the problem of superinfection of 3,095 hospitalized patients who received one or more antibiotics as treatment for an infectious disease. The over-all incidence of superinfection was 2.19 percent. The secondary infection often affected the same organs as those affected by the primary disease. A benign, self-limiting disease may be converted by the appearance of superinfection into a serious, prolonged, and even fatal one. The presently available antibacterial drugs are often ineffective against the organisms responsible for the superinfection. These occurred after treatment of the primary infection with penicillin, aureomycin, streptomycin and p e n i c i l l i n-streptomycin combination. Weinstein also found that where antibiotics were administered prophylactically, (a practice to be deplored) that the frequency of superinfection after prophylaxis of respiratory poliomyelitis was more than seven times the average for the whole group and after prophylaxis of measles it was over 16 times higher than the average.

One additional factor in the complications of the use of antibiotic drugs is that reported by Tompsett (29). The masking of signs and symptoms as a result of antimicrobial therapy is well known in that suppression of clinical manifestations of infection and negative blood cultures can be obtained without actually producing a cure. Also antimicrobial therapy can obscure signs of localized infection which require further management, usually surgery.

A few years ago chloramphenicol was incriminated in a number of cases as producing fatal aplastic anemia. This disease has fortunately been rare, but has also been attributed to other antibiotics and other drugs.

Research in the development of drugs effective against molds and yeasts has been stimulated by the appearance of moniliasis or thrush (*Candida albicans*) as a sometimes fatal, but more frequently annoying, side effect in antibiotic therapy. Drug therapy of these diseases has been ineffectual until recently and still leaves much to be desired.

A distressing report was recently issued in Lancet by Thomas (30) against an old enemy of man — tuberculosis. Nine patients who had received no previous chemotherapy for tuberculosis were found to be infected with drug-resistant tuberculosis bacilli: 4 to streptomycin, 4 to Para-Aminosalicylic acid, and one to both. At least three were

* **Antibiotic** (*continued on page 82*)

cells which results in erosions and ulcers. Blindness results in the following manner: The virus is carried to the mucous membrane of the eye where it causes severe reddening. This is followed by a sero-mucous discharge from the eyes. This mucous may cause the eyelids to stick together and thus the animal can't see.

ARSENICAL & LEAD POISONING

This can occur in any species of animal if they ingest the chemical. These chemicals are absorbed into the blood stream and they are carried to the nervous system. They affect the eye by causing the pupils to dilate, if these animals so affected get into bright light the retinal cells will become paralyzed and blindness will result.

The use of these chemicals in weed sprays, rodent poisons, insecticides and paints has increased the incidence of this condition in animals.

MISCELLANEOUS CAUSES

There are a number of things that may affect the eye directly and cause blind ness. These are foreign bodies such as pieces of weeds, thorns, seeds and sticks; chemical irritants such as acids; scrathces such as those from a barbed wire fence or from bites as occurs in dogs. These conditions may also allow secondary infections to enter the eye and produce blindness.

Blindness may also result from congenital defects such as absence of one or both eyes, failure of development of optic foramina as a result of vitamin A deficiency and improper development of any part of the eye of the fetus.

BIBLIOGRAPHY

1. Australian Vet. J.: Bovine infectious ophthalmia. AVMA Journal, 125, (1954): 313.
2. Bloom, Frank: Diabetes mellitus. Canine Medicine, (1953): 288–292.
3. Cunningham, Chas. H.: Fowl pox. Disease of Poultry, (1952): 635–644.
4. Eddy & Dalldorf: Vitamin A deficiency. The Avitaminoses, (1944): 137–172.
5. Hambridge, Gove: Avian leukosis complex. Keeping Livestock Healthy, (1942): 81–82.
6. Hutyra, Marek, & Manninger: Special Pathology and Therapeutics of the Diseases of Domestic Animals, 1, (1938).
   Canine Distemper ..... pp. 224–238.
   Sheep Pox ..... pp. 353–368.
   Rinderpest ..... pp. 256–284.
   Fowl Pox ..... pp. 380–389.
7. Hutyra, Marek, & Manninger: Special Pathology and Therapeutics of the Disease of Domestic Animals, 3, (1938).
   Diabetes Mellitus ..... pp. 244–250.
   Leukosis ..... pp. 118–126.
8. Innes, J. R. M.: Distemper. Canine Medicine, (1953): 480–487.
9. Innes, J. R. M.: Infectious canine hepatitis. Canine Medicine, (1953): 491–497.
10. Jungherr, Erwin: Avian leukosis complex. Disease of Poultry, (1953): 467–470.
11. KKelser & Schoening: *Hemophilus bovis*. Manual of Veterinary Bacteriology, (1948): 246–248.
12. Maynard, Leonard A.: Vitamin A. Animal Nutrition, (1951): 170–173.
13. Merchant, Ival A.: Avian-leukosis virus. Veterinary Bacteriology and Virology, (1950): 850–852.
14. Mott & Seibold: Periodic ophthalmia of horses. Keeping Livestock Healthy, (1942): 402–408.
15. Price & Harwood: Eye worms, Keeping Livestock Healthy, (1942): 1165.
16. Ramsey & Chivers: Mucosal disease of cattle. North American Veterinarian, 34, (1953): 629–633.
17. Roberts, Seymour R.: The nature of corneal pigmentation in the dog. AVMA Journal, 124, (1954): 208–211.
18. Runnells, Russell A.: Animal Pathology, (1954):
   Pregnancy Disease ..... pp. 664–665.
   Listeriosis ..... pp. 571–572.
   Rinderpest ..... pp. 637–638.
   Fowl Pox ..... pp. 610–613.
   Leukosis ..... pp. 648–656.
19. Udall, B. H.: The Practice of Veterinary Medicine, (1947).
   Pregnancy Disease ..... pp. 379–382.
   Listerosis ..... pp. 298–302.
   Rinderpest ..... pp. 553–556.
   Bovine Infectious Keratitis pp. 736–738.
20. Vigue, R. F.: Use of Radon Implants in the Treatment of Bovine Ocular Neoplasms. AVMA Journal, 126, (1955): 23–25.

---

* **Antibiotic**

(*continued from page 76*)

known to have tuberculosis before the revalent drug was in general use, and it is presumed that their original bacilli were drug-sensitive and they were superinfected with resistant bacilli. To them the future is drugless.

Finally, an important economic problem is presented in the dairy industry. It is known (31) that there may be serious interference with lactic acid fermentations if minute amounts of antibiotics are present in the milk. Since

pasteurization does not destroy the antibiotics (or are not proven to be destroyed) we can only surmise at the amount of antibiotics disseminated unknowingly (or willfully) to the general population.

There is a definite need in the field of veterinary medicine for more information on the changing picture in antibiotic therapy. This is particularly true for studies under field conditions, where the information is most needed and least available. Factual information, sufficient in quantity to be statistically significant and carefully balanced with control studies, would assist immeasurably in providing more rational therapeutic regimes than are now used. It would also reduce the deplorable practice of empirical therapy which was reintroduced with the advent of sulfonamides and antibiotics. Since the practitioner is faced more and more with resistant strain diseases, diagnosis before treatment is more imperative than ever.

1. Finland, M. and Haight, T. Antibiotic resistance of pathogenic staphylococci: Study of 500 strains isolated at boston city hospital from October, 1951, to February, 1952. Arch. Internal Medicine 91:143, 1953.
2. Kirby, W. M. and Ahern, J. Changing pattern of resistance of staphylococci to antibiotics. Antibiotics and Chemotherapy 3:831, 1953.
3. Gagne, F. Staphylococcal pneumonia in infancy: A review of 40 autopsied cases. Can. Medical Assn. Jour. 73:551, 1955.
4. --- Antibiotic resistant staphylococci. Lancet II:1003, 1954.
5. Wilson, R. and Cockcroft, W. The problem of penicillin resistant staphylococcal infection. Can. Medical Assn. Jour. 66:548, 1952.
6. Martin, W. et al. Changes in sensitivity of **micrococcus pyogenes** to erythromycin over a period of 2 years. Proc. Staff Meetings, Mayo Clinic 29:379, 1954.
7. Wright, S. et al. Susceptibility of pseudomonas to ten antibiotics *in vitro*. Am. Jour. Clin. Path. 24:1121, 1954.
8. Schalm, O. and Woods, G. The mastitis complex. Jour. Am. Vet. Medical Assn. 122:462, 1953.
9. Rantz, L. Consequences of the widespread use of antibiotics. California Med. 81:1, 1954.
10. Speare, G. Staphylococcus pseudomembranous enterocolitis, a complication of antibiotic therapy. Am. Jour. Surg. 88:523, 1954.
11. -- Micrococcus pseudomembranous enterocolitis. J.A.M.A. 157:346, 1955.
12. Tyson, R. et al. Antibiotics and intestinal flora with a study of terramycin effect on intestinal flora. Penn. Med. Jour. 56:627. 1953.
13. Sieburgh, J. and Skinner, C. The effect of terramycin on the antagonism of certain bacteria against species of proteus. Jour. Bact. 64:163, 1952.
14. Scaletti, J. et al. Effect of terramycin on fecal microflora of rats. I. Interrelationship of diet and terramycin. Proc. Soc. Exper. Biol. & Med. 81:552, 1952.
15. Poth, E. Intestinal antisepsis in surgery. J.A.M.A. 153:1516, 1953.
16. Hay, P. and McKenzie, P. Side effects of oxytetracycline. Lancet I:945, 1954.
17. Calesnick, B. et al. Antithyroid action of antibiotics. Science 119:128, 1954.
18. Stevens, K. The effect of antibiotics upon the immune response. J. Immunol. 71:119, 1953.
19. Slanetz, C. The influence of antibiotics on antibody production. Antibiotics & Chem. 3:629, 1953.
20. Manheim, S. and Alexander, R. Further observations on anorectal complications following aureomycin, terramycin and chloramphenicol therapy. N. Y. State J. Med. 54:231, 1954.
21. Rostenberg, A. and Webster, J. Mechanisms of cutaneous drug reactions, especially to antibiotics. J.A.M.A. 154:221, 1955.
22. Strauch, J. et al. Penicillin reactions. Texas State J. Med. 50:699, 1954.
23. Welch, H. et al. Antibiotics in fluid milk. Antibiotics & Chemo. 5:571, 1955.
24. Barr, et al. Resistance of calf scour-producing organisms to broad spectrum antibiotics. Am. J. Vet. Res. 16:515, 1955.
25. Lang, L. and Clagett, H. Anaphylactic reaction following oral administration of penicillin. New Engl. J. Med. 253:652, 1955.
26. Coleman, M. and Siegel, B. Studies in penicillin hypersensitivity. J. Allergy 26:253, 1955.
27. Blanton, W. and Blanton, F. Unusual penicillin hypersensitiveness. J. Allergy 24:405, 1953.
28. Weinstein, L. et al. Infections occuring during chemotherapy. New Engl. Jour. Med. 251:247, 1954.
29. Tompsett, R. Complications of the use of antimicrobial drugs. N. Y. State J. Med. 55:49, 1955.
30. Thomas, O. et al. Infection with drug-resistant tubercle bacilli. Lancet I:1308, 1954.
31. Johns, C. Differences in sensitivity of lactic starters to antibiotics. J. Dairy Science 36:1241, 1953.
32. Von Oettingen, R. Antibiotics Annual, 1954–55. Medical Encyclopedia, Inc., New York, p. 374.
33. Packer, R. Six year summary of laboratory diagnosis of mastitis in Iowa. North Am. Vet. 33:777, 1952.

A good anesthetic for birds of the parakeet variety is ether. However it must be given by the intermittent method. General anesthetics are much better than is the use of local anesthetic such as procaine.