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Effectiveness of Penicillin in Eliminating Mastitis Infections in the Bureau of Dairy Industry Herd [1]

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INTRODUCTION

In October 1942, the Bureau of Dairy Industry began a survey of the extent of mastitis infection in its herd at the Agricultural Research Center, Beltsville, Md. At the same time it began a study of the effectiveness of sulfonamide preparations in the eradication and control of the disease. During the first 10 months' work, two sulfonamide preparations were used. One preparation was sulfanilamide in oil, and the other was a combination of sulfanilamide and sulfadiazine in oil.

Treatments with sulfonamides containing urea were begun in August 1943 and continued until October 1944. Two reports describing the results obtained with the sulfonamides during this 2-year period (October 1942 to October 1944) have been published (*12*, *13*).[3]

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[3] Italic numbers in parentheses refer to Literature Cited, p. 22.

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Treatments with penicillin were begun in December 1944. This bulletin gives the results of treating udder infections with infusions of penicillin (injections into the teat canal) from the time the new drug was first used on December 11, 1944, until December 31, 1947. The results obtained with penicillin are also compared with the results obtained previously with infusions of various sulfonamides.

REVIEW OF LITERATURE

A comprehensive review of reports on the treatment of mastitis with various therapeutic agents previous to 1946 is given by Little and Plastridge (*3*). In that review Kakavas (*1*) was credited with being the first to report on the use of crude penicillin and purified sodium salt of penicillin in the treatment of mastitis. His results were most encouraging. Penicillin since has been used extensively in the treatment of mastitis in this country both in experimental studies and as a practical means of controlling the disease.

Reports of experimental studies have been numerous. They have dealt with the use of penicillin in various forms, dosages, and methods of administration in treating mastitis resulting from many different infecting organisms. One of the first authoritative reports on the use of penicillin, which was prepared by a subcommittee and published with the approval of the Committee on Animal Health, National Research Council (*2*), indicated that 25,000 to 50,000 units of penicillin per infected quarter infused once a day for four consecutive days is adequate to effect a cure in the majority of *Streptococcus agalactiae* infections. The report also implied that, even though penicillin was less effective against infections of *Staphylococcus aureus*, it was the best method then in use for the treatment of this kind of infection.

Other investigators (*4*, *5*, *6*, *10*, *11*) have reported results indicating that the efficiency of penicillin infusions may vary from 33 to as high as 100 percent in eliminating streptococcal infections. The various reports are nearly unanimous in showing that, in general, penicillin is less effective in eliminating staphylococcal than in eliminating streptococcal infections. Effectiveness of penicillin therapy appears to depend to some extent on the total amount of penicillin administered, the number and frequency of the infusions, the duration and severity of the infections involved, and the relative activity of the gland at the time of treatment.

It has been shown by a number of investigators (*4*, *6*, *7*) that good results can be obtained with a total of 100,000 units or less of penicillin. Schalm and Ormsbee (*9*) found that in treating infections of *Staphylococcus pyogenes* 100,000 units was as effective as 400,000 units for lactating quarters, that optimum results were obtained with 200,000 units in dry quarters, and that little was gained by continuing penicillin therapy beyond the third treatment.

Strong evidence has been presented (*6*, *8*) to show that a given dosage of penicillin administered in three or more infusions is much more effective than when it is given in a single infusion. Packer (*5*), however, found that multiple infusions were of little if any advantage in treating streptococcal infections but were advantageous in treating staphylococcal infections.

Spencer and Kraft (*11*) obtained good results by using 25,000 units per infusion in only 10 milliliters of vehicle containing 1 part of distilled water and 9 parts of mineral oil. On the contrary, Plastridge and Hale (*6*) found that the efficiency of penicillin tends to increase with the volume of vehicle used. Others have recommended the use of at least 50 milliliters of vehicle per infused quarter.

Penicillin was found by Plastridge and Hale (*6*) to be more highly effective in treating infections in dry than in lactating quarters. Schalm and Ormsbee (*9*) found the difference in effectiveness of penicillin in treating staphylococcal infections in lactating and in dry quarters to be very marked (27.6 percent in lactating and 66.8 percent in dry quarters). They stress the importance of the volume of milk secreted in determining the effectiveness of treatment.

METHODS AND MATERIALS

Taking Milk Samples

In the studies with penicillin, as in the studies with sulfonamides, milk samples for laboratory analysis were obtained from all cows in the herd as soon as practicable after the beginning of each lactation period. Samples were taken thereafter, at any time during the lactation, when cows showed swollen quarters, flakes in their milk, or any other mastitic condition. Ordinarily the samples were taken prior to the regular afternoon milking. The end of each teat was wiped with a pledget of cotton wet with alcohol, particular attention being given to cleaning the teat orifice. A sample from each quarter of the udder was drawn into a separate sterile container, and each container was marked with the number of the cow and the quarter from which the sample was taken. The samples were refrigerated overnight and sent to the laboratory the following morning for examination.

Diagnosis of Mastitis

The detection of symptoms of mastitis and the determination of the presence and identity of infecting organisms by examining the foremilk from the separate quarters of the udder have been accepted, generally, as reliable procedures in the diagnosis of mastitis. These procedures formed the basis of diagnosis in this study and included the microscopic examination of the milk for number of leucocytes, the determination of the percentage of chlorides of the milk, the use of the Hotis test for presence of infection, the plating of the milk on aesculin-blood agar for the isolation of infecting organisms, and the testing of purified isolates on a series of differential media for the identification of the infecting organisms.

The presence of large numbers of leucocytes and abnormally large concentrations of chlorides in the milk, and alkalinity of the milk to brom-cresol-purple as indicated by the Hotis test, are indicative of mastitis. The correlation of one or more of these symptoms with a positive growth in the incubated sample of milk in the Hotis test provides a presumptive diagnosis. Finally, isolation and identification of the infecting organisms completes the diagnosis. A schematic outline of the diagnosis procedure is shown in figure 1.

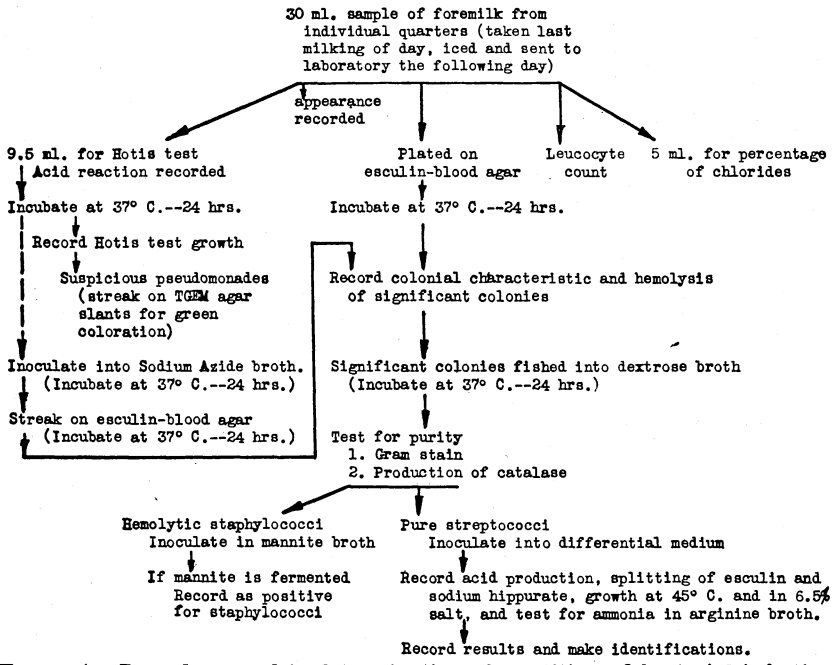

FIGURE 1.—Procedure used in determination of mastitis and bacterial infection.

ADMINISTERING TREATMENT

Solutions or suspensions of penicillin were administered, by infusion, to infected udder quarters that had not been treated previously and also to infected quarters that had failed to respond to single or repeated treatments with sulfonamide preparations. Except in unusual cases only the quarters known to be infected were treated. In a few cases treatment consisted of a single infusion, and in some cases it consisted of one infusion daily on two successive days. But in most cases treatment consisted of two infusions daily on two successive days—a total of four infusions. In lactating cows infusions were made as soon as possible after milking, and the material was left in the udder until the next regular milking. In some cases treatment was administered to dry cows, and all of the material was left in the udder.

A 50-cc. glass and metal serum syringe with Luer type nozzle fitting was used. Injection cannulas having as large a bore as possible and still being small enough to allow easy access into the teat canal were used. A sterilized cannula was used for each quarter treated. Following the infusion the quarter was massaged upward for the purpose of distributing the injected material through the cistern and into the larger milk ducts.

Milk samples were taken from all treated udders, approximately 10 days after treatment, to determine the effectiveness of the treatment. If the infecting organisms were not found in the first sample, a second sample was taken about 2 weeks later for confirmation. If the organisms were present in either posttreatment sample, treatment was repeated; if absent, they were considered as eliminated.

Vehicle, Dosage, and Number of Infusions Per Treatment

As previously stated, insufficient knowledge about the proper dosages for infusing cow udders made it necessary to determine arbitrarily the number of units of penicillin to be used in the initial treatments. A dosage of 50,000 units per infected quarter was agreed on for use at the start. Sodium penicillin was available at the time, and it was administered in either an aqueous or a physiological salt solution. Later, in a few cases, glycerin was used as a carrying vehicle. Still later, when calcium penicillin became available, mineral oil was used in some cases as an agent for suspending the penicillin.

At the start, a treatment consisted of 50,000 units of penicillin administered as a single infusion. In some later cases the 50,000-unit dosage was divided into two equal parts. A treatment then consisted of 25,000 units, infused once daily on two successive days. Still later a change was made so that each treatment consisted of two infusions, each containing 25,000 units, on each of two successive days—the four infusions making a total of 100,000 units. When penicillin became available in larger quantities and at lower cost, the dosage was increased through various levels to a high point of 92,800 units in each of the four infusions—making a total of 371,200 units for the treatment of an infected quarter.

Four cows with seven infected quarters were treated with penicillin incorporated in peanut oil and beeswax. (See Romansky and Rittman (7).) The material was injected intramuscularly in the region of the neck. Each treatment consisted of three injections administered at intervals of approximately 12 hours. One cow received three injections of 900,000 units each, followed by three injections of 1,500,000 units each. The other three cows each received three injections of 1,500,000 units each, making a total of 4,500,000 units per treatment.

Except for three or four quarters treated by infusion at the very beginning, and the four cows treated intramuscularly with penicillin in peanut oil and beeswax, the volume of the material used for each infusion was 50 cubic centimeters. This has been the volume of the infusion regardless of the nature of the vehicle in which the penicillin was incorporated, and regardless of the number of units of penicillin administered.

DISCUSSION OF RESULTS

Procedures Followed in Analyzing Results

The penicillin studies may be divided into two fairly distinct phases. The first (preliminary) phase includes treatments at the beginning in which the dosage was 50,000 units, in vehicles of water, physiological salt solution, glycerin, or mineral oil, and administered either as one infusion of the full amount or as two infusions of 25,000 units each on consecutive days.

The second phase includes all treatments that consisted of two infusions daily on two consecutive days, the number of units in each infusion varying from 25,000 to 92,800—a total of 100,000 to 371,200 units for each infected quarter.

This analysis includes only the cases in which the nature of the infection and the results of treatment are known. The following are excluded from all tabulations: (1) Treatments mistakenly or otherwise administered to uninfected quarters; (2) treatments for infections or abnormal conditions of the udder or the milk in which an offending organism could not be found or identified; and (3) treatments for infections and conditions in which the causative organisms may have been identified, but for which adequate posttreatment samples were not available for bacteriological analysis.

No attempt was made in this study to show the effectiveness of penicillin in treating infections that had failed to respond to sulfonamide preparations, as compared with the effectiveness of penicillin in cases not previously treated. This comparison was omitted in order to avoid making the analysis too complicated. All cases were included even though inclusion of the more persistent cases that had failed to respond to sulfonamides previously tends to make the results with penicillin appear in a less favorable light.

In this analysis, each organism is considered separately in determining the effectiveness of treatment. That is, if a quarter was infected with both streptococci and staphylococci and both were eliminated by treatment, credit was given for two "cures." If only one of the two was eliminated, the treatment was credited with one "cure" and one "failure." If neither was eliminated, the treatment was charged with two failures. In cases where one organism was present before treatment and an entirely different organism was found in posttreatment milk samples, credit was given for eliminating the organism for which treatment was given even though the quarter was infected with another organism after treatment. Thus the results are calculated according to the organisms eliminated rather than the number of quarters cleared of infecting organisms. This appears to be the most equitable way of evaluating the response of various infecting organisms to penicillin infusions.

Throughout the text and tables of this bulletin, references to "infections eliminated" or "specific organisms eliminated" are used to show that the specific causative organisms present before treatment were absent from samples of milk obtained subsequent to treatment. In the treatment of dry cows, the posttreatment samples were obtained at the beginning of the next lactation. The absence of causative organisms from the posttreatment samples of milk usually was accompanied by a definite recession of symptoms of mastitis and a marked reduction in the numbers of leucocytes and percentage of chlorides.

Effectiveness of Penicillin Treatments

Preliminary Phase (Total of 50,000 Units in 1 or 2 Infusions)

During the 11-month period from December 1944 to October 1945, inclusive, infusions of penicillin were administered to 47 infections in which the nature of the infection was known, and the effects of treatment were determined by analysis of posttreatment milk samples. In all of these cases the total dosage per treatment was 50,000 units of penicillin. Not more than two treatments were given in any of these cases. The results obtained with the 47 cases are given in table 1.

TABLE 1.—*Effectiveness of penicillin in single infusions of 50,000 units or in two infusions of 25,000 units each on consecutive days*

Infecting organism	Infections eliminated	Infections not eliminated	Percentage eliminated
	Number	*Number*	*Percent*
S. agalactiae	8	5	61. 54
S. uberis	9	3	75. 00
S. dysgalactiae	2	1	66. 67
S. (viridans group)	3	1	75. 00
S. (enterococcus group)	2	3	40. 00
All streptococci	24	13	64. 86
Staphylococci (hemolytic)	3	6	33. 33
Pseudomonades		1	0
All infections	27	20	57. 45

The data show that treatment eliminated 24 of the 37 streptococcal infections (64.86 percent) and 3 of the 9 staphylococcal infections (33.33 percent), but that it failed to eliminate the 1 pseudomonadal infection. For all types of infection combined, the treatment was effective in 27 of the 47 cases (57.45 percent).

A break-down of the data on these 47 cases leaves numbers too small in the various groups to justify definite conclusions with regard to (1) the merits of various vehicles in which penicillin was incorporated, (2) the relative value of dividing the total dosage into two parts, or (3) the desirability of treating cows when dry instead of during lactation. However, the results are given as a matter of interest.

In eight cases the infused penicillin was suspended in mineral oil. Three of the eight infections were eliminated; five were not. The infections that were eliminated were all streptococcal. Of those that were not eliminated, one was pseudomonadal, three were staphylococcal, and one was a streptococcal infection.

Physiological salt solution was used as a vehicle in 21 cases. Infusions eliminated 12 infections and failed to eliminate 9. Of the 12 eliminated, 11 were streptococcal infections and 1 was a staphylococcal infection. Of those that were not eliminated, 8 were streptococcal infections and 1 was a staphylococcal infection.

Glycerin was used as a vehicle in 14 cases. Infusions eliminated 10 infections (8 streptococcal and 2 staphylococcal) and failed to eliminate 4 infections (2 streptococcal and 2 staphylococcal).

In four cases the infected quarter was infused with penicillin in salt solution at one time and with penicillin in glycerin at another. Two of the infections were eliminated; the other two were not. All four infections were streptococcal.

Although definite conclusions are not warranted, the best results seem to have been obtained with the glycerin solution (71.43 percent) and the poorest results with the mineral-oil solution (37.50 percent).

In 9 of the 47 cases, treatment was administered to nonlactating quarters. In each case the total dosage was given as a single infusion

of 50,000 units. Five of the infections were eliminated; 4 did not respond to treatment. Those that were eliminated were all streptococcal; those that were not eliminated included 2 streptococcal and 2 staphylococcal infections. The effectiveness of the treatment for the dry quarters was 55.55 percent, or about the same as the average (57.45 percent) for the entire group of 47, which includes both lactating and nonlactating quarters.

The total dosage of 50,000 units of penicillin was given in a single infusion in 39 cases. Of these, 29 were streptococcal infections. Eighteen were eliminated and 11 persisted. Nine were staphylococcal, of which only 3 were eliminated. Treatment failed to eliminate the 1 pseudomonadal infection. For all types of infection 21 were eliminated and 18 were not, showing an effectiveness of 53.85 percent. In 8 cases, the total dosage was divided into two infusions. All 8 were streptococcal infections. Six responded and 2 failed to respond.

The data in table 1 suggest that the staphylococcal and pseudomonadal infections may have been more resistant to penicillin than the streptococcal infections. This is indicated again by the fact that 62.07 percent of the streptococcal infections were eliminated, as compared with 30.00 percent of the staphylococcal and pseudomonadal infections, when the 50,000-unit dosage of penicillin was given as a single infusion. Despite the small number of cases available for comparison, it is noteworthy that 62.07 percent of the streptococcal infections were eliminated by single infusions of 50,000 units of penicillin, whereas 75.00 percent were eliminated when the 50,000-unit dosage was administered in two infusions of 25,000 units each on consecutive days.

SECOND PHASE (2 INFUSIONS DAILY ON 2 CONSECUTIVE DAYS)

The information obtained in the preliminary phase indicated that extending the treatment through 2 days was more effective than administering it as a single infusion. It seemed desirable also to increase the frequency of the infusions in order to insure a more constant presence of penicillin in the udder. When an adequate supply of penicillin again became available, it was possible to use higher dosages.

Therefore, the procedure adopted and followed for the period April 1946 through December 1947 was to treat infected quarters by infusing them twice daily on two consecutive days.[4] The four infusions are considered as one treatment in all tabulations. Infusions were administered as soon as practicable after the morning and afternoon milkings. Cows milked three times daily were given no infusions after the late evening milking. The amount of the infused material was 50 cubic centimeters. The minimum dosage at each infusion was 25,000 units of penicillin except for 10 cases treated during 1 week when the potency of the penicillin used proved to be low and the dosage amounted to only 12,000 units at each infusion. The dosage varied from the minimum indicated to a maximum of 92,800 units at each infusion—a total of 371,200 units of penicillin for the treatment. For a period of approximately 6 months—from April to Sep-

[4] Actually, for the sake of convenience, in many cases the first infusion of a treatment was given on the afternoon of one day and the fourth infusion was given on the morning of the third day.

tember 1946—mineral oil was used in some cases as a vehicle for the penicillin. In all subsequent infusions the penicillin was in aqueous solution.

NATURE OF INFECTIONS FOUND

According to reports from many sources, *Streptococcus agalactiae* has been held responsible for a very high percentage of mastitic infections found in single herds or in herds covered by area surveys. Before giving the results of treatment it may be of interest to show the nature of udder infections found in the dairy herd at Beltsville during this period of 21 months, by following the procedure of analyzing quarter samples of milk from all cows near the beginning of each lactation, from cows showing indications of mastitis at any time, and from cows recently treated. The number of infections and the kinds of infecting organisms identified by bacteriological analyses in connection with this study are shown in table 2.

TABLE 2.—*Organisms found responsible for udder infections in the Beltsville herd during a 21-month period*

Kind of organism	Infections	Percentage of all infections
	Number	*Percent*
S. agalactiae	36	10. 56
S. uberis	85	24. 93
S. dysgalactiae	25	7. 33
S. (viridans group)	17	4. 99
S. (enterococcus group)	16	4. 69
S. (unidentified)	7	2. 05
All streptococci	186	54. 55
Staphylococci (hemolytic)	105	30. 79
Coliform bacteria	15	4. 40
Pseudomonades	26	7. 62
Yeast	6	1. 76
Cocci	3	. 88
All organisms	341	100. 00

The most frequently found infections were staphylococcal (30.79 percent). *Streptococcus uberis* was the second most common offender (24.93 percent), accounting for nearly half of all streptococcal infections and about one-fourth of the infections of all kinds. Pseudomonadal infections, which have caused many severe cases of mastitis in the past, represented only 7.62 percent of all infections during this period. The data show that, although slightly more than half (54.55 percent) of the infections were streptococcal, only 10.56 percent were caused by *S. agalactiae.*

Either the incidence of *Streptococcus agalactiae* in the Beltsville herd was very much lower than that reported from most sources or else the highly refined techniques followed in the bacteriological analyses have more accurately differentiated between the different kinds of streptococcal infections in this study. At any rate, 45 percent of the total infections were other than streptococcal.

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EFFECTIVENESS OF PENICILLIN IN ELIMINATING VARIOUS KINDS OF INFECTIONS

The results of treatment were determined for 337 of the 341 infections listed in table 2, by analyzing posttreatment samples of milk. The 337 treated infections were infused twice daily on two consecutive days according to the procedure outlined above. A tabulation of these results is given in table 3.

The effectiveness of penicillin in eliminating streptococcal infections is gratifying. It will be noted that 97.22 percent of *Streptococcus agalactiae* infections were eliminated. The lowest effectiveness (85.71 percent) was obtained with *S. uberis*, the most common streptococcal offender during this period. For all streptococcal infections, the penicillin treatments eliminated 90.81 percent.

Somewhat surprising is the fact that staphylococci and coliform bacteria were so successfully eliminated by penicillin (85.44 and 93.33 percent, respectively). Satisfactory results were obtained also in treating pseudomonadal infections with penicillin (76.00 percent). Attention is directed also to the unusually high percentage of effectiveness (87.83 percent) for all kinds of infections. All of these results speak well for penicillin therapy as a means of eliminating a wide variety of infecting organisms from cow udders. However, one reason for the high degree of effectiveness undoubtedly is the fact that most of the infections were detected at an early stage before clinical mastitis had become evident. It is recognized also that in any study of mastitis some infections disappear without benefit of treatment.

QUICK RESPONSE OF INFECTIONS TO PENICILLIN THERAPY

The data in table 3 indicate also that a high proportion of the infections were eliminated by the first treatment and that the proportion increased considerably up to the third. This is shown in two ways: (1) On the basis of the percentage of the total number of infections treated, and (2) on the basis of the percentage of infections effectively eliminated, that were found to be absent after one treatment, after two treatments, and after three treatments. When calculated on the basis of all of the streptococcal infections treated, 73.51 percent were eliminated by the first treatment, 87.03 percent by the first two treatments, and 89.73 percent by three treatments. The corresponding percentages for all kinds of infections were 69.73, 82.79, and 86.35.

Obviously, when efficiency of successive treatments is calculated on the basis of the proportion of the number of infections eliminated rather than on the total number treated, the percentages will be relatively higher—particularly in the case of the more resistant organisms. The first treatment eliminated more than 80 percent (80.95) of the streptococcal infections and 79.39 percent of the infections of all kinds that responded to penicillin therapy. Two treatments—when the first was ineffective—resulted in the elimination of 95.83 percent of the streptococcal and 94.26 percent of infections of all kinds. Three treatments—when the first and second were ineffective—eliminated 98.81 percent of the streptococcal and 98.31 percent of the infections of all kinds that finally responded to treatment. The fact that more than 98 percent of the infections that responded to treatment were eliminated by three treatments or less indicates that there is little to be gained by continuing penicillin infusions beyond the third treatment.

TABLE 3.—*Effectiveness of infusing the udder with penicillin twice daily on two consecutive days, in eliminating various kinds of infections*

Infecting organism	Infections treated	Infections eliminated		Percentage of total number of infections treated that were eliminated by the—			Percentage of infections effectively eliminated, that were eliminated by the—		
				First treatment	First two treatments	First three treatments	First treatment	First two treatments	First three treatments
	Number	*Number*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*	*Percent*
S. agalactiae	36	35	97. 22	69. 44	91. 67	94. 44	71. 43	94. 29	97. 14
S. uberis	84	72	85. 71	69. 05	83. 33	84. 52	80. 56	97. 22	98. 61
S. dysgalactiae	25	22	88. 00	72. 00	80. 00	88. 00	81. 82	90. 91	100. 00
S. (viridans group)	17	17	100. 00	88. 24	94. 12	100. 00	88. 24	94. 12	100. 00
S. (enterococcus group)	16	15	93. 75	81. 25	93. 75	93. 75	86. 67	100. 00	--------
S. (unidentified)	7	7	100. 00	100. 00	--------	--------	100. 00	--------	--------
All streptococci	185	168	90. 81	73. 51	87. 03	89. 73	80. 95	95. 83	98. 81
Staphylococci (hemolytic)	103	88	85. 44	64. 08	77. 67	82. 52	75. 00	90. 91	96. 59
Pseudomonades	25	19	76. 00	68. 00	76. 00	76. 00	89. 47	100. 00	--------
Coliform bacteria	15	14	93. 33	80. 00	93. 33	93. 33	85. 71	100. 00	--------
Yeast	6	6	100. 00	50. 00	66. 67	100. 00	50. 00	66. 67	100. 00
Cocci	3	1	33. 33	33. 33	33. 33	33. 33	100. 00	--------	--------
All infections	337	296	87. 83	69. 73	82. 79	86. 35	79. 39	94. 26	98. 31

RESULTS WITH PENICILLIN AND WITH SULFONAMIDES COMPARED

This study was not undertaken with the idea of comparing the effectiveness of penicillin with that of the sulfonamides previously used in treating mastitis infections in the dairy herd at Beltsville. However, bringing together the summaries of results for comparison at this point seems appropriate. The percentages showing the proportion of total infections eliminated by treatment with sulfonamides and penicillin are given in table 4.

TABLE 4.—*Efficiency of penicillin as compared with that of sulfonamide preparations previously used*

Kind of infection	S, or S+SD [1]		SUG [2]		Penicillin [3]	
	Infections		Infections		Infections	
	Treated	Eliminated	Treated	Eliminated	Treated	Eliminated
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Streptococcal	91	80. 22	56	62. 50	185	90. 81
Staphylococcal	10	90. 00	5	80. 00	103	85. 44
Pseudomonadal	18	55. 55	22	77. 27	25	76. 00
Coliform	6	83. 33	2	100. 00	15	93. 33
All kinds	125	77. 60	85	68. 24	328	88. 11

[1] Sulfanilamide, or sulfanilamide+sulfadiazine (*12*).
[2] Sulfanilamide, urea, and glycerin (*13*).
[3] Penicillin administered twice daily on two consecutive days.

During a period of approximately 2 years (from October 1942 to October 1944), the sulfanilamide-sulfadiazine preparations (S+SD) eliminated the various infecting organisms from 97 of the 125 infected quarters treated (77.60 percent). The sulfanilamide-urea preparations (SUG) eliminated the organisms from 58 of the 85 infected quarters treated (68.24 percent). The preparations containing urea appeared to be substantially less effective against streptococcal infections, but definitely more effective against pseudomonadal infections, than the sulfanilamide-sulfadiazine preparations. An absolute comparison of the two sulfonamides could not be made because of differences in concentrations of sulfanilamide and in dosage, and because in some instances the urea preparations were used in treating cases that had failed to respond to sulfanilamide-sulfadiazine preparations. However, it was concluded that the addition of urea to sulfonamide preparations was not sufficiently beneficial to compensate for the greater difficulty of administering the treatments. In neither case did the administration of the sulfonamide result in a decline in milk production that could be considered excessive or significantly greater than the decline to be expected during corresponding periods of time in untreated udders.

The various streptococcal infections were grouped together as less attention was given to the identification of the different streptococci

while sulfonamides were used than when penicillin was used. Yeasts and cocci are omitted as they were not listed in the earlier studies when sulfanilamide and sulfadiazine (S or S+SD), and sulfanilamide, urea, and glycerin (SUG) were being used. It would appear that, because of the greater numbers of infections treated, the results obtained with penicillin should have even greater significance than those obtained with sulfonamides.

Penicillin was definitely more effective than either of the sulfonamide preparations in eliminating streptococcal infections. For staphylococcal infections, penicillin appeared to be of about the same effectiveness, on an average, as the sulfonamides. For pseudomonadal infections, penicillin appeared to be much more effective than S or S+SD and of approximately the same effectiveness as SUG. There was little difference, on an average, between penicillin and the sulfonamides with regard to efficiency in eliminating coliform infections. For all kinds of infections listed in table 4, penicillin had a higher efficiency than the sulfonamides—particulary SUG—even though some of the infections treated with penicillin had failed to respond favorably to previous treatments of sulfonamide.

Mention has been made of the quick response of udder infections to penicillin administered twice daily on two consecutive days. Table 5 shows the total number of infections eliminated by treatments with the sulfonamide preparations (S and S+SD, and SUG) and with penicillin, and the percentage of the total number eliminated by each preparation, that were eliminated by the first, the first two, or the first three treatments. From this standpoint, penicillin seemed to have about the same effectiveness as SUG for streptococcal infections but to be more effective than S or S+SD. For staphylococcal infections, there was little difference for the first treatment but the percentages for penicillin were considerably higher than for SUG for the first two or the first three treatments. In the case of pseudomonadal infections, penicillin and S or S+SD were of about the same effectiveness, both being somewhat higher than SUG. The response was somewhat quicker for penicillin than for S or S+SD in the case of coliform infections, but all preparations seem to have reached the same level by the third treatment.

The results with the various kinds of infection were more uniform for penicillin than for the sulfonamides. Consequently, when all kinds of infections are considered together, penicillin is shown to have a higher efficiency than either of the sulfonamides for the first, the first two, and the first three treatments. Again it seems noteworthy that the results may be more significant in the case of penicillin because of the greater number of infections treated, and that there seems to be little advantage to be gained by continuing penicillin therapy beyond the third treatment.

TREATMENT OF DRY COWS

Many workers on the problem of mastitis have advocated the treatment of infected udders during the nonlactating state, and have claimed better results in treating dry than lactating cows. It has been the practice in the Beltsville herd to treat infections when they occur—which usually is during lactation—but in some cases to treat

TABLE 5.—*Total number of infections eliminated by treatments with sulfonamide preparations and with penicillin, and the percentage of the total number eliminated by the first, the first two, or the first three treatments*

Kind of infection	S or S+SD		SUG		Penicillin	
	Total infections eliminated	Cumulated proportion of total infections eliminated	Total infections eliminated	Cumulated proportion of total infections eliminated	Total infections eliminated	Cumulated proportion of total infections eliminated
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Streptococcal	73		35		168	
Eliminated by—						
First treatment	47	64. 38	29	82. 86	136	80. 95
First two treatments	64	87. 67	33	94. 29	161	95. 83
First three treatments	67	91. 78	34	97. 14	166	98. 81
Staphylococcal	9		4		88	
Eliminated by—						
First treatment	6	66. 67	3	75. 00	66	75. 00
First two treatments	8	88. 89	3	75. 00	80	90. 91
First three treatments	9	100. 00	3	75. 00	85	96. 59
Pseudomonadal	10		17		19	
Eliminated by—						
First treatment	9	90. 00	11	64. 71	17	89. 47
First two treatments	9	90. 00	15	88. 24	19	100. 00
First three treatments	10	100. 00	15	88. 24		
Coliform	5		2		14	
Eliminated by—						
First treatment	3	60. 00	2	100. 00	12	85. 71
First two treatments	3	60. 00			14	100. 00
First three treatments	5	100. 00				
All kinds [1]	97		58		289	
Eliminated by—						
First treatment	65	67. 01	45	77. 59	231	79. 93
First two treatments	84	86. 60	53	91. 38	274	94. 81
First three treatments	91	93. 81	54	93. 10	284	98. 27

[1] The data for all kinds of infection treated with penicillin differ from the data in table 3 because the yeast and cocci infections are omitted.

infections during the dry period that have failed to respond to treatment during lactation.

Only four infections were treated during the dry stage after the adoption of the program of infusing twice daily on two successive days. In each case only one treatment was administered because, obviously, by the time the results were known the cows were again in lactation. One of these (*Streptococcus uberis*) was eliminated by one treatment in which the total dosage was 100,000 units of penicillin. The other three infections failed to respond to treatment. Of those that failed, one (*S. uberis*) was given a total of 100,000 units.

The other two that failed to respond to treatment were staphylococcal infections in different quarters of the same udder. One of these previously had failed to respond to five treatments with dosages varying from a total of 100,000 to 259,000 units, and the other to three treatments having the same range in dosage. In addition to these two infusion treatments, the cow was given 4,500,000 units of penicillin intramuscularly in peanut oil and beeswax a short time before she went dry. The treatments administered without success, to the staphylococcal infections in two quarters of the same udder, consisted of a relatively heavy dosage (371,000 units) of penicillin.

The number of cases, of course, is too small to justify conclusions with regard to the relative merits of treating during the dry stage as compared with treating during lactation. It is recognized, too, that two of the cases that failed to respond were persistent, having failed to respond to several previous treatments during lactation. However, since no unfavorable reactions were noted in connection with cases treated during lactation, it appears that the logical time to administer treatment is the time at which the infection occurs. The data obtained in this work indicate that there is no advantage in treating infections while the cows are dry instead of during lactation.

DOSAGE AND SEVERITY OF INFECTION

Two important factors must be taken into account in interpreting the results obtained in these analyses. One is the dosage (number of units of penicillin) used. The other is the severity of the infections treated.

It has been shown that, with the exception of 10 cases (see text, page 8), the total number of units of penicillin used per treatment of four infusions varied from 100,000 to 371,000 for each infected quarter of the udder. In order to get some idea of the relative effectiveness of various dosages, all treated infections were divided for tabulation into four groups, as follows: (1) Those receiving up to 100,000 units, (2) those receiving between 100,000 and 200,000 units, (3) those receiving between 200,000 and 300,000 units, and (4) those receiving between 300,000 and 400,000 units.

Setting up a classification for severity of infection was equally important but much less easily accomplished. Since the number of organisms in any given sample of foremilk did not appear to be directly correlated with any available, tangible data on severity of infection, it was necessary to select other criteria to provide a basis for evaluating severity.

The criteria used were (1) leucocyte count, (2) percentage of chlorides, and (3) the physical appearance of the milk. On the basis of these criteria, pretreatment samples were sorted for tabulation into three groups designated as mild, moderate, and severe, in the order of increasing severity of the infection.

Infections designated as mild included samples with leucocyte counts of less than 500,000, chlorides below 0.10 percent, and milk of normal appearance.

Those designated as moderate generally included samples with leucocyte counts between 500,000 and 10,000,000, chlorides between

TABLE 6.—*Distribution showing success or failure of the various dosages of penicillin in eliminating infecting organisms, classified according to severity of infections treated* [1]

Infecting organism	Eliminated			Not eliminated		
	Mild	Moderate	Severe	Mild	Moderate	Severe
100,000 UNITS OR LESS						
	Number	*Number*	*Number*	*Number*	*Number*	*Number*
S. agalactiae	6	4		2		
S. uberis	10	7	2	3	9	1
S. dysgalactiae					1	1
S. (veridans group)	4					
S. (enterococcus group)		2				
S. (unidentified)	2	2				
All streptococci	22	15	2	5	10	2
Staphylococci	19	2		7	12	
Coliform bacteria						
Pseudomonades	1		1		1	
Yeast			2			
Cocci						
All organisms	42	17	5	12	23	2
100,000 TO 200,000 UNITS						
S. agalactiae		1				
S. uberis	4	1	1			
S. dysgalactiae	2	1			1	
S. (viridans group)	5	1				
S. (enterococcus group)	1	1	1			
S. (unidentified)						
All streptococci	12	5	2		1	
Staphylococci	3	4				
Coliform bacteria	2	1		1		
Pseudomonades		1	1		1	1
Yeast					2	1
Cocci						
All organisms	17	11	3	1	4	2
200,000 TO 300,000 UNITS						
S. agalactiae	5	5		3	3	1
S. uberis	20	6	3	1	6	2
S. dysgalactiae	6	3	2		1	
S. (viridans group)	1	2		1	1	
S. (enterococcus group)	3	4	1	1		2
S. (unidentified)		2	1			
All streptococci	35	22	7	6	11	5
Staphylococci	15	15	4	4	8	1
Coliform bacteria	2	3	2			
Pseudomonades	9	2	1		2	1
Yeast		1				
Cocci		1		1		1
All organisms	61	44	14	11	21	8

See footnote at end of table.

TABLE 6.—*Distribution showing success or failure of the various dosages of penicillin in eliminating infecting organisms, classified according to severity of infections treated* [1]—Continued

300,000 TO 400,000 UNITS

Infecting organism	Eliminated			Not eliminated		
	Mild	Moderate	Severe	Mild	Moderate	Severe
	Number	*Number*	*Number*	*Number*	*Number*	*Number*
S. agalactiae	2	2			2	
S. uberis	2	2			2	2
S. dysgalactiae	1		3		1	2
S. (viridans group)		2				
S. (enterococcus group)						
S. (unidentified)						
All streptococci	5	6	3		5	4
Staphylococci	3	1		1	4	
Coliform bacteria	1	1		2		
Pseudomonades		1			1	1
Yeast						
Cocci						
All organisms	9	9	3	3	10	5

[1] Results based on success or failure of first treatment in each case.

0.10 and 0.18 percent, and milk with little if any abnormality in appearance.

Those designated as severe generally showed leucocyte counts above 10,000,000, chlorides in excess of 0.18 percent, and/or distinct abnormality in appearance of the milk.

Table 6 shows the distribution of the mild, moderate, and severe infections treated, arranged according to the dosages used. Results, based on the success or failure of the first treatment administered in each case, are shown for each kind of infection. It was necessary to limit this phase of the study to the first treatment because in some cases, where more than one treatment was administered, subsequent treatments involved different dosages and the severity of the infections often increased or decreased between treatments. It is regrettable that the number of cases receiving dosages between 100,000 and 200,000 units and dosages between 300,000 and 400,000 units is so much smaller than the number receiving the other dosages. Little discussion is given to this table, as the data contained are broken down for various comparisons in other tables that follow.

Table 7 is an abbreviation of table 6, arranged to show the proportion of the streptococcal infections, staphylococcal infections, and infections of all kinds that fell in the three groups representing severity of infection, and that received various dosages. The data in this table emphasize the fact that the greatest proportion of infections found in the herd were mild and that a somewhat lower proportion were moderate, but that the number of severe infections was very low. This was particularly true of the staphylococcal infections, of which more than 50 percent were in the group of mild infections and less than 5 percent were in the group of severe infections.

TABLE 7.—*Proportion of total infections classified as mild, moderate, and severe infections and treated by each of the various dosages of penicillin*

Infecting organism and dosage used	Mild infections		Moderate infections		Severe infections	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Streptococci:						
100,000 units or less	27	48. 21	25	44. 64	4	7. 14
100,000 to 200,000 units	12	60. 00	6	30. 00	2	10. 00
200,000 to 300,000 units	41	47. 67	33	38. 37	12	13. 95
300,000 to 400,000 units	5	21. 74	11	47. 83	7	30. 43
All dosages	85	45. 95	75	40. 54	25	13. 51
Staphylococci:						
100,000 units or less	26	65. 00	14	35. 00	------	--------
100,000 to 200,000 units	3	42. 86	4	57. 14	------	--------
200,000 to 300,000 units	19	40. 43	23	48. 94	5	10. 64
300,000 to 400,000 units	4	44. 44	5	55. 56	------	--------
All dosages	52	50. 49	46	44. 66	5	4. 85
All organisms:						
100,000 units or less	54	53. 47	40	39. 60	7	6. 93
100,000 to 200,000 units	18	47. 37	15	39. 47	5	13. 16
200,000 to 300,000 units	72	45. 28	65	40. 88	22	13. 84
300,000 to 400,000 units	12	30. 77	19	48. 72	8	20. 51
All dosages	156	46. 29	139	41. 25	42	12. 46

The data given in table 6 are greatly abbreviated in a different way in table 8 to show the proportion of the infections that were eliminated by treatment. In order that the percentages might be based on larger numbers, the results are shown for only three groups of organisms: Streptococci, staphylococci, and all organisms combined. The results are not interpreted easily because of the probable counteracting effects of variations in dosage and severity, both of which are taken into account. It appears, however, that regardless of the dosage used the penicillin therapy was more effective in the mild cases than in the more severe ones. There is also some indication that dosages above 100,000 and up to 300,000 units were more effective than dosages of 100,000 or less, but that increasing the dosage above 300,000 units was not beneficial.

Table 9 gives the percentage of effectiveness of various dosages by first treatment when the severity of the infections is disregarded. It is quite definitely indicated here that increasing the dosage above 100,000 units increases the efficiency of the penicillin treatments but that raising the dosage above 300,000 units probably is not justified. The greatest efficiency is shown for dosages between 100,000 and 200,000 units, but because of the smaller number of cases represented it can hardly be concluded that this is the optimum dosage for maximum efficiency.

Table 10 gives the percentage of efficiency for infections of different severity when the dosage used is disregarded. The results show rather

TABLE 8.—*Effectiveness of various dosages of penicillin in eliminating infecting organisms, in relation to the severity of infection*

Dosage and infecting organism	Proportion of total infections eliminated by first treatment with dosage indicated					
	Mild infections		Moderate infections		Severe infections	
100,000 units or less:	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
All streptococci	22	81. 48	15	60. 00	2	50. 00
Staphylococci	19	73. 08	2	14. 29	------	------
All organisms	42	77. 78	17	42. 50	5	71. 43
100,000 to 200,000 units:						
All streptococci	12	100. 00	5	83. 33	2	100. 00
Staphylococci	3	100. 00	4	100. 00	------	------
All organisms	17	94. 44	11	73. 33	3	60. 00
200,000 to 300,000 units:						
All streptococci	35	85. 37	22	66. 67	12	58. 33
Staphylococci	15	78. 95	15	65. 22	4	80. 00
All organisms	61	84. 72	44	67. 69	14	63. 64
300,000 to 400,000 units:						
All streptococci	5	100. 00	6	54. 55	3	42. 86
Staphylococci	3	75. 00	1	20. 00	------	------
All organisms	9	75. 00	9	47. 37	3	37. 50

TABLE 9.—*Effectiveness of various dosages of penicillin in eliminating infecting organisms, without regard to severity of infection*

Infecting organism	Infections eliminated by first treatment with dosage of—							
	100,000 units or less		100,000 to 200,000 units		200,000 to 300,000 units		300,000 to 400,000 units	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
All streptococci	39	69. 64	19	95. 00	64	74. 42	14	60. 87
Staphylococci	21	52. 50	7	100. 00	34	72. 34	4	44. 44
All organisms	64	63. 37	31	81. 58	119	74. 84	21	53. 85

TABLE 10.—*Effectiveness of penicillin in treating infections of different degrees of severity (without regard to dosage used)*

Infecting organism	Infections eliminated by first treatment					
	Mild infection		Moderate infection		Severe infection	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*
All streptococci	74	87. 06	48	64. 00	14	56. 00
Staphylococci	40	76. 92	21	45. 65	4	80. 00
All organisms	129	82. 69	81	58. 27	25	59. 52

definitely that, for streptococcal infections and for infections of all kinds treated, the mild infections were eliminated more readily than those that were classed as moderate or severe. But the severe infections were eliminated with about the same efficiency as the moderate ones. In fact, in the case of staphylococci, the percentage of efficiency is higher for the severe than for the moderate infections, but the results in this case should be discounted because of the small number of severe cases represented.

SUMMARY AND CONCLUSIONS

From late 1944 until October 1945 penicillin was used in a limited way in treating mastitis infections in the Bureau of Dairy Industry herd at Beltsville. The total dosage used was 50,000 units of penicillin at each treatment. In some cases this amount was administered as a single infusion. In other cases two infusions of 25,000 units each were given once daily on successive days. The penicillin was given in aqueous and in physiological salt solutions, and in suspensions of mineral oil and glycerin. The amount of the infused material given at each infusion was 50 cubic centimeters.

Forty-seven infections were treated during this preliminary period. Treatment was effective in eliminating 64.86 percent of 37 streptococcal infections and 33.33 percent of 9 staphylococcal infections, but failed to eliminate the 1 pseudomonadal infection. Although the number of cases compared was small, the effectiveness seemed to be definitely higher in the cases where the total dosage was divided into two infusions and extended through a 2-day period.

Beginning in April 1946, when penicillin again became available, udder infections were treated by administering 4 infusions—2 infusions daily on successive days. The amount of infused material used was 50 cubic centimeters at each infusion. Except in 10 cases the minimum dosage at each infusion was 25,000 units—a total of 100,000 units for the treatment of each infected quarter. The dosage varied from this minimum to a maximum of 92,800 units per infusion—a total of 371,200 units for the treatment. This summary includes only the results of treatments during a 21-month period from April 1946 through December 1947. The total number of infections treated was 337.

Unlike the findings reported from many sources, *Streptococcus agalactiae* accounted for only about 10 percent of all infections in the Beltsville herd during this 21-month period. *S. uberis*, however, accounted for 25 percent. Streptococci of all kinds accounted for 54 percent, staphylococci for 30 percent, and coliform bacteria, pseudomonades, and other bacteria for the balance.

Penicillin, administered as four infusions, twice daily for two days, eliminated 97.22 percent of the *Streptococcus agalactiae* infections, 85.71 percent of the *S. uberis* infections, and 90.81 percent of all streptococcal infections. It eliminated 85.44 percent of the staphylococcal infections, 93.33 percent of the coli infections, 76.00 percent of the pseudomonadal infections, and 87.83 percent of all kinds of infections treated.

Of all infections effectively treated, 98.81 percent of the streptococcal infections and 98.31 percent of the infections of all kinds were eliminated by the first, second, or third treatments. It appears that little is to be gained by administering more than three treatments.

Increasing the number of infusions at each treatment from one or two to four, and raising the dosage from 50,000 units to 100,000 units or more, increased the effectiveness of penicillin in treating infections of all kinds from 57.45 percent to 87.83 percent.

A comparison of percentages of effectiveness in treating infections—77.60 for sulfanilamide-sulfadiazine preparations, 68.24 for sulfanilamide-urea preparations, and 87.83 for penicillin—indicates that penicillin therapy was more effective than the sulfa drugs used. Moreover, penicillin was prepared and administered much more easily than either of the sulfonamides used.

Classifying the infections according to severity showed that the greatest proportion of the infections found in the herd were mild, and that a somewhat smaller proportion were moderate, but that the number of severe infections was very low. This was particularly the case with staphylococci. More than 50 percent of the cases of this infection were classed as mild and less than 5 percent as severe.

Disregarding the matter of severity of infection, the effectiveness of penicillin therapy (based on first treatment) was increased for all kinds of infections by raising the dosage beyond a total of 100,000 units per treatment, but no advantage was found in administering more than 300,000 units. Percentages showing the average effectiveness were 63.37, 81.58, 74.84, and 53.85, respectively, for dosages of (1) less than 100,000 units, (2) 100,000 to 200,000 units, (3) 200,000 to 300,000 units, and (4) 300,000 to 400,000 units.

Disregarding the dosage used, it was found for all kinds of infecting organisms that 82.69 percent of the mild infections, 58.27 percent of the moderate infections, and 59.52 percent of the severe infections were eliminated by the first treatment.

When the dosage was 100,000 units or less, there was comparatively little difference in effectiveness whether infections were mild or severe. But for each of the higher dosages, the effectiveness declined steadily as the severity of the infections increased.

It appears from our observations that there is little to be gained by administering a total of more than 200,000 units of penicillin in treating an infected quarter.

Infusions of infected udders with antibiotics or other preparations is not the entire answer to the problem of mastitis control. Effective herd management—including milking methods—must be stressed as of even greater importance. If it had been possible to maintain the desired standards of management during the period represented by this study, the number of infected quarters requiring treatment undoubtedly would have been very much smaller and the condition of the herd with reference to mastitis would have shown greater improvement.

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