A Review of the Comparative Efficacy of Sulfonamides in Cattle and Economics of Their Use*

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Sulfonamides started a new era of veterinary medicine, providing the practitioner a real tool to control bacterial disease losses. History (1) shows progress in the beginning was extremely slow. Some of the milestones were:

1908 — Gelmo synthesized sulfanilamide but activity was not known.

1910 — Erlich developed arsphenamine and neoarsphenamine for syphilis and trypanasomiasis.

1913 — Eisenberg suggested use of an azo dye in chemotherapy.

1919 — Heidelberger and Jacobs noted *in vitro* antibacterial action of azosulfamide compounds.

1932 — After a lag of 24 years, Domagk showed Prontosil protected mice infected with streptococci.

1936 — Trefouel *et al.*, reported para-aminobenzene sulfonamide was the active portion of Prontosil.

1938 — Sulfapyridine synthesized.

1939 — Sulfathiazole synthesized.

1940 — Sulfadiazine, sulfamerazine, and sulfamethazine were synthesized.

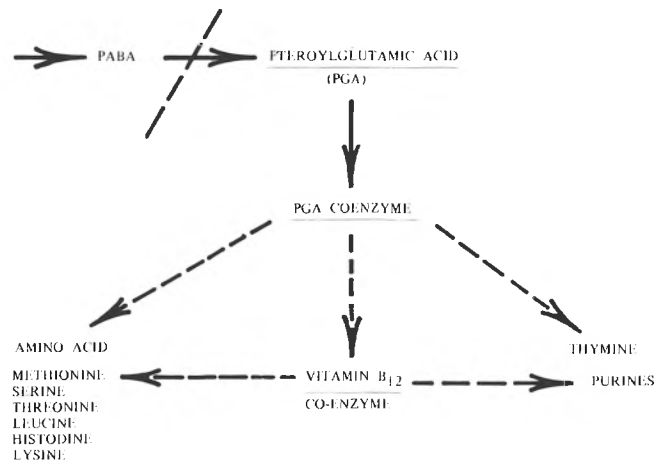
Through the forties, sulfamilamide, sulfaguanadine, sulfathiazole, sulfaquinoxaline and sulfapyridine were used to a limited extent in domestic animals. In 1946, Cyanamid conducted blood level studies with seven systemic sulfonamides in seven domestic animal species (2). From this study, SULMET(R) sulfamethazine was chosen for development and was marketed in 1948.

In the fifties, SULFABROM** (sulfabromomethazine) and SOXISOL sulfisoxazole becomes available followed in the sixties by SPANBOLETS (sustained release sulfamethazine), ALBON (sulfadimethoxine), VETASULID (sulfachloropyridazine) and S.E.Z. (sulfaethoxypyridazine). The trend has been to orally administer sulfonamides and particularly those which are rapidly absorbed and slowly excreted, thus providing a therapeutic blood level over a period of 24 hours or longer. Concurrently in the fifties and sixties a number of antibiotics were introduced, providing the veterinarian with a wide variety of antibacterial agents. This led to combination formulas and use on a preventive as well as treatment basis. It is understandable that the large number of antibacterial agents created a problem of selection and also led to the postulation that sulfonamides would eventually be completely replaced with antibiotics. Now, in the beginning of the seventies, we have the benefit of two decades of experience and can confidently state sulfonamides are firmly established in veterinary medicine.

Mode of Action

Generally, antibacterials exert their activity on one of three sites; on the cell wall, on the cytoplasmic membrane or blocking metabolic reactions within the cell. Sulfonamides act in the latter way. See Figure 1.

FIGURE 1
MODE OF ACTION
SULFONAMIDE



Most bacteria do not utilize pre-formed folic acid (pteroylglutamic acid) (PGA) but synthesize it from paraminobenzoic acid (PABA). Folic acid (PGA) is converted to PGA coenzyme which is essential for organisms in the synthesis of amino

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***SULFABROM, sulfabromomethazine, Merck Co.; SOXISOL, sulfisoxazole, Fort Dodge Co.; SPANBOLETS, sustained release sulfamethazine boluses, Smith, Kline & French Co.; ALBON, sulfadimethoxine, Roche Co.; VETASULID, sulfachloropyridazine, Squibb Co.; S.E.Z., sulfaethoxypyridazine, American Cyanamid Company.*

acids, vitamin B_{12}, and thymine.

Sulfonamides interfere with folic acid synthesis by competing with PABA for enzymes needed for folic acid synthesis. To put it another way, sulfonamides "jams the lock" of the bacteria's folic acid production.

Some of the important characteristics of sulfonamide activity include:

- Active against both gram-negative and gram-positive bacteria.
- Bacteriostatic action is most effective when bacteria are rapidly multiplying.
- The effect on bacteria is not immediate. There is a lag phase until stored PGA is used up.
- Bacteria that do not require PGA or can utilize their own PGA are not effected. (These are in the minority.)
- Sulfonamides are antagonized by PABA, procaine and any of the end products of PGA metabolism. (See Figure 1.)

It is important to emphasize that ALL SULFONAMIDES HAVE THE SAME MODE OF ACTION. The differences between sulfonamides are mainly accounted for by variations in pharmacological activity viz. absorption, distribution and excretion.

In Vitro and In vivo Activity

The relative *in vitro* potency of sulfonamides varies greatly due to many factors. Generally *in vitro* sulfonamide activity is not regarded as a good guide to selecting a sulfonamide. Stowe (2) states, "There is little point in trying to select a sulfonamide for therapeutic use on the basis of *in vitro* potency." Glantz (4) tested 530 strains of *E. coli* against 10 sulfonamides *in vitro* and concluded all were effective. As an illustration, see Table 1.

TABLE 1

IN VITRO POTENCY OF SULFONAMIDES

	Value
SULFATHIAZOLE	50
SULFAMERAZINE	20
SULFAMETHAZINE	13
SULFAPYRIDINE	13
SULFACETAMIDE	8
SULFAGUANIDINE	4
SULFANILAMIDE	1

(Hawking and Lawrence – 1950)

This shows sulfathiazole as the most active followed by sulfamerazine, sulfamethazine and sulfapyridine. In contrast, the *in vivo* activity shows an entirely different relative activity. (See Table 2.)

The comparative activity of an antibacterial can only be accurately determined in a standardized

TABLE 2

SULFONAMIDE ACTIVITY AGAINST PASTUERELLA MULTICIDA IN MICE

	Median Effective Dose	Activity Ratio	Blood Conc. Activity Ratio
	Mg./Kg./Day		
SULFATHIAZOLE	210	1.0	1.0
SULFADIAZINE	54	3.89	0.45
SULFAMERAZINE	43	4.88	0.38
SULFAMETHAZINE	96	2.19	0.47

experimental infection test system such as the pasteurella mouse test. In this test sulfathiazole saved 50% of the mice at the lowest blood level, but the dose of sulfathiazole required to produce effective blood levels was two to five times that of sulfadiazine, sulfamerazine or sulfamethazine. The net result shows sulfathiazole to be far less active than the other three. Table 3 shows relative activity in a mouse *Salmonella choleraesuis*

TABLE 3

SULFONAMIDES VS. EXPERIMENTAL SALMONELLA CHOLERA SUIS

Sulfonamide	Estimated Relative Activity
Sulmet	1
30,256	1/8
27,297	1/8
30,255	1/8
27,287	1/8
4,454	1/2
483	1/2
36,720	1/2
30,638	3/4
502	1-1/3

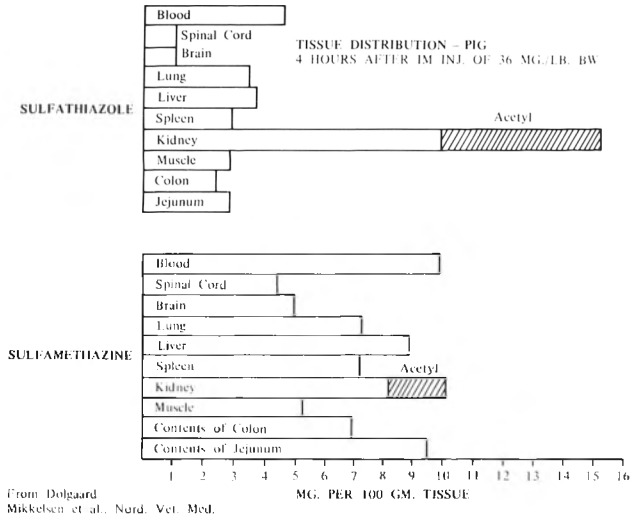
infection. Against a series of experimental sulfonamides, very few have activity comparable to sulfamethazine. Our experience in the past 25 years has established that sulfonamides with high *in vivo* activity are the most effective under field conditions. *Again, the differences in sulfonamide activity is due to differences in pharmacology.*

Absorption and Distribution

Except for the so-called enteric sulfonamides, such as sulfasuxidine, sulfathalidine and sulfaguanidine, most sulfonamides are readily and efficiently absorbed from the rumen and intestine. They dissolve in lipids and are thus transported through membranes to the tissues. The rate of absorption with some may be quite rapid. Experimentally (3) in a calf with an empty rumen it was demonstrated that twelve percent of a dose of sulfamethazine is absorbed in 15 minutes. By three hours, 60% was absorbed.

The distribution of sulfonamides in the tissues may vary considerably (see Figure 2). A 36 mg./lb. intramuscular dose of sulfathiazole and

FIGURE 2



sulfamethazine in the pig shows three fold higher levels of sulfamethazine in all tissues except the kidney. Note both sulfonamides are distributed in all tissues, including brain and spinal cord.

Blood Levels

The blood level pattern is the best single criteria for judging efficacy potential of a sulfonamide. After an oral dose, the desired pattern calls for a rapid rise of blood level to 5 mg.% in four hours, a peak of 10 to 15 mg.% in 12 hours and gradual decline to a 24 hour level of 5 mg.%. The blood level goal of 5 mg.% was established in the forties as an average therapeutic level, one which would inhibit most common pathogenic bacteria. It was based entirely on quantitative data derived from *in vivo* mouse experimental infection blood level models. Levels less than 5 mg.% (2-3%) are effective against early infections of the most susceptible bacteria. But levels higher than 5 mg.% are necessary for persisting or deep seated infections. Preventive or subtherapeutic levels generally were at a blood level of 1 to 2 mg.%.

To illustrate variations in blood level patterns a few of the more commonly used sulfonamides are presented. These figures express the values as free sulfonamide indicating the active form. Total sulfonamide includes the acetylated form, a liver metabolite which is inactive. With pyrimidine sulfonamides 15% of the total may occur in the acetylated form. Sulfaquinoxaline may be acetylated to 50% of that in blood.

Figure 3 presents the blood level pattern (5) of sulfamethazine and sulfisoxazole at an oral dose of 4/5 grain or 54 mg./lb. Here sulfamethazine levels are therapeutic but sulfisoxazole are not.

If a similar dose is given *intravenously* instead of *orally* an entirely different blood level pattern is seen (see Figure 4). As one would expect, intravenous administration gives immediate and

FIGURE 3

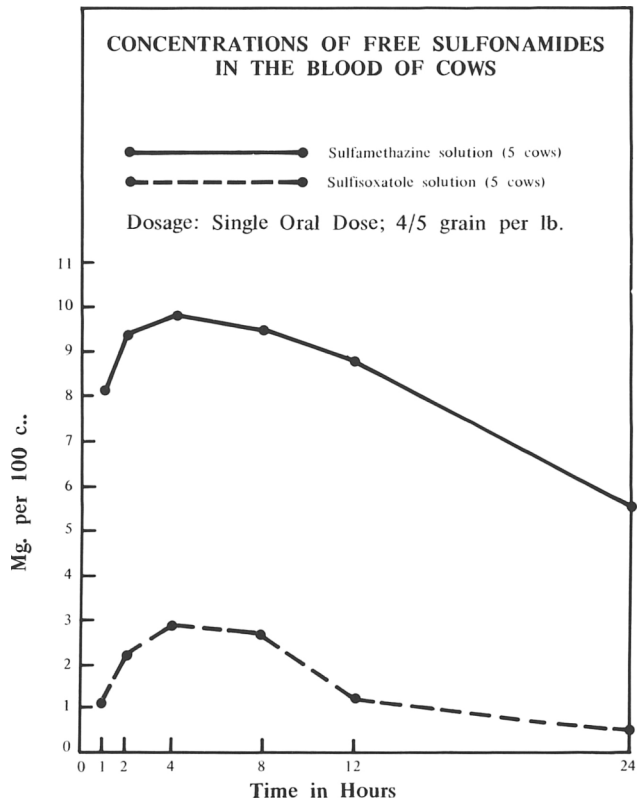
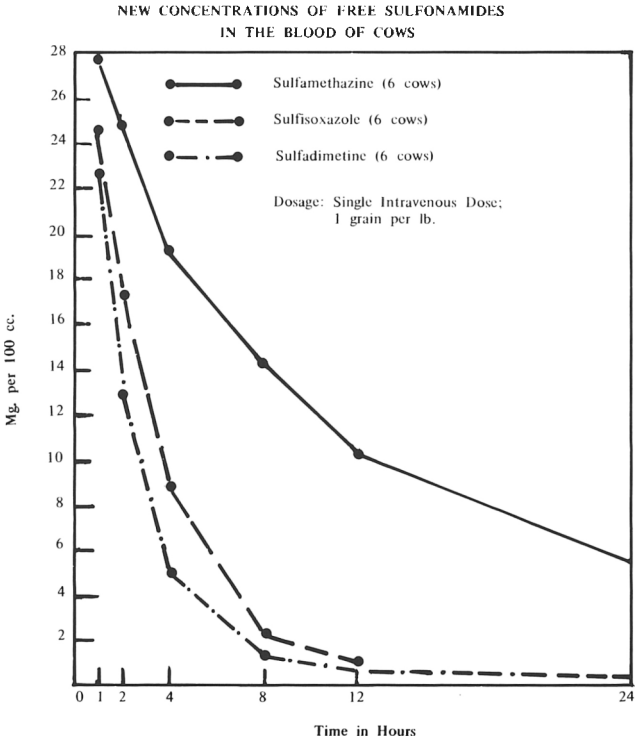


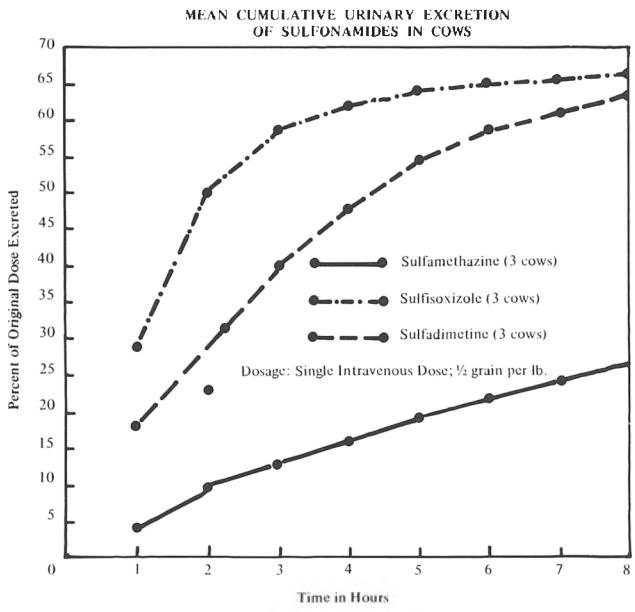
FIGURE 4



very high levels. Sulfisoxazole and sulfadimetine fall to subtherapeutic levels in four to eight hours.

The explanation for this blood level pattern is seen in Figure 5, which presents the excretion rate.

FIGURE 5



Sulfisoxazole and sulfadimetine are rapidly excreted, whereas SULMET is slowly excreted. It follows, that the slower the excretion the more persisting the blood levels. But, sulfonamides that are rapidly excreted, provide higher urine levels and are therefore particularly useful for urinary tract infections.

Another facet of blood level patterns are the sulfonamide levels in blood and milk. Figure 6 shows that an oral dose of 97 mg./lb. initial and 65 mg./lb. maintenance, resulted in high therapeutic blood and milk levels. This pattern stimulated the oral use of sulfamethazine for the treatment of acute and septic mastitis, which was confirmed by clinical trial.

Rumen absorption of sulfonamides is excellent. It is particularly good in the calf up to three months of age. If a calf, newborn to two months of age, is dosed at 1/2 that of a mature cow the blood levels are approximately equivalent! See Figure 7.

Previously, we mentioned that sulfathiazole has good *in vitro* activity but requires higher and 4-hour repeat doses to obtain the efficacy equivalent to sulfamethazine. Figure 8 shows that at equivalent oral doses in cattle effective blood levels of sulfathiazole last only four to five hours whereas sulfamethazine is good for 24.

In this figure we also see the blood level pattern of three equal component combinations, sulfa-

FIGURE 6

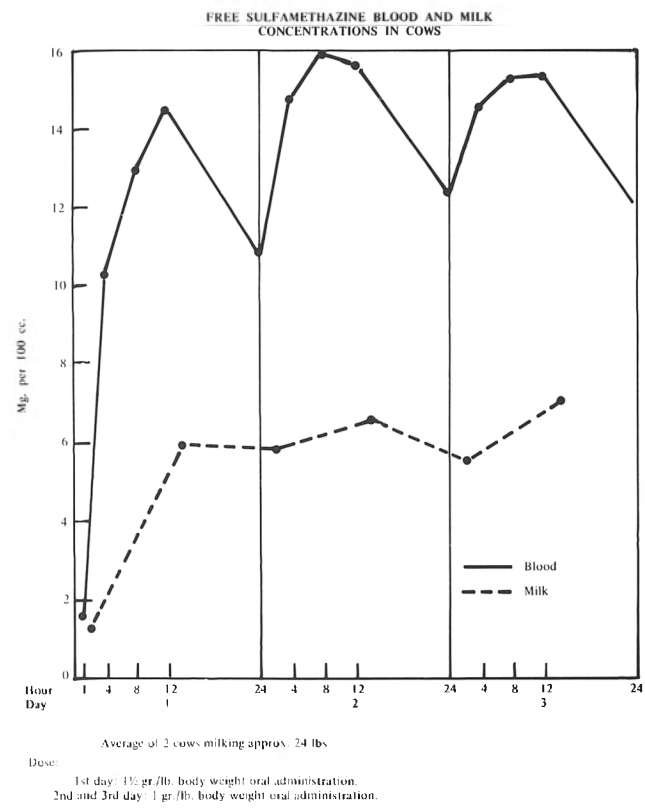


FIGURE 7

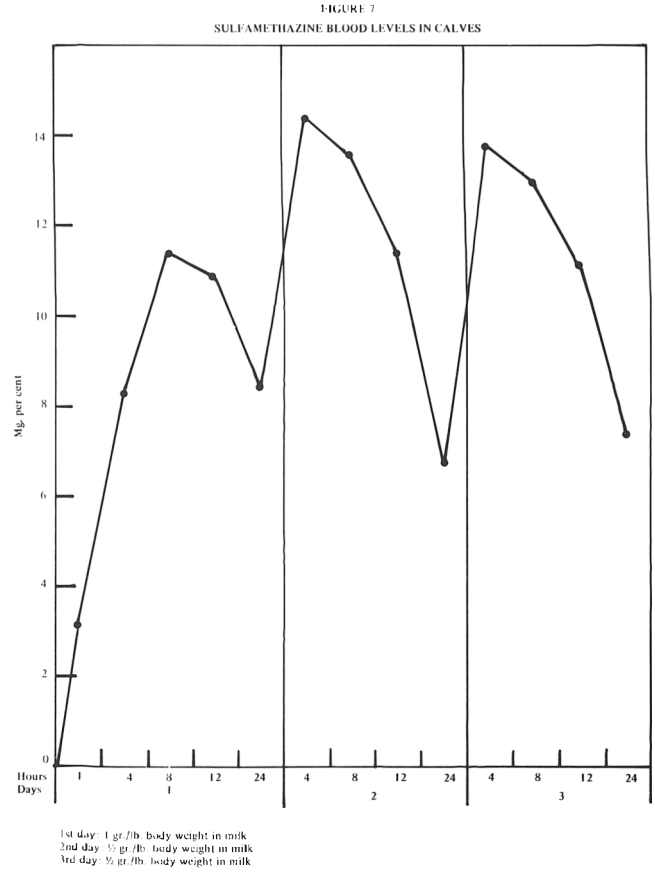
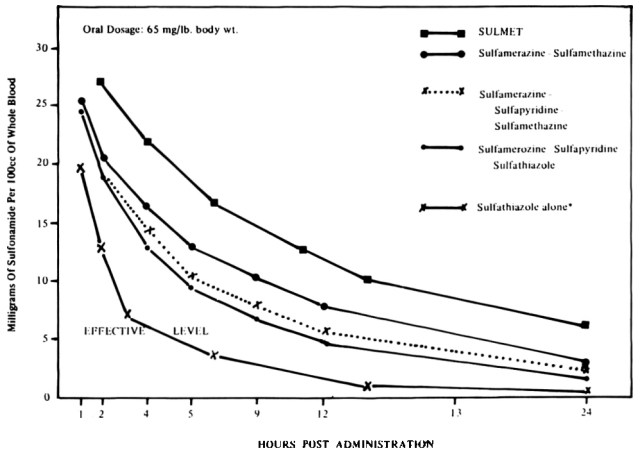


FIGURE 8

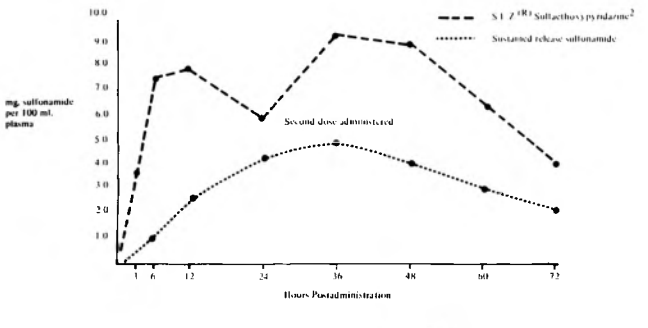


*Data taken from Jones, L. M., Smith, H. A., and Roepke, M. H., Am. J. Vet. Res., 10, (1949) 318.

merazine and sulfamethazine; and sulfamerazine-sulfapyridine-sulfathiazole. Combinations of two or more sulfonamides permit a greater total sulfonamide solubility than any one alone. This reduces potential renal toxicity of advantage with sulfapyridine. However, there is no blood level advantage and the patterns here show all combinations to be inferior to sulfamethazine alone.

In Figure 9, the blood level patterns of S.E.Z. and a sustained release sulfamethazine bolus are

FIGURE 9



COMPARISON OF SULFONAMIDE BLOOD LEVELS ADMINISTERED AT RECOMMENDED LEVELS[1]

[1]From Cyanamid Experiment No. BH-67-22-FT.
[2]Note, the third dose of sulfaethoxypyridazine was not administered.

presented (6). A single dose of a sustained release sulfamethazine bolus gradually approached a therapeutic level, then slowly declined. This pattern favors a preventive application. For therapeutic effect supporting initial parenteral administration is indicated. S.E.Z. at a dose of 25 mg./lb. illustrates a good therapeutic pattern with 5 mg.% being reached in four hours and a peak of 7.5 to 8 in six hours. A second dose of 25 mg./lb. produced a rise to 10 mg.% giving a therapeutic level lasting to beyond 72 hours.

One of the pharmacological features of sulfonamides producing satisfactory blood level patterns is plasma binding. *Plasma Binding* occurs with many drugs including sulfonamides. It is a physico-chemical bond primarily with albumin. However, the bond is a loose one. Some characteristics are:

- Drugs prone to binding are more soluble in plasma than water.
- The bound fraction is not available for renal excretion.
- The bound fraction is inactive.
- It is a source of active drug since the drug is released as concentration of unbound falls.

Generally it is a desirable characteristic.

Toxicity

Another important factor to consider in the choice of a sulfonamide is toxicity. To make a critical comparison, one might start with the mouse established oral LD_{50} dose in mg./kg. See Table 4. On this basis sulfathiazole is the least

TABLE 4

ORAL MOUSE LD_{50} DOSE IN MG./KG.

SULFATHIAZOLE	6000
SULFAETHOXYPYRIDAZINE	5000
SULFANILAMIDE	3300
SULFAMERAZINE	2500
SULFAMETHAZINE	1900
SULFADIAZINE	1800
SULFAPYRIDINE	1700
SULFABROMOMETHAZINE	700

toxic while sulfapyridine and sulfabromomethazine are the most toxic of the pyrimidine sulfonamides, sulfaethoxypyridazine is the least toxic. Unfortunately, sufficient published data on comparative toxicity in cattle is not available.

Dosage and Cost Comparison

Table 4 presents a comparison of eight sulfonamide formulations taken from the most recent label instructions. It will be seen that the newest entries to the market, S.E.Z., ALBON, and VETASULID, all carry low dosages, 12.5 to 25 mg./lb. body weight. This illustrates the trend to sulfonamides which are *quantitatively* more active. The cost shown here is derived from the listed price to the veterinarian for convenient calculation, the cost/gram of activity was determined. The cost of treatment is based on a four day regime, which was recommended for each product except SPANBOLETS, where only treatment was given. The cost for boluses are higher than drinking water solutions or soluble powder, reflecting the added cost for formulations.

As we compare the cost for one treatment with another, we must remind ourselves that the products are not equivalent in activity. Also the cost of labor is not included and this cost may, in some cases, equal or exceed the cost of drugs. (With large operations water treatment should always be considered not only for maintenance dosing but initial treatment as well.)

TABLE 5

SULFONAMIDE COST COMPARISON

SULFONAMIDE	Dose Mg./Lb. Body Wt. Initial	Maintenance	Cost Per Gram of Active*	Cost to Treat A 600 Lb. Cow For 4 Days
SULMET (sulfamethazine)	65	32.5	.015 DW** .036 OB***	1.46 3.46
S.E.Z. Sulfaethoxypyridazine	25	25	.03 DW .034 OB	1.80 2.04
SULFABROM Sulfabromamethazine	60-90	every 2 days	.03 DW	2.70
ALBON Sulfadimethoxine	25	12.5	.066 BO****	2.47
VETASULID Sulfachloropyridazine	25	25	.044 BO	2.64
SPANBOLET Sulfamethazine	120	---	.03 BO	2.16 (5 days)
SULFATHIAZOLE	65	65	.008 DW .012 BO	1.25 1.92
TRIPLE SULFA Sulfanilamide 90 gm. Sulfathiazole 90 gm. Sulfamethazine 60 gm.	65	65	.013 DW	1.92

*Calculated from price to the Veterinarian 9/70
**DW = Drinking Water
***OBLETS
****BOLETS

Label claims (see Table 6) vary to some degree from product to product. Most claims are listed for SULMET and SULFABROM. Sulfathiazole and

TABLE 6

SULFONAMIDE LABEL CLAIMS

	Sulmet	S.E.Z.	Sulfabrom	Albon	Vetasulid	Spanbolet	Sulfathiazole	Triple Sulfa
Foot rot	X	X	X	X		X		
Shipping fever	X	X	X	X		X	X	X
Pneumonia	X	X	X	X		X	X	X
Diptheria	X		X	X		X	X	X
Peritonitis			X					
Septicemia	X							
Enteritis	X			X	X	X	X	X
Metritis	X	X						
Mastitis	X	X	X					
Coccidiosis	X		X					

triple sulfas, although used extensively have not been field evaluated sufficiently to develop data for publication. Most sulfonamides have foot rot, shipping fever and pneumonia claims. The mastitis claim is limited to three sulfonamides and coccidiosis to two.

Sulfonamide label restrictions are presented in Table 7. On milk withdrawal ALBON has the shortest, 48 hours, while SULFABROM and SULMET require 96 hours. This is partly related to the dose required. On days to slaughter S.E.Z., SULFABROM and SPANBOLETS require a minimum of 10 to 16 days.

TABLE 7

SULFONAMIDE LABEL RESTRICTIONS

	Milk Withdrawal Hours	Minimum Days to Slaughter
Sulmet	96	7
S.E.Z.	72	16
Sulfabrom	96	10
Albon	48	5
Vetasulid	Not Approved	Not Stated Calves Only
Spanbolet	Not Approved	15
Sulfathiazole	No Data	No Data
Triple Sulfa	No Data	No Data

One method of judging acceptance or trends in formulation use, is a survey. Table 8 shows of all sulfonamide formulations offered, drinking water

TABLE 8

SULFONAMIDE FORMULATIONS 1969

	% Sales
Drinking Water	65
OBLETS(R) – Bolets – Tablets	30
Injectable	5

administration forms are in the greatest demand. Some reasons are:

- Rising cost of labor
- The realization that handling can reduce feed intake and gains for three days.

From a technical point of view, drinking water administration is good therapy:

- In the first day or two of illness many animals will drink when they refuse to eat.
- Most sulfonamides are palatable and lower dosage helps to assure acceptance.
- The margin of safety and efficacy is acceptable and permits good blood levels in spite of variation in intake.
- Blood levels rise rapidly and are maintained throughout the treatment period.

One disadvantage is the lack of suitable or sufficient watering troughs in some facilities.

Boluses are also widely used. Injectable forms are the least used due to the preference for antibiotics by this route.

In conclusion:

- We believe sulfonamide therapy will continue to be widely used.
- Sulfonamides should not be selected on the basis of *in vitro* activity alone.

- All sulfonamides have the same mode of action. The differences are mainly due to pharmacological activity.
- Blood level patterns are the best single criteria to judge potential activity.
- Water administration is widely accepted, effective and economical.

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TRANSPORT OF PASSIVE IMMUNITY TO THE CALF

(Continued from page 39)

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