A COMPARISON OF THE PHYSICAL PROPERTIES AND ABSORPTION RATES OF COMPRESSED TABLETS MADE FROM MICROCRYSTALLINE AND REGULAR SULFADIAZINE

by
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INTRODUCTION

There are several references in the literature (2,4,9,11,14) pointing out that many substances become more active physiologically when their particle size is reduced to microscopic dimensions. J. G. Reingold, F. J. Phillips, and H. F. Flippin report:

> Microcrystalline sulfonamides have shown differences from ordinary sulfonamides in both pharmacodynamic behavior and therapeutic activity. In general, such differences suggest that in microcrystalline form the activity is enhanced, but the information available is limited, and it is desirable that further investigations be made. (11)

These microcrystalline drugs have been shown to be more active when taken internally as a suspension, (4,11) when applied locally as a powder (6) or ointment, (9) or when inhaled as a powder, (8) than the regularly used crystalline form. However, there is no mention in the literature of any compressed tablets being made from microcrystalline drugs. Since compressed tablets provide one of the most economical, stable, and satisfactory forms of medication, it was considered worthwhile to investigate the possibilities of making tablets from microcrystalline drugs. Sulfadiazine was selected for the experiment since it is readily available in both microcrystalline and macrocrystalline forms, it is widely used in the form of tablets, and its rate of absorption from the gastrointestinal tract can be followed by well established methods for determining its concentration in the blood.

HISTORICAL BACKGROUND

The use of microcrystalline drugs and chemicals is relatively new because only in recent years has it been possible to produce a powder with a maximum particle size of less than ten microns. Several machines are in use today which will reduce the particle size of a powder to the microcrystalline and semi-microcrystalline state. In 1938, M. A. Lissman (10) described a machine, the "Micronizer", which is a jet induction mill developing its pulverizing properties from jets of compressed gas or superheated steam. These jets are set at an angle into a cylindrical structure with an aperture in the center for withdrawing the finely ground powder. The force of the compressed gas causes a whirling motion into which the substance to be ground is introduced. The grinding action comes from the particles colliding with each other at great speed. One advantage of the jet induction mill is that the sudden expansion of the gases upon entering the grinding chamber causes a refrigerating effect which holds to a minimum the heat generated by friction. In 1946, C. E. Berry (1) described several different machines, both rotor and jet induction types, which are used in the production of microcrystalline products. The rotor type mill differs from the jet induction type in that the pulverizing action comes from the grinding of the material between a rotating wheel known as a rotor and a stationary abrasive surface.

Powdered insecticides were among the first relatively insoluble substances investigated with the purpose of determining the specific effect of microcrystalline particle size. In 1941, L. M. Bertholf and J. E. Pilson (2) experimented with the toxicity of lead arsenate on the

honeybee, Apis mellifera. They compared the toxicity of this poison in relation to its particle size and found that the median lethal dose of the lead arsenate with a particle size of eighteen microns was one hundred and eighty-five micrograms per bee, while that of lead arsenate with a particle size of two microns was only five micrograms. These men concluded that, "When materials of different particle size were used, the fine fractions were on the whole more toxic than the coarse." (2) In 1942, C. M. Smith and L. D. Goodhue (14) reviewed the literature concerning the effectiveness of powdered insecticides and concluded that the smaller the particle size, the more effective the insecticide.

L. A. Chambers, T. N. Harris, F. Schuman, and L. K. Ferguson (6) reported in 1942 that microcrystalline sulfathiazole had been used advantageously in trauma and minor surgery. They found that a more rapid solution and absorption was obtained with microcrystalline sulfathiazole than was obtained with the regular crystals. They also reported that the microcrystalline sulfathiazole was much less likely to clump when put into a suspension or sprinkled on a wound. L. E. Silcox and H. P. Schenck (13) used microcrystalline sulfathiazole in 1942 in cases of acute upper respiratory infections, acute and chronic sinusitis, and chronic suppurative otitis media. These men report:

> The drug (sulfathiazole) is finely divided and is in direct contact with infected tissues over a large surface area. . . . . The microcrystals are removed completely from sinus cavities within four or five days, either by ciliary movement or by absorption, and are found experimentally to be diffused over the surface of the membrane rather than deposited in one area as a powder. (13)

They also reported that the microcrystalline drug gave better results, less toxic reactions, and that less complications resulted in those cases treated with microcrystalline sulfathiazole than in those

treated with the usual therapeutic measures.

In 1943, T. N. Harris, H. E. Sommer, and C. C. Chapple (8) used microcrystalline sulfathiazole experimentally in mice as an inhalant. The crystals were suspended in a fine mist, and as the water evaporated, a "smoke" was produced. The mice showed a high blood level of the drug very soon after inhaling this "smoke", and its use in pneumonia seemed indicated. Also in 1943, T. N. Harris (7) used microcrystalline sulfathiazole in cases of Impetigo contagiosa. He reported a much better result from the use of the microcrystalline drug than with the ordinary powdered drug. In his report, Harris sets forth his beliefs as to why the microcrystalline sulfathiazole is better than the regularly used powder.

> The improved results in the treatment of impetigo reported here are due only to the physical form of the agent and its chemical simplicity. Ordinary sulfonamide powders cake on lesions of impetigo for the same reason that they cake in pure aqueous suspension, presumably because the grains of powder are not naturally crystalline in shape. The microcrystalline drug maintains the separation of the crystals, assuring a much greater surface for solution into local tissue fluids and a continued distribution over the lesion. (7)

J. W. Bigger and G. A. Hodgson (3) corroborated this report in 1944, stating that microcrystalline sulfathiazole caused a more rapid healing than the regular crystalline form in all cases of Impetigo contagiosa that they had treated.

In 1945, J. G. Reingold, F. J. Phillips, and H. F. Flippin (11) reported that they had conducted clinical experiments on the absorption rate of regular and microcrystalline sulfadiazine when taken internally in the form of a suspension. They state:

> 1. Patients receiving by mouth suspensions of microcrystalline sulfadiazine (3 gm.) showed significantly higher concentrations of sulfadiazine in serum during the first six hours following its ingestion than did those who received ordinary sulfadiazine.

2. The excretion of sulfadiazine in the urine of those receiving microcrystalline material was likewise significantly higher during this period. These observations indicate that microcrystalline sulfadiazine is absorbed more rapidly than is ordinary sulfadiazine. (11)

In 1947, E. M. Boyd and R. W. Dingwall (4) duplicated this experiment using a four gram dose, and obtained approximately the same results. However, they also found that when the dosage was continued, there was no significant difference in the blood levels which were maintained by the microcrystalline and the regular drug after the first six hours.

In 1949, B. Levy and C. L. Huyck (12) reported that there was a faster diffusion rate from ointment bases of the microcrystalline sulfadiazine than the regular crystalline form. For this test the ointment was placed on a 4% agar gel containing Ehrlich's Aldehyde Reagent, which turns yellow when in contact with sulfadiazine. The rate of diffusion was then determined by the depth of color formation in the gel in a specified period of time.

EXPERIMENTAL

Manufacture of Tablets

The tablets used in this experiment were made by the wet granulation method. An attempt was made to manufacture the tablets by the dry granulation method, but this was found to be impractical on the small machine available since the fine powder would not flow smoothly into the die to make the "slugs". Several formulas using different binders were tried to determine which formula would make the most satisfactory tablet. In each formula 25% corn starch was used as a disintegrating agent. Binders of starch paste, light syrup, acacia, and sucrose were tried. The formula which seemed to make the best tablets with the most satisfactory disintegration and hardness is given below.

Sulfadiazine, USP	70%
Corn Starch, USP	25%
Acacia Powder, USP	2%
Magnesium Stearate, Medicinal	3%

Mix the sulfadiazine, corn starch, and acacia thoroughly and granulate by moistening with water and forcing the mass through a #12 seive. Dry the granulation in a hot air oven, pass again through the #12 seive and mix lightly with the magnesium stearate, which acts as a lubricant. Compress into tablets using a 3/8" die.

The above formula and procedure were followed in making both the tablets of the microcrystalline sulfadiazine and those of the regular sulfadiazine. The microcrystalline sulfadiazine used was obtained from the Calco Chemical Company, while the regular sulfadiazine used was obtained from Abbott Laboratories.

The particle size of both types of sulfadiazine was determined with the aid of a microscopic red blood cell counting chamber. It was found that the particle size of the regular sulfadiazine was fifteen to

thirty microns in length and five microns in width, while the particle size of the microcrystalline sulfadiazine was two to four microns in length and one and one-half microns in width.

Three hundred tablets were made from each type of sulfadiazine, each tablet containing 0.265 grams of sulfadiazine. It was not possible to compress both types of sulfadiazine with the same pressure setting on the tablet machine since the microcrystalline product is very light and gram for gram occupies considerably more space than does the regular product. The tablets were made on a type "F" single punch Stokes tablet machine.

Physical Properties of Tablets

Some differences were noted in the physical properties of the tablets made from the regular and from the microcrystalline sulfadiazine. The tablets of microcrystalline sulfadiazine were more glossy in appearance, had a more brittle fracture with a clean break and little crumbling, and had less tendency to break when dropped or handled roughly than had the tablets made from the regular sulfadiazine.

It was also noted that the tablets made from the microcrystalline sulfadiazine disintegrated in water more rapidly than did the other group. To test the disintegration time, the tablet was laid across two wires which were about 1/8" apart. Another wire in the form of a large hook with a weight suspended from it was placed over the tablet in such a way that when the tablet disintegrated the weight would fall to the bottom of the container holding the apparatus. To time the disintegration of a tablet, the apparatus with the tablet in place was lowered into the water and the time recorded from the moment the tablet came in contact with the water until the weight dropped. Twenty tablets were

picked at random from each group of tablets and were tested in the above manner. It was found that the average disintegration time of the microcrystalline tablets was 46.1 seconds, while the time for the regular tablets was 57.3 seconds. This represents a decrease of approximately 20% in the disintegration time of the tablets made from the microcrystalline sulfadiazine over those of the regular sulfadiazine. Since both types of tablets disintegrated in less than one minute, this factor does not seem significant. Figure I represents a breakdown of the disintegration times of the individual tablets.

Absorption Rate of Sulfadiazine in Dogs

The method used for determining the blood level of the sulfadiazine and thereby showing the absorption rate of the drug was the method developed by Marshall and Bratton (5) and described below.

Reagents:

1. 15% trichloracetic acid
2. 1:1000 sodium nitrite
3. 0.5% ammonium sulfamate
4. 1:100 n-(1-naphthyl)ethylenediamine dihydrochloride

Method:

1. For setting up standard curve:
   a. Make known dilutions of sulfadiazine covering the expected range of blood levels.
   b. To 2 cc of each known dilution, add 8 cc of the trichloracetic acid solution and 30 cc of distilled water. This makes a 1:20 dilution.
   c. To a 10 cc aliquot of each dilution prepared above add 1 cc of the sodium nitrite solution. Let stand for 3 minutes.
   d. Add 1 cc of the ammonium sulfamate solution. Let stand for 2 minutes.
   e. Add 1 cc of the n-(1-naphthyl)ethylenediamine dihydrochloride solution. Let stand for about ten minutes for optimum color formation, and read the percent transmission of light on a spectrophotometer. Plot the results on semi-logarithmic graph paper.

2. For determining the sulfadiazine level in blood:
   a. Lake 2 cc of the blood with 30 cc distilled water and add 8 cc of the trichloracetic acid solution. Let stand for about 15 minutes and filter.
   b. Take a 10 cc aliquot and add 1 cc of the sodium nitrite solution. Let stand for 3 minutes.
   c. Add 1 cc of the ammonium sulfamate solution. Let stand for 2 minutes.
   d. Add 1 cc of the n-(1-naphthyl)ethylenediamine dihydrochloride solution. Let stand for about 10 minutes for optimum color formation.
   e. Read the percent transmission on a spectrophotometer and compare with the standard curve for milligrams of sulfadiazine per 100 cc whole blood.
   f. If the expected blood level is very high or extremely low, the dilution can be made stronger or weaker than the 1:20 described above. This dilution is then compared the same as those above with a standard curve made from the same dilution.

A standard curve was set up for this experiment by preparing known standards of one, two, three, four, and five milligrams of sulfadiazine to each one hundred cubic centimeters of solution. These known dilutions were treated as described above, and readings were taken from a Central Scientific Company Spectrophotometer using a green filter. On four different occasions the standard dilutions were prepared and the results recorded. These results were then averaged, and the final result was plotted on semi-logarithmic graph paper (Figure II).

To test the accuracy of this method in recovering the sulfadiazine from blood, five samples of beef blood containing varying known amounts of sulfadiazine were prepared. The sulfadiazine was determined by the above method, and the results were found to be accurate to within one-half of a milligram per one hundred cubic centimeters of blood.

It was felt that dogs would be the most satisfactory animal to use in comparing the absorption rates of the two types of tablets. It has been shown that the absorption curve of sulfonamides in dogs is more regular and predictable than is the curve in other animals such as cats

or rabbits. (15) Since sulfonamides are not acetylated in dogs as they are in most animals, (12) the determination of the blood level is simplified since it is not necessary to hydrolize the acetylated compound to the sulfonamide base before testing. Another factor which made dogs a practical animal for the purpose of this experiment is that dogs are large enough to be fed the tablets orally without difficulty and also have large enough veins to permit the withdrawal of numerous samples of blood for the purpose of determining the blood level of the sulfadiazine without seriously injuring the vein.

For this experiment two dogs were used, one a male animal weighing twelve and one-half kilograms (dog #1), the other a female weighing five and seven-tenths kilograms (dog #2).

In the comparison of the tablets prepared for the experiment from the microcrystalline and from the regular sulfadiazine, the dogs were fed the tablets of sulfadiazine and blood samples were taken at approximately one-half, one, two, three, four, six, eight, and twenty-four hours. Since the blood of dogs clots very rapidly, (15) the inside of the syringe was wetted with a 1% solution of heparin. This procedure made possible the accurate measurement of two cubic centimeters of blood. Approximately three cubic centimeters of blood were withdrawn for each determination and placed in a test tube. Two cubic centimeters of blood could then be accurately measured with a two cubic centimeter pipette. Food was withheld from the animals for twenty-four hours prior to the test and water for at least thirty minutes prior to the test. The water and food were also withheld during the first eight hours after feeding the tablets. A rest period of at least three days was allowed between each series of tests to allow the sulfadiazine to be completely excreted.

The two types of sulfadiazine tablets were compared three separate times on the small female dog and twice on the large male dog. In the first two comparisons on the small dog and the first comparison on the large dog, only whole tablets were used with the result that the dosages were not exactly the same for each dog. In the final test on both dogs, the dosage was adjusted by breaking a tablet in such a way as to have both dogs receive the same dose per kilogram of body weight.

Results of all the tests are plotted on the graphs marked Figures III and IV. The results were then averaged in order to get a more concise picture of the differences in the absorption rates, and this average is shown on the graph marked Figure V.

Discussion

It seems that tablets made from microcrystalline sulfadiazine possess somewhat better physical properties than the tablets made from the regularly used sulfadiazine. They have a hard, glossy surface which is pleasing to the eye and a hard finish which does not chip easily. These tablets of microcrystalline sulfadiazine also break more cleanly with a brittle fracture. Scored tablets provide more accurate dosage with less waste of tablets where it is necessary to administer one-half tablet per dose. The fact that there is approximately a 20% decrease in disintegration time in the microcrystalline tablets over the regular does not seem to be of significant importance since both types of tablets disintegrate in a matter of seconds. However, with drugs which form slowly disintegrating tablets, the use of the microcrystalline form might prove important in assuring disintegration in the gastrointestinal tract.

A comparison of the absorption rates in the two dogs does not definitely prove or disprove the possibility of a faster and/or higher

blood level by the administration of tablets made from microcrystalline sulfadiazine. In the first place, the results are not statistically important since only two dogs were available for the experiment. Moreover, it is possible that the great difference in the weights of the two dogs used may have had some influence on the absorption rates.

After each feeding of the tablets, it was observed that at least an hour lapsed before there was an appreciable rise of the blood level of the sulfadiazine. On one occasion there was a delay of three hours before a significant amount of sulfadiazine appeared in the blood of either dog. It is suspected, although impossible to prove, that the animals were inadvertantly fed just prior to the feeding of the tablets on that particular day.

The difference in the reactions of the two dogs was much more noticeable than was the difference in the absorption rates of the two types of tablets. The small dog (dog #2) consistently showed a higher blood level with the microcrystalline sulfadiazine than with an equivalent dose of the regular drug. However, the large dog (dog #1) showed no significant difference in the blood level obtained from either type tablet.

The different reactions received from the two dogs make a definite conclusion impossible as to the speed of absorption of the microcrystalline sulfadiazine as compared with the speed of absorption of the regular sulfadiazine; therefore, more experimentation seems indicated.

CONCLUSIONS

1. Compressed tablets of microcrystalline sulfadiazine are glossier, more easily divided accurately, and faster disintegrating than are compressed tablets made from the regularly used sulfadiazine.

2. There is enough evidence to show a possibility that compressed tablets made from microcrystalline sulfadiazine will produce a higher blood level of the drug in the blood of dogs, but more extensive experimentation is needed before a definite conclusion can be drawn.

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FIGURE I

DISINTEGRATION TIMES OF MICROCRYSTALLINE AND REGULAR SULFADIAZINE TABLETS

Disintegration Times of Tablets Made From Microcrystalline Sulfadiazine	Disintegration Times of Tablets Made From Regular Sulfadiazine
Seconds	Seconds
32	47
33	49
35	49
36	50
39	50
39	50
40	55
40	55
43	56
43	58
43	59
43	59
46	60
50	60
52	62
56	64
57	73
60	75
67	76
67	90
Median - 43	Median - 58
Mean - 46.1	Mean - 57.3

FIGURE II

STANDARD CURVE FOR DETERMINING BLOOD LEVELS OF SULFADIAZINE

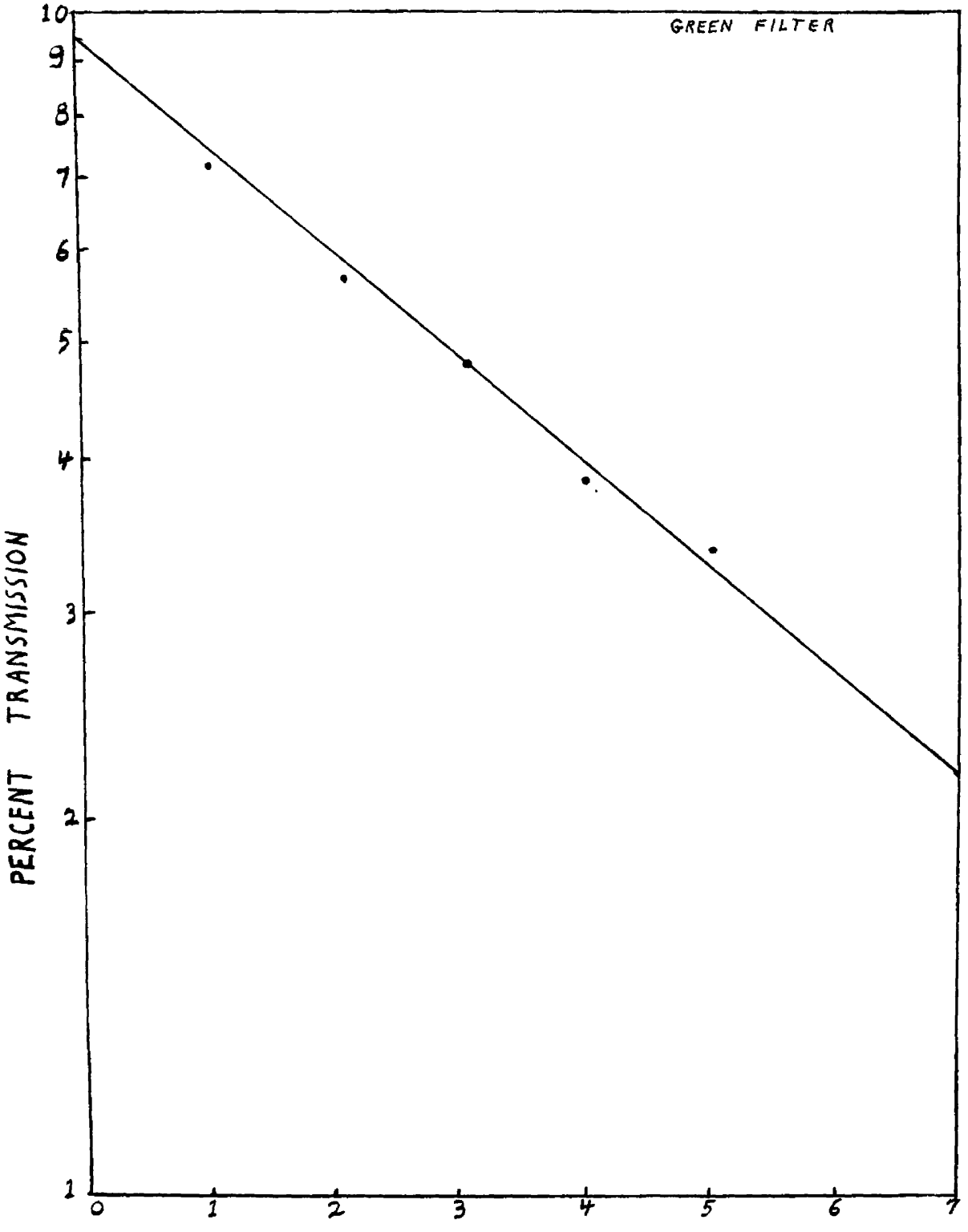

FIGURE III

BLOOD LEVELS OF SULFADIAZINE IN DOG # 1

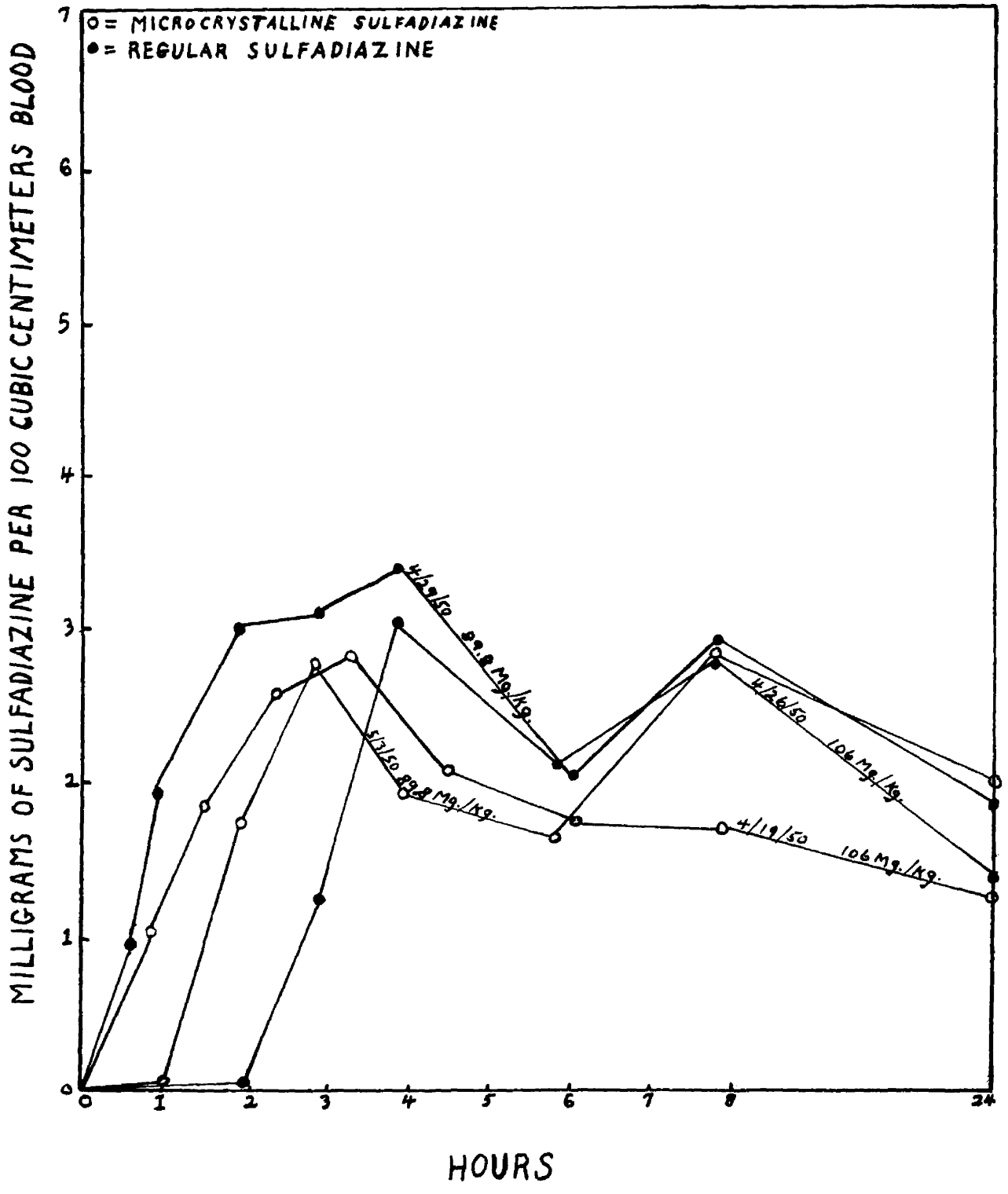

FIGURE IV

BLOOD LEVELS OF SULFADIAZINE IN DOG #2

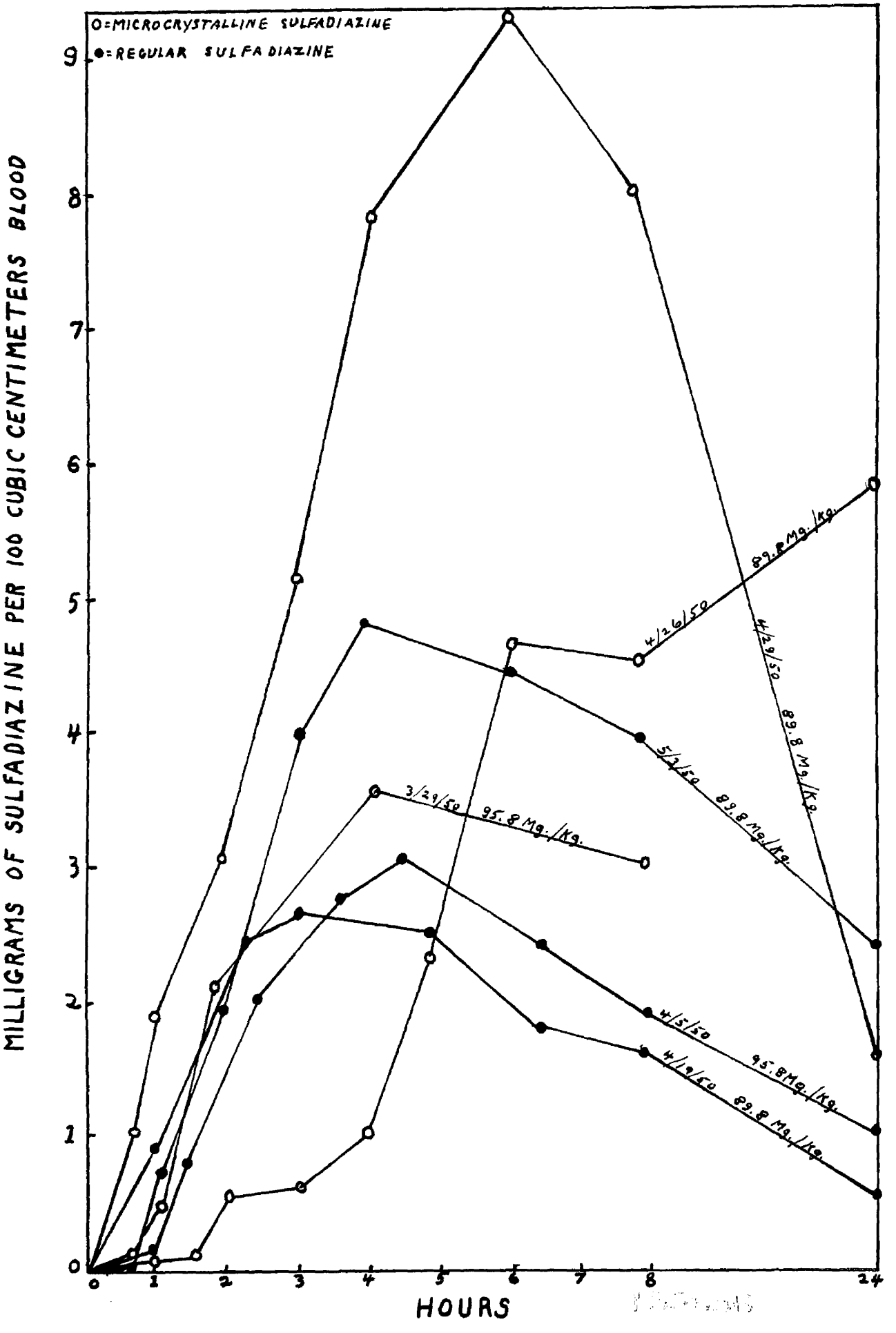

FIGURE V

AVERAGE BLOOD LEVELS OF ALL TESTS