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A COMPARATIVE STUDY OF THE BLOOD CONCENTRATIONS AND URINARY EXCRETION OF SULFAPYRIDINE AND SULFANILAMIDE AFTER SINGLE DOSES OF SULFAPYRIDINE AND RELATED COMPOUNDS ADMINISTERED BY VARIOUS ROUTES

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Research Article

A COMPARATIVE STUDY OF THE BLOOD CONCENTRATIONS AND URINARY EXCRETION OF SULFAPYRIDINE AND SULFANILAMIDE AFTER SINGLE DOSES OF SULFAPYRIDINE AND RELATED COMPOUNDS ADMINISTERED BY VARIOUS ROUTES

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We have recently had available a solution containing a high concentration of sulfapyridine in 50 per cent glucose which can be conveniently administered orally, subcutaneously and intravenously (1). This offered an opportunity to study the effect of the route of administration of a drug containing sulfapyridine on the blood level and urinary excretion and to compare it with other derivatives of sulfanilamide. The results of the biochemical studies are presented in this paper. The bacteriological and clinical results are presented elsewhere (1, 2).

METHODS AND MATERIALS

Four subjects were studied. They were maintained on a house diet and their average fluid intake was about 3 liters daily. There was no demonstrable kidney damage present in any of these patients. In the case of Subject B, who is reported in detail, the phenolsulfonphthalein excretion was normal and showed no change after the investigation was completed. In no instance did vomiting occur following the administration of any of the drugs investigated, nor was there any diarrhoea during the period of observation. Subject A was a 26-year-old white man weighing 127 pounds (58 kgm.), suffering from gonococcal arthritis. Subject B was a 43-year-old white male, weighing 152 pounds (69 kgm.), who had arthritis thought to be of gonococcal origin. Subject C was a 62-year-old white male, weighing 150 pounds (68 kgm.), who was under treatment for a parotid abscess which followed facial erysipelas. Subject D was a 39-year-old white male weighing 156 pounds (70 kgm.), who had active gonococcal arthritis.

The glucose-sulfapyridine solution used in this study was prepared for us by the Research Division of the Lederle Laboratories. It contained[1] 9.5 per cent total sulfapyridine in 50 per cent glucose solution. Approximately 97 per cent of the sulfapyridine was reported to be in the form of a glucose-sulfapyridine compound, as determined by a direct nitrous acid method. Hydrolysis of the compound takes place rapidly in the presence of cold dilute acids. For this reason the colorimetric method of Marshall and Litchfield (3) cannot be used to determine the amount of sulfapyridine in combination with glucose either in the original solution or in the blood.

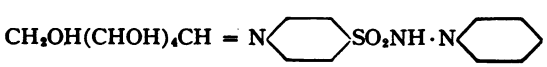
During this investigation the glucose-sulfapyridine solution and sulfanilamide were administered intravenously, subcutaneously and orally; sodium sulfapyridine was given intravenously, and sulfapyridine was given orally. Each drug was given in 4.75 gram amounts in 500 ml. of fluid. Physiological saline was used for the parenteral injections and tap water for the oral doses. The intravenous injections were given over a period of an hour, the subcutaneous ones in about 1½ hours, and the oral doses were divided into 6 parts and given over a period of an hour. Some of the studies were repeated in individual subjects.

All urine samples were saved. Specimens were obtained simultaneously with the blood samples as far as possible. Determination of sulfapyridine or sulfanilamide was made on all samples. Collection of urine was continued until it showed no appreciable amounts of the drug. Before commencing a study of a second drug or changing the route of administration, a further period of 24 hours was usually allowed to elapse.

In vitro studies were conducted by adding sufficient amounts of the compound under investigation to oxalated whole blood to give concentrations of the substance between 8 and 10 mgm. per 100 ml. The hematocrit was determined in each instance and corrected for the oxalate effect. Samples were removed at various times and the concentration of the drug in the whole blood and plasma was determined.

Determinations of sulfapyridine or sulfanilamide were made by Marshall and Litchfield's method (3), and glucose determinations by the method of Folin and Wu (4).

[1] We are indebted to the Research Division of the Lederle Laboratories for assays on the drug. They report the glucose-sulfapyridine compound to be a glucose anil of the general formula:



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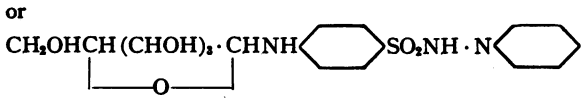

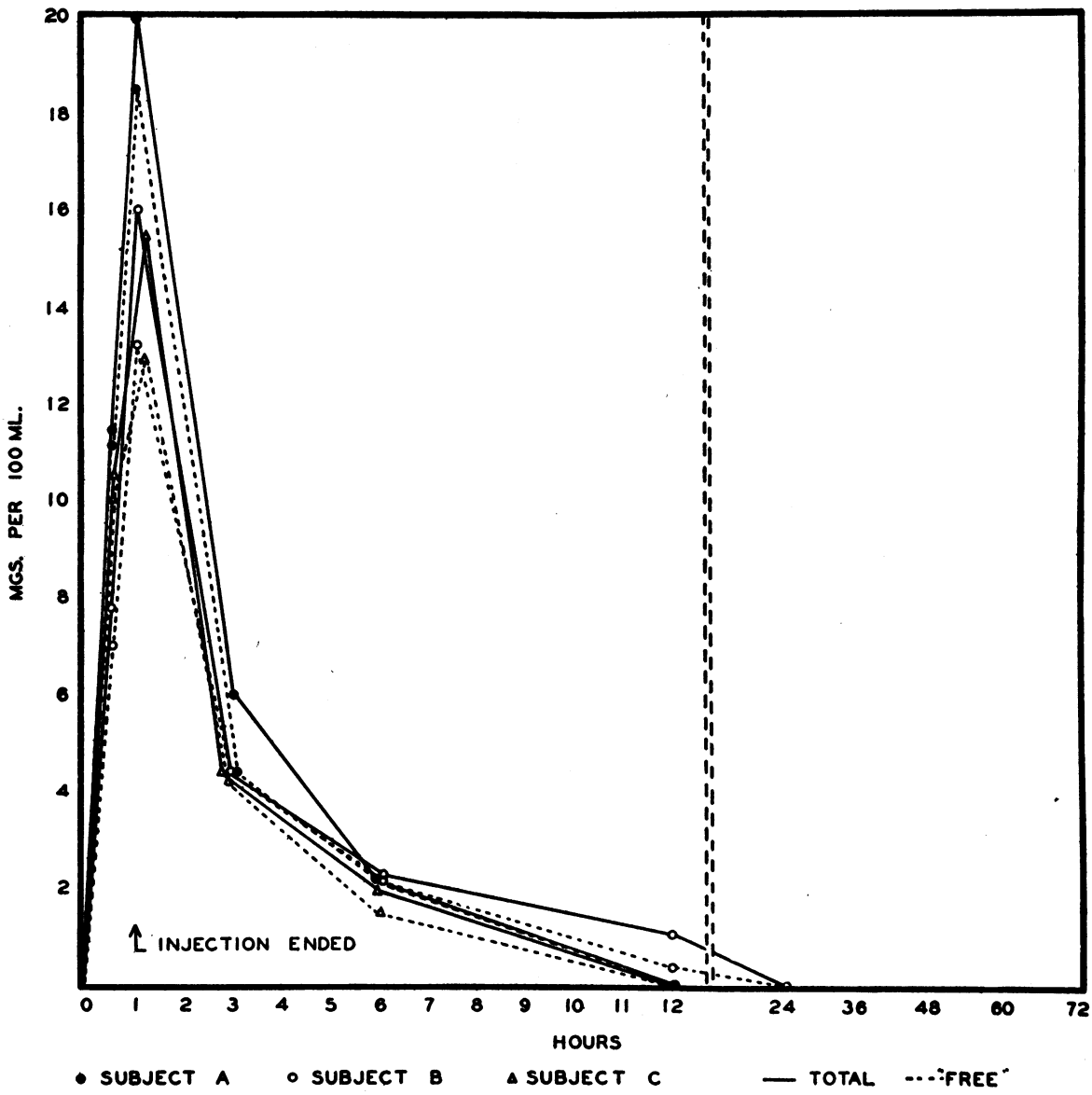

FIG. 1. EFFECT OF INTRAVENOUS INJECTION OF GLUCOSE SULFAPYRIDINE ON THE BLOOD LEVEL

EXPERIMENTAL

The effect of the intravenous administration of glucose sulfapyridine, sodium sulfapyridine and sulfanilamide on the blood level and urinary excretion of sulfapyridine and sulfanilamide, respectively

The sulfapyridine concentrations of the blood in three subjects injected with glucose sulfapyridine intravenously are shown in Figure 1. The data for subject B, who was given all the drugs by all the routes used in this study, are shown in Table I. (This subject's excretion differed in some respects from the other subjects studied in spite of good phenolsulphonphthalein excretion.) During the period of administration the blood level of sulfapyridine rose rapidly, reaching levels between 15 and 20 mgm. per 100 ml. of blood at the end of the injection. The fall in concentration of the drug was equally rapid, only traces being present in the circulating blood 11 hours after the injection ended.

There was a rise in blood glucose comparable to that found after the intravenous injection of an

equivalent amount of glucose over a period of 1 hour (Table II). However, this temporary hyperglycemia was not accompanied by a glycosuria. The sulfapyridine was rapidly excreted into the urine and was recovered completely in 24 hours. Between 11 and 27 per cent was recovered while the injection was still in progress.

About 70 per cent of the drug was present in the urine in the conjugated form as determined by Marshall's method (3). Whether this conjugated compound is the acetyl-derivative was not determined. Even in the samples containing large amounts of conjugated sulfapyridine, there was no detectable glycosuria (Table II). Presumably the glucose compound was not being excreted as such.

The urinary excretion of the drug was somewhat dependent on diuresis. There was, however, a direct relationship between the blood level of sulfapyridine and the amount of the drug excreted in the urine.

Following the injection of sodium sulfapyridine the maximum blood levels were not as high as those obtained for the glucose compound, but significant amounts of both free and total sulfapyridine were present 12 hours after the injection. The blood contained traces of free sulfapyridine and determinable amounts of total sulfapyridine 36 hours after injection (Table I and Figure 2). Between 88 and 100 per cent of the circulating sulfapyridine at the end of the injection period was in the free form. In two patients this partition was rapidly reduced so that in 12 hours be-

TABLE I

Effect of administration of certain derivatives of sulfanilamide on the blood level and urinary excretion of these substances in Subject B

Compound	Route	Time*	Blood			Urine							Remarks
			Concentration of drug			Volume	Water excretion	Concentration of drug		Excretion of drug		Per cent of administered dose excreted (cumulative)		
			Free†	Total	Conjugated			Free	Total	Free	Total	Free	Total	
		hours	*mgm. per 100 ml.*		*per cent*	*ml.*	*ml. per minute*	*mgm. per 100 ml.*		*mgm. for period*		*per cent*		
Glucose Sulfapyridine	Intravenous	½	10.6	11.0										
		1	18.4	20.0		120	2.0	107.5	468	129	562	2.7	11.8	Injection ended at 1 hour
		3	4.5	5.8		300	2.5	174.7	775	524	2325	13.7	60.7	
		6	2.2	2.3		800	4.3	49.5	180	396	1440	22.0	91.2	
		12½	T	T		1400	3.7	12.4	44	174	615	25.7	104.1	All values as sulfapyridine
		24½	T	T		1350	1.9	4.5	17	61	230	27.0	109.0	
		46	0	0		2600	2.0	T	3		78		110.6	
Sodium Sulfapyridine	Intravenous	½	4.4	5.3	17	620		4.7	6.3	29	39	0.6	0.8	
		1	9.5	10.3	8	30	1.0	47.1	65.6	14	20	0.9	1.2	Injection ended at 1 hour
		3	6.9	8.5	19	300	2.5	40.8	64.1	122	192	3.5	5.3	
		6	5.0	7.4	32	600	3.3	26.8	74.3	161	446	6.9	14.7	
		12	2.9	5.4	46	980	2.7	22.6	84.0	222	823	11.5	32.0	All values as sulfapyridine
		24	T	3.2	100	780	1.1	23.6	179.1	184	1397	15.4	61.4	
		36	T	1.8	100	1640	2.3	4.7	45.2	77	741	17.0	77.0	
		48	T	T		1000	1.4	3.4	40.7	34	407	17.7	85.5	
		72	T	T		2900	2.0	0.8	6.9	23	200	18.2	89.7	
		94				2800	2.1	T	1.3		36		90.5	
		119				240		T	1.5		4		90.6	
Sulfanilamide	Intravenous	¼	8.1	8.1	0	75	5.0	24.8	24.8	19	19	0.4	0.4	
		¾	11.7	13.4	13	215	7.2	54.0	58.7	116	126	2.8	3.0	Injection ended ¾ hour
		2¾	8.3	9.5	13	430	3.6	55.8	70.0	240	301	7.9	9.3	
		5¾	7.1	8.6	17	1150	6.4	24.8	30.6	285	352	13.9	16.7	
		12	4.3	7.2	40	740	1.8	42.5	70.2	314	519	20.5	27.6	All values as sulfanilamide
		24	2.7	4.9	45	1400	1.9	29.1	65.7	407	920	29.1	47.0	
		36	1.6	3.6	56	1850	2.6	13.1	43.7	242	808	34.1	64.0	
		48	T	2.8	100	680	0.9	12.2	60.1	83	408	35.8	72.6	
		68½				1300	1.1	6.2	30.9	81	402	37.5	81.1	
		71½	T	T		610	3.3	3.8	24.8	23	151	38.0	84.3	
Glucose Sulfapyridine	Subcutaneous	1	1.8	2.5										
		3	4.6	6.6		650	3.6	18.2	117.0	118	761	2.5	16.0	
		6	4.0	5.2		380	2.1	62.5	290.1	237	1102	7.0	39.2	Injection ended 1½ hours
		12	2.0	3.3		1000	2.8	32.2	165.5	322	1655	13.8	73.9	
		24	T	T		1100	1.5	27.3	86.2	306	948	20.1	93.9	
		36	Sl.T.	Sl.T.		2000	2.8	1.3	8.1	26	162	20.6	97.3	All values as sulfapyridine
		48	Sl.T.	Sl.T.		900	1.2	1.2	5.9	10.8	53	20.8	98.4	
		69				2900	2.3	T	1.3		37		99.2	
		72	0	0		250	1.4	T	1.7		4		99.3	

TABLE I—*Continued*

Compound	Route	Time*	Blood: Concentration of drug: Free†	Blood: Concentration of drug: Total	Blood: Concentration of drug: Conjugated	Urine: Volume	Urine: Water excretion	Urine: Concentration of drug: Free	Urine: Concentration of drug: Total	Urine: Excretion of drug: Free	Urine: Excretion of drug: Total	Urine: Per cent of administered dose excreted (cumulative): Free	Urine: Per cent of administered dose excreted (cumulative): Total	Remarks
		hours	*mgm. per 100 ml.*		*per cent*	*ml.*	*ml. per minute*	*mgm. per 100 ml.*		*mgm. for period*		*per cent*		
Sulfanilamide	Subcutaneous	¼	T	1.9	100	180	4.0	2.8	12.7	5	23	0.1	0.5	
		1½	1.8	3.1	41.9	20	0.4	10.6	21.6	2	4	0.1	0.6	Injection ended at 1½ hours
		3	3.8	5.0	24.0	190	2.1	24.7	41.7	47	79	1.1	2.3	
		6	9.0	10.6	15.1	450	2.5	53.4	77.0	240	346	6.1	9.6	
		12	4.7	6.7	29.9	1600	4.4	46.9	74.1	750	1186	21.9	34.5	All values as sulfanilamide
		24	2.1	3.5	40.0	1160	1.6	43.8	110.0	508	1276	32.6	61.4	
		50	1.2	3.0	60.0	2350	1.5	19.9	52.3	468	1229	42.5	87.3	
		74	T	2.1	100.0	1840	1.2	6.2	30.3	114	558	44.9	99.0	
		92½				3000	2.7	1.0	5.8	30	174	45.5	102.7	
		95	T	T		200	1.3	1.6	12.2	3	24	45.6	103.2	
Glucose Sulfapyridine	Oral	1	T	T		400	6.6	0.8	1.6	3	6	0.1	0.1	
		3	T	1.7	100	25	0.2	22.6	59.2	6	15	0.2	0.4	Administered over first hour
		6	T	1.8	100	150	0.8	26.6	96.1	40	144	1.0	3.4	
		12	T	1.9	100	700	2.0	10.5	43.5	73	304	2.5	9.8	
		24	1.6	2.9	45	650	0.9	23.5	119.0	153	773	5.7	26.1	All values as sulfapyridine
		36	1.5	3.0	50	1450	2.0	16.3	73.7	236	1069	10.7	48.6	
		48	T	2.0	100	720	1.0	20.0	128.2	144	923	13.7	68.0	
		72				2800	2.0	3.1	23.4	87	655	15.5	81.8	
		94				2500	1.9	1.0	2.5	25	62	16.0	83.1	
		96	0	0		15	0.5	1.5	5.9		1			
Sulfanilamide	Oral	6	6.6	7.8	15.4	1600	4.4	27.5	40.0	440	640	9.3	13.5	
		12	4.7	6.9	31.9	800	2.2	52.5	88.8	420	713	18.1	28.5	Administration over 1 hour
		24	3.3	7.1	53.5	1050	1.4	39.2	99.0	412	1040	26.8	50.1	1st sample at 6 hours
		36	1.9	3.8	50.0	1200	1.7	9.6	26.4	115	316	29.2	57.1	
		48	1.3	3.2	59.1	1000	1.4	11.8	43.7	118	437	31.7	66.3	All values as sulfanilamide
		72	T	2.0	100.0	2700	1.9	5.4	21.8	146	588	34.8	78.7	
		96	T	1.5	100.0	3100	2.2	1.8	6.5	56	201	36.0	82.9	
		120	0	T		2900	2.0	T	3.9		115		85.3	
		141	0	Sl.T.		2900	2.3	T	1.0		29		85.9	
		144				300	1.7	T	2.1		6		86.0	
Sulfapyridine	Oral	6	4.4	6.5	32.3	1600	4.4	10.8	19.7	173	315	3.6	6.6	
		12	3.2	7.4	56.8	820	2.3	26.4	84.4	216	692	8.1	21.2	Administration over 1 hour
		24	1.4	3.6	61.1	550	0.8	30.2	15.0	166	1182	11.6	46.1	
		48	Sl.T.	T		2800	1.9	5.2	41.8	146	1170	14.7	70.7	1st sample at 6 hours
		72½	0	V.Sl.T.		2950	2.0	1.1	8.6	32	254	15.4	76.0	
		96				2950	2.1	0.5	1.6	15	47	15.7	77.0	All values as sulfapyridine
		120				3400	2.4	T	0.6	T	20		77.4	

* All times recorded from commencement of administration of drug.

† The values given for " free " sulfapyridine following the administration of *glucose sulfapyridine* refer only to the values given by the Marshall method without hydrolysis (3) and *do not imply* that the sulfapyridine was present in the free form.

T = Trace. Sl.T. = Slight trace. V.Sl.T. = Very slight trace.

TABLE II

The effect of the intravenous administration of glucose and of glucose sulfapyridine on the concentration of glucose in the blood and urine of Subject B

Time	Glucose: Blood glucose	Glucose: Urine glucose	Glucose sulfapyridine: Blood glucose	Glucose sulfapyridine: Urine glucose
hours	*mgm. per 100 ml.*	*grams per 100 ml.*	*mgm. per 100 ml.*	*grams per 100 ml.*
Fasting	90.9	Less than 0.10	115.0	0.25
½ hour after injec.	144.5	Less than 0.10	181.1	
1 hour after injec.	171.8	Less than 0.10	227.5	0.20
2 hours after injec.	115.6	Less than 0.10		
3 hours after injec.	96.6	Less than 0.10	95.8	0.20
4 hours after injec.	84.4	Less than 0.10		
6 hours after injec.				Less than 0.10
12 hours after injec.				Less than 0.10

tween 40 and 46 per cent was circulating as the conjugated drug.

The excretion of sulfapyridine into the urine after the injection of sodium sulfapyridine was much slower than in the case of the glucose compound (Table I). In 96 hours, however, 90 per cent of the administered sulfapyridine had been excreted. About 75 per cent of the total sulfapyridine excreted was in the form of the conjugated drug and this percentage was approximately the same whether the sodium salt or the glucose compound was injected.

The effect of diuresis on the urinary excretion of sulfapyridine was not marked in Subject B, but in the other two individuals the maximum excretion of the drug into the urine corresponded to a period of maximum diuresis. There was no parallelism between the blood level and the ex-

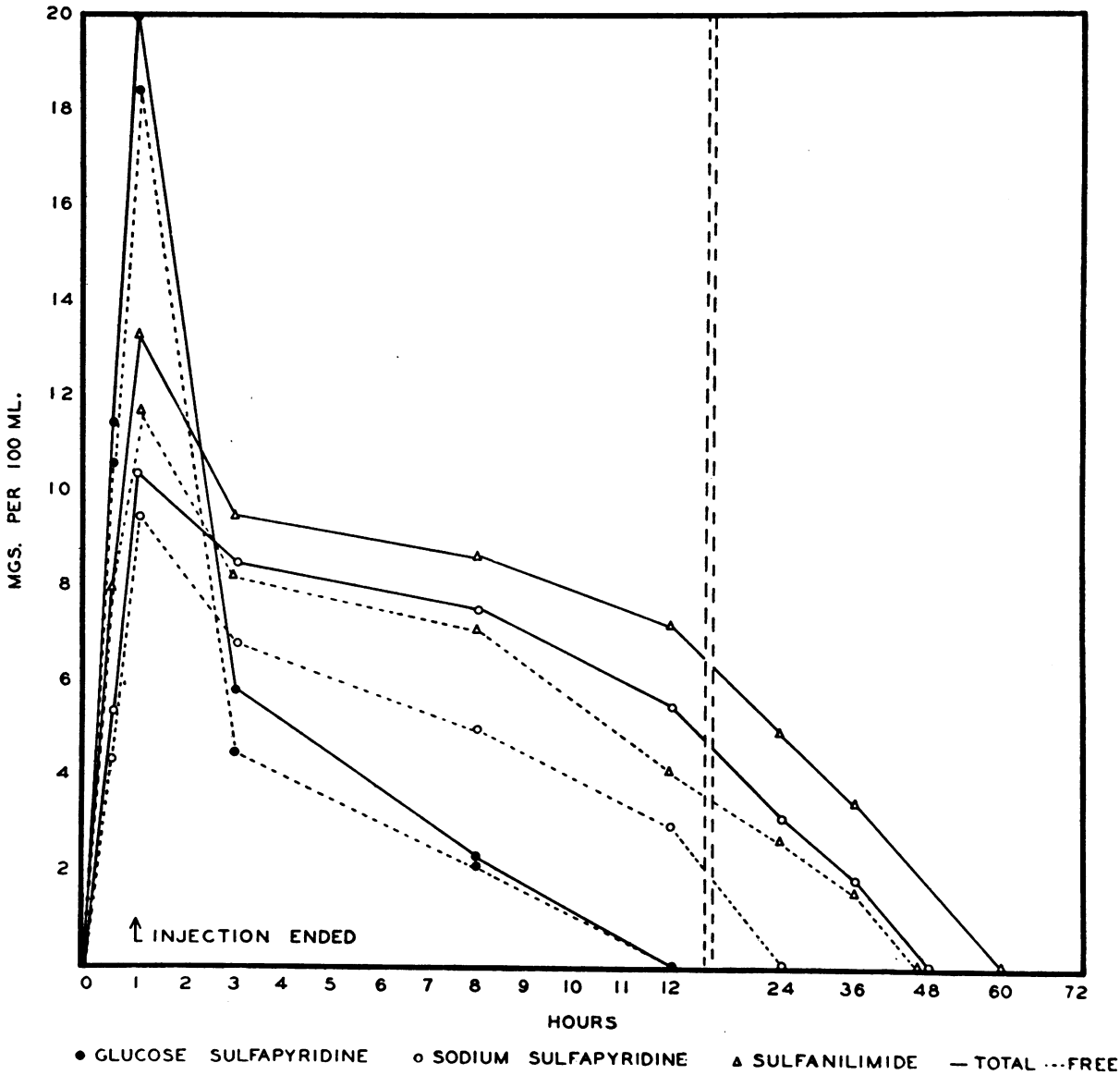

FIG. 2. (SUBJECT B.) BLOOD LEVELS AFTER INTRAVENOUS ADMINISTRATION OF THREE SULFANILAMIDE DERIVATIVES

cretion rate of sulfapyridine such as obtained for the glucose compound.

The injection of sulfanilamide gave similar results except that there was a somewhat lower concentration of conjugated sulfanilamide present in the urine than that found after the injection of a corresponding amount of sodium sulfapyridine.

The effect of the subcutaneous administration of glucose sulfapyridine and sulfanilamide on the blood level and urinary excretion of sulfapyridine and sulfanilamide respectively

The blood concentrations of sulfapyridine following the subcutaneous injection of glucose sul-

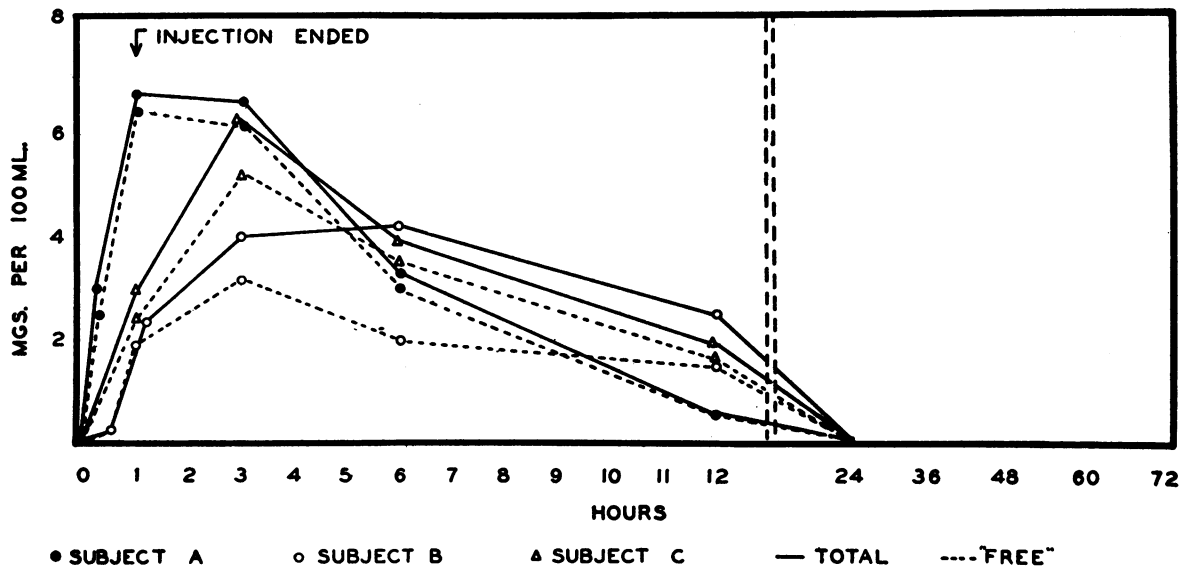

FIG. 3. EFFECT OF SUBCUTANEOUS INJECTION OF GLUCOSE SULFAPYRIDINE ON THE BLOOD LEVEL

fapyridine are shown for the three subjects in Figure 3, and the data obtained on a second occasion in Subject B are shown in Table I. The concentration of sulfapyridine in the blood rose more slowly and to a lower maximum than when glucose sulfapyridine was given intravenously. Determinable amounts were present in the circulating blood for at least 12 hours. There was no marked increase in the conjugated form as was the case when the sodium salt or sulfanilamide was given intravenously.

The subcutaneous injection of glucose sulfapyridine was followed by a hyperglycemia comparable to that produced by a similar amount of glucose. There was, however, no corresponding glycosuria. All of the sulfapyridine was recovered in the urine within 24 to 48 hours, from 77 to 87 per cent appearing in the conjugated form.

Following the subcutaneous injection of sulfanilamide, the blood levels rose slowly to a maximum of between 8 to 10 mgm. per 100 ml. 6 hours after the injection was started. In Subject B (Table I and Figure 4) determinable amounts of free sulfanilamide were present 50 hours after commencement of injection; in a second subject only traces were present at this time. In both instances, however, levels between 2 and 3 mgm. of free, and 3 to 5 mgm. of total sulfanilamide per 100 ml. of blood were present 24 hours after injection. During the time when the blood levels were high, between 70 and 89 per cent of the drug was present in the free form.

All of the subcutaneously injected material was recovered from the urine in 96 hours; 38 per cent of this was present as the free and 62 per cent as the conjugated drug. The maximum excretion occurred during or shortly after a period of maximum diuresis. The essential difference between the urinary excretion of sulfapyridine after injection of the glucose compound and the excretion of sulfanilamide, when both were given subcutaneously, was the greater rapidity of the removal of glucose sulfapyridine from the blood.

The effect of the oral administration of glucose sulfapyridine, sulfapyridine, and sulfanilamide on the blood levels and urinary excretion of sulfapyridine or sulfanilamide

The blood levels after oral administration of glucose sulfapyridine in three subjects are shown in Figure 5, and the data for Subject B appear in Table I. The absorption from the gastro-intestinal tract was very slow. Appreciable concentrations did not appear in the blood until 24 hours after the beginning of ingestion. Unlike the findings after parenteral administration of the drug, there were large amounts of conjugated sulfapyridine present in the circulating blood.

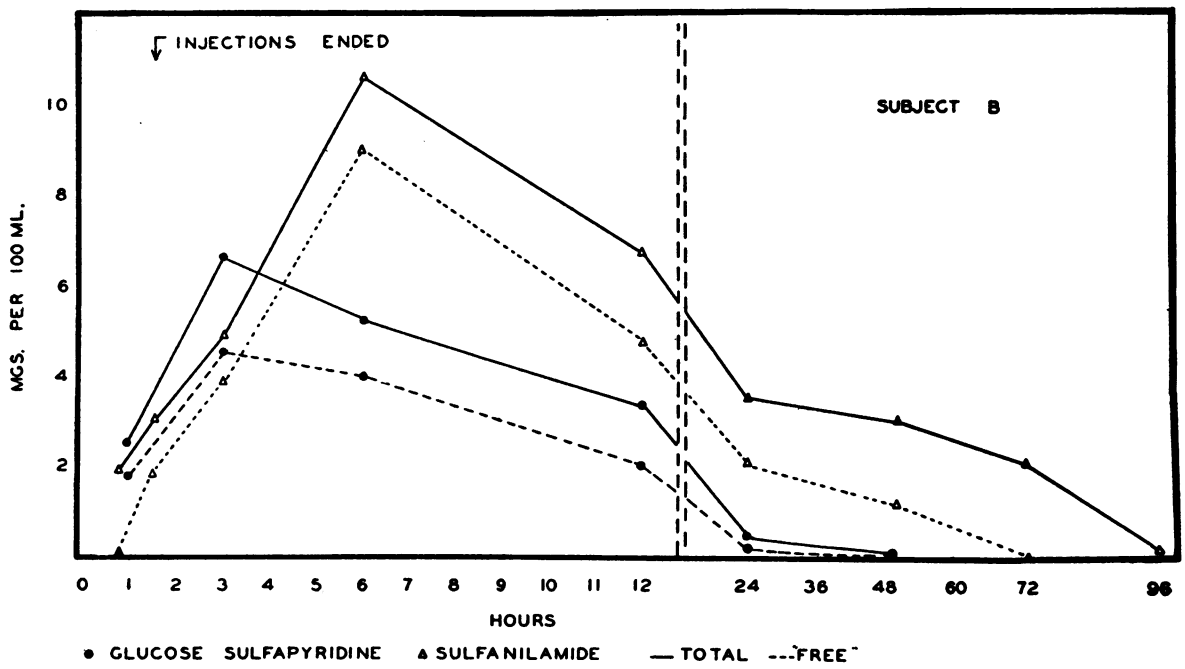

FIG. 4. GLUCOSE SULFAPYRIDINE AND SULFANILAMIDE: EFFECT OF SUBCUTANEOUS INJECTION ON THE BLOOD LEVEL

About 80 per cent of the drug administered was recovered from the urine in 72 hours. Approximately 25 per cent of this amount was in the free form. The maximum excretion of the drug occurred during the interval between 24 and 36 hours, which corresponded to maximum levels in the blood.

For purposes of further comparison, additional data on the effect of the administration of glucose sulfapyridine by the three different routes on the blood levels of sulfapyridine in Subject A are shown in Figure 6. The data on the recovery of this drug from the urine of the same subject are shown in Figure 7.

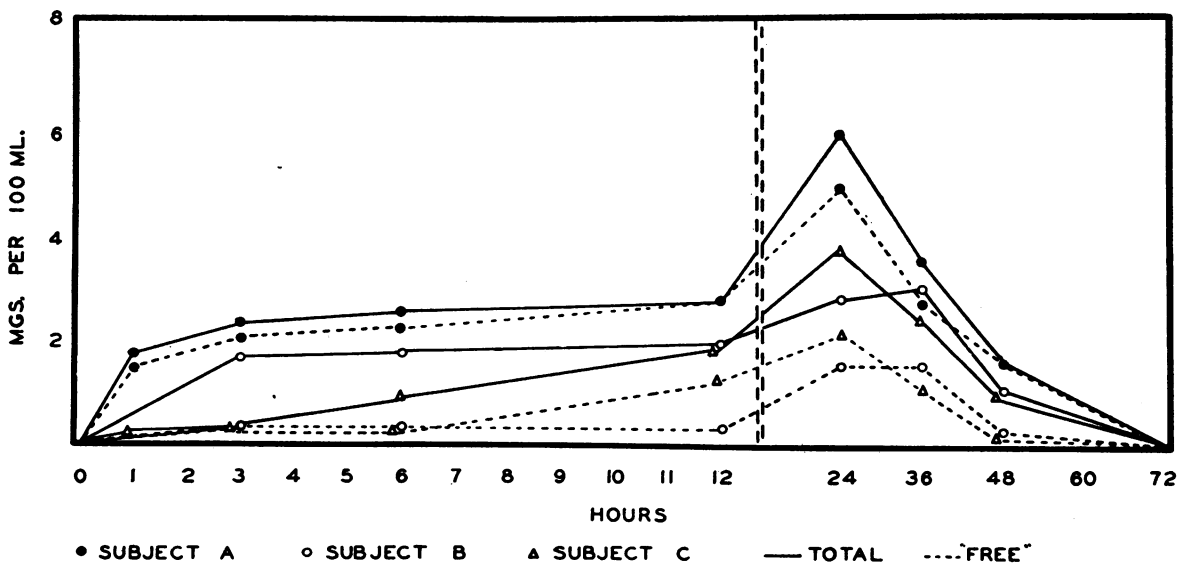

FIG. 5. EFFECT OF ORAL ADMINISTRATION OF GLUCOSE SULFAPYRIDINE ON THE BLOOD LEVEL

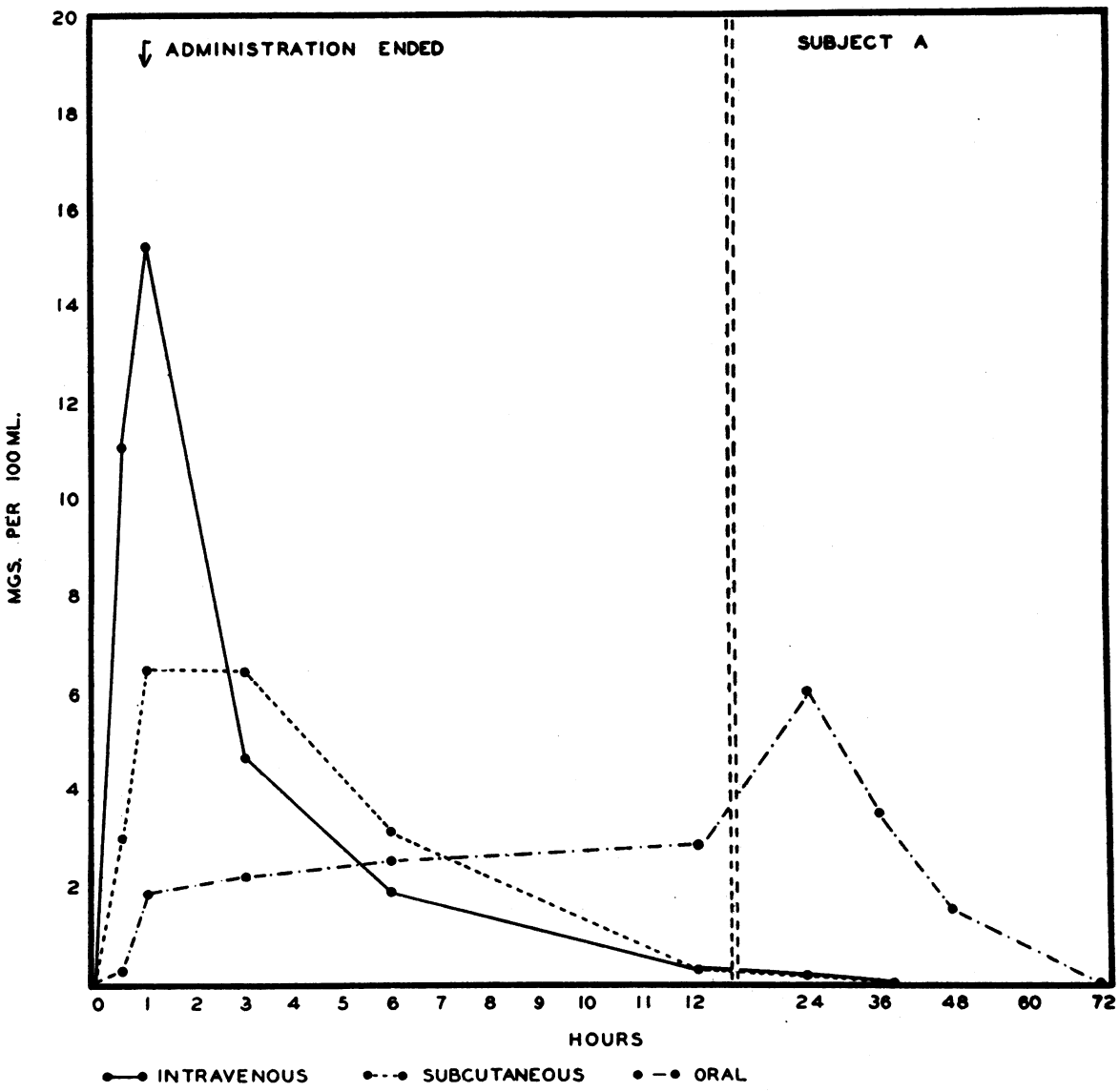

FIG. 6. GLUCOSE SULFAPYRIDINE: EFFECT OF ROUTE OF ADMINISTRATION ON BLOOD LEVEL

When equivalent amounts of sulfapyridine or sulfanilamide were given orally, the rate of absorption from the gastro-intestinal tract was much faster than for the glucose compound. Values of 4 to 8 mgm. of free sulfapyridine or sulfanilamide per 100 ml. of blood were obtained 6 hours after the beginning of ingestion and determinable levels were present in the blood 24 hours later. A comparison of the effect of the administration of these two drugs with glucose sulfapyridine is shown in Figure 8 and in Table I. Similar results for the absorption and excretion of sulfapyridine and sulfanilamide after oral ingestion have been reported by others (5, 7, 8).

The distribution between red blood cells and plasma of certain derivatives of sulfanilamide in vitro

The fundamental differences in the behavior of glucose sulfapyridine and other sulfanilamide derivatives given intravenously and subcutaneously made appropriate a further consideration of the data in the light of blood clearance and distribution in the body. However, since the investi-

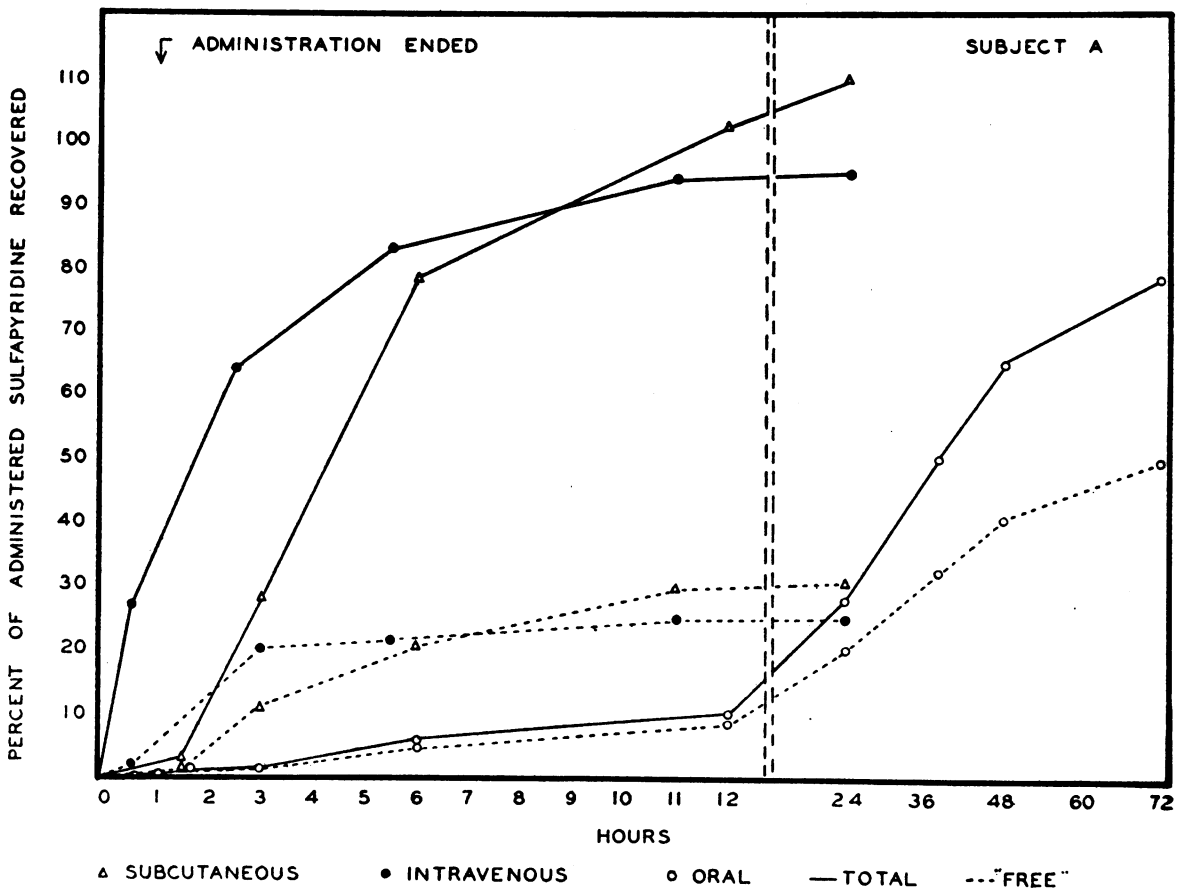

FIG. 7. GLUCOSE SULFAPYRIDINE: EFFECT OF ROUTE OF ADMINISTRATION ON URINARY ELIMINATION

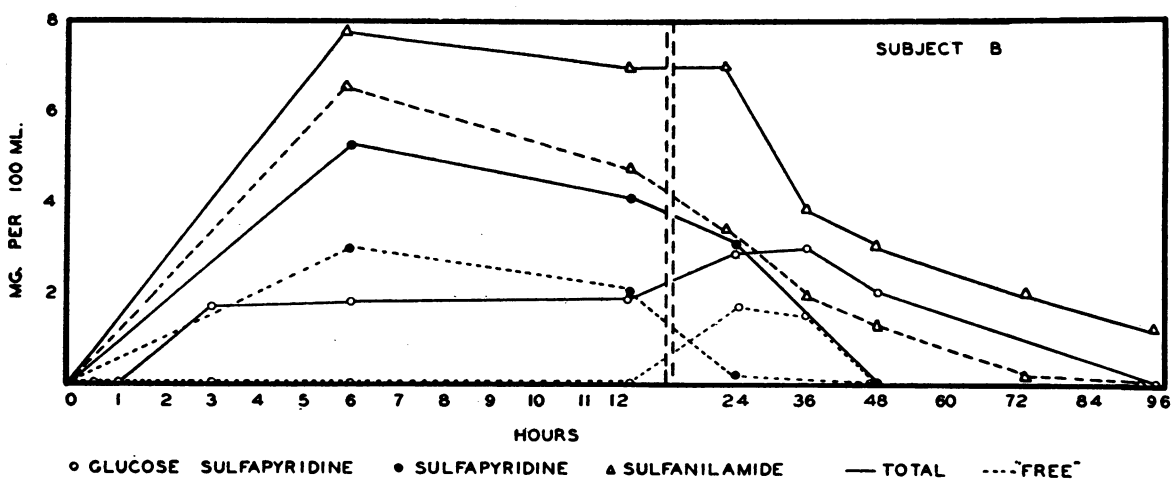

FIG. 8 BLOOD LEVELS AFTER ORAL ADMINISTRATION OF THREE SULFANILAMIDE DERIVATIVES

TABLE III

Distribution between whole blood and plasma of glucose sulfapyridine, sodium sulfapyridine and sulfanilamide in vitro

Subject	Compound given	Time from mixing	Whole blood values*	Plasma values*	Calculated values* in plasma for 100 ml. blood	Calculated values* in cells for 100 ml. blood	Hematocrit (corrected)
			mgm. per 100 ml.	*mgm. per 100 ml.*			
T	Glucose Sulfapyridine	10 minutes	9.0	16.4	8.4	0.6	48.8
T	Sodium Sulfapyridine	10 minutes	8.7	9.6	4.9	3.8	48.8
Lo	Glucose Sulfapyridine	10 minutes	11.2	19.8	11.5	0	41.8
Lo	Sodium Sulfapyridine	10 minutes	7.7	8.2	4.8	2.9	41.8
F	Glucose Sulfapyridine	10 minutes	9.1	15.6	8.3	0.8	46.9
F	Glucose Sulfapyridine	1 hour	9.0	16.1	8.5	0.5	46.9
F	Glucose Sulfapyridine	3 hours	8.9	16.0	8.5	0	46.9
F	Sodium Sulfapyridine	10 minutes	8.3	8.7	4.6	3.7	46.9
F	Sodium Sulfapyridine	1 hour	8.2	8.6	4.6	3.6	46.9
F	Sodium Sulfapyridine	3 hours	8.2	8.6	4.6	3.6	46.9
F	Sulfanilamide	10 minutes	9.7	7.7	4.1	5.6	46.9
F	Sulfanilamide	1 hour	9.4	7.4	3.9	5.5	46.9
F	Sulfanilamide	3 hours	9.3	7.5	4.0	5.3	46.9
Low	Glucose Sulfapyridine	10 minutes	9.9	18.9	9.5	0	50.2
Low	Glucose Sulfapyridine	1 hour	9.7	17.6	8.8	0.9	50.2
Low	Glucose Sulfapyridine	3 hours	9.9	18.5	9.3	0.6	50.2
Low	Sodium Sulfapyridine	10 minutes	8.1	8.7	4.4	3.7	50.2
Low	Sodium Sulfapyridine	1 hour	8.1	8.8	4.4	3.7	50.2
Low	Sodium Sulfapyridine	3 hours	8.1	8.2	4.1	4.0	50.2
Low	Sulfanilamide	10 minutes	8.5	7.6	3.8	4.7	50.2
Low	Sulfanilamide	1 hour	9.3	7.5	3.8	5.5	50.2
Low	Sulfanilamide	3 hours	9.7	7.4	3.7	6.0	50.2

* Sulfapyridine or sulfanilamide.

gation had been made on whole blood, the distribution of these compounds between red blood cells and plasma was studied.

The distribution of glucose sulfapyridine, sodium sulfapyridine and sulfanilamide between red blood cells and plasma was determined *in vitro* at various times up to 3 hours after their addition to oxalated blood. The results are given in Table III. Glucose sulfapyridine was present only in the plasma, sodium sulfapyridine was equally distributed between the red blood cells and the plasma, and sulfanilamide showed a slightly greater concentration in the red cells than in the plasma. This increased concentration in the red cells of sulfanilamide was pointed out previously by Sise (6). This slight increase in concentration in the red blood cells was disregarded in subsequent calculations.

The distribution of glucose sulfapyridine between red cells and plasma in vivo

Two subjects were given 4.75 grams of glucose sulfapyridine intravenously, two others received the same amount subcutaneously and three were given 12.5 grams of the drug orally. Hematocrits were determined and estimations of sulfapyridine were made on the whole blood and plasma at appropriate intervals. The data are shown in Table IV. Like the *in vitro* results, glucose sulfapyridine showed little penetration into the red blood cells when given intravenously or subcutaneously, while following oral administration approximately one-third of the sulfapyridine found in the whole blood was present in the red cells.

TABLE IV

Distribution of sulfapyridine between red blood cells and plasma when glucose sulfapyridine was administered by various routes

Subject	Route	Time after administration	Whole blood sulfapyridine	Plasma sulfapyridine	Calculated sulfapyridine in plasma for 100 ml. blood	Calculated sulfapyridine in cells for 100 ml. blood	Hematocrit (corrected)
			mgm. in 100 ml.	*mgm. in 100 ml.*			
I	Intravenous	1 hour	10.8	17.2	10.5	0	38.9
I	Intravenous	3 hours	7.4	10.8	6.6	0.8	38.9
II	Intravenous	1 hour	9.1	16.3	9.3	0	43.3
II	Intravenous	3 hours	4.1	7.1	4.0	0	43.3
III	Subcutaneous	3 hours	3.9	5.5	3.4	0.5	38.6
III	Subcutaneous	4 hours	3.3	4.6	2.8	0.5	38.6
IV	Subcutaneous	3 hours	4.3	7.8	4.4	0	42.8
IV	Subcutaneous	4 hours	3.9	5.6	3.2	0.7	42.8
V	Oral	17 hours	10.5	12.5	6.8	3.7	46.4
VI	Oral	11½ hours	10.6	11.0	6.1	4.5	45.1
VII	Oral	11½ hours	12.0	14.6	8.3	3.7	43.2

The distribution of glucose sulfapyridine in the body water after both intravenous and subcutaneous injection shows that the drug is confined essentially to the extra-cellular water (Table V).

TABLE V

Distribution of glucose sulfapyridine

Patient	Route	Time after beginning of injection in hours	Total sulfapyridine in serum water at end of period	Total sulfapyridine excreted in urine through end of period	Liters of body water	Per cent of body weight
		hours	*mgm.*	*mgm.*	*liters*	*per cent*
B	Intravenous	3	8.4	2887	25	36
A	Intravenous	3	6.4	3024	31	53
C	Intravenous	3	7.4	2558	33	49
B	Subcutaneous	12	4.8	3518	23	33
A	Subcutaneous	6	4.6	3734	28	48

Sodium sulfapyridine, sulfapyridine and sulfanilamide, when given by each of the three routes, were distributed over the total body water. Unfortunately, variations in the amounts of free and conjugated sulfapyridine or sulfanilamide, and secretion of these compounds into the gastrointestinal tract prohibit determination of the distribution. In all instances, however, the *apparent* distribution of sulfanilamide and sulfapyridine or its sodium salt was in a volume of water in excess of 70 per cent of the body weight, and this was also true following the *oral* administration of glucose sulfapyridine.

The renal clearance of sulfanilamide and certain of its derivatives when administered by different routes

The clearance values given in Table VI were obtained by recalculation of the whole blood data on three subjects, making use of the distributions between red cells and plasma to obtain serum levels. When given by the intravenous route, glucose sulfapyridine differed sharply from either sodium sulfapyridine or sulfanilamide. The latter two substances were cleared at rates indicating a considerable degree of tubular reabsorption while the glucose compound was cleared at a rate usually associated with simple glomerular filtration.

When glucose sulfapyridine and sulfanilamide were given subcutaneously, the clearances for the glucose compound were elevated above that for sulfanilamide. With one exception (Subject B) the values for the clearances were similar to those found after intravenous administration.

When given by the *oral route* glucose sulfapyridine, sulfapyridine and sulfanilamide all gave

TABLE VI

Blood clearances of glucose sulfapyridine, sodium sulfapyridine and sulfanilamide when administered by different routes

Patient	Compound	Route	Time of period	Average serum* concentration (calculated)		Total drug* excreted in urine for period		Blood cleared per minute		
				Free	Total	Free	Total	Free	Conjugated	Total
			minutes	*mgm. per 100 ml.*		*mgm.*	*mgm.*	*ml.*	*ml.*	*ml.*
B	Glucose Sulfapyridine	Intravenous	120		15.3		2325			125
A	Glucose Sulfapyridine	Intravenous	120		12.7		1737			114
C	Glucose Sulfapyridine	Intravenous	120		12.0		1718			90
B	Sodium Sulfapyridine	Intravenous	120	7.3	8.5	122	192	14	48	19
A	Sodium Sulfapyridine	Intravenous	180	7.5	7.7	429	508	32		37
C	Sodium Sulfapyridine	Intravenous	120	7.8	10.0	181	256	20	28	21
B	Sulfanilamide	Intravenous	120	10.0	11.5	240	301	20	34	23
D	Sulfanilamide	Intravenous	195	5.7	7.1	475	728	41	92	52
B	Glucose Sulfapyridine	Subcutaneous	360		6.2		1102			49
A	Glucose Sulfapyridine	Subcutaneous	120		9.0		1267			117
C	Glucose Sulfapyridine	Subcutaneous	180		7.9		1714			120
B	Sulfanilamide	Subcutaneous	180	5.8	7.0	240	346	23	49	27
D	Sulfanilamide	Subcutaneous	360	5.1	6.8	645	1057	36	68	43
B	Glucose Sulfapyridine	Oral	720	1.4	2.7	236	1069	23	89	55
A	Glucose Sulfapyridine	Oral	720	3.6	4.3	592	954	23	72	32
C	Glucose Sulfapyridine	Oral	720	1.7	2.9	299	986	24	80	47
B	Sulfapyridine	Oral	720	2.1	5.0	166	1182	11	49	33
A	Sulfapyridine	Oral	720	3.6	4.0	606	804	23		28
C	Sulfapyridine	Oral	360	3.7	5.6	506	1183	38	99	59
B	Sulfanilamide	Oral	720	1.4	3.2	118	437	12	25	19
A	Sulfanilamide	Oral	360	3.5†	4.5†	596	995	47	111	61
C	Sulfapyridine	Oral	360	4.0	5.7	530	1400	37	142	69

* = Sulfapyridine or sulfanilamide.
† = Determinations were done on serum instead of whole blood.

similar values. For all the compounds given orally the clearance values indicated marked tubular reabsorption. The clearance of the conjugated form of sulfanilamide or sulfapyridine was always higher than the free form. The tubules apparently selectively reabsorb the free form of sulfapyridine and sulfanilamide.

DISCUSSION

The data presented show that, when glucose sulfapyridine is given intravenously or subcutaneously, its behavior is quite different from that of the other derivatives of sulfanilamide used in this study when they are given by the same route. The levels of total sulfapyridine in the blood are comparatively higher but these high levels are not maintained. After a brief interval no circulating sulfapyridine is demonstrable.

From the clearance data it is possible to say that intravenous glucose sulfapyridine is eliminated with very little reabsorption while sulfapyridine and its sodium salt, given by parenteral or oral routes, and glucose sulfapyridine, *given* by *mouth,* undergo considerable tubular reabsorption. This would indicate that glucose sulfapyridine given intravenously or subcutaneously is not converted to sulfapyridine or sodium sulfapyridine but retains its identity in the blood and is excreted at a different rate. The low clearance values following the oral administration are of the same order of magnitude as those obtaining for sulfapyridine. There is a corresponding increase in the concentration of sulfapyridine in the red blood cells. It would appear, therefore, that orally administered glucose sulfapyridine is largely converted to sulfapyridine or its sodium salt before absorption.

Calculations of the distribution of glucose sulfapyridine given by parenteral route show that the drug is distributed over the extracellular fluid. In this regard it behaves in sharp contrast to sulfapyridine and sodium sulfapyridine which, by approximate calculation, appear to be distributed over the total body water. The distribution of the various compounds between red blood cells and plasma offers still further confirmation of these observations. The oral administration of glucose sulfapyridine differs from that of sulfapyridine and sulfanilamide. The absorption is slower, maximum concentrations are lower and are found 24 hours or longer after the ingestion of the drug.

These observations are interpreted as meaning that, following intravenous or subcutaneous administration, glucose sulfapyridine circulates in the blood unchanged. However, it would appear that the material present in the urine was not glucose sulfapyridine. This is suggested by the failure to show any glycosuria comparable to the amount of sulfapyridine present in the urine, and also by the presence of a conjugated compound determinable as such by the Marshall and Litchfield method (3).

The results of studies on the pneumococcidal activity of glucose sulfapyridine in human blood were in accord with these findings (2). The addition of glucose sulfapyridine to blood in high concentration *in vitro* produced no pneumococcidal activity. On prolonged standing at 37° C. only slight bacteriostasis became evident. When blood was withdrawn from patients to whom glucose sulfapyridine was given intravenously or subcutaneously, no pneumococcidal power was evident. Even should some activity occur in the blood after prolonged standing, the present data show that the drug is removed too quickly from the circulating blood for such a possibility to arise *in vivo* after parenteral administration. Following the oral administration of glucose sulfapyridine the pneumococcidal power of the circulating blood was practically the same as that demonstrable with blood having similar concentrations of drug after sulfapyridine itself had been given. These studies offer further evidence that the substance present in the blood after intravenous or subcutaneous administration of glucose sulfapyridine is not free sulfapyridine. They also suggest that the oral administration of glucose sulfapyridine results in its decomposition with the formation of active sulfapyridine.

It is of interest that such a slight procedure as boiling a drug in glucose solution should so change its biochemical and physiological activity. It is suggested that such studies as the ones presented, when applied to new therapeutic substances of this type, may be helpful in determining the potentialities of a drug. Glucose sulfapyridine by these criteria, when given by the

parenteral route, has characteristics which indicate that it is probably not useful therapeutically. The rapidity with which it leaves the blood stream, its poor distribution and its apparent failure to hydrolize into an active substance all militate against its usefulness.

CONCLUSIONS

1. Glucose sulfapyridine administered intravenously or subcutaneously gives high levels of the drug in the blood but is rapidly excreted and appears to circulate in a form which does not behave like sulfapyridine.

2. The data for the clearances of glucose sulfapyridine after its intravenous or subcutaneous administration indicate that little or no reabsorption of glucose sulfapyridine takes place.

3. Glucose sulfapyridine administered orally is absorbed slowly. In other respects, however, the drug present in the blood after its absorption from the gastro-intestinal tract behaves in the same manner as when sulfapyridine itself is given.

4. Glucose sulfapyridine given intravenously or subcutaneously does not enter the red blood cells, and is apparently distributed only in the extracellular fluids.

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BIBLIOGRAPHY

1. Finland, M., Lowell, F. C., Spring, W. C., Jr., and Taylor, F. H. L., Parenteral sulfapyridine. The intravenous use of sodium sulfapyridine and a report of clinical and laboratory observations on the use of a glucose-sulfapyridine solution. Ann. Int. Med. (In press).
2. Lowell, F. C., Spring, W. C., Jr., and Finland, M., Bactericidal action of sodium sulfapyridine and of a glucose-sulfapyridine solution in human blood. J. Clin. Invest., 1940, **19**, 215.
3. Marshall, E. K., Jr., and Litchfield, J. T., Jr., Determination of sulfanilamide. Science, 1938, **88**, 85.
4. Folin, O., A Laboratory Manual of Biological Chemistry. D. Appleton-Century Co., New York, 1934, 5th Edition, pp. 301–307.
5. Stewart, J. D., Rourke, G. M., and Allen, J. G., Excretion of sulfanilamide. J. A. M. A., 1938, **110**, 1885.
6. Sise, H. S., The distribution of sulfanilamide and acetylsulfanilamide between cells and extracellular fluid. Proc. Soc. Exp. Biol. and Med., 1939, **40**, 451.
7. Baines, E. J., and Wien, R., The absorption and excretion of 2-sulphanilyl-aminopyridine. Quart. J. Pharm. and Pharmacol., 1939, **12**, 4.
8. Marshall, E. K., Jr., and Long, P. H., The intravenous use of sodium sulfapyridine. J. A. M. A., 1939, **112**, 1671.