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Observations upon the Absorption and Excretion of Sulfapyridine* (2 Sulfanilyl Aminopyridine).

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We[1] have already discussed the concentrations of sulfapyridine noted in the blood of mice, dogs and human beings following the administration of single doses of this drug. In this communication we wish to submit additional data concerning the absorption, distribution and excretion of sulfapyridine. In all of our experiments we have used Marshall's method[2, 3] and have found it highly satisfactory for the determination of sulfapyridine in body fluids.

In Table I are recorded the concentrations of the drug obtained in the blood of mice, dogs and human beings following single peroral doses. It is to be noted that the concentrations of sulfapyridine observed in these experiments are definitely lower in each species than those which have been reported for corresponding doses of sulfanilamide. It is also of interest that in the same dog, marked variations in the absorption of sulfapyridine were noted in experiments carried on at different times. In human beings also, a definite variation in the ability of individuals to absorb this compound was observed.

The absorption rate of sulfapyridine would seem to be slower than that of sulfanilamide, and because of this factor, the peak concentration of the drug observed in the blood of human beings occurs at somewhat later periods than have been noted for sulfanilamide. Because of this, we have concluded that in human beings the dosage of this compound should be based on a 6-hour schedule rather than upon a 4-hour schedule, as is the case in sulfanilamide therapy.

In Table II we have recorded observations of the concentrations of sulfapyridine in the blood of patients who were being regularly treated with this drug at 6-hour intervals. The bloods were obtained between 9 and 10 A.M.

It would seem from the data in this table, that regardless of size

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TABLE I.
Blood Levels of Sulfapyridine Following Single Peroral Doses in Mice, Dogs and Man.

		Blood levels in mg%, hours following administration of sulfapyridine															
		1		2		4		5		8		24		36		48	
Species	Dose, g/kilo	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T
Mouse	0.5	15.4		15.6		12.5				6.9		3.2					
,,	1.0	23.6	22.9			21.1	21.4			16.0	16.5	0.7	0.6			0	0
Dog I	1.0	0.8	0.8			6.25	6.25			9.1	9.1	1.0	1.0				
,,	1.0					19.4	19.5			16.7	16.8	1.3	1.4				
,,	1.0	T	T			9.35	9.44			17.1	17.3	1.2	1.3				
Man	0.05	0.55	0.53			3.26	3.2			2.77	2.6	1.8	1.7	1.1	1.0		
,,	0.05	T	T			5.0	4.9			4.1	4.4	2.5		1.6			
,,	0.05	0.5	0.6			4.2	4.0			3.0	3.4	3.1	3.1	1.9	1.9		
,,	0.05	1.6	1.7			3.4	3.4			3.1	3.2	3.1	3.1			1.3	1.3
,,	0.10	0.9	1.1					4.6	6.4	4.7	7.4	1.9	2.9	0.9	2.4	0.4	0.7
Infant	0.1			3.2	3.2	5.6	5.6			5.3	5.4	2.4	2.5			VFT	VFT
,,	0.1			4.1	4.1	3.3	3.6			3.2	3.5	2.0	2.3			VFT	VFT

T = Total sulfapyridine (including conjugated fraction).

TABLE II.
Concentrations of Sulfapyridine Noted in Blood of Patients Receiving This Compound.

			Blood Levels mg%—Day of Administration of Drug															
			2		3		4		5		6		7		8		9	
Subject	Wt, kilo	Dose per day, g	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T
G.B.	62	4			1.7				7.1	7.1					6.3	7.1		
S. D.	—	6	1.6	1.8	3.1	4	2	3.8	2.8	4.6	1.5	3.2	1.8	3.9			1.9	3.8
N.M.	38	6.9 + 2	6.2	6.3	3.1	3.5	3.8	3.8			1.1	1.1	0.8	0.8				
J.B.	60	3.6	2.6	3.5														
J.R.	60	3.6					6.5	6.5					9.0	9.5				
L.A.	42	3.6			T	1.0			3.0	4.2			3.7				2.4	3.2
D.C.	49	3.6	1.1						2.0				2.1				1.7	2.2
F.P.	71	4.8	7.7				6.5						3.0				4.9	
B.F.	63	3.6	6.7	6.7			4.5	5.0					5.3	5.2				
G.J.	70	12.0	4.8	8.6	2.8	6.6	3.8	6.2	4.6	6.8			2.3	5.7	3.8	9.6	4.0	10.0

F—Free sulfapyridine.
T—Total sulfapyridine (including conjugated fraction).

TABLE III.
Urinary Excretion of Sulfapyridine Following Administration of Single and Repeated Doses of the Compound.

Subject	Dose of compound	Volume of Urine, Excretion in mg%, Days												Total drug excreted, g	% of dose excreted
		1			2			3			4				
		U.V. cc	F	T	U.V. cc	F	T	U.V cc	F	T	U.E. cc	F	T		
J.C.	Single 0.05 g/kilo Total = 3.0	1875	32.6	48.6	2775	23.5	36.6	1875	11.6	25	1660	6.4	13.2	2.37	79
S.B.	Single 0.1 g/kilo Total = 5.7	2850	25	48.8	2600	11.9	45.5	1650	4	22.5		T	T	2.9	51
E.P.	Single 0.1 g/kilo Total = 6.8	1675	50	79	900	31.2	141.5	1000	4	16.8		T	T	2.34	39
J.B.	3.6 g per day	1440	30	155	1520	40.8	137	1350	53.6	166				6.55	60
H.W.	3.6 g per day	1840	62.5	105	1780	47	89.9	2640	40	77				5.52	51
D.J.	3.6 g per day	2130	36.4	107	2240	31.3	95.7	2310	38.1	111				6.97	64

U.V. = Urine volume.
F = Free sulfapyridine.
T = Total sulfapyridine (includes conjugated fraction).

of the dose of the drug, marked variations occur in the concentrations observed in bloods from various patients. These findings are in contrast to the rapid and nearly complete absorption of sulfanilamide observed in human beings. These marked irregularities in the absorption of the drug necessarily make accurate therapy with sulfapyridine difficult.

Marshall and his associates[2] first observed that sulfanilamide was almost totally excreted in the urine of individuals possessing normal renal function. This has been confirmed by Stewart, *et al.*[4] In Table III are presented experiments dealing with the urinary excretion of sulfapyridine.

It seems quite definite that, following the administration of a single dose of sulfapyridine, its excretion in the urine is not complete until 3 or 4 days have passed and that the amount of the drug excreted varies markedly in normal individuals. If, on the other hand, repeated doses of the compound are given to patients at 6-hour intervals over a period of days, and estimations be made of the total amount of the drug excreted over a 3-day period, it will be seen that from 50 to 65% of the ingested sulfapyridine has been excreted. This is a decidedly lower figure than was obtained with sulfanilamide, and suggests that large doses of sulfapyridine are not necessarily indicated because much of the drug may not be absorbed.

It has been observed[2] that from 10 to 20% of circulating sulfanilamide exists in a conjugated form (acetyl sulfanilamide) in the blood of patients treated with this drug. Our studies tend to indicate that the percentage of conjugated sulfapyridine in the circulating blood of patients treated with sulfapyridine, may reach a high figure and that, in general, relatively more of the drug is conjugated than is the case when sulfanilamide is administered to human beings. This is again a detriment to therapy because conjugated sulfapyridine probably has little chemotherapeutic activity.

We have observed that sulfapyridine passes over into the spinal fluid of human beings in from one-half to three-quarters of the concentration of the drug which exists in the blood. It is present in purulent pleural exudates in concentrations of about 75% of that which exist in the blood. Hence, it seems that the drug diffuses into the tissues somewhat less readily than does sulfanilamide.

Conclusions. Sulfapyridine (2-sulfanilyl aminopyridine) is less readily and more irregularly absorbed by human beings than is sulfanilamide. Our experience leads us to believe that from a half to two-thirds of the ingested drug is excreted in the urine. Sulfapyri-

[4] Stewart, J. D., Rourke, G. M., and Allen, J. G., *J. A. M. A.*, 1938, **110**, 1885.

dine is found in purulent pleural exudates and spinal fluids in concentrations of a half to two-thirds of those observed in the blood. In the blood of human beings a considerable fraction of the drug is frequently found in the conjugated form. Because of the irregular absorption of the drug and its tendency towards conjugation, accurate therapy with sulfapyridine is more difficult than with sulfanilamide.

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Note on the Mechanism of Specific Agglutination.

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One consequence of the "lattice"-theory of serological reactions* is that if 2 or more independent antigens and their respective antibodies are all mixed together, each system should aggregate independently. By using microscopically visible and distinguishable particulate antigens† (*e.g.*, bacteria and/or erythrocytes) this prediction has been recently tested.[1-5] In many cases the individual aggregates were chiefly or entirely composed of only one of the 2

* "This view differs from the hypothesis that the antibody globulin is denatured in that the aggregation of the particles of antibody combined with antigen is ascribed not only to a loss of attraction for water, but also to a *specific* attraction between the particles. *This mutual attraction is due to the link provided by further antigen molecules.*" (Italics ours.) ". . . . the formation of a continuous lattice fails progressively more and more as no further antigen molecules are available to provide links for the formation of larger structures when aggregates of larger size . . . . . are formed." (Marrack[6]).

Heidelberger and associates similarly picture the precipitate[7] (or agglutinate[8]) as a lattice-structure *in which antibody and antigen alternate.*

† Landsteiner reported similar experiments long ago (*Hand. Biochem.*, 1909, **2**, 400).

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