

clusion of the external secretion of the pancreas by stated methods produces an abnormal deposition of fat in the liver and concomitant degeneration and atrophy of the liver cells. 5. Lipid deposition and degeneration of the liver does not occur in pancreatic transplants.

10306

Absorption, Acetylation, and Excretion of 2 Sulfanilamido Pyridine (Dagenan, M & B 693).*

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Preliminary reports in English journals¹ on the effectiveness of M & B 693 in pneumonia have been either clinical or bacteriological in nature. Since the administration of this drug will doubtless become widespread in this country, precise knowledge of its absorption and excretion should be made available. Analytical data are herewith presented showing the fate of M & B 693 in both laboratory animals and human patients.

Quantitative estimation of M & B 693 and its conjugated derivative in body fluids is similar to that of sulfanilamide. The original Fuller² method was employed using sulfanilamide standards with a factor to account for the difference in molecular weight and color intensity of the pyridine derivative. Determinations of the conjugated form, 2(N-acetylsulfanilamido) pyridine,³ were similarly made after hydrolysis with p.-toluenesulfonic acid. The percent acetylated values appearing in the tables were calculated from the hydrolyzed values minus the free (unhydrolyzed) times 100.

It was found, as with sulfanilamide, that the rabbit and human detoxify the drug by acetylation; the dog excretes it completely and unchanged in the urine. In all 3 species, the drug is detectable in the blood stream directly after ingestion, and the unchanged, therapeutically active form is completely eliminated from circula-

* Since this was written the name of the drug has been changed officially to sulfapyridine.

¹ *Lancet*, 1938, **1**, 1210, 1230, 1305, 1391, 1402.

² *Lancet*, 1937, **232**, 194.

³ Nomenclature suggested by Crossley, M. L., Northey, E. H., Hultquist, M. E., *J. A. C. S.*, 1938, **60**, 2217.

tion within 24 hours after the last administration, though the drug itself has but limited solubility in water (0.04% at 20°C).

2-(N-acetylsulfanilamido)pyridine has been isolated from both rabbit and human urine. The crystals deposit spontaneously in rabbit and in human urine, occasionally. 1.82 and 2.4 g of the crystalline acetyl derivative were recovered from two 24-hour specimens from a female patient, age 67, given 9.5 g M & B 693 over a period of 3 days. Upon one recrystallization from alcohol the M.P. was 226-7°C. Synthetic 2-(N-acetylsulfanilamido)pyridine, M.P. 230-231°C. Mixed M.P. 225-227°C.

Analysis: Dumas N found, synthetic, 14.40%, found natural 13.92%, calculated for $C_{13}H_{13}O_2N_3S$ 14.40%.

Dosage: The dosages were varied between the following rough limits: human patients 0.030-0.1 g per kg, per diem; rabbits 0.16-0.64 g per kg; dog 0.20-0.25 g per kg.

Toxic Effects: Laboratory animals show no effects but among patients, nausea is common, often accompanied by mental confusion which passes off upon withdrawal of the drug. Parenteral injection into a rabbit of a solution of the crystalline sodium salt (pH 10.7) was tolerated in a dose 0.4 g per kg but proved lethal at twice that dosage.

Absorption and Elimination of M & B 693. Rabbits: Immediate absorption from the gastrointestinal tract into the blood of rabbits fed varying doses of M & B 693 by stomach tube is shown in the accompanying graphs of 2 typical cases selected from 8. Curves I and II represent the blood levels of unchanged drug at definite time intervals after a single dose of 0.32 g and 0.64 g per kg body weight respectively; curves Ia, IIa, represent the acetylated form. The concentration of M & B 693 reaches a maximum in about 3 hours, begins to fall after 6 or 7, and becomes practically zero after 18-20 hours. Appreciable amounts of the acetylated form still circulate after 26 hours. As far as has been ascertained, however,* this conjugated form is therapeutically inactive, as is N-acetylsulfanilamide. In another experiment on parenteral injection of the sodium salt of M & B 693 of 0.4 g per kg into a rabbit, all of the free drug had disappeared from the blood stream in 11 hours with but 2.5 mg % of the acetylated form remaining.

Dog: 2.0 g M & B 693 was fed to a 12 kg dog in each of 2 separate experiments. Quantitative determinations on the urine showed es-

* The extreme insolubility of 2-(N-acetylsulfanilamido)-pyridine renders proper testing of the bacteriostatic action against pneumococcus growth difficult. Kindly performed by Miss Hobby on Pn type II.

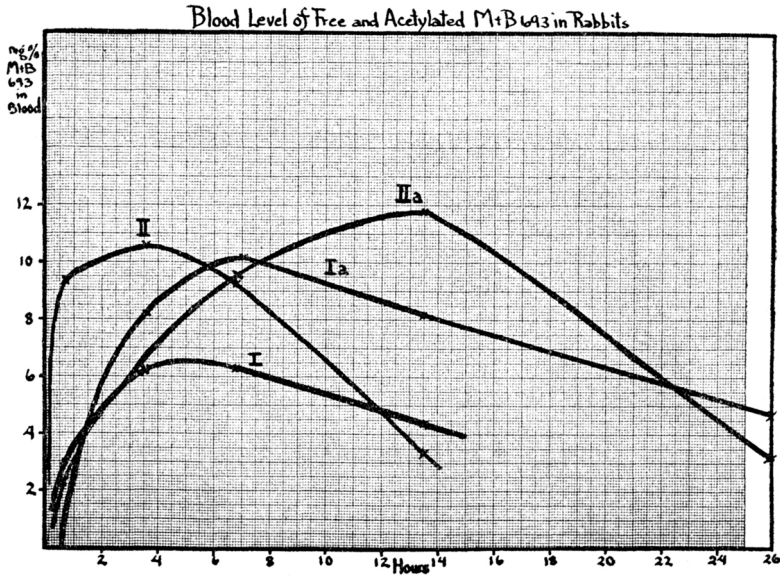


FIG. 1.

Curve I—Blood concentration of free M & B 693 of Rabbit No. 5.49, 3.1 kg, fed 1 g M & B 693.

Curve Ia—Blood concentration of acetylated M & B 693 of Rabbit No. 5.49, 3.1 kg, fed 1 g M & B 693.

Curve II—Blood concentration of free M & B 693 of Rabbit No. 5.48, 3.1 kg, fed 2 g M & B 693.

Curve IIa—Blood concentration of acetylated M & B 693 of Rabbit No. 5.48, 3.1 kg, fed 2 g M & B 693.

essentially complete recovery in 48 hours post administration. None was acetylated. Rates of elimination of M & B 693 were respectively: 13.5 and 21.0% in 4 hours, 71.5 and 73.0% during the next 18 hours, and 6.3 and 8.4% in the next 26 hours, representing a recovery of 98.8 and 94.9%.

Hospitalized Patients: Blood analyses have been made on 75 patients between the ages of 5 and 84 years that had been given a dosage of 2.0-6.0 g M & B 693 per diem over periods varying from 3 to 22 days. In all cases in which no gastrointestinal obstruction was present, rapid absorption into the blood stream was observed and a balance among rates of absorption, acetylation and excretion generally was attained after 24 hours. Accordingly, to insure maximum blood levels, samples for analysis were taken at least 24 hours after the initial dose unless otherwise indicated. Cases 1, 2, 3 (see also footnotes of Table I) show blood concentration of both free and acetylated M & B 693 at the initial phase of drug therapy. Low blood levels and percentage acetylation prevail. Case 4 is characteristic of the final phase. Twenty-four hours after withdrawal of

the drug only the acetylated form is present. The remaining cases are typical of the general findings on a group of patients. In case 5 the normal rate of absorption of the drug was modified by a gastrointestinal block which gradually cleared (analyses 2, 3, Case 5). Although this allowed high blood levels, the amount of acetylated product varies but slightly around 50%.

The amount of acetylated (inactivated) drug varies widely in different individuals (30%, cases 1, 6, 7, against 60-80%, case 8), and is somewhat greater than that for sulfanilamide. In general, roughly 50% is acetylated by the human. This is confirmed by urine analysis.

As was to be expected from preliminary rabbit experiments, patients on larger dosages (Cases 1, 7) produced higher blood levels, but the amount and type of circulating drug seems to depend

TABLE I.
Blood Levels of Free and Acetylated M & B 693 in Human Patients.

Case	Patient	Age	Dosage M & B 693 g per diem	M & B 693 Blood Levels		
				Free mg%	Total mg%	Acetylated %
1	Male	27	5.5, 6, 6, 6	5.5	5.5	0*
				10.5	14.2	30
2	Female	58	2, 2.5	2.5†	4.1	39
				1.2	3.3	64
3	"	66	3, 3	2.0‡	2.4	16
				3.7	6.5	43
4	Male	18		0.0	4.0	100§
5	"	74	4, 3.5, 3, 3, 1.5	2.0	3.5	43
				3.5	8.0	56
				5.5	10.5	48
6	Female	16	4, 3.5, 1.5	3.0	4.5	33
				10.5	13.0	19
7	"	40	5, 5, 2	7.5	10.0	25
8	Male	59	3 g for 22 days	1.2	3.0	60
				1.5	8.5	83
				3.0	10.0	70
				2.5	6.2	60
				1.5	6.5	77
				1.0	5.3	81
9	"	71	3 g for 5 days	6.9	14.1	51

*Sample for analysis after 1 g every 4 hr for 20 hr.

†Sample for analysis after 1 g every 4 hr for 10 hr.

‡Sample for analysis after 1 g every 4 hr for 6 hr.

§Sample for analysis 24 hr after last dosage.

on 3 variable factors, (1) rate of absorption, (2) rate of acetylation, (3) rate of elimination of free and acetylated forms. Case 8 is an example in point, and is to be compared with case 9 on the same dosage. In the former, the rapid rate of acetylation may be interpreted as contributing to the low blood levels of the free drug. (Nine urine analyses over a period of 13 days revealed 80-90% of the drug in the acetylated form.)

All of the active form of the drug is removed from general circulation 24 hours after the last dose (Case 4). Urine analyses again bear this out.

TABLE II.
Patient's Excretion of M & B 693 in Urine.

Days	Dosage M & B 693 g per diem	Volume 24 hr specimen cc	Excretion M & B 693			Total daily Excretion M & B 693 g
			Free mg/cc	Total mg/cc	Acetylated %	
1	3					
2	3	800	1.38	2.49	45.0	2.00
3	3	575	3.12	5.90	47.0	3.40
4	3	520	3.50	5.00	30.0	2.60
5	2	245	5.00	7.10	29.6	1.75
6	2	225	6.00	8.50	29.4	1.90
7	0.5	225	2.25	5.35	58.0	1.20
8		360	1.25	1.65	24.0	0.60
9		410	0.17	0.30	43.0	0.12
10		810	0.00	traces		(0.03)
Total 16.5						13.60

Urinary Excretion of Drug: Table II shows the results of daily urine analysis made on a nephrotic youth fed a total of 16.5 g M & B 693 over a period of 7 days. 13.6 g of free and acetylated drug represent a recovery of 82.5%. Both forms had been practically completely excreted 2 days after the last dose. Total drug recovery on 6 other patients varied from 15-85%.

Summary. The concentration of M & B 693 has been determined in the body fluids of the rabbit, dog, and human, following its administration in varying doses. Blood analyses show the appearance of free M & B 693 directly after ingestion; no acetylated form is detectable until later. The percent acetylated is roughly constant for an individual and varies widely around 50% among human subjects. No free drug can be detected in general 24 hours after the last dose and essentially all the acetylated form is eliminated in 48 hours. Urine analyses confirm these findings.