orators.[5,6] Similar efforts to confirm by electrocorticography the gross motor responses described are in process in this laboratory.

The implication of these findings in terms of normally operative physiological activity can, of course, only be conjectured. Observations of the effect of emotional stress on muscle strength, and clinical notes of movements of paralyzed limbs and production of ejaculatory speech in the hemiplegic aphasic[7,8] under conditions of excitement, anger, or joy may have their basis in hypothalamic-cortical facilitation.

5 Morison, R. S., and Dempsey, E. W., *Am. J. Physiol.*, 1942, **135**, 281.

6 Dempsey, E. W., and Morison, R. S., *Am. J. Physiol.*, 1942, **135**, 293.

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14864

Carboxythiazole (2-Sulfanilamido-5-Carboxythiazole) in Blood, Urine and Feces After Oral Administration in Humans.

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Two general types of sulfonamide compounds have been used with some success in the treatment of certain enteric infections and in attempts to reduce the numbers of coliform and other bacteria in the intestinal contents in relation to surgical procedures. One type is represented by sulfaguanidine[1] which is fairly soluble in water, poorly absorbed from the gastro-intestinal tract, and, generally speaking, is about as active as sulfanilamide. The second type is one in which a substitution is made on the *p-amino* group of a more active sulfanilamide derivative, the resulting compound being totally inactive until the added group is released by hydrolysis which occurs within the intestinal tract. Glucose sulfapyridine,[2] succinylsulfathiazole,[3] and phthalylsulfathiazole[4] are examples of such compounds. They, too, are highly soluble, but only a small fraction of the active compound is released in the bowel and low concentrations of the active drug appear in the blood.

Carboxythiazole (2-sulfanilamido-5-carboxythiazole) is a third type of derivative in which a simple substitution is made on the thiazole ring of sulfathiazole.* This results in a compound which, though less active than the original sulfathiazole, is highly soluble and is poorly absorbed. In the present paper are presented the results of studies in human subjects on the occurrence of this drug in the blood, urine, and feces after single and repeated oral doses. The relevant findings in a small number of cases of enteric infections in which this drug was used are also summarized.

Materials and Methods. A single 5 g dose

1 Marshall, E. K., Jr., *et al.*, *Bull. Johns Hopkins Hosp.*, 1940, **67**, 163.

2 Taylor, F. H. L., *et al.*, *J. Clin. Invest.*, 1940, **19**, 201; Lowell, F. C., Spring, W. C., Jr., and Finland, M., *ibid.*, 1940, **19**, 215.

3 Poth, E. J., and Knotts, F. L., PROC. SOC. EXP. BIOL. AND MED., 1941, **48**, 129.

4 Mattis, P. A., Benson, W. M., and Koelle, E. S., *J. Pharm. Exp. Therap.*, 1944, **81**, 116.

* This compound was received from the American Cyanamid Co. with the following information: It has a melting point of 215.5°C; water solubility at 37°C and at pH 3.0 of 42.7 mg per 100 cc and a buffer solubility at pH 5.0 of 4920 mg per 100 cc. It is poorly absorbed from the intestinal tract, rapidly excreted from the blood stream, and practically non-toxic in mice, rats, rabbits, and dogs. Experimentally, its antibacterial activity is about equal to that of sulfaguanidine. (Personal communication from Dr. Harold J. White.)

TABLE I.
Recovery of Carboxythiazole from Urine and Feces after a Single Oral Dose of 5 Grams.

Subject A						Subject B					
Urine			Feces			Urine			Feces		
Hr after dose	Free mg	Total mg	Hr after dose	Free mg	Total mg	Hr after dose	Free mg	Total mg	Hr after dose	Free mg	Total mg
0-12	216	230	0-27	1788	1870	0-12	159	236	0-38	0	0
12-24	32	35	27-35	347	354	12-24	31	39	38-46	15	17
24-36	17	26	35-62	347	347	24-36	31	44	46-55	143	148
36-48	17	25	62-120	476	476	36-48	38	58	55-73	127	134
48-72	30	52	120-144	15	16	48-72	40	47	73-84	702	714
72-96	14	19				72-96	56	82	84-107	867	884
96-120	12	28				96-120	71	104	107-149	221	221
0-120	338	415	0-144	2973	3063	0-120	426	610	0-149	2075	2118
Conjugated		19%		3%			30%			2%	
Total amt recovered = 3.478 g or 69.6%								2.728 g or 54.6%			

Blood levels at 3, 6, 12, 27, and 77 hours all 1 mg% (trace) in both subjects.

of carboxythiazole was given by mouth to each of 2 male subjects. One of them (A) was given a mild laxative the night before and each night thereafter for the duration of the study. Both had a cleansing enema an hour before and emptied the bladder just before the dose was given. Blood samples were taken 3 times the first day and twice thereafter. The entire urine output for each 12-hour period was collected for 5 days and all stools were saved *in toto* for 6 days. The method of Bratton and Marshall[5] was used for the carboxythiazole determinations. The drug content of the feces was determined as follows: the total contents of each stool were immersed in water and the mixture was made alkaline with concentrated NaOH, boiled, homogenized, made up to a given volume (usually 500 to 1500 cc) with water, strained through several layers of gauze, and an aliquot was treated like blood samples for the sulfonamide determination.†

The study was later repeated, each subject this time being given an initial dose of 4 g followed by 1 g every 4 hours until a total of 29 g were given in 100 hours. Blood samples were obtained daily for 5 days and all urine and feces were collected for 10 to 13 days. During this study, too, Subject A was given a laxative (cascara sagrada) each evening.

Four patients with bacillary dysentery and one with acute gastro-enteritis were treated with carboxythiazole. Each was given 4 g followed by 1 g every 4 hours, the former for 8 to 15 days and the latter for 3 days. Cultures of the stools were made frequently before and after the treatment was started and until the patient left the hospital.‡ Blood levels of carboxythiazole were determined daily.

Results. The results obtained following the ingestion of 5 g of carboxythiazole are shown in Table I. The amount of the drug recovered from the urine was greatest in the first 12 hours in both subjects. Only traces, however, were detectable in the blood samples obtained during this time or in the later ones. The largest amount was recovered from the first stool passed after 27 hours in Subject A who was receiving a daily laxative. In Subject B, whose bowels were sluggish, only small amounts were found in the stools during the first 3 days, and the largest amounts were recovered from the stools passed 84 and 107 hours after the dose was given. Some of the drug was still present in the urine on the fifth day and in the stool on the sixth day, the amounts being larger at these times in B than in A.

[5] Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, 1939, **128**, 537.

† The chemical determinations were carried out by Ellen J. Doyle and Clare Sacco.

‡ The bacteriological studies were carried out by Miss Marion E. Lamb and her associates at the Mallory Institute of Pathology.

TABLE II.
Recovery of Carboxythiazole from Urine and Feces after Oral Administration of 4 Grams Followed by 1 Gram Every 4 Hours for a Total of 29 Grams.

Subject A						Subject B					
Urine			Feces			Urine			Feces		
Hr after initial dose	Free mg	Total mg	Hr after initial dose	Free mg	Total mg	Hr after initial dose	Free mg	Total mg	Hr after initial dose	Free mg	Total mg
0-24	239	235	0-5	224	224	0-24	153	176	0-6	100	138
24-48	262	306	5-10	3754	3816	24-48	352	404	6-26	80	128
48-72	360	401	10-33	1238	1238	48-72	410	502	26-36	228	242
72-96	322	372	33-37	1420	1420	72-96	494	548	36-53	95	95
96-120	218	218	37-77	4508	4508	96-120	257	257	53-62	280	315
120-144	162	179	77-105	6702	7579	120-144	381	461	62-98	80	88
144-168	120	149	105-171	2924	3060	144-168	281	328	98-108	231	231
168-192	118	137	171-216	39	45	168-192	178	243	108-130	3917	3917
192-216	31	64	216-241	65	68	192-216	159	213	130-150	3156	3156
216-240	5	20				216-240	73	100	150-179	2240	2378
240-264	5	12				240-264	70	96	179-194	2346	2394
264-288	0	0				264-288	58	64	194-217	722	850
						288-312	0	13	217-242	1196	1538
									242-265	560	568
									265-291	94	94
									291-315	28	28
0-288	1842	2093	0-241	20892	21958	0-312	2866	3405	0-315	15353	16160
Conjugated 12%				5%			16%			5%	
Total amt recovered = 24.051 g = 82.9%						19.565 g = 67.5%					
Blood levels 4, 26, 52, 73, and 100 hrs after initial dose all <1 mg%.						Blood levels 4, 26, 52 and 73 hours after initial dose = <1 mg%; after 100 hrs = 1.4 mg% (free and total).					

The total amount recovered in A (69.6% of the administered dose) was greater than in B (54.6%). Of these total recoveries 12% was obtained from the urine in A as compared with 22% in B. Only 2-3% of the amount recovered from the feces was in the conjugated form. In the urine, on the other hand, 19% of the drug recovered in A and 30% in B were in this form.

The results obtained with repeated doses are shown in Table II. In both of the subjects only traces of drug were found in the blood except in the sample taken at the time of the last dose in Subject B which showed a level of 1.4 mg per 100 cc. In both subjects, the amounts recovered from the urine were greatest during the third and fourth day of the drug administration and then decreased progressively after the last dose. With respect to the amounts of drug recovered from the feces, the 2 subjects differed as they did after the single dose. Large amounts were recovered from the feces on the first day in Subject A who was receiving daily laxatives, whereas, in B large amounts were not recovered from the feces until the sixth day. Only small amounts were recovered from urine and stools beyond the fourth day after the last dose was given in A while fairly large amounts were still present in both the urine and feces collected on the seventh day after the last dose in B.

In this instance, too, the total amount of drug recovered was greater in A (82.9% of the administered drug) than in B (67.5%). Of this amount only 9% was found in the urine in A as compared with 17% in B. Of the amount of drug recovered in the feces, 5% was determined as the "conjugated" form in both subjects while 12% of the drug recovered from the urine in A and 16% in B were found in this form.

The 5 patients treated with carboxythiazole were only moderately ill, afebrile and having 3 or 4 loose bowel movements a day when the treatment was started. Each of the 4 patients with dysentery previously had 2 to 4 positive stool cultures, strains of Sonne (Duval) being

obtained in 3 cases and of Flexner dysentery bacilli in the fourth. The fifth patient had an unidentified pathogen in the stool obtained before the treatment was begun. All stool cultures were negative for pathogens after 1 day of treatment in 2 of the cases with the Sonne strains and in the case of acute gastro-enteritis, while in the third case of Sonne infection and in the case of Flexner dysentery positive cultures were obtained during the first 2 days of treatment and all the cultures taken on the following day and thereafter were negative for pathogens.‡

The total dose of carboxythiazole was 46-81 g (average 64) in the dysentery cases and was given over an average of 10 days. The case of acute gastro-enteritis received 22 g in 3 days. Daily blood samples showed only traces of the drug in almost every instance. In one case a blood level of 2.0 mg% was obtained on the eleventh day and in another a level of 1.2 was obtained on the second and eighth days. In each of 2 other patients levels of 1.5-5.1 were obtained in the first 2 morning samples of blood after the night nurse had given 2 or 3 doses of sulfathiazole by error.

Clinically, the patients were improved and the diarrhea subsided in each case within 1 or 2 days after the treatment was started. No toxic reactions of any sort were encountered in these patients or in the experimental subjects.

Discussion. These observations in humans confirm the findings in animals that carboxythiazole is poorly absorbed after oral administration and as far as could be determined from these few trials, is non-toxic. The failure to obtain positive cultures for the pathogenic strains after its use also suggests that it may be effective and deserves a place with the other drugs used in intestinal infections. Its relative value as compared with other drugs now used for this purpose would require an extensive clinical trial under controlled conditions.

Of interest is a comparison of the findings in Subject A who received laxatives daily and in Subject B who had rather sluggish bowels. In both of them the maximum urinary excretion of the drug occurred within a few hours after it was ingested. In the former, however, the drug appeared rapidly and in large amounts in the stools, whereas large amounts did not appear in the stools of B until after the third day. An appreciably greater percentage of the administered drug was recovered from A than from B after both the single dose and the multiple doses and there was less conjugated drug in the urine of A in each instance. In addition, the amount of carboxythiazole recovered from the urine in A constituted a much smaller proportion of the total drug recovered than was the case in B. These findings are in keeping with the prolonged though slight absorption of the drug in B which permitted a greater urinary output and also a longer time for conjugation to occur. Only a small part of the drug found in the feces was determined in the conjugated form.

It seems likely that there was still an appreciable amount of drug in the bowel after the completion of the studies particularly in Subject B, and this may have accounted for the smaller percentage of the administered drug which was recovered in that case. The possibility that part of the drug is destroyed in the body cannot be excluded.

Conclusions. "Carboxythiazole" (2-sulfanilamido-5-carboxythiazole) is poorly absorbed after oral administration to man and produced no toxic symptoms in 5 patients receiving 4 g initially and 1 g every 4 hours for 3-15 days. The drug may be useful in the treatment of enteric infections and in bowel surgery.