presence of bile and pancreatic secretions) seems to be necessary for release and subsequent absorption of EECPE but not EE from the lipid vehicle. Storage in body fat and brain of the unaltered EECPE is increased by its administration as an oily solution instead of an aqueous suspension. The nature of the vehicle of administration, however, had no influence on the degree of biological activity of EECPE as well as EE.

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The Excretion of Taurine During Deoxypyridoxine Administration in Downs' Syndrome Patients and Controls.* (31433)

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The metabolism of the sulfur-containing amino acid cysteine involves, as shown in Fig. 1, a number of anabolic and catabolic reactions. Among the principal catabolic reactions is the oxidation of cysteine to form cysteine sulfinic acid. Cysteine sulfinic acid or its oxidation product cysteic acid are in turn decarboxylated by a vitamin B_6 dependent reaction to hypotaurine or taurine. Urinary taurine is the most frequently measured metabolite that is used as an indicator of sulfur amino acid metabolism. The excretion of taurine in mammals is influenced in varying degrees by protein intake(1), cysteine loading(2), by irradiation(3,4), by trauma(5) and by vit B_6 intake(2). Decreased taurine excretion has been proposed as an indicator of inadequate vit B_6 levels(6). It has been shown by Goodman *et al*(7) that Downs' syndrome patients have a low base line excretion of taurine. Administration of the vit B_6 antagonist deoxypyridoxine was studied to determine if the effect on taurine excretion was similar to that of actual vit B_6 deficiency and if these effects were similar in a group of Downs' syndrome patients and matched controls. Of further interest was to determine if the previously demonstrated greater effect of deoxypyridoxine on the excretion of certain tryptophan metabolites in Downs' syndrome also resulted in greater changes in taurine excretion compared to control subjects. The results indicated that, after a significant ini-

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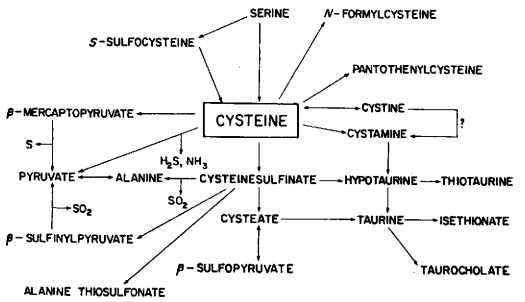

FIG. 1. Pathways for metabolism of cysteine.

tial decrease, a significant increase in taurine excretion above base line levels occurred in both groups with continued deoxypyridoxine administration. There was no significant difference in excretion of taurine between Downs' syndrome and control patients.

Methods. Eight female subjects ranging in age from 9 to 15 years were studied. Four of the patients had trisomy for chromosome 21 proven Downs' syndrome, and four patients were matched for age and weight. The subjects all lived in the Higginsville State School and ate the same diets which were adequate in quality and variety for good nutritional states. The children were examined, were in good health, and continued to eat normally during the test period. During the collection days the children voided every 2 hours around the clock to avoid missing specimens. The urine was collected under toluene, then frozen at $-20°$ until used for analysis. Two base line urines were collected, then deoxypyridoxine 200 mg/day was given for 10 consecutive days. Twenty-four-hour collections were obtained on days 1, 2, 4, 7 and 10 during deoxypyridoxine administration. The day following the last deoxypyridoxine administration 100 mg pyridoxine was administered by intramuscular injection and a 24-hour urine collection obtained.

One two-thousandth of the 24-hour urine volume was applied to a 0.63 $\times$ 140 cm column of a Technicon amino-acid analyzer packed with chromobeads Type A and equilibrated with citrate buffer pH 2.875. The sample was washed once with 0.5 ml of 0.2 N citrate buffer pH 2.875. Elution was carried out using only 0.2 N citrate buffer pH 2.875.

As taurine is an early emerging peak, the analyzer was run until the urea peak emerged and returned to the base line. The column was regenerated by washing with 0.5 N NaOH for 45 minutes. The longer wash period was necessary in order to elute off ninhydrin positive substance left after the short run. It was then washed with the citrate buffer 0.2 N pH 2.875 for 90 minutes prior to the next run. Cysteic acid 0.1 μM was run as the internal standard. Taurine gives 0.94 as much color with ninhydrin as an equivalent molar amount of cysteic acid (personal communications, Dr. H. Goodman and Dr. J. King). The cysteic acid standard value was converted to an equivalent μM value for taurine and the amount of taurine excreted was calculated as mg taurine per 24 hours. Statistical analysis was done on the data expressed as mg taurine/24 hours.

Previous studies(8) on these subjects showed that after 7 days of deoxypyridoxine abnormal vit B_6 metabolism was present as evidenced by increased excretion of xanthurenic acid and 3-hydroxy-kynurenine.

Results. 1. Base line taurine excretion. As shown in Table I there is not only considerable variation in excretion by different individuals but variation in excretion by the same individual. A comparison of the average urinary taurine excretion in paired subjects as mg/24 hours shows that Downs' syndrome patients excreted an average of 45 mg/24 hours while controls averaged 64 mg/24 hours. The lesser excretion in Downs' syndrome subjects was significant at the $p<0.01$ level.

2. Taurine excretion during the first day of deoxypyridoxine. The administration of deoxypyridoxine resulted in an increased taurine excretion from 46 mg/24 hours to 65 mg/24 hours in Downs' syndrome patients and from 64 mg to 77 mg/day in their controls. Six of the 8 subjects had increased excretion of taurine; one mongoloid and one non-mongoloid had a decrease in excretion. The increase in excretion above base line values for both groups was significant at $p<0.01$ level. A comparison of the increase in Downs' syndrome to their controls showed it to be similar and without statistical significance.

3. Taurine excretion Day 2 to Day 10 of

TABLE I.

Subjects	Results expressed in mg taurine/24 hr							
	Pre-deoxy.		Deoxypyridoxine					Pyridoxine, 100 mg
	1	2	Day 1	Day 2	Day 4	Day 7	Day 10	
M	75	67	53	46	51	95	131	106
NM	85	62	45	53	59	68	98	105
M	26	31	44	33	27	10	77	41
NM	98	*	74	40	68	86	104	98
M	67	67	109	59	35	20	34	83
NM	65	39	56	44	56	62	65	68
M	23	17	49	14	23	59	64	81
NM	82	58	136	72	105	124	132	122
Mean value Downs' syndrome	47	45	64	38	34	46	76	78
Mean value controls	82	49	78	52	72	85	100	98

* Incomplete collection.

Two 24-hr urine collections were obtained then deoxypyridoxine 200 mg/day started. Twenty-four-hour urine collections were obtained on days indicated while deoxypyridoxine was administered. Taurine determinations were done using an amino acid analyzer as outlined in *Methods*. Results are expressed as mg taurine/24 hr. Subjects are grouped as pairs. M = Downs' syndrome, NM = controls.

deoxypyridoxine. The data from Table I were taken and the values for each group averaged and deviations from base line values plotted for each collection period (Fig. 2).

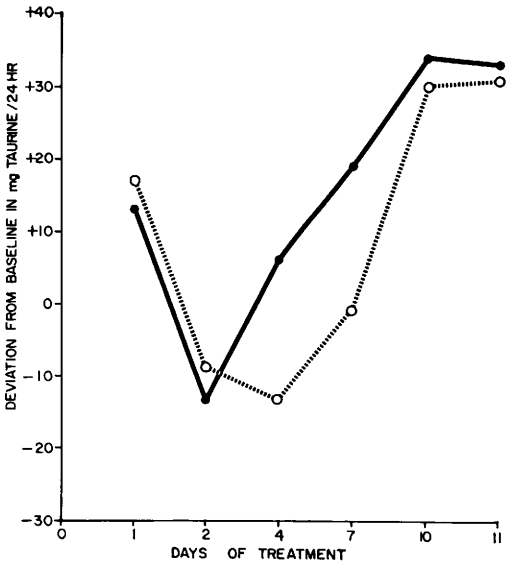

FIG. 2. Average deviation from base line taurine excretion of Downs' syndrome subjects and controls during deoxypyridoxine administration. The deviation from the average base line taurine excretion of Downs' syndrome and control subjects as averaged and plotted for each day is shown. Day 10 - 11 shows average taurine excretion of both groups following 100 mg pyridoxine. ●——● Non-mongoloids ○ - - - - ○ Mongoloids.

On the second day of administration of deoxypyridoxine 200 mg/day a decrease in taurine excretion occurred in 7 of the 8 subjects to below base line levels. In the eighth subject the excretion was slightly above the base line. There was no difference in excretion between the 2 groups. However, by trend analysis for a quadratic component the decrease in both groups was significant at $p<0.01$ level.

On the fourth day of deoxypyridoxine administration taurine excretion had increased above average base line values in 3 of 4 controls but was below average base line values in 3 of 4 Downs' syndrome subjects. The differences between groups were, however, not statistically significant (t test $p>0.05$). On Day 7 of deoxypyridoxine, taurine excretion was greater than average base line values in the 4 control subjects and in 2 of 4 Downs' syndrome patients. By Day 10 taurine excretion was 50 to 100% greater than base line values in 7 of the 8 subjects studied. There was no significant difference in excretion between the two groups but trend analysis for a quadratic component of both groups showed that the increase in excretion was significant at $p<0.05$ level.

4. Effect of pyridoxine on taurine excretion. The day following the last deoxypyridoxine,

pyridoxine 100 mg by intramuscular injection was administered to determine its effect on taurine excretion. In all cases taurine excretion persisted above base line values. There was no consistent pattern compared to the last day of deoxypyridoxine; in some instances the excretion increased while in others it decreased. Though both groups showed increases and decreases, the changes in the non-mongoloid group were small (range −10 to +7 mg) compared to a range of −36 to +49 mg for the mongoloid group. This may be a reflection of metabolic instability of the mongoloid.

Discussion. Goodwin, King and Thomas(7) have shown that the base line excretion of taurine in subjects with Downs' syndrome is less than in controls. Our data for base line values confirm their findings. The data of Wainer *et al*(9) indicate that the decreased excretion is due to low excretion and not a decrease in plasma levels.

The range of values for the present base line studies is similar to that of Pentz(1) but lower than that of Koyanagi *et al*(10). The results of Koyanagi *et al*(10) were similar after administration of thiamine, riboflavin, ascorbic acid and vit A to his subjects. It is of interest that vit A administration decreased taurine excretion in the Japanese children who were thought to have a suboptimal vit A intake.

On the first day of administration of deoxypyridoxine a significant increase in excretion of taurine occurred, followed by a decrease below base line excretion on the second day of administration. The increased excretion on the first day was unexpected. It was expected that after phosphorylation, deoxypyridoxine, acting as a competitive inhibitor of pyridoxal phosphate, would decrease the activity of cysteine sulfinic acid and cysteic acid decarboxylase decrease the formation of taurine and result in a decrease in urinary taurine excretion. The increase in excretion would indicate that perhaps initially the other pathways of cysteine metabolism-transamination to β mercaptopyruvic acid or the desulfhydration reaction to pyruvate + H_2S + NH_3 were more affected than the decarboxylation reaction.

On the second day of deoxypyridoxine, the expected decrease in taurine excretion in both groups occurred. A further decrease in excretion occurred in the Downs' syndrome group at 4 days but not in the control group. By trend analysis for a quadratic component the decrease in both groups was significant at $p<0.01$ level. The decreased excretion may have been due to the effect on the decarboxylation reaction with the formation of less taurine. On Day 7, but more marked on Day 10, an increase in excretion of taurine occurred in both groups. Trend analysis for a quadratic component showed this increase in excretion to be significant at $p<0.05$ level. Because deoxypyridoxine is a competitive inhibitor of pyridoxal phosphate, it had been expected that taurine excretion would remain below base line levels during the entire period of deoxypyridoxine administration. The following points may be considered in the explanation of increasing taurine excretion while deoxypyridoxine was administered. The non-vitamin B_6 deficient adult excretes between 1 and 3% of an administered cysteine load as taurine(2). Thus the great majority of ingested cysteine is disposed of by routes other than taurine excretion. A slightly greater effect of deoxypyridoxine on one of the alternate pathways could shunt small amounts to taurine formation and affect the observed increased excretion. One such pathway could be conversion of cysteine to cystine which is in turn converted to cystine disulfoxide. This compound then undergoes decarboxylation to form taurine. All reports of vit B_6 deprivation in humans and animals show decreased taurine excretion. It is evident then that deoxypyridoxine administered to non-vitamin B_6 deficient individuals results in a different pattern of cysteine metabolism than that observed with true B_6 deficiency.

A number of factors have been shown to influence taurine excretion. Colchicine(11) administered to rats resulted in a 4- to 8-fold increase of urine taurine excretion. Boquet and Fromageot(3) showed that post irradiation increased urinary taurine originates from a pre-existing tissue pool. Vitamin B_6 deficient animals had no increase of urinary taurine excretion following irradiation. The above

results indicate that following a severe insult, increased taurine is excreted that is derived from a tissue pool. An alternate theory to that previously mentioned, the shift of taurine metabolic pathways, could be that deoxypyridoxine results in a release of tissue taurine stores with subsequent urinary excretion.

Summary. Deoxypyridoxine, a vitamin B_6 antagonist, was administered to 4 patients with Downs' syndrome and controls matched for age and weight. Taurine excretion was measured in 24-hour urine samples collected before and during the period of deoxypyridoxine administration. Taurine excretion in the Downs' syndrome patients before deoxypyridoxine was significantly less than their controls ($p<0.01$). During deoxypyridoxine administration, average taurine excretion of both groups increased on Day 1, decreased on Day 2, then increased significantly above base line levels by Day 10. There was no significant difference in taurine excretion between Downs' syndrome patients and their controls. Trend analysis for a quadratic component showed that the decrease and subsequent increased excretion of taurine was of statistical significance. Possible reasons for the observed changes were discussed. Taurine excretion during deoxypyridoxine administration differs from that found during vit B_6 depletion in man.

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Influence of Propranolol on Hemodynamic Changes and Plasma Catecholamine Levels Following Cigarette Smoking and Nicotine.* (31434)

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It is well known that cigarette smoking and nicotine administration stimulate man's cardiovascular system(1). Among the effects commonly seen are an increase in blood pressure, heart rate, stroke volume and cardiac output(2-4). Many of these effects can be attributed to the release of catecholamines from the adrenal medulla and adrenergic nerve endings as observed by Westfall and Watts(5-7) and Kershbaum *et al*(8,9).

At present it is popular to attribute the pharmacological action of catecholamines to their combination with certain receptors. One such classification of adrenergic receptors is that of Ahlquist(10) who arbitrarily chose the names of *alpha* and *beta* based on the relative

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