as peripheral resistance fell slightly but not significantly. 4. Both right and left ventricular work decreased significantly while left ventricular myocardial oxygen consumption was unchanged and calculated cardiac efficiency decreased. 5. These hemodynamic effects are similar to those of hexamethonium, pentolinium, mecamylamine and SKF 6890.

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Received January 15, 1962. P.S.E.B.M., 1962, v110.

Serotonin Metabolism in Paralysis Agitans.* (27429)

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An abnormality of serotonin release or metabolism in paralysis agitans is suggested by two lines of evidence. In the first place, the mesencephalic and diencephalic structures contain the highest 5-hydroxytryptamine (5-HTA) content in human brain(1). Certain anatomic foci within these areas—the substantia nigra, globus pallidus and locus caeruleus—appear to undergo cellular destruction in paralysis agitans(2). Secondly, extrapyramidal syndromes may be pharmacologically induced by agents which release 5-HTA from tissue stores (*i.e.*, reserpine)(3) or exert chemical antagonism to serotonin (*i.e.*, phenothiazine derivatives)(4,5).

The purpose of this study is to investigate the urinary excretion of 5-hydroxyindole compounds in patients with paralysis agitans under basal conditions and following administration of the serotonin precursor, 5-hydroxytryptophan. The latter procedure has been utilized to detect the possible existence of impaired decarboxylation and/or oxidative deamination(6).

Procedure. Patients. This report concerns metabolic observations in 10 cases of paralysis agitans and 12 (control) patients afflicted with other neurologic diseases, including cerebrovascular accidents, multiple sclerosis, anoxic brain disease, spastic paraplegia, and peripheral neuropathy. All were hospitalized within the same ward, permitting some control of nutrition and physical activity. Cases selected for investigation were free of liver dysfunction(6) and azotemia, and did

* This work was supported in part by grants from U. S. Public Health Service and Gastrointestinal Fund of Peter Bent Brigham Hospital.

TABLE I. Urinary 5-Hydroxyindole Metabolites in Paralysis Agitans.*

	Paralysis agitans (10 patients)	Neurologic controls (11 patients)
Baseline 5-HTA (mean)	262 γ (S.D. ± 218 γ)	328 γ (S.D. ± 253 γ)
(range)	0-725 γ	57-567 γ
" 5-HIAA (mean)	2.7 mg (S.D. ± 2.0 mg)	3.3 mg (S.D. ± 1.4 mg)
(range)	0-7.1 mg	1.1-5.9 mg
Post 5-HTP loading		
5-HTA (mean)	1384 γ (S.D. ± 1130 γ)	2592 γ (S.D. ± 1660 γ)
(range)	447-4248 γ	210-5439 γ
5-HIAA (mean)	7.3 mg (S.D. ± 4.1 mg)	8.9 mg (S.D. ± 5.3 mg)
(range)	0.4-13.2 mg	4.3-22.9 mg
% 5-HTP recovered		
As 5-HTA		
mean	3.0% (S.D. ± 2.7%)	5.7% (S.D. ± 3.5%)
range	0-10.2%	0.7-12.9%
As 5-HIAA		
mean	11.3% (S.D. ± 7.2%)	13.7% (S.D. ± 10.8%)
range	1.1-27.8%	5.1-45.8%
As total 5-hydroxyindoles		
mean	51.3% (S.D. ± 17.4%) 7†	54.6% (S.D. ± 23%) 10†
range	21.9-66.9%	23-100%

* Values based on total quantities excreted/24 hr. † No. of patients in group.

not receive rauwolfia compounds, phenothiazines, or drug therapy for Parkinsonism during the period of study.

Methods. In both groups endogenous 24-hour urinary excretion of serotonin and its major metabolic derivative 5-hydroxyindoleacetic acid (5-HIAA) were measured by standard chemical technics(7,8). These measurements were repeated following intravenous administration of DL-5-hydroxytryptophan (5-HTP) (0.66 mg/kg body weight) (6). Determination of total 5-hydroxyindole excretion by a modification of Udenfriend's procedure(7) and paper chromatographic analysis†(9) were also carried out on urines collected following 5-HTP infusion. The accuracy of all urine collections was confirmed by measurement of urinary creatinine excretion.

Results. The baseline and post-5-HTP excretion of urinary indoles for both groups is recorded in Table I. The findings indicate no significant alteration in metabolism of 5-hydroxyindoles in patients with paralysis agitans ($p>.05$). Marked variability of indole excretion within each group was noted. Large standard deviations resulted so that occasional substantial differences between the mean values of the 2 groups were statistically insignificant (*cf.* 5-HTA excretion after 5-hydroxytryptophan loading).

It is of interest that approximately half of the administered 5-hydroxytryptophan did not appear as urinary 5-hydroxyindolic compounds, suggesting the possibility of tissue storage as 5-HTA(10) or degradative catabolism by unknown alternate pathways. In malignant carcinoidosis, serotonin may be deaminated, undergo N-acetylation, conjugation with glucuronic acid or possibly oxidation(11).

5-Hydroxytryptophan, serotonin, and 5-hydroxyindoleacetic acid were the only indoles demonstrated by paper chromatography. Quantitatively, 5-HTP predominated, confirming the predictions derived from the chemical analyses, *i.e.*, the per cent 5-HTP recovered as 5-HTP should equal % 5-HTP recovered as total 5-hydroxyindole minus (% 5-HTP recovered as 5-HTA plus % 5-HTP recovered as 5-HIAA). Applying this formula to the values in Table I, it is apparent that urinary 5-HTP comprises the largest fraction of total 5-hydroxyindoles in both groups of subjects.

† Six cases of paralysis agitans and 7 controls were studied by the chromatographic technic.

Discussion. Data presented here indicate that the metabolism of 5-hydroxyindolic compounds in paralysis agitans is similar to that observed in other unselected neurological disorders. This conclusion, however, is based upon measurements of urinary indoles which largely reflect gastrointestinal synthesis and degradation of these substances(12). For this reason an anomaly of serotonin metabolism confined to cerebral function cannot be excluded in paralysis agitans.

Biochemical abnormalities involving related substances—catecholamines(13) and specifically, dopamine(14)—have recently been suggested. Barbeau has shown a high incidence of positive Simola reactions and contractility of rabbit-aorta preparations in the presence of urine obtained from Parkinsonian patients. Both tests are considered to be unusually sensitive to catecholamines. The specificity of these findings and their ultimate significance, however, must await confirmation.

Unfortunately, precise chemical measurements of the small quantities of 5-hydroxyindole compounds in human cerebrospinal fluid are not currently available for application to this problem. Nevertheless, a discrete central nervous system defect involving serotonin seems unlikely. Preliminary studies in our laboratory, for example, show that repetitive daily infusions of 5-hydroxytryptophan (1.3 mg/kg body weight) do not influence Parkinsonian tremor or rigidity or effect the quantitative excretion of urinary 5-hydroxyindoles (15).

These observations clearly shed no light on the possibility that drug-induced extrapyramidal syndromes may be induced by serotonin deficiency.

Summary. Urinary excretion of 5-hydroxyindole compounds before and after 5-hydroxytryptophan infusion was studied in paralysis agitans and a control group of other neurological disorders. The findings appear to rule out a systemic defect of serotonin metabolism associated with basal ganglia dysfunction in these patients. However, a localized biochemical or physiological lesion within the central nervous system involving 5-hydroxyindoles remains a speculative possibility.

The authors wish to express their thanks to Dr. George Berryman of Abbott Laboratories. We also gratefully acknowledge the technical assistance of Betty Dorsey, Donna Gould and Ina Phelps.

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Received January 15, 1962. P.S.E.B.M., 1962, v110.