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The relation between vanilyl mandelic acid and 5-hydroxyindoleacetic acid excretion in a patient with a carcinoid tumour

SIR,—There is convincing evidence from experiments with several species (Werle & Aures, 1959; Rosengren, 1960; Lovenberg, Weissbach & Udenfriend, 1962; Reid, Riley & Shepherd, 1963; Reid & Shepherd, 1964) that the non-specific histidine decarboxylase, dopa- and 5-hydroxytryptophan decarboxylases are, in fact, one and the same enzyme. An opportunity to study this relationship in man was afforded recently by a carcinoid tumour showing an exceptionally high output of 5-hydroxyindoleacetic acid (5-HIAA).

5-HIAA was estimated by the method of Macfarlane and others (1956) and vanilylmandelic acid (VMA) by Connelian & Godfrey's (1964) modification of the method of Pisano, Crout & Abraham (1962), in 24-hr urine specimens collected from the patient (F.N., male, age approx. 50 years) over a period of six months During most of this time the patient was under treatment with methysergide to reduce the symptomatic effects of released 5-HT. The results are recorded, in chronological order, in the Table 1.

TABLE 1. VMA AND 5-HIAA CONTENT OF URINE SPECIMENS FROM A MALE WITH CARCINOID SYNDROME DURING SIX MONTHS

	Urinary excretion, mg/24 hr	
Date	VMA	5-HIAA
25/3/65	7·12	336
26/3/65	8·00	417
27/3/65	9·92	510
28/3/65	9·18	538
9/4/65	10·20	680
21/4/65	9·18	500
4/5/65	8·88	410
7/5/65	10·08	590
31/5/65	9·02	548
12/7/65	11·00	575
5/9/65	13·90	692
1/10/65	7·16	275
Upper limit of normal	7·00	10·0
	Correlation between VMA and 5-HIAA: $r = 0{\cdot}859$; $P = <0{\cdot}01$	

The highly significant correlation of the excretion levels of the metabolites of 5-HT and catechol amines supports the theory of a common decarboxylase responsible for the formation of these amines. On the other hand, in the carcinoid tumour, 5-HIAA formation is very much more rapid than VMA formation, since, in this particular patient, the output of 5-HIAA is increased to as much as 70 times the normal level, whereas the highest value for VMA excretion is only twice that of the upper limit of normal. In fact, there is no noticeable increase in VMA excretion above the normal range until the 5-HIAA excretion rises to 300–400 mg/24 hr, so that it would be unlikely that this relation would be observed in the average case of carcinoid, in which the 5-HIAA output rarely exceeds 100 mg/24 hr. This would suggest that there is a big difference in the

availability of substrates to the enzyme in the carcinoid tumour, 5-hydroxytryptophan penetrating much more readily than dopa.

I wish to thank Miss Maureen Raffan for carrying out the VMA estimations.

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Liberation of noradrenaline from the dog spleen

SIR,—Recently, Haefely, Hürlimann & Thoenen (1965) published evidence on the relation of the rate of stimulation and the quantity of noradrenaline liberated from sympathetic nerve endings in the isolated spleen of the cat. This is an account of similar experiments on the isolated spleen of the dog.

Mongrel bitches were anaesthetised with pentobarbitone, 30 mg/kg, intravenously. A midline incision was made in the abdomen and the animal eviscerated from mid-duodenum to the terminal colon. The spleen was isolated and removed to a chamber containing liquid paraffin and maintained at 37°. It was perfused with McEwen's solution maintained at 37° and at a rate of 20 ml/min. The perfusion fluid contained 1 μg/ml each of cocaine hydrochloride and phenoxybenzamine. The splenic nerves were laid over bipolar electrodes and stimulated with supramaximal square wave pulses of 1 msec duration. Stimulation was for 2 min at 0·5, 1·0, 2·0 and 5·0 c/s, applied successively without interruption. The perfusate was collected in the last 30 sec of each period of stimulation in tubes containing hydrochloric acid, ascorbic and ethylenediaminetetra-acetic acids and the noradrenaline assayed spectrofluorometrically. The method of assay also served to identify the substance as noradrenaline, and fully accounted for the vasopressor activity of the samples assayed in the pithed rat.

The combined results of three experiments are shown in Fig. 1. A resting output of approximately 20 ng/ml noradrenaline was observed; whether arising from the spontaneous release of noradrenaline from the nerve terminals, or from an indirect sympathomimetic action of cocaine is not known. The output of noradrenaline increased by 20 ng/ml at 0·5 c/s which is approximately twice the resting output; the noradrenaline output per stimulus was 1·2 ng. At a frequency of 1·0 c/s the output of noradrenaline rose to 110 ng ml, i.e. about 4 ng/stimulus. When the rate of stimulation was increased to 2·0 c/s the