Chapter 4

Occurrence of indolealkylamines in nature

By

VITTORIO ERSPAMER

With one Figure

I. Introduction

Quantitative data on the occurrence of 5-HT and related indolealkylamines in nature are presented in Tables 1—23 of this chapter and in Tables 1—6 of chapter 13. The interest of these data is obvious, especially for the interpretation of the physiological significance of indolealkylamines in their different localizations. However, it seems opportune to call attention at once to a few points.

The occurrence of 5-HT or another indolealkylamine in a tissue does not of necessity imply that the amine has particular importance in this tissue. In fact, it is obvious that one is authorized to surmise that a given localization of an indolealkylamine has a general biological significance only if this localization occurs in all or in a great number of species.

Quantitative data on the concentration of indolealkylamines in a tissue reflect only a static situation, and they give no indication of the rapidity of synthesis and metabolism of the amines. There is no doubt that knowledge of the turnover rate of the amines in a tissue is considerably more important, from every point of view, than knowledge of the content of the amines at a given moment.

To give only one example, it is probable that the amount of 5-HT synthetized and destroyed in a 24-hour period in the rat brain is considerably larger than that metabolized in the skin of *Bombina variegata pachypus* or *Discoglossus pictus*. Yet, it will be seen that the first tissue contains as little as 0.4—0.6 μg/g 5-HT, the second 200—450 μg/g. Obviously, the functional significance of 5-HT in these two localizations cannot be the same.

II. Vertebrates

1. Gastro-intestinal tract

Found for the first time in extracts of rabbit's gastric mucosa (VIALLI and ERSPAMER 1937, ERSPAMER 1940b), 5-HT has since been recognized in extracts of the gastrointestinal mucosa of all examined vertebrates, as well as of ascidians (ERSPAMER 1946, 1953b, 1954a, 1954b, FELDBERG and TOH 1953, DALGLIESH et al. 1953). At variance with previous negative results, small amounts of 5-HT could be detected also in gastrointestinal extracts of *Telostei* (ERSPAMER unpublished observations).

The general occurrence of 5-HT within the gastrointestinal mucosa of all vertebrates represents the most convincing proof of the general biological significance of the 5-HT of enterochromaffin origin. It has been conclusively demonstrated that, with a few exceptions, the alimentary canal is the only source of the 5-HT found in blood of vertebrates.

Table 1. *The 5-HT content of rat extracerebral tissues*

Tissue	5-HT content (in μg/ml or μg/g)
Blood	
Whole blood	0.31[1]; 0.43[2]; 0.87 ± 0.07[3]; 0.73 ± 0.06[4]; 1.04[5]
Serum	0.57—1.72[6]; 0.65[7]; 0.53—0.82[8]; 0.4—0.6[9]; 0.3—0.54[10]
Platelet protein (1 mg)	1.0—2.0[11]
Plasma (platelet free)	0.008[32]
Spleen	2.8[6]; 2.15[7]; 1.9—3.0[8]; 2.5[12]; 2.99 ± 0.16[4]; 0.8 ± 0.1[13]; 1.8—2.2[5]; 4.43 ± 0.44[31]; 3.2—9.2[34]
Gastrointestinal tract	2.1[7]; 1.87—2.45[20]
Stomach	1.4[6]; 1.45 ± 0,07[14]; 1.8 F, 2.1 P[15]; 5.6[16]; 3.9 P[18], 1.9 P[17]; 9.31 ± 0.7 P[31]; 0.68 ± 0.09 F, 0.80 ± 0.19 P[35]
Small intestine	1.2[6]; 4.18[5]; 6.5[16]; 2.8 ± 0.6[17]; 1.06—1.35[10]; 5.04 ± 0.23[4]; 2.9[19]; 1.1—4.0[21]; 3.48 ± 0.25[38]
cranial third	5.6[15]; 2.9[18]; 2.3 ± 0.13[20]; 6.26 ± 0.48[31]; 3.28 ± 0.52[35]
medium third	3.2[15]; 1.6[18] } 2.57 ± 0.16[20]
caudal third	5.5[15]; 3.3[18] }
Large intestine	3.8[15]; 4.75—6.0[18]; 5.9 ± 1.4[17]; 5.76[19]; 6.32 ± 0.5[20]
Liver	0.14[15]; 0.27—0.45[8]; 0.18[7]; 0.65 ± 0.08[31]; 0.48—0.68[36]
Lung	1.16[12]; 1.0[1]; 0.55 ± 0.16[22]; 3.9[15]; 2.7—3.5[21]; 1.9—3.3[8]; 1.3[7]; 2.43 ± 0.25[31]
Heart	0.15[7]; 0.58[19]; 0.7—0.8[30]
Uterus	0.15 ± 0.05[13]
Testicles	0.05[7]
Kidney	0.08[7]
Thyroid gland	2.5—5.0[23]; 3.55[37]
Salivary glands	0.56 (parotid), 0.25 (submaxill.), 0.8 (sublingual)[23]
Uvea and retina	2.70—5.20[33]
Lid	1.53[33]
Skin	
ear	1.0[24]; 3.20 (base), 1.40 (margin)[25]; 1.9[15]; 0.32—0.67[8]; 0.55[7]
groin	1.5[24]; 4.36[25]
throat	4.26[25]
abdomen	1.3[24]; 1.9[15]; 0.66—1.56[26]; 0.8—1.1[27]
tail	0.33[24]; 0.9[25]
feet	0.7[24]; 1.5[15]; 1.5—4.0[28]; 0.75[29]
Paws	0.34[7]; 0.15—0.44[8]
Adipose tissue	
interscapular brown fat	1.04 ± 0.054[38]
epididymal white fat	0.154 ± 0.018[38]

P = pyloric or glandular stomach; F = fundic stomach.

References to Table 1. [1] SKILLEN et al. (1961a). — [2] GORDON (1961). — [3] ERSHOFF and GAL (1961). — [4] ERSHOFF et al. (1962). — [5] GAL and DREWES (1961). — [6] ERSPAMER (1954a, 1954b). — [7] ERSPAMER and BERTACCINI (1962). — [8] BERTACCINI (1960). — [9] SCHMIDT et al. (1960). — [10] CASS and MARSHALL (1962). — [11] SHORE et al. (1956). — [12] PARRATT and WEST (1957a). — [13] BORÉUS and WESTERHOLM (1962). — [14] NIKODIJEVIĆ and TRAJKOV (1963). — [15] TELFORD and WEST (1960). — [16] TOH (1960). — [17] RESNICK et al. (1961). — [18] NOBILI, unpublished data. — [19] SCHONE and LINDNER (1960). — [20] BERTACCINI and ERSPAMER (1962). [21] WEISSBACH et al. (1958). — [22] KINDWALL et al. (1962). — [23] PAASONEN (1958). — [24] PARRATT and WEST (1956a). — [25] PARRATT and WEST (1958). — [26] BROCKLEHURST et al. (1960). — [27] JOHANSSON (1960). — [28] MÖRSDORF (1959, 1961). — [29] SUPEK et al. (1961). — [30] SKILLEN et al. (1962). — [31] UUSPÄÄ and UUSPÄÄ (1962). — [32] KÄRKI and PAASONEN (1960). — [33] LEVENE (1962). — [34] VARAGIĆ et al. (1963). — [35] MORAN and WESTERHOLM (1963). — [36] BOGGS et al. (1963). — [37] MAGUS et al. (1964). — [38] STOCK and WESTERMANN (1963a, 1963b).

In the mucosa of the digestive tract 5-HT is localized, to a great extent at least, in the enterochromaffin cells, which the writer considers to constitute a "diffuse endocrine organ", in the sense of FEYRTER (1953), designed for the production and storage of 5-HT. The abundant evidence definitely supporting this view has been discussed elsewhere (see pages 138, 140 and 203).

From the enterochromaffin cells 5-HT is released into the circulatory stream, where most of it is taken up by the platelets (Toh 1954, Erspamer and Testini 1959, Adams 1960, Bertaccini 1960, Kärki et al. 1960a).

It has been claimed that elevation of the intraluminal pressure and/or motility of an isolated or *in situ* loop of the guinea-pig intestine causes the appearance in the intestinal lumen of detectable amounts of 5-HT (Bülbring and Crema 1959a, 1959b) and similarly that a fraction of the 5-HT released by HCl from the wall of an obstructed loop of the rat intestine can be recovered intraluminally (Resnick and Gray 1962). Although an external secretion by the enterochromaffin

Table 2. *The 5-HT content of dog and cat extracerebral tissues*

Tissue	5-HT content (in µg/ml or µg/g)	
	Dog	Cat
Blood		
Whole blood	0.2—0.8[1]	0.9—4.5[1]; 1.8[2]
Serum	0.08—0.57[3]; 0.2—0.6[1]; 0.55[4] 0.28[5]; 0.2—0.6[6]	1.2—7.4[3]; 0.3—5.7[1]; 4.3[2]
Plasma (platelet free)	0.002—0.005[5]; <0.006[7]	
Spleen	0.61—2.5[3]; 4.6[9]	5.7—10.5[3]; 8.5[9]
Gastrointestinal tract		
Stomach	5.2[3]; 1.6—2.3[8]	0.45[3]; 0.52[8]
Small intestine		
cranial half	2.0[8]; 3.7[3]	1.4[8]; 0.9[3]
caudal half	1.7[8]; 4.3[3]	1.0[8]; 0.5[3]
Large intestine	1.5[8]; 2.8[3]	1.7[8]; 1.2[3]
Lung	0.1[1]; 0.26[9]	0.2[1]; 0.62[9]
Liver	0.54[9]	0.56[9]
Heart	0.02—0.26[12]	=
Skin	<0.03[9]	0.08—0.13[9]
Salivary glands		
parotid	0.017[10]	=
submaxillary	0.012[10]; 0.35—1.4[11]	=
Thyroid gland	0.025[10]	

References to Table 2. [1] Sanders et al. (1959). — [2] Smith and Smith (1955). — [3] Erspamer (1954a, 1954b). — [4] Rosenberg et al. (1960). — [5] Cambridge and Holgate (1958). — [6] Erspamer and Testini (1959). — [7] Toh (1956). — [8] Nobili, unpublished data. — [9] Parratt and West (1957a). — [10] Paasonen (1958). — [11] Iachello et al. (1962). — [12] Bhatt et al. (1963).

cells cannot be excluded (the chromaffin cells of the posterior salivary glands of octopods, for example, possess both an internal and an external secretion) there is as yet no decisive evidence that the enterochromaffin cells discharge, under strict physiological conditions, part of their 5-HT into the intestinal lumen.

Evidently, the problem is whether the delicate intestinal epithelium may be considered completely normal in isolated or obstructed intestinal loops. Moreover, it should not be forgotten that the typical normal enterochromaffin cells of the pancreatic islets of some mammals and of the thymus of some birds lack the anatomical possibility of an external secretion.

Administration of a diet of meat or liver or of a diet containing added tryptophan to rats or mice produces an increase in the 5-HT content of the small intestine (Stacey and Sullivan 1957, Eber and Lembeck 1958, Sullivan 1960). The opposite can be observed in rabbits, guinea-pigs, rats and mice on feeding a low-tryptophan diet (Eber and Lembeck 1958, Zbinden et al. 1958, Gal and Drewes 1962). This observation points to the decisive role of tryptophan in the biosynthesis of 5-HT.

Of interest is the finding of BEAVER and WOSTMANN (1962) that the 5-HT content of the intestines may vary conspicuously (up to 100%) in different mouse strains kept on the same diet.

5-HT levels in the intestinal wall of conventional animals having a normal intestinal flora are lower than those found in the intestinal wall of germ-free

Table 3. *The 5-HT content of guinea-pig and rabbit extracerebral tissues*

Tissue	5-HT content (in μg/ml or μg/g)	
	Guinea-pig	Rabbit
Blood		
Whole blood	0.2[1]	3.2—6[1]; 4—6[2]; 3.5[3]; 2.52 ± 0.3[4]
Serum	0.07—0.27[5]; 0.15—0.7[6]	1.8—5.6[5]; 4.4[6]; 2.0[7]; 3.3—10[8]
Platelets	0.3—0.5 μg/mg platelet protein[9]	2.7 per 10^8 platelets[10]
Plasma (platelet free)	=	0.01—0.07[11]
Spleen	0.25—1.6[5]; 1.1[12]; 3.7 ± 0.5[13]	16.4—22.5[5]; 11.7[14]; 24.3[12]
Gastrointestinal tract		
Stomach	1.4[5]; 3.9[15]; 1.15[16]	0.85 P, 4.9 F[5]; 0.9 P, 5.7 F[16]; 6.2[14]
Duodenum	7.2[15]; 3.3[16]	3.2[16]
Jejunum	5.0[5]; 6.2[15]; 2.0[16]	3,3[5]; 1.8[16]
Ileum	3.4[5]; 4.5[15]; 2.0[16]; 3.6[13]	3.7[5]; 1.5[16]
Caecum	0.8[15]; 0.9[16]	0.7[16]
Large intestine	0.7[5]; 0.8[15]; 0.45[16]	2.7[5]; 2.2[16]; 3.5[14]
Intestine (?)		10—17[2]; 17[1]; 5.9[17]
Liver	< 0.02[12]	0.55[12]; 2.3[1]; 0.27[14]; 0.6[17]
Lung	0.06[12]; 0.2—0.3[2]; 0.2[1]; 0.21[22]	1.6[12]; 1.2—4,7[1]; 5—5.5[2]; 0.13[14]; 0.1[17]; 1.7—7.1[18]
Uterus	< 0.003[13]	=
Heart	=	0.4[1]; < 0.1[17]; 0.02[14]
Kidney	=	< 0.1[17]; 0.09[14]
Thyroid gland	=	0.09—0.29[20]; 0.09[14]
Salivary glands	=	0.13—0.16[20]; 0.07[14]
Skin	< 0.02—0.18[12]; < 0.01[13]	< 0.04—0.11[12]; < 0.04[19]
Thymus, pancreas, bladder, skeletal muscle	=	< 0.1[14]
Uvea and retina	1.5—2.1[21]	0.45—1.3[21]
Lid	0.92[21]	0.24[21]
Adipose tissue	0.015—0.03[23]	=

P = pyloric stomach; F = fundic or glandular stomach.

References to Table 3. [1] WAALKES and COBURN (1959, 1960a, 1960b). — [2] WEISSBACH et al. (1957, 1958). — [3] SHORE et al. (1956). — [4] CERHOVÁ (1962). — [5] ERSPAMER (1954a, 1954b). [6] MACHAFFIE et al. (1960). — [7] VANE (1958). — [8] DAVIS et al. (1961). — [9] HAVERBACK et al. (1957). — [10] WOOLLEY and EDELMAN (1958). — [11] KÄRKI et al. (1960a). — [12] PARRATT and WEST (1957a). — [13] BORÉUS and WESTERHOLM (1962). — [14] HAGMÜLLER et al. (1961). — [15] GARVEN (1956). — [16] NOBILI, unpublished data. — [17] KAKIMOTO and ARMSTRONG (1962). — [18] SANYAL and WEST (1958). — [19] WAALKES and COBURN (1960b). — [20] PAASONEN (1958). — [21] LEVENE (1962). — [22] ROBILLARD and ALARIE (1963). — [23] STOCK and WESTERMANN (1963b).

animals. BEAVER and WOSTMANN (1962) have observed 20—40% differences in rats, and 30—90% differences in mice, PHILLIPS et al. (1961) 10—55% differences in chickens. Oral administration of antibiotics causes a significant increase in intestinal 5-HT in mice, whereas in rats the increase is not considered to be significant. Sterilization of the gut acts probably by preventing bacterial metabolism of dietary tryptophan (STACEY and SULLIVAN 1957, SULLIVAN 1961). With the exception of neomycin, antibiotics only affect the 5-HT content of the intestine in mice.

The 5-HT content of the stomach and the duodenum of the hedgehog shows no statistically significant differences during activity and hibernation (UUSPÄÄ 1963).

The small intestine of thiamine-deficient rats presents, like blood and spleen, reduced levels of 5-HT; that of starved rats normal levels (GAL and DREWES

Table 4. *The 5-HT content of hamster and mouse extracerebral tissues*

Tissue	5-HT content (in μg/ml or μg/g)	
	Hamster	Mouse
Blood		
Whole blood	=	1.8—4.6[1]
Serum	0.37[2]	1.48[2]
Spleen	20.5[3,12]	1.8[2]; 2.7[3]; 5.9[4]; 3.5[5]
Gastrointestinal tract		
Stomach	1.7—3.7[6]; 0.85[12]	25 P, 2.15 F[6]; 8.85[2]; 5.2[7]; 1.1[12]
Small intestine		1.6[2]; 3.5—4.5[1]; 3.1[4]; 2.8—3.7[9]
cranial third	0.95[6]	2.5[6]; 2.8[7]
medium third	0.95[6]	1.7[6]
caudal third	0.85[6]	0.7[6]; 2.6[7]
Caecum	0.73[6]	2.1[6]; 2.2[7]
Colon	1.3[6]	4,5[6]; 8.7[7]; 3.1[2]
Liver	0.22[3]	0.6—1.1[1]; 0.24[5]
Lung	2.75[3]	1.4—6[1]; 2.7[4]; 2.59 ± 0.37[10]; 1.9[8]
Kidney	=	1.3[4]
Skin	0.08[3,12]; < 0.08[13]	0.37 (abdomen), 1.12 (ears)[3]
Adipose tissue	=	0.12 (interscapular), 0.025 (epididymal)[14]
Placenta	=	0.14—0.52[15]
Whole body	=	1.5[11]

P = pyloric stomach; F = fundic stomach.

References to Table 4. [1] WAALKES and COBURN (1959, 1960a). — [2] ERSPAMER (1954a, 1954b). — [3] PARRATT and WEST (1957b). — [4] DONALDSON et al. (1960). — [5] MELCHING et al. (1960). — [6] NOBILI, unpublished data. — [7] HAGMÜLLER et al. (1961). — [8] WEISSBACH et al. (1957). — [9] SMITH (1960). — [10] KIND et al. (1961). — [11] SJOERDSMA et al. (1957). — [12] WEST (1958b). — [13] CHIECO BIANCHI et al. (1963). — [14] STOCK and WESTERMANN (1963b). — [15] ROBSON and SENIOR.

Table 5. *The 5-HT content of the gastrointestinal tract of some large domestic mammals* (FAUSTINI 1955)

	5-HT content (in μg base per g fresh tissue)							
	Stomach				Intestine			
	Rumen	Reticulum	Omasum	Abomasum	Small intest. proximal	Small intest. distal	Large intest. proximal	Large intest. distal
Ox	0	0	0	1.6	5.1	1.6	1.2	4.9
Calf	0	0	?	1.2	3.6	3.0	3.7	4.5
Goat	0	0	?	3.2	4.1	2.0	2.5	2.9
Hog	0.5				4.0	0.5	0.3	0.5
Horse	?				0.7	0.3	0.5	1.0

1961). Pyridoxine-deficiency causes in chickens a fall in the 5-HT content of the intestine from 5.0 to 1.2 μg/g, possibly owing to lessened activity of dopadecarboxylase (UDENFRIEND et al. 1957). Chronic administration of ethanol to mice and guinea-pigs, up to 3—7 months, does not produce significant changes either in the number of enterochromaffin cells or in the 5-HT content of the gastrointestinal tract (HAGMÜLLER et al. 1961).

Table 6. *The 5-HT content of the gastrointestinal tract of other vertebrate species* (in μg 5-HT base per g fresh tissue)

Animal species	Stomach	Small intestine			Large intestine	Reference
		proximal	medium	distal		
Monkey *(Papio hamadryas)*	1.2—1.5	2.1	1.65	1.4	1.8—2.5	1
Marmot	0.2	1.1	0.6	0.9	1.1—2	2
Hedgehog	6.3		2.8		3.9	3
Bat *(Rhinolophus ferrum equinum)*			1.6			3
Chicken	0—0.65	2.0	3.4	1.0	1.3—1.9	1
	1.4	4.9		4.5	4.1	3
		8.3 ± 1.3		6.1 ± 0.8		4
Pigeon	0.3—0.7	0.7	0.8	1.0	1.3—1.9	1
Duck	=	3.1		4.1	3.6	3
Tortoise			3.2			3
Rana pipiens	3.0		5.4, 1.4—2.0		=	6,7
Hyla cinerea	3.6		4.8		=	6
Hyla radiana			0.9			5
Hyla faber			0.6			5
Pleurodema tucumana			0.8			5
Calyptocephallela gayi			0.3			5
Phyllomedusa sauvagi			0.8			5
Leptodactylus ocellatus			1.4			5
Leptodactylus chaquensis			1.5			5
Leptodactylus bufonius			0.7			5
Leptodactylus pentadactylus labyrinthicus			1.0; 4.9			1
Leptodactylus laticeps			1.7			5
Bufo bufo bufo	2.2		1.6			3
Bufo americanus	2.6		5.1		=	6
Bufo marinus	2.7		7.1		=	6
Bufo marinus			0.4, 0.77			5,7
Bufo arenarum			1.5			1
Bufo spinulosus			0.7			5
Bufo granulosus major			2.0			5
Odontophrynus americanus			3.0			5
Bombina variegata pachypus	1.0		0.75			3
Desmognatus fuscus	3.0		5.0		=	6
Ambystoma tigrinum	1.1		2.1		=	6
Necturus maculosus	1.8, 0.28		1.4, 0.26		=	6,7
Scyliorhinus canicula	0.6		2.6			3
Scyliorhinus stellaris	0.3		2.3			3
Torpedo marmorata	1.35		2.5			3
Acipenser naccarii	0.3		0.34			3
Acipenser sturio			0.38			3
Ameiurus catus, Anguilla anguilla, Tinca tinca			<0.2—0.4 (?)			3
Carassius auratus	1.1		1.1		=	6
Amia calva	1.6 (mucosa)		1.2		=	6
Ameiurus nebulosus	0.15—0.36		0.4—0.74		=	7
Petromyzon planeri			0.2			3

References to Table 6. [1] NOBILI, unpublished data. — [2] BERTACCINI, unpublished data. — [3] ERSPAMER (1954a, 1954b). — [4] PHILLIPS et al. (1961). — [5] ROSEGHINI, unpublished data. — [6] BOGDANSKI et al. (1963), BRODIE et al. (1964). — [7] WELSH (1964).

Quantitative data on the occurrence of 5-HT in foetal tissues have been collected in bovine foetuses by FAUSTINI (1955) and by BERTACCINI et al. (unpublished observations). They are shown in Table 7.

It clearly appears from the tabulated data that small amounts of 5-HT are detectable very early in the intestinal tract of bovine foetuses, at the time of the first appearance of the enterochromaffin cells in the mucosa and, similarly, that spleen tissue contains considerable amounts of 5-HT from the time of its first differentiation.

Table 7. *Occurrence of 5-HT in some tissues during foetal life (bovine foetuses)* (FAUSTINI 1955, BERTACCINI et al. to be published)

Gestation time	Content of 5-HT base (in μg per g fresh tissue)		
	Gastrointestinal tract*	Spleen	Brain
up to 30 days	non detectable	=	=
30—60 days	trace amounts	=	=
60—90 days	0.35—0.7	3—3.3	=
90—120 days	0.65—0.7	3.1—3.3	=
120—150 days	0.7	3.4	=
	A 0.9—2; S 0.6—1.6; L 0.9—2	1.7—2.7	0.2—0.4
150—180 days	A 1.6—1.7; S 2.6—3.4; L 2.7—3.5	2.2—5.0	0.15—0.25
180—210 days	A 2.7; S 2.4; L 2.2	6.0	0.16
240 days	A 1.6; S 1.6; L 2.0	5.8	0.12

* A = abomasus, S = small intestine, L = large intestine.

In guinea-pigs, 5-HT first appears in the small intestine in measurable amounts after 30—40 days of intrauterine life, i.e. only half way through the gestation period. Thereafter the concentration in the gut rises rapidly till at birth it reaches a level about 60% of the adult. The rise in concentration of the 5-HT in the platelets follows the rise in the intestine, a result which supports the view that platelet 5-HT is derived from the intestine (STACEY and YOUNG 1964).

Data on the subcellular localization of 5-HT in the enterochromaffin cells and on the turnover rate of 5-HT in the gastrointestinal tract are presented in Chapter 5.

2. Blood

As early as 1912, O'CONNOR, as a result of his careful experimental observations, supposed that the serum vasoconstrictor did not pre-exist in the circulating plasma, but was released, during coagulation or defibrination of the blood, from the blood cells or, more probably, from the platelets. The hypothesis of the thrombocytic origin of the serum vasoconstrictor was later supported, with ever more convincing evidence, by ZUCKER and STEWART (1913), JANEWAY et al. (1918), HIROSE (1918), FREUND (1920a, 1920b), SIMON (1938, 1939), ZUCKER (1944, 1947, 1951), BRACCO and CURTI (1953, 1954), BRACCO et al. (1956) and finally by RAND and REID (1951, 1952) and by ZUCKER and RAPPORT (1954) and ZUCKER et al. (1954). By fractional centrifugation of ox blood rendered non-coagulable with sodium citrate, RAND and REID succeeded in establishing definitively that the presence of platelets at the time of clotting was a necessary condition for the appearance of 5-HT in the serum. ZUCKER and co-workers, in their turn, found that the content of 5-HT in bovine platelets was more than sufficient to account for all the 5-HT present in bovine serum. No other indolic or phenolic substances were found in the platelet extracts.

It is evident that the thrombocytes contain substances or active groups capable of anchoring 5-HT with especial selectivity and tenacity. This anchoring is very important in that, amongst other things, it provides a defence for 5-HT against amine oxidase and other enzymes, to which the substance would otherwise inevitably be exposed.

HUMPHREY and TOH (1954) first demonstrated that washed dog platelets possess the capacity of absorbing 5-HT from their suspending medium and these results have since then been confirmed, both *in vitro* and *in vivo*, by a number of research workers. From all the studies on this topic it clearly emerged on the one hand that there exists for every animal species a definite limit to the capacity of the thrombocytes to take up 5-HT and, on the other hand, that the absorption capacity of 5-HT by the thrombocytes is by no means saturated under normal conditions.

In fact, the maximum uptake of 5-HT observed by BORN and GILLSON (1959) for human platelets was 1.08 μg per 10^8 platelets, the normal content being 0.025—0.038 μg.

In fractioning experiments, carried out on suspensions of destroyed human thrombocytes, 95% of the platelet 5-HT was found by SCHULTZ et al. (1964) in the hyalomer fraction and only 5% in the granulomer fraction.

5-Hydroxy-α-methyltryptamine is taken up by ox platelets in the same way as 5-HT and the uptake is inhibited competitively by α-methyltryptamine (LONG 1962). Tryptamine is taken up by the platelets by a different mechanism and in the presence of tryptamine the uptake of 5-HT is depressed. Tryptophan, 5-HTP and DOPA do not affect 5-HT uptake by the platelets (STACEY 1961).

Specific hetero-antibodies (anti-human-platelet serum prepared in the rabbit) and iso-antibodies (serum from patients who have received multiple blood transfusions) strongly inhibit the *in vitro* uptake of 5-HT by platelets (BRIDGES et al. 1963).

When thrombocytes disintegrate, in the spleen, in other tissues or in the blood itself, 5-HT is of necessity set free either into the plasma or inside the macrophages. The further fate of the substance may then be very different inasmuch as, according to the circumstances, it may either be taken up by other thrombocytes, or undergo enzymatic inactivation, or finally act on the effector structures to provoke its peculiar biological actions.

There is at present no doubt that platelet 5-HT is of intestinal origin, with the possible partial exception of the few animal species containing 5-HT in their mast cells. Mature platelet is, in fact, not capable of forming 5-HT from its precursor 5-HTP (GADDUM and GIARMAN 1956).

Through the use of radioactive tryptophan it has been calculated that the half-life of platelet 5-HT is 24 to 73 hours, i.e. that the platelets lose their 5-HT only when disintegrating (UDENFRIEND and WEISSBACH 1958; MELMON and SJOERDSMA 1963).

Assuming in man a daily production of 5—20 mg 5-HT — as inferred from the urinary excretion of 5-HIAA (ERSPAMER and TESTINI 1959) — and a total 5-HT content in the platelets of 0.5—1 mg 5-HT (TODRICK et al. 1958), it should be concluded either that the turnover rate of 5-HT in the platelets is considerably faster than that calculated or that barely 2.5—20% of the 5-HT produced by the enterochromaffin cells is absorbed by the platelets.

Recent studies have concordantly shown that platelet 5-HT exchanges with other body depots of the amine and that it may be re-utilized after release from the platelets (PARKER-WILLIAMS et al. 1963; JACKSON et al. 1963, ZUCKER et al. 1964).

If we allow that thrombocytic 5-HT has its origin in the enterochromaffin cells of the gastrointestinal mucosa, then it must of necessity be admitted that a part of the 5-HT, though perhaps a very small part, does exist and circulates free in the plasma. In fact, the exchange of 5-HT between thrombocytes and enterochromaffin cells can take place only through the mediation of plasma, and the substance released following damage or lysis of the platelets must obviously

penetrate, at least in part, into the plasma. The well-known extreme fragility of thrombocytes accounts for the circumstance that unambiguous quantitative data on plasma 5-HT are very difficult to collect.

HUMPHREY and JAQUES (1954b) indicate for dog, rabbit, and human plasmas a possible 5-HT content of 2 to 5 ng/ml, ARMIN and GRANT (1957a) a content in dog plasma of less than 0.1 ng/ml. It may be inferred that normal plasma 5-HT values exceeding 10 ng/ml are to be considered erroneous.

Table 8. *The 5-HT content of the serum (or whole blood) and spleen of other vertebrates* (in μg 5-HT base per g fresh tissue or ml serum)

Animal species	Serum (whole blood*)	Spleen	Reference
Ox	1.48	7.8	1
Goat	2.2	4.8	1
Sheep	0.85	3.8	1
Horse	0.4	1.75	1
Ass	0.4	3.1	1
Hog	0.26; 0.4*	1.2	1,2
Hedgehog	1.8	1.8	1
Bat *(Rhinolophus ferrum equinum)*	3.6	19	1
Chicken	2.8; 2—3*	12.5	1,3
Guinea-hen	2.7	=	1
Turkey	0.1	=	1
Duck	1.15	4.1	1
Goose	350 μg/g platelets	=	4
Pigeon	0.33	=	1
Sea gull	0.7	=	1
Stork	0.03	=	1
Tropidonotus natrix	0.4	0.16	1
Testudo graeca	0.01	0.01	1
Rana esculenta	0.18	0.08	1
Bufo bufo bufo	0.02	=	1
Scyliorhinus canicula	<0.02	<0.06	1
Scyliorhinus stellaris	<0.04	<0.06	1
Torpedo marmorata	<0.02	<0.06	1
Acipenser naccarii	0.01	0.03	1
Acipenser sturio	0.025	0.03	1
Anguilla anguilla	<0.05	<0.05	1
Tinca tinca	<0.04	<0.05	1
Ameiurus catus	<0.05	=	1
Petromyzon planeri	<0.05	=	1
Petromyzon marinus	<0.03	=	1

References to Table 8. [1] ERSPAMER (1954a, 1954b). — [2] GRETTE (1957). — [3] WEISSBACH et al. (1958). — [4] BRACCO and CURTI (1954).

For a better understanding of the data shown in the Tables 1—4 and 8 it should be emphasized that blood serum contains only part (43—59%) of the 5-HT present in the blood. The remainder is lost during the separation of serum owing to irreversible absorption by red cells or to enzyme attack (see page 746).

Blood 5-HT is reduced in thiamine-deficient rats (from 1.04 to 0.7 μg/ml) and in tryptophan-deficient rats (from 0.86 to 0.12 μg/ml), but not in starved rats (GAL and DREWES 1961, 1962). Similarly, there is a very conspicuous reduction of the 5-HT level in blood of pyridine-deficient chickens (from 5.5 to 0.4 μg/ml) (UDENFRIEND 1957).

Removal of the large intestine in rats does not cause any change in serum 5-HT levels, in spite of reduced biosynthesis of 5-HT. On the contrary, total removal of the gastrointestinal tract produces a conspicuous decrease in the serum 5-HT content. Decrease is of 50% after 24 hr, and of 85% after 3 days (BERTACCINI 1960). A similar 90% decrease of platelet 5-HT has been described by HAVERBACK and DAVIDSON (1958) in a patient with resection of large and small intestine.

This demonstrates unequivocally that the enterochromaffin cells of the gastrointestinal mucosa represent both in man and in the rat the main, if not the only, source of blood 5-HT.

Data on the content of 5-HT in foetal blood are scanty, but it may be supposed that, as in spleen tissue, 5-HT in blood makes its appearance rather early.

PEPEU and GIARMAN (1962) observed that whereas in the goat foetal blood contains more 5-HT than maternal blood (1.83—8 μg/ml as compared with 0.27 to 4.2 μg/ml) in the rabbit the level of 5-HT in maternal blood is almost twice as high as that found in foetal blood (1.2—2.5 μg/ml as compared with 0.53 to 2 μg/ml).

3. Spleen

5-HT is regularly present, in considerable amounts, in spleen tissue. The substance is contained to the greatest extent in the thrombocytes and thrombocyte fragments caught in the spleen. Mast-cell 5-HT contributes scarcely, even in rats and mice, to the total spleen 5-HT (PARRATT and WEST 1957b). Generally, the amine is particularly abundant in the spleen tissue of animal species whose blood is rich in 5-HT (ERSPAMER 1940b, 1954b, c).

FAUSTINI (1955) has been able to establish that 5-HT appears in the spleen from the earliest stages of its embryonic development (cf. Table 7).

4. Mast cells

The occurrence of 5-HT in mast cells was first demonstrated by BENDITT et al. in 1955 (b). Since then, considerable work has been dedicated to the study of this peculiar localization of 5-HT in the mammalian organism and some fundamental facts may now be considered as firmly established:

a) Only rat and mouse mast cells contain important amounts of 5-HT. The amine is not detectable in the mast cells of other mammalian species, either under normal or pathological conditions (BHATTACHARYA and LEWIS 1956, PARRATT and WEST 1957a, ADAMS-RAY et al. 1964). The consequence of this statement is that, from a general biological point of view, 5-HT in the mast cells of the above rodents is little more than a biochemical rarity, and exactly the same may be said of the occurrence of 5-HT in the hypobranchial body of some molluscs or in the coelenteron tissue of some coelenterates.

It is obvious that those animal species which contain 5-HT in their mast cells display considerable 5-HT levels in nearly all their parenchymatous tissues (cf. Tables 1 and 4). However, a correlation between mast-cell population and 5-HT concentration is not always evident, i.e. mast cells do not necessarily contain the same quantity of 5-HT in the different rat tissues, nor is the 5-HT/histamine ratio everywhere the same (BHATTACHARYA and LEWIS 1956). PARRATT and WEST (1957a), for example, maintain that the abundant 5-HT which is found in the outer layer of the rat skin is not held in mast cells, at least in the typical metachromasia-yielding mast cells. This opinion is shared by SMITH and LEWIS (1961) on the basis of results obtained in rats treated with an anti-mast-cell serum, which caused no fall of skin 5-HT at the time when histamine and mast cells in the skin were very low. Similarly, mast-cell origin is doubtful in the case of the 5-HT found in the rat thyroid gland.

GREEN et al. (1960a, 1960b) found that heparin from rat tissues and from a mouse mastocytoma yielded, on fractionation, an unusual heparin fraction. They suggest that the anomalous occurrence of 5-HT in the mast cells of rats and mice may be explained by the presence of this unique heparin.

b) In the mouse 5-HT is present not only in normal mast cells, but also in neoplastic mast cells, namely in those of mastocytoma and of mast cell leukaemia.

Moreover, during chemical skin carcinogenesis in the mouse the 5-HT content of the skin at different stages of papilloma formation rises from 0.3 to 4.5 μg/g. 5-HT is apparently contained in cells giving a golden-yellow fluorescence with no

or very little metachromasia (RILEY 1958, COUPLAND and RILEY 1960, FIORE-DONATI et al. 1962).

On the contrary, animals lacking 5-HT in their normal mast cells do not show any detectable 5-HT either in tissues abnormally rich in mast cells (mastocytosis) or in mastocytomas (Table 9).

Table 9. *The 5-HT content of mast cells*

Animal species and mast cell type	Content of 5-HT base	Reference
Rat Normal mast cells		
peritoneal cavity	630—700 μg/ml cells	BENDITT et al. (1955b)
peritoneal cavity	0.35—0.46 μg/10^6 cells	KELLER (1957)
peritoneal cavity	1.02—1.59 μg/10^6 cells	MORAN et al. (1962, 1963)
feet, areolar tissue	760 μg/ml cells	BENDITT (1957)
feet, dermis	780 μg/ml cells	BENDITT (1957)
back, areolar tissue	800 μg/ml cells	BENDITT (1957)
back, dermis	1150 μg/ml cells	BENDITT (1957)
Mouse Mastocytoma		
tumoral tissue	6—714 μg/g tissue	FURTH et al. (1957) SJOERDSMA et al. (1957a) ONO et al. (1959)
tumoral cells in culture	0.06—1.5 μg/10^6 cells	SCHINDLER et al. (1959) GREEN and DAY (1960b)
Mast cell leukemia	7.74 μg/ml blood	ONO et al. (1959)
Dog Mastocytoma		
tumoral tissue	<0.2 μg/g fresh tissue	SJOERDSMA et al. (1957a) PARRATT and WEST (1957a)
tumoral tissue	0.32—0.83 μg/g lyophilized tissue	MEIER (1959)
Cow Mastocytoma		
tumoral tissue	no detectable 5-HT	PARRATT and WEST (1957a)
Man Mastocytoma	no detectable 5-HT	PARRATT and WEST (1957a)
Urticaria pigmentosa	<0.25 μg/g skin	PARRATT and WEST (1957a) SJOERDSMA et al. (1957a)
Spleen mastocytosis	no increase in 5-HT level	ENDE and CHERNISS (1958)
Liver mastocytosis	no 5-HT detectable	GARDNER and TYCE (1958)
Cutaneous mastocytosis	<0.05 μg/g skin or ml blister content	STURM and STÜTTGEN (1962)

RICE and MITCHENER (1961) claim to have obtained histochemical evidence of the occurrence of 5-HT in a dog mast cell tumour. Unfortunately, the investigators were unable to support their not completely persuasive histochemical data (variable silver reaction!) with any biochemical or biological evidence.

ENERBACK (1963) in his turn affirms that mast cells occurring in human carcinoid tumours exhibit histochemical reactions suggesting that they contain 5-HT and that a large number of mast cells with positive enterochromaffin reactions may occur even in so-called anargentaffin carcinoids.

Apart from the fact that it is difficult to accept, in the case of a neoplastic tissue, the statement of ENERBACK that a cell which contains metachromatic granules *must* be a mast cell (why not an enterochromaffin cell with abnormal content in metachromatic granules?) the above finding demonstrates only that under conditions of enhanced 5-HT secretion, human mast cells are capable of "storing" 5-HT. Biosynthesis of 5-HT has never been demonstrated in human mast cells.

Similarly, the possible occurrence of 5-HTP in extracts of human skin affected by mastocytosis, as described by STURM and STÜTTGEN (1962) in a single clinical

case, awaits confirmation. Perplexity seems justified not only by the meagre direct evidence, but even more by the lack of detectable 5-HT in the extracts.

It should be stressed at this point that, in a study by MEIER (1959), eight canine mastocytomas revealed only negligible quantities of 5-HT (?), averaging 0.49 μg per g dry lyophilized tumour material, although histochemically large amounts of indole compounds could be demonstrated, and that FIORE-DONATI et al. (1963) were unable to find any increase of 5-HT during chemical skin carcinogenesis in the hamster.

c) 5-HT in the mast cells is probably of completely autochthonal origin, i.e. it may be synthesized from L-tryptophan within the mast cells themselves. This has been shown by SCHINDLER et al. (1959) and by DAY and GREEN (1959) and GREEN and DAY (1960b), who found that neoplastic mast cells obtained from a mouse mastocytoma after many generations in culture maintained, or even increased, their high intracellular level of 5-HT. Of necessity, 5-HT is formed at the expense of the L-tryptophan in the cultural medium.

The above statement does not exclude the possibility that exogenous 5-HT may contribute to the store in mast cells. In fact, mast cells from the peritoneal fluid of the rat are capable of taking up 5-HT and histamine (not dopamine and noradrenaline) both in vitro and in vivo. The distribution ratios of 5-HT and histamine between cells and medium are 78 and 9.2, respectively (FURANO and GREEN 1964).

d) The turnover rate of mast-cell 5-HT is not known. Indirect evidence supports the view that under normal conditions it is probably rather slow, but that in the case of mastocytoma it may become more rapid. In fact, BERTACCINI (1960) has shown that removal of the entire gastrointestinal tract in rats causes the practical disappearance of 5-HIAA in urine, while leaving largely unaffected the mast-cell 5-HT in the skin, which accounts for more than 50% of the total 5-HT in the body. On the other hand, SJOERDSMA et al. (1957) have found that mouse mastocytoma provokes not only a huge increase in the 5-HT content of the mouse body (from 1.5 to 20 μg/g) but also a similar increase in the urinary 5-HIAA (from 6 to 70 μg/ml).

STOLK (1963) has described in the lizard a mast cell reaction during chemical skin carcinogenesis identical, in every detail, to that seen in the mouse by FIORE-DONATI et al. (1962). This raises the problem of the occurrence of 5-HT in mast cells of vertebrates other than mammals.

LEWIS (1957) considers each mast cell of rats and mice to be a minute pharmacological armamentarium destined not only to serve as outer defence in the body defence mechanism against tissue injury, but also as a store-house of vasoactive substances which may well be released physiologically to control the vasculature of the connective tissue. This view has recently been strengthened by the observation that mast cells may contain not only histamine and 5-HT but, at least in ungulates, dopamine also (COUPLAND and HEATH 1961).

5. Other extracerebral tissues of mammals

Concerning unusual localizations of 5-HT in animal species not containing 5-HT in their mast cells, two seem of particular interest: that in the rabbit lung and that in the sheep thyroid gland.

The 5-HT in the rabbit lung clearly originates from blood platelets, as shown by the fact that during anaphylactic shock, in which circulating platelets are caught in the lung, lung 5-HT may increase by 5 to 10 times (WAALKES and COBURN 1959).

The origins of the 5-HT contained in the sheep thyroid gland (2.4—7.5 μg/g fresh tissue) and the rat thyroid gland (2.4—5 μg/g) are unknown. The rabbit thyroid contains 0.09—0.29 μg/g 5-HT, the dog thyroid only 0.025 μg/g PAASONEN 1958). FALCK (1962) has recently shown that in the rat thyroid gland 5-HT may be localized in peculiar fluorescent cells. It would seem advisable to extend the search for typical enterochromaffin cells or fluorescent 5-HT-containing cells to the thyroid gland of the sheep and other animal species.

No significant changes in the 5-HT content of the rat thyroid gland are seen following single doses of methimazole or potassium thiocyanate. Repeated administration of methimazole, however, produces a significant increase of the total 5-HT in the gland (PAASONEN and PELTOLA 1960). As expected, the 5-HT level in the rat thyroid gland is raised also by administration of iproniazid and 5-HTP (PAASONEN et al. 1961).

Table 10. *The 5-HT content of miscellaneous vertebrate tissues*

	Tissue	Content of 5-HT base (μg/g fresh tissue)	Reference
Man	Placenta	0.13 ± 0.04	KURIAKI and INOUE (1956)
	Lung	0.1	SANDERS et al. (1959)
	Skin	0.03	PARRATT and WEST (1957a) JOHANSSON (1960)
Monkey	Uvea and retina	0.15—0.97	LEVENE (1962)
	Lid	0.25	LEVENE (1962)
Goat	Placenta	0.25—0.27	PEPEU and GIARMAN (1962)
	Lung	0.8—2.2	PEPEU and GIARMAN (1962)
Sow	Urinary tract	0.13 (mucosa) 0.02 (muscular layer)	KOCH and ENGELHARDT (1959)
Hedgehog	Liver	1.46—2.79	UUSPÄÄ (1963)
	Lung (perfused)	0.71—0.94	UUSPÄÄ (1963)
	Kidney	0.21—0.59	UUSPÄÄ (1963)
Pigeon	Liver	0.22—0.48	APRISON et al. (1962)
	Heart	0.11—0.30	APRISON et al. (1962)
	Lung	0.08—0.26	APRISON et al. (1962)
Ameiurus nebulosus (fish)	Skin	< 0.02	WELSH (1964)

Minute amounts of 5-HT have been described in a variety of tissue extracts (see Tables 2, 3 and 10) but very often one cannot avoid the impression that this 5-HT may be referred to the blood contained in the tissues (GARVEN 1956), or that colour reactions, fluorescence reaction or pharmacological effects considered specific for 5-HT may in reality depend on substances other than 5-HT. It is hoped that the histochemical fluorescence method of FALCK (1962) will be of decisive importance, owing to its extreme sensitivity and high specificity, in solving many of the present doubts.

The 5-HT content of nearly all rat tissues shows a progressive increase during postnatal development. For example, the lung, liver and gastrointestinal tract of male rats weighing 36 g contains 0.52, 0.03 and 1.45 μg/g 5-HT, respectively; the same organs of rats weighing 300 g 2.02, 0.14 and 2.8 μg/kg, respectively (BERTACCINI 1958).

It is interesting to note that two days after weaning, the 5-HT and histamine values for ears, abdominal skin and skin of feet are about double those found in the unweaned rats of the same age. No detectable difference has been found in

the 5-HT content of tissues secured from male and female rats of similar age (PARRATT and WEST 1956b).

Several parenchymatous tissues (lung, liver, kidney) contain apparently small amounts (0.05—0.2 μg/g) of tryptamine (HESS and UDENFRIEND 1959, HESS et al. 1959). This is all we know at present about the occurrence and distribution of this amine in the mammalian organism.

6. Central and peripheral nervous system

The occurrence of 5-HT in the CNS was first demonstrated by AMIN et al. (1954) and by TWAROG and PAGE (1953) and was soon confirmed by numerous other research workers. It may be seen from Tables 11 and 12 that all vertebrate species examined contain 5-HT in the brain. This fact represents again, as in the case of gastrointestinal mucosa, strong evidence that 5-HT in the brain has a general biological significance.

Table 11. *The 5-HT content of the central nervous system of the rat*

	The 5-HT content (in μg per g fresh tissue) as estimated by	
	Bioassay	Spectrofluorometric method
Whole brain	Rat uterus: 0.23—0.38[1]; 0.26—0.50[2]; 0.25—0.52[3]; 0.41—0.48[4]; 0.2—0.25[40] Rat stomach: 0.35[5]; 0.346 ± 0.01[6]; 0.286 ± 0.05[7] Venus heart: 0.34—0.42[8]; 0.21—0.45[9]; *0.36[10]; *0.36 ± 0.007[11]; *0.38 ± 0.02[12]	0.4[13]; 0.54[14]; 0.48—0.53[15]; 0.41—0.77[16]; 0.4—0.45[17]; 0.6 ± 0.1[18]; 0.63 ± 0.14[19]; 0.58 ± 0.014[20]; 0.78 ± 0.1[21]; 0.53[22]; 0.47[23]; 0.41[24]; 0.5—0.8[25]; 0.474[26]; 0.371 ± 0.048[27]; 0.81 ± 0.05[28]; 0.54 ± 0.08[29]; 0.57[32]; 0.49—0.62[33]; 0.58 ± 0.033[34]; 0.78—0.80[39] *0.54—0.59[10]; *0.43—0.52[11]; *0.52 ± 0.02[12] °0.62 (r.h.)—0.60 (l.h.)[42]
Frontal cortex		0.162 ± 0.014[31]
Cerebellum		0.029 ± 0.002[31]; 0.31[25]
Hippocampal gyrus		0.328 ± 0.07[31]
Hypothalamus		0.429 ± 0.123[31]
Anterior hypothalamus		3.8 ± 1.4[30]
Midbrain + stem		0.94[25]
Pons + mesencephalon + diencephalon		1.07—1.34[39]
Whole brain bound 5-HT		60—75%[35]; 85%[36]; 70%[37]; 82%[38]; 55%[41]
free 5-HT		25—40%; 15%; 30%; 18%; 39%

° r.h. = right hemibrain; l.h. = left hemibrain.
* Comparative assays with the Venus heart method and the spectrofluorometric method.

References to Table 11. [1] BERTACCINI (1959). — [2] BERTACCINI (1960). — [3] ERSPAMER and BERTACCINI (1962). — [4] BERTACCINI and ERSPAMER (1962). — [5] PAASONEN and KÄRKI (1959). [6] KIVALO et al. (1961). — [7] GÖRÖG and SZPORNI (1962). — [8] BONNYCASTLE et al. (1957). — [9] PAASONEN and GIARMAN (1958). — [10] FREEDMAN (1961). — [11] BONNYCASTLE et al. (1962). — [12] ANDERSON et al. (1962). — [13] BOGDANSKI et al. (1956). — [14] PLETSCHER (1956), PLETSCHER et al. (1956). — [15] MAAS and NIMMO (1959). — [16] TABACHNICK and RUBIN (1959). — [17] UDENFRIEND et al. (1958). — [18] RESNICK et al. (1961). — [19] SKILLEN et al. (1961). — [20] YUWILER and LOUTTIT (1961). — [21] SCHWABE et al. (1961). — [22] MOORE and BRODY (1961). — [23] EHRINGER et al. (1961). — [24] GAL and DREWES (1961). — [25] HESS and DOEPFNER (1961). — [26] GREEN et al. (1962). — [27] MAYNERT et al. (1962). — [28] ERSHOFF and GAL (1961). — [29] ERSHOFF et al. (1962). — [30] QUAY and HALEVY (1962). — [31] JOYCE (1962). — [32] SCHONE and LINDNER (1960). — [33] PUT and HOGENHUIS (1962). — [34] TOWNE et al. (1962). — [35] WHITTAKER (1959). — [36] GLUCKMAN (1960). — [37] SCHANBERG and GIARMAN (1962). — [38] GREEN and SAWYER (1962). — [39] MAAS (1963). — [40] WALASZEK and ABOOD (1959). — [41] CARLINI and GREEN (1963). — [42] HARVEY et al. (1963).

Table 12. *The 5-HT content of the whole brain in representatives of different vertebrate classes*

Animal species	5-HT content (in μg per g fresh tissue)
Rhesus monkey	0.43—0.53[22]
Rabbit	0.57 ± 0.08[1]; 0.46 ± 0.03[2]; 0.45—0.67[3]; 0.35 ± 0.014[4]
Guinea-pig	0.46 ± 0.05[2]; 0.6[5]; 0.44 ± 19[6]; 0.428[7]; 0.68—0.72[21] 0.56 ± 0.23[27]; 0.49 ± 0.24[28]
Mouse	0.85—1.0[8]; 0.48—0.62[9]; 0.66 ± 0.01[10]; 0.82 ± 0.02[11]; 0.59 ± 0.04[12]; 0.52 ± 0.05[13]; 0.78—0.93[14]; 0.53 ± 0.03[4]; 0.32[15]
Marmot	0.13[16]
Hedgehog	0.56—0.96[24]
Goat	0.08—0.12 parietal and frontal lobes, 0.11—0.12 hippocampus and basal ganglia[17]
Chicken	1.13[18]; 1.0[23]; 0.88 ± 0.08 hemispheres, 0.70 ± 0.10 midbrain, 0.51 ± 0.96 pons-medulla, 0.16 ± 0.05 cerebellum[26]
Pigeon	0.7[23]; 0.78—1.24 telencephalon, 0.6—1.2 diencephalon + optic lobes, 0.12—0.44 cerebellum, 0.93—1.5 pons-medulla[20]
Turkey	0.4[19]
Water snake	0.2[19]
Sceloporus cyanogenys	3.1[23]
Alligator mississipiensis	0.21—0.68 telencephalon, 0.46—1.56 diencephalon, 0.34—0.69 rhombencephalon, 0.5 cerebellum, 0.51—0.87 optic lobes[30]
Rana esculenta	0.25—0.35[29]
Rana pipiens	3.7[23]; 0.23—0.62 telencephalon, 0.75—1.6 diencephalon; 0.32—0.71 rhombencephalon, 1.1—1.6 optic lobes[30]
Rana catesbiana	0.36—0.7 telencephalon, 1.29—1.8 diencephalon, 0.36—1.0 rhombencephalon[30]
Hyla cinerea	2.0[23]
Bufo americanus	9.1[23]
Bufo marinus	1.5[23]
Bufo arenarum	0.8—1.3[25]
Bufo paracnemis	0.8[25]
Leptodactylus chaquensis	0.6—1.0[25]
Telmatobius hauthali	0.57[25]
Desmognatus fuscus	2.8[23]
Ambystoma tigrinum	2.9[23]
Necturus maculosus	1.1[23]
Scyliorhinus canicula	0.2[19]
Carassius auratus	0.15[23]
Amia calva	0.48[23]

References to Table 12. [1] Brodie et al. (1956); Shore and Brodie (1957). — [2] Bogdanski et al. (1956). — [3] Gursey et al. (1959), Gursey and Olson (1960). — [4] Haggendal et al. (1957). — [5] Pletscher (1956a). — [6] Whittaker (1962). — [7] Ryall (1962). — [8] Pletscher (1956)b. — [9] Bartlet (1960). — [10] Dubnick et al. (1960, 1962). — [11] Wiegand and Perry (1961). — [12] Wiegand and Scherfling (1962). — [13] Leroy (1962). — [14] Albrecht et al. (1956). — [15] Melching et al. (1960). — [16] Bertaccini, unpublished observations. — [17] Pepeu and Giarman (1962). — [18] Udenfriend et al. (1957). — [19] Correale (1956). — [20] Aprison et al. (1962). — [21] Haverback et al. (1957). — [22] Weissman and Finger (1962). — [23] Bogdanski et al. (1963), Brodie et al. (1954). — [24] Uuspää (1963). — [25] Nobili, unpublished observations. — [26] Pscheidt and Himwich (1963); Pscheidt (1964). — [27] Hsia et al. (1963). — [28] Michaelson and Whittaker (1963). — [29] de Caro and Roseghini, to be published. — [30] Welsh (1964).

Tables 13 and 14 of this chapter and Table 4 of chapter 13 show that, at least in mammals, 5-HT is preferentially contained in specific areas of the brain (brain stem structures, rhinencephalic structures, neostriatum) some of which are part of, or are functionally connected with, the autonomic system or the reticular activating system.

Although the problem of the origin of cerebral 5-HT is not solved, indirect evidence seems to support the view that brain 5-HT may originate locally from

L-tryptophan. We refer to the experiments of BERTACCINI (1960) showing that 5-HT is present, in nearly normal amounts, in the brain of rats deprived operative-

Table 13. *Regional distribution of 5-HT in the brain of the dog, cat and rabbit*

	5-HT content in μg base per g fresh tissue		
	Dog	Cat	Rabbit
Brain stem	0.75[1]; 0.43 ± 0.10[3]; 1.28[16]	0.79[1]	0.65[1]; 0.58—0.7[2]; 0.425 ± 0.05[3]
Spinal cord cervical	0.26 ± 0.013 (above Th2)[14]	0.24[4]	
sacral	0.25 ± 0.02 (below Th2)[14]	0.82[4]	
Medulla	0.55—0.62[5]	0.55—1.2[5]	
Area postrema	0.26[7]		
Floor 4th ventricle	0.17—0.37[7]		
Medulla-pons	0.56[15]	0.88[15]	0.63[9]
Pons	0.42—0.38[5]	0.33[6]; 0.7[5]	
Pontile reticular formation		0,89[6]	
Cerebellum	0.07—0.09[5]; 0.11 ± 0.04[16]	0.3—0.27[5]	0.12[9]
Cerebellar cortex	0.007—0.012[7]		
Inferior colliculus		0.76[6]	
Midbrain	0.97—1.0[5]	1.23—1.7[5]	0.83[9]
Midbrain reticular formation		2.6[6]	
Midbrain-hypothalamus	1.31[15]	0.5 ± 0.08[10]; 1.45[15]	
Hypothalamus	1.75[5]; 0.37[8]; 1.28[16]	1.78—2.0[5]	0.43 ± 0.12[11]
anterior		2.4[6]	
posterior		2.5[6]	
Thalamus	0.65[5]; 0.48[15]	0.78[5]; 0.43[6]; 0.91[15]	
Basal thalamic area		0.88[6]	
Caudate nucleus	0.27[8]; 0.72[5]; 0.48—0.63[12]; 0.61[15]; 0.51[16]	1.6[6,5]; 0.84[15]	
Intralaminar and midline nuclei		0.56[6]	
Olfactory bulb	0.38[5]; 0.04[7]; 0.08[8]		
Septal region	0.46[8]	2.0[6]	
Brain gyri	0.17[5]	0.24[5]	
White matter	0.07—0.13[5]; 0.02[8]	0.13[5]	
Cortical grey matter	0.27—0.34[5]	0.68[5]	
Central grey matter		1.6[6]	
Amygdala	2.1[5]; 0.48[8]	1.6[6]	
Hippocampus	0.64[5]; 0.25[8]; 0.46[15]	0.71[15]	0.33 ± 0.07[11]
Putamen	0.11[8]		
Hypnogenic zone of HESS		1.8[6]	
Neocortex		0.69[6]	
Frontal cortex			0.055 ± 0.002[11]
Auditory cortex		0.41[6]	
Pyriform cortex	0.94[5]; 0.18—0.48[8]	1.4[6]	
Posterior pituitary	0[7]		
Sympathetic ganglia	0[7]	0.2[13]	

References to Table 13. [1] BRODIE et al. (1959). — [2] SPECTOR et al. (1960). — [3] MAYNERT et al. (1962). — [4] ANDERSON and CUDIA (1962). — [5] BOGDANSKI and UDENFRIEND (1956), BOGDANSKI et al. (1957). — [6] KUNTZMAN et al. (1961). — [7] PAASONEN and VOGT (1956). — [8] PAASONEN et al. (1957). — [9] COSTA and APRISON 1958). — [10] ANTONELLI et al. (1961). — [11] JOYCE (1962). — [12] ASHCROFT and SHARMAN (1962). — [13] GERTNER et al. (1959). — [14] CARLSSON et al. (1963). — [15] PSCHEIDT et al. (1964). — [16] TYCE et al. (1964).

ly of the whole gastrointestinal tract, and to the occurrence of considerable quantities of 5-HT in ganglia and peripheral nerves of molluscs containing only traces of the amine in all other tissues.

Quite recently direct evidence that brain tissue is capable of hydroxylating L-tryptophan has been furnished by several groups of research workers [e.g. GREEN, H., and J. L. SAWYER, Fed. Proc. 24, 604 (1965)].

Concerning the problem of the distribution of 5-HT at cellular and subcellular levels within the brain tissue, there is still considerable uncertainty and perplexity. Three main possibilities should be kept in mind, namely that:

a) 5-HT is contained, at least in some areas, in glia cells instead of in true nervous cells. This possibility is supported, α) by the finding that in autoradiographs of brain tissue obtained after injection of radioactive 5-HTP, the 5-HT appears to be distributed fairly evenly throughout the brain with no relation to nervous elements (LEWIS 1958), β) by the observation that in the dog whole CNS the highest concentrations of 5-HT are found in the area postrema which consists of highly vascular neuroglia tissue and only some nervous cells (STACEY 1959), γ) by the observation that in mount rabbit brain cortex cultures and subtransplants some glial elements and fibers contain yellow fluorescent monoamines (5-HT ?) (GEIGER et al. 1964), and finally, γ) by the stimulating experimental results of UTLEY (1963), who found that removal in the cat of cortical areas known as A I, A II, Ep, S II, temporal and insular (which results in retrograde degeneration and gliosis in all portions of the principal division of the medial geniculate body, with a 45% decrease in weight) produced a 70% increase of 5-HT in the residual atrophic tissue (from 1.2 to 2.05 μg/g). This 5-HT concentration persisted even after successive lesions of the brachium of the inferior colliculus.

Table 14. *Regional distribution of 5-HT in the brain of the monkey (Macacus rhesus)* (PSCHEIDT and HIMWICH 1963)

	5-HT content, in μg base per g fresh tissue*
Pons-medulla	0.49 ± 0.11
Midbrain (hypothalamus)	0.77 ± 0.16
Caudate	0.36 ± 0.06
Thalamus	0.56 ± 0.15
Hippocampus (amigdala)	0.29 ± 0.08
Various cortical structures	0.17 ± 0.04
Temporal pole	0.20—0.24
Lenticular thalamic mass	0.29—0.35

* Spectrofluorometric method.

JOYCE (1963) has recently shown that glioma tissue contains less 5-HT than normal surrounding cerebral tissue. However, in the writer's opinion this observation, while certainly not in favour of the theory that 5-HT is localized in glia cells, does not disprove this theory. In fact, data obtained in neoplastic cells can hardly be transferred to normal cells.

b) 5-HT is present in the body of the nervous cell. This is the opinion shared, tacitly or expressly, by the majority of research workers. According to WALASZEK and ABOOD (1959) most of the 5-HT present in rat brain is bound to the mitochondria, but other investigators (GLUCKMAN 1960, GIARMAN and SCHANBERG 1959, INOUYE et al. 1962, KATAOKA 1962, CARLINI and GREEN 1963) while confirming that 60—80% of the brain 5-HT resides in granules, eschew a more precise definition of the nature of these granules.

c) 5-HT is contained in the nerve endings, more precisely in the synaptic vesicles or in particles quite similar to them. This theory, which has been advanced by WHITTAKER (1959, 1961, 1962) and MICHAELSON and WHITTAKER (1962, 1963) is at present the most satisfactory and attractive. WHITTAKER suggests that, like acetylcholine, 5-HT also may be bound to the particles partly in a highly labile state and partly in a more stable state. Subcellular particles containing 5-HT are distinct from those storing acetylcholine (cf. also RYALL 1963, 1964).

CARLSSON et al. (1963) have recently shown that a week after transection of the rabbit spinal cord at the 2nd thoracic segment the 5-HT in the portion below the

section was only about 15% of that found in the cervical portion (0.04 ± 0.015 as compared to 0.32 ± 0.02 μg/g). According to the Swedish investigators this fact may be interpreted to mean that 5-HT in the cord is mostly localized, like noradrenaline, in the fibres descending from more centrally sited cell bodies. The interpretation is not in contrast with the WHITTAKER's theory.

The turnover rate of 5-HT in the CNS is high. With the aid of powerful, promptly-acting monoamineoxidase inhibitors it has been demonstrated that the half-life of cerebral 5-HT is not longer than 10 to 20 min (UDENFRIEND et al. 1958), and according to 5-HT estimates in brains of rats anaesthetized with pentobarbital sodium it is even shorter (2 minutes) (ANDERSON and BONNYCASTLE 1960).

ALBRECHT et al. (1956) found that the brain 5-HT level is slightly higher in female mice than in male adult mice (0.93 and 0.78 μg/g, respectively) and that a small but significant decrease in 5-HT concentration of brain pools is noted prior to the usual time of arousal. On the average the concentration of 5-HT in brain is higher before and around noon than at or after 4.30 p.m. (difference 0.12 μg/g).

MAAS (1963) has recently called attention to the possible existence of neurochemical differences among different strains of mice. He found that whereas the 5-HT in total brain did not differ significantly in the two examined strains (0.807 and 0.783 μg/g), the 5-HT in pons + mesencephalon + diencephalon was 1.34 ± 0.046 μg/g in strain BABL/CJ and 1.07 ± 0.037 μg/g in strain C57BL/10J.

Data on the appearance of brain 5-HT during embryonic life are still incomplete and in part contrasting.

NACHMIAS (1960) found that 5-HT is present in the brain of newborn rats at about a third of the concentration in adult brain and increases in a linear fashion thereafter; KÄRKI et al. (1960, 1962) observed that three days before birth rat brain 5-HT is about 25% (norepinephrine 15%), at birth 50% (norepinephrine 20%), and two weeks later 70% (norepinephrine 40%) of normal, with values of the mature animals (0.47 ± 0.02 μg/g) being approached in seven weeks; finally WANG et al. (1962) noted, in full confirmation of the above results, that in rat brain 5-HT increases gradually from birth, attaining 0.45 ± 0.02 μg/g at 20 days of age and 0.77 ± 0.03 μg/g at 39 days of age.

Rabbits behave like rats (brain 5-HT levels in newborn and adult rabbits= 0.33 ± 0.05 and 0.60 ± 0.02 μg, respectively), whereas in guinea-pigs the amount of 5-HT stored in the brain of newborn animals approaches the adult figure (0.26 ± 0.01 μg/g, as compared to 0.33 ± 0.01 μg/g) (KÄRKI et al. 1962, SMITH et al. 1961, PEPEU and GIARMAN 1960, 1962).

It has been suggested that the above biochemical differences should be correlated with differences in the functional development or degree of maturity of the various species at birth. However, this hypothesis does not seem to have a general value since in goat foetuses, late in gestation, the 5-HT content of different brain areas is considerably larger than that of the corresponding maternal brain areas (foetus and mother, respectively: parietal lobe 0.36 and 0.10, occipital lobe 0.29 and 0.09, hippocampus 0.25 and 0.15, basal ganglia 0.27 and 0.17 μg/g) (PEPEU and GIARMAN 1960, 1962).

The observations on the influence of the diet on brain 5-HT levels in rats are of considerable interest.

Young rats maintained for 1 to 7 weeks on a diet supplemented with 2—7% phenylalanine regularly present a marked decrease (20—35%) in the brain 5-HT level. This decrease is even greater (70%) in animals kept on a tryptophan-free diet. On the contrary, rats kept on a high-tryptophan diet show a consistent

increase (30—35%) in 5-HT levels. Finally, rats kept on a diet supplemented with both phenylalanine and tryptophan present, depending on the ratio between the two aminoacids, increased, unchanged or decreased 5-HT concentrations in the brain (WANG et al. 1961, 1962; YUWILER and LOUTTIT 1961; GAL et al. 1961; SCHANBERG et al. 1962; GREEN et al. 1962; GAL and DREWES 1962; CULLEY et al. 1963). The depressive effect of a low-tryptophan diet on brain 5-HT has been confirmed by ZBINDEN et al. (1958) in the guinea-pig and in the mouse, that of a high-phenylalanine diet by HSIA et al. (1963) in the guinea-pig.

Excess dietary tyrosine (7%) causes little or no change in brain 5-HT, excess valine (6—9%) a 17% decrease of the amine, phenylacetic acid (5%) a 22% increase (BOGGS et al. 1963).

The mode of action of tryptophan excess or deficiency is obvious; phenylalanine is believed to act as a depressor of dopadecarboxylase via its metabolites.

Table 15. *The 5-HT content (in μg/g) of the hedgehog brain during activity and hibernation* (UUSPÄÄ 1963)

	Summer active state	Cold season	
		active state	hibernating
Whole brain	0.56 ± 0.026	0.85 ± 0.056	0.96 ± 0.045
Cerebellum	0.05 ± 0.004	0.07 ± 0.02	0.06 ± 0.02
Medulla and pons	0.78 ± 0.02	1.00 ± 0.07	1.21 ± 0.08
Mesencephalon	1.37 ± 0.04	1.76 ± 0.07	1.79 ± 0.08
Diencephalon	1.00 ± 0.05	1.25 ± 0.08	1.22 ± 0.06
Cerebral hemispheres	0.37 ± 0.04	0.75 ± 0.08	0.89 ± 0.06
Olfactory bulbs	0.27 ± 0.08	0.41 ± 0.04	0.47 ± 0.04

UUSPÄÄ (1963) has carried out a comparative study on the 5-HT content of the hedgehog brain during activity and hibernation. Results are shown in Table 15.

It may be seen that whereas an increase in the 5-HT content occurs during the cold season, this increase seems to be independent of the activity of the animal. In fact, no significant differences are found in brain 5-HT levels between hibernating hedgehogs and animals kept at room temperature during the cold season.

Neither starvation nor thiamine deficiency produces any change in the brain 5-HT levels of rats (GAL and DREWES 1961). Pyridoxine-deficiency causes only a small decrease in the 5-HT concentration of the rat brain (YEH et al. 1959), but a conspicuous decrease in the brain 5-HT level of chickens (UDENFRIEND et al. 1957).

TOH (1960) observed that the 5-HT content of the brain of rats exposed to extreme heat or cold was lower (0.20 and 0.24 μg/g) than that of control rats (0.38 μg/g).

BARCHAS and FREEDMAN (1963) noted that swimming to exhaustion produced a 13—15% increase in brain 5-HT levels and wheel a 10% increase, whereas a number of other stressors (exposure to cold, electroshock, 72 hours of food and water deprivation, anoxia in a nitrogen chamber, adrenalectomy) failed to evoke significant changes.

TYCE et al. (1962) could not find any change in the brain 5-HT levels of dogs submitted to hepatectomy or of Eck-fistula dogs.

Results obtained in the rat were at variance. In fact, TYCE et al. (1963) observed that in this species 24 hr after hepatectomy the concentration of 5-HT

in the brain showed a twofold, and that of 5-HIAA a 3-fold increase, indicating a rapid turnover of 5-HT. Tryptophan showed a 4- to 5-fold increase.

Not only 5-HT but also tryptamine must be considered a normal constituent of brain tissue. The brain content of this amine seems, however, to be rather low (HESS et al. 1959, HESS and DOEPFNER 1961) and information about regional differences in its distribution is lacking.

Among the metabolites of 5-HT the only one so far detected in brain tissue is 5-HIAA, but there is the possibility that other acidic or basic 5-hydroxyindole compounds are present (ASHCROFT and SHARMAN 1962).

According to PLETSCHER et al. (1963) rat brains contain 0.37 ± 0.01 μg 5-HIAA per g tissue, as compared to the 0.57 ± 0.02 μg/g 5-HT found in the same brains.

Among the areas of the CNS, the pineal gland occupies a unique position since, in addition to large amounts of 5-HT and 5-HIAA, it contains two unusual 5-hydroxyindole derivatives: melatonin and its metabolite 5-methoxyindoleacetic acid (LERNER and CASE 1960). Table 16 shows that the 5-HT levels in the pineal gland are the highest ever reported in any neuronal structure of all species examined. However, it should be stressed that only part and less than half of the material that is measured in the rat pineal by the fluorescence method is 5-HT (QUAI and HALEVY 1962).

Table 16. *Indole derivatives in the pineal gland*

	Content in μg per g fresh tissue				Reference
	5-HT	5-HIAA	Melatonin	5-Methoxy IAA	
Steer. . .	0.2—0.63	2	0.2	2	1, 2, 3, 4
Monkey .	1.2—10.1				3
Man . . .	0.36—22.8				3
Rat . . .	11; 10—90;	4—18	1—3	1	5, 8
	56.9—72.6				7
Goat. . .	1.2—7				6

References to Table **16.** [1] GIARMAN and DAY (1958). — [2] GIARMAN et al. (1959). — [3] GIARMAN and FREEDMAN (1960). — [4] LERNER et al. (1959 b), LERNER et al. (1960). — [5] QUAY (1963 c, 1964). — [6] PEPEU and GIARMAN (1962). — [7] OWMAN (1963). — [8] DE IRALDI et al. (1963).

The content of 5-HT and related indole amines in the rat pineal gland nearly doubles during the second postnatal week and attains nearly adult levels. Continuous artificial light for either $4^1/_2$ or $21^1/_2$ weeks significantly reduces the amine content (from 89 to 45.3 μg/g and from 120.7 to 71.7 μg/g, respectively). A similar reduction is produced by transection of the optical tracts $4^1/_2$ weeks before removal of the pineals for analysis (QUAI and HALEVY 1962).

DE IRALDI and DE ROBERTIS (1961) suggest that 5-HT is contained, together with other amines, in the secretory processes of the pinealocyte, and more precisely in the heterogeneous vesicles of these processes. This suggestion is supported by the disappearance of the heterogeneous vesicles following reserpine administration.

However, fluorescence microscopy seems to indicate that in the rat, mouse, guinea-pig and dog pineal gland indolealkylamines may be contained also in pineal nerves, more precisely in the network of nerve fibres enclosing the vessels. In cat and rabbit pineals, on the contrary, the fluorescence reaction in the nerves indicates the presence of a primary catecholamine. In the rat, an intense tryptamine-fluorescence also develops in the parenchymal cells.

After bilateral cervical sympathectomy and after single reserpine injections no fluorescence occurs in the nerves and the 5-HT of the rat pineal gland is decreased to 50% (OWMAN 1963).

The decrease in the pineal 5-HT content following bilateral gangliectomy has been confirmed by DE IRALDI et al. (1963), who similarly suggest, continuing

their previous studies, that there are probably two different pools of 5-HT in the rat pineal gland, one located in the parenchymal cells and the other in the sympathetic nerve fibres and endings.

Of considerable importance are the recent observations of QUAY (1963c, 1964) on the existance of a daily cycle or circadian rhythm of surprising amplitude for the 5-HT, 5-HIAA and melatonin contained in the pineal body of the rat.

Pineal 5-HT rises from a nocturnal minimum of 10 ng/pineal to a midday maximum of over 90 ng/pineal and falls rapidly at the start of darkness (Fig. 1). If the start of darkness is delayed, the nocturnal drop of pineal 5-HT is reduced or even abolished. The time at which the lights turn on in the morning has much less effect on 5-HT levels.

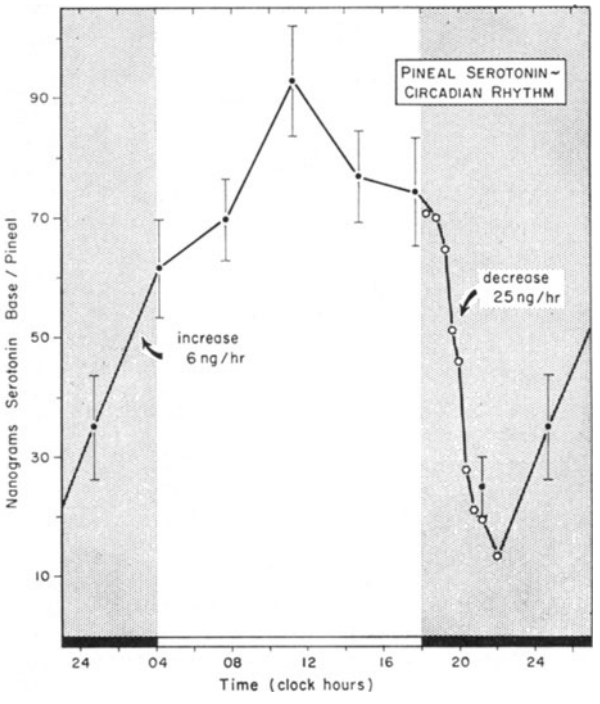

Fig. 1. Rat pineal gland. Circadian rhythm of 5-HT

Pineal 5-HIAA similarly rises from a nocturnal basal level of about 4 ng/pineal to an early afternoon maximum of about 18 ng/pineal and again falls sharply at the start of darkness. However, the time of maximum 5-HIAA content of the pineal is significantly later than the time of maximum 5-HT content. In sharp contrast to 5-HT and 5-HIAA-pineal melatonin rises on the start of darkness, from 1 to 3 ng/pineal. 5-Methoxyindoleacetic acid, averaging 0.98 ng/pineal, shows no circadian change.

The physiological meaning of the circadian rhythm in pineal 5-HT is not clear. QUAY suggests that the slow daily increase in pineal 5-HT may represent an intrinsic rate of continuous uptake or formation of 5-HT as a precursor to melatonin and related compounds, and that the sharp decline in the pineal 5-HT in the evening may represent a triggered release of melatonin-synthesizing activity. The rhythm in melatonin content of the pineal body is in agreement with the above hypothesis that melatonin is formed from 5-HT at the start of darkness.

The 5-HT, 5-HIAA and melatonin content of the rat pineal is, to a slight but significant degree, modified by, or shows fluctuations correlated with, the estrous cycle. Early morning pineal 5-HT, for example, shows a trend of increasing during the estrous period, and evening 5-HT a trend in reduction. The behaviour of melatonin is similar, the behaviour of 5-HIAA opposite to that of 5-HT (QUAY 1964).

Feeding a high-tryptophan diet leads to a 250% increase in pineal 5-HT levels, feeding a high-phenylalanine diet to a 30% reduction (QUAY 1963b).

Other very important studies on melatonin in the pineal gland were carried out by AXELROD and co-workers. The main results so far obtained are summarized below, but research on this topic is still in progress.

Exposure to light reduces the ability of the rat pineal gland to synthesize melatonin (from 5 to 2 ng/hr/pineal) and decreases the weight of the gland (from 1.2 to 0.95 mg in female rats weighing 160—180 g). When the sympathetic nerves to the pineal are cut, light no longer has an effect on melatonin synthesis or pineal weight. The response of the gland does not require that the gonads or the pituitary gland be present (WURTMAN et al. 1964).

In surprising contrast with the rat pineal gland, the hen pineal gland shows a highly significant decrease in the activity of the melatonin-forming enzyme when the animals are kept in darkness for 5 days. The activity of hydroxyindole-O-methyl transferase per mg of pineals in hens is at least 200 times that of the rat (AXELROD et al. 1964).

The 5-HT content in the vertebrate eye which is, in part, derived from the central nervous system, has been thoroughly investigated by WELSH (1964). He found that 5-HT was present in the retina and pigment epithelium-choroid complex of several representative vertebrates, in amounts ranging from 2—2.5 μg/g (*Pomolabrus pseudoharengus*, a fish) to <0.05 μg/g (retina of *Bos taurus*). Where the retina could be cleanly separated from pigmented tissue, the values for the two layers were about the same. Other values of 5-HT in the retina and pigment epithelium-choroid complex were as follows: *Rana pipiens* 0.7—0.8 μg/g, *Rana catesbiana* 0.2—0.4 μg/g, *Bufo marinus* 0.4—0.6 μg/g, *Alligator mississipiensis* 0.25—0.41 μg/g, *Rattus norvegicus* 0.22—0.27 μg/g, *Lepus cuniculus* 0.1—0.2 μg/g.

The problem of whether the autonomic ganglia of mammals contain 5-HT or are capable of synthesizing the substance cannot be considered solved by the partially positive results of GERTNER et al. (1959), which contrast with the negative results of AMIN et al. (1954). At any rate no measurable 5-HT appears in the perfusate from the functioning superior cervical ganglion of the cat *in situ* unless iproniazid is added to the perfusion liquid. But even in this case there is a delay of 2 hr before 5-HT appears in the effluent (GERTNER et al. 1959).

Peripheral nerves apparently do not contain 5-HT (AMIN et al. 1954, GARVEN 1956). However, a melatonin-like substance has been described in some of them (LERNER et al. 1959).

The occurrence of 5-HT in normal cerebrospinal fluid has never been demonstrated with certainty either in man or in the dog. In fact, the values given by the different investigators (2—20 ng/ml) are beyond the practical limits of sensitivity of the available biological and fluorometric methods (AMIN et al. 1954; FELDMAN et al. 1957; TURNER and MAUSS 1959; ASHCROFT and SHARMAN 1960, 1961; DERRY et al. 1961; BOWERS 1962; PERRY et al. 1964). This statement is more relevant when one considers that cerebrospinal fluid may contain substances disturbing both bioassay (BOWERS 1962) and spectrofluorometric estimation of 5-HT (ASHCROFT and SHARMAN 1962).

5-HT is not detectable in cerebrospinal fluid even after MAO inhibitors (BOWERS 1962, PERRY et al. 1961) or after intravenous infusion of large amounts of 5-HT (SOUTHERN 1960). The same significance has the lack of 5-HT in the cerebrospinal fluid of carcinoid patients (SJOERDSMA et al. 1957b).

According to ASHCROFT and SHARMAN (1960, 1961) and ROOS (1963) the cerebrospinal fluid contains acidic 5-hydroxyindole derivatives, among which the most important is 5-HIAA (0.03—0.04 μg/ml).

The occurrence of tryptamine in pooled human cerebrospinal fluid, at a concentration of about 0.02 μg/ml has been reported by JENSEN (1962), but not confirmed by PERRY et al. (1964).

7. Venom of reptiles

ZARAFONETIS and KALAS (1960) have described the presence of minute amounts of 5-HT in the venom of certain reptiles: *Heloderma horridum*, 2,2 μg 5-HT base/ml venom; *Crotalus atrox*, 0.15—0.3 μg/ml; *Crotalus adamanteus*, 0.1 μg/ml; *Agkistrodon piscivorus*, 0.35 μg/ml. 5-HT is accompanied by other known (tryptamine, 5-HIAA, IAA) and unknown indole compounds.

It seems futile to ascribe to these unimportant amounts of indolealkylamines any significance in the complex action of the snake venom.

8. Amphibian skin

Amphibian skin represents one of the most conspicuous localizations of indolealkylamines in the living organism. No tissue can compete with the parotoid glands of some toads as regards the absolute values of indolealkylamines, and in no tissue is there such a variety of indolealkylamines. It is therefore conceivable that comparative studies of the skin of adult and larval amphibians may contribute substantially to a better understanding of the metabolic possibilities of these substances in the living organism.

Table 17 shows the indolealkylamine content of the skin of a number of amphibians studied in the writer's laboratory since 1957.

In the skin of the following species of amphibians, none of the tabulated indole derivatives could be found in detectable amounts: *Euproctes rusconi*, *Pleurodeles waltlii*, *Triton cristatus*, *Ambystoma tigrinum* (Axolotl), *Leptodactylus chaquensis*, *Leptodactylus ocellatus*, *Leptodactylus bolivianus*, *Leptodactylus prognatus*, *Leptodactylus bufonius*, *Physalaemus fuscumaculatus*, *Physalaemus centralis*, *Pleurodema tucumana*, *Pleurodema cinerea*, *Pleurodema bibroni*, *Ceratophrys ornata*, *Cycloramphus fuliginosus*, *Eleutherodactylus ranoides*, *Corythomantis brunoi*, *Trachycephalus nigromaculatus*, *Gastrotheca boliviana*, *Batracophrynus macrostomum*, *Sphoenorhyncus aurantiacus*, *Thoropa petropolitana*, *Telmatobius hauthali*, *Elosia aspera*, *Elosia lateristrigata*, *Phyllomedusa sauvagi*, *Phyllomedusa annae*, *Phyllomedusa hypochondrialis*, *Phyllomedusa burmeisteri*, *Hyla lanciformis*, *Hyla faber*, *Hyla radiana*, *Hyla trachytorax*, *Hyla nasica*, *Hyla raniceps*, *Hyla semiguttata*, *Hyla albomarginata*, *Hyla ansper*, *Rana megapoda*, *Rana limnocharis*, *Hynobius nebulosus*, *Triturus pyrrhogaster*, *Polypedates buergeri*, *Dicroglossus occipitalis*, *Racophorus madagascariensis*, *Rana fuscigola*, *Chiromantis rufescens*, *Phyctimantis verrucosus*, *Ptychadena mascariniensis*, *Leptopelis karissimbensis*, *Arthroleptis adolphi-friederici*, *Callixalus* sp., *Chrysobatrachus* sp. *Hyla spegazzini*, *Hyla multilinea*, *Telmatobius montanus*, *Lepidobathracus hanensis*, *Lepidobathracus salinicola*, *Eleutherodactylus bufoniformis*, *Leptodactylus sibilatrix*, *Eupsophus roseus*, *Eupsophus nodosus*, *Pseudis paradoxa*, *Physalaemus bresslaui*.

It may be seen that nearly all indolealkylamines so far found in the animal kingdom are present also in the amphibian skin, and it is certain that other indolealkylamines will be discovered in the systematic screening of skin extracts from new amphibian species.

In all probability indolealkylamines in this localization are of completely autochthonal origin, i.e. they are fully independent, in regard to biosynthesis, of gastrointestinal mucosa. In fact, whereas the 5-HT content of the gastrointestinal mucosa is practically the same in the different amphibian species (0.5—3 μg/g), that of the skin may vary within extremely wide limits (0 to 1000 μg/g).

Indolealkylamines in the skin of amphibians are destined exclusively for external secretion and their biosynthesis is therefore strictly connected with the

Table 17. *The content of indolealkylamines in the amphibian skin*[1] (in μg per g dry or fresh[+] tissue)

Amphibian species	5-HT	N-Methyl-5-HT	Bufotenine	Bufotenidine	Dehydrobufotenine	Bufothionine	Tryptamine
Bufo bufo bufo[+]	20	10	450	50	130	260	0
Bufo viridis[+]	5—10	20—30	350—630	30	0	0	(Bufoviridine 450—520)
Bufo calamita[+]	6—8	13—15	95—110	30—40	0	0	(Bufoviridine 220—230)
Bufo arenarum	40—250	40—200	800—2600	40—130	250—700	150—450	0
Bufo paracnemis							
whole skin	25—70	10—200	2.8—4.3 mg	180—220	120—180	110—290	0
a) parotoid glands	100—150	=	13—20 mg	650—1600	500—700	220—350	0
b) coxal glands	150	=	16—20 mg	500—1000	300—400	120	0
c) remaining skin	20—70	=	0.4—0.5 mg	30—50	30—100	100—270	0
Bufo marinus	30—140	40—130	<2—4	0	2200—6000	30—375	0
Bufo marinus poeppigi	160	100—140	0	0	270—1100	210—240	0
Bufo ictericus	5—70	<4—50	<2—15	0	1800—4500	35—375	0
Bufo granulosus major	60—250	25—130	140—200	0	<10—1000	300—750	0
Bufo granulosus fernandezae	60—750	300—650	80—150	0	1200—2400	900—1500	0
Bufo spinulosus spinulosus	5—50	0	15—230	<3—80	180—4000	360—3600	0
Bufo spinulosus trifolium	0	0	550	100	0	0	0
Bufo terrestris	0	0	0	80	0	0	0
Bufo boreas	0	3—10	230—300	20—50	0	250—360	0
Bufo valliceps	1600	traces	0	0	0	0	0
Bufo alvarius	4—6	30—40	250—1500	0	0	0	15—30 mg 5-Methoxy-N,N-dimethyltryptamine
Bufo cognatus	600	20	0	0	20	0	0
Bufo speciosus	600—4500	80—450	0	0	50—300	0	0
Bufo canaliferus	3000	120—130	0	80	0	200	0
Bufo debilis[+]	24—30	30	0	15 (?)	750	450	0
Bufo horribilis	500—520	300	30	25—30	3000	? (<30)	0
Bufo typhonius	5—10		0	0	450	630	0
Bufo variegatus	0	0	8500	750	0	0	0
Bufo woodhousei	500—800	40	0	950—1200	150—200	0	0
Bufo punctatus	0	0	20	0	125—1000	100—750	0
Bufo haematiticus	2100	0	0	0	9000	0	0
Bufo americanus	++	+	++	++		+	0
Bufo fowleri	++	+	++	++		+	0
Bufo mauretanicus	150—300	0	0	0	0	0	0
Bufo funereus	180	0	0	0	0	0	0
Bufo regularis	550—2500	0	0	0	0	0	0
Bufo berghei	150	0	0	0	0	0	0
Bufo kisoloensis	600	0	0	0	0	0	0
Bufo formosus	80—100	60	150	130—150	15—30	300	0
Bufo gargarizans Chan Su	++	+	?	++			0
Bufo melanostictus	125	0	15	1250	8—9	0	0
Pseudobufo subasper	8—10	0	0	0	0	0	0
Leptodactylus laticeps	570	0	0	0	0	0	0
Leptodactylus pentadactylus pentadactylus	130—150	0	0	0	0	0	0
Leptodactylus pentadactylus labyrinthicus	100—1800	0	0	0	0	0	0
Leptodactylus pentadactylus dengleri	40—65	0	0	500—700	3	0	0

Table 17. (Continued)

Amphibian species	5-HT	N-Methyl-5-HT	Bufotenine	Bufotenidine	Dehydrobufotenine	Bufothionine	Tryptamine
Leptodactylus podicipinus podicipinus	640	0	0	15—20	0	0	0
Leptodactylus podicipinus petersi	1—1.5	0	0	2.5—3	0	0	0
Leptodactylus rubido cope	7	0	0	40—45	0	0	0
Leptodactylus melanonotus	35	10	0	25	0	0	0
Odontophrynus americanus	300—1700	0	0	0	0	0	0
Odontophrynus occidentalis	500	0	0	0	0	0	0
Scaphiopus hammondi	550—600	0	0	70	0	0	0
Scaphiopus couchi	320	0	0	0	0	0	0
Xenopus laevis+	100—200	0	0	600—1800	0	0	0
Melanophryniscus moreirae	40—70	0	2400—3000	30	0	0	0
Thoropa miliaris	2—10	0	0	0	0	0	0
Osteocephalus taurinus	2—3	0	0	0	0	0	0
Bombina variegata pachypus+	400—450	0	0	0	0	0	0
Bombina bombina	++	0	0	0	0	0	0
Discoglossus pictus+	200—350	0	0	0	0	0	0
Rana esculenta+	20—40	0	0	0	0	0	0
Rana temporaria+	20—200	3—10	7—100	0—22	0	0	0
Rana latastei+	4—16	2—10	12—95	10—15	0	0	0
Rana dalmatina	100	?	1900	200	0	0	0
Rana japonica	60—70	0	0	0	0	0	0
Rana nigromaculata	70—80	0	0	0	0	0	0
Rana rugosa	750	0	0	0	0	0	0
Rana palmipes	4—60	0	0	0	0	0	0
Rana pipiens	3—60	0	0	0	0	0	0
Rana clamitans	?	0	0	0	0	0	0
Rana palustris	+	0	0	0	0	0	0
Rana madagascariensis	+	0	0	0	0	0	0
Rana labrosa	+	0	0	0	0	0	0
Pleurodema bufonina							
coxal glands	230—250	0	0	0	0	0	0
remaining skin	0	0	0	0	0	0	0
Phyllomedusa rohdei	0	0	7—25	0	0	0	0
Hyla caerulea	200	0	0	0	0	0	0
Hyla infrafrenata	500	0	0	0	0	0	0
Hyla arborea (europea)+	10—100	0	0	0	0	0	0
Hyla arborea (japonica)	10	0	0	0	0	0	0
Hyla fuscovaria	10—15	0	0	0	0	0	0
Hyla peroni	250	12	15	0	0	0	0
Lepidobathracus asper	5	0	0	0	0	0	0
Salamandra salamandra+	10	0	0	0	0	0	45
Salamandra atra+	10	0	0	0	0	0	2.5

0 = not detectable (<2—3 μg/g).
[1] Erspamer (1954a, 1954b), Erspamer, Cei and co-workers (to be published).

biosynthesis of the other constituents of the "cutaneous venom". This suggests that, in spite of all appearances, the turnover rate of the amines in the skin must be very slow.

The biological significance of the indolealkylamines in the amphibian skin is largely obscure. It may be that they play some part in the defence of the animal, but it is also possible that they simply constitute metabolic end products.

Before concluding it should be emphasized that amphibian skin may represent a formidable store-house not only of indolealkylamines, but also of phenyl-

alkylamines, imidazolealkylamines and highly active polypeptides (ERSPAMER 1958; ERSPAMER et al. 1962a, 1962b, 1963).

9. Fish tissues and venoms

Male reproductive tract of the dogfish. The undiluted secretion of clasper siphons of sexually mature specimens of *Squalus acanthias* (250 mg of fluid per pair of clasper siphons) contains, according to MANN (1960), the tremendous amount of 25—34 mg 5-HT base per g secretion; the siphon tissue itself (2.8—3.6 g per kg body weight) 1.2 mg 5-HT per g wet tissue. This would correspond to not less than 10 mg 5-HT per animal weighing 1 kg. 5-HT is absent or present only in traces in the sperm removed directly from the seminal ducts and in the so-called seminal vesicles. Clasper siphons of immature males, weighing 100 mg, contain only 0.07—0.2 mg 5-HT per g tissue.

It has been suggested that the 5-HT present in a secretion which represents an integral part of semen might play a part in the reproductive process, either by affecting the mechanism of copulation and ejaculation in the male, or by eliciting contractions of the female reproductive tract, thus influencing passage of sperm and fertilization.

Fish venoms. The dried venom obtained from the dorsal spines of the lesser weever-fish, *Trachinus vipera*, contains about 1—20 μg 5-HT per mg. According to CARLISLE (1962) the 5-HT appears to be responsible for the immediate pain about wounds inflicted by this fish.

10. Urine

Table 18 summarizes the most important available data on the occurrence of indolealkylamines and indole acids in normal urine.

The origin of the 5-HT found in normal human urine is obscure. A first possibility is that urinary 5-HT originates from plasma 5-HT either by glomerular filtration or tubular excretion; a second possibility that at least part of the 5-HT in urine is contributed directly by kidney metabolism (RODNIGHT 1956, AIRAKSINEN and UUPÄÄ 1961). This would, however, require the presence of 5-HTP in the blood or in kidney tissue.

In the chicken, exogenous 5-HT is excreted by tubular excretion. In fact, 80 μg of 5-HT base given to normal chicken or to chicken pre-treated with a MAO inhibitor by unilateral leg vein infusion produces an ipsilateral excess of excretion of 5-HT of such magnitude that it proves a tubular excretion of the compound (SANNER and WORTMAN 1962).

Apparently 5-HT is transported in the chicken tubule by the ordinary organic base system (SANNER 1963).

According to DESPOPOULOS (1956, 1957) 5-HIAA is excreted by the kidney both by glomerular filtration and by tubular excretion, and this opinion is shared by BARAC (1961). In fact, the intravenous administration of 2 g of probenecid to patients with a high rate of excretion of 5-HIAA is followed by a decrease in the rate of excretion of 5-HIAA and an increase in its concentration in plasma.

Neither in man nor in the rat is there any significant change in the excretion rate of 5-HIAA with varying urinary pH. The mean excretion rate in human acid urine (pH 5.5—6.5) is 240 μg/hr, and in alkaline urine (pH above 7.8) 280 μg/hr (MILNE et al. 1960, DEGKWITZ et al. 1962).

Data on the diurnal rhythm in the excretion of urinary 5-HIAA are at variance. According to JOHNSEN et al. (1958) and SOCHOR and LAKATUA (1964) the peak in the daily 5-HIAA excretion occurs in the 3-hour period on either side of

Table 18. *Indolealkylamines and indole acids in urine*

	Indolealkylamines		Indole acids	
	5-HT	Tryptamine	5-HIAA	Other acids
Man . . .	20—100[1], 45—120 μg/24 hr[2]; 0.01—0.7[3], 0.23 μg/ml[4]	20—100[1], 45—120[2], 25—250[35] 30—120[5], 30—126 μg/24 hr[6]	2—9[7]; 3.2—13.7[8], 1.3—5.6[9]; 2—7[10]; 5.7 ± 1.4[11]; 4.77 ± 0.32[12]; 3.54 ± 0.18[13] mg per day 229[14]; 203[15]; 240—280[16]; 238[17]; 206 ± 53 μg per hour[18] 3.9 mg per g creatinine[19]	indoleacetic, indolelactic, indoleacetylglutamic, indole-3-carboxylic, indoleacrylic, indoleglycolic acids; indoleacetylglutamine; acetyltryptophan[20]; indoleacetamide[20,21]
Rat		4.4—8.2 μg per 10 mg creatinine[28]	146[22]; 145—200[23]; 113—133[24]; 110—140[25]; 130[26]; 250—280[27] μg/kg/24 hr	166 μg IAA per 100 mg creatinine[28]
Guinea-pig.		0.6 mg/24 hr/animal[29]	60—150 μg/day/animal[34]	
Mouse. . .			6 μg/ml[32]; 130—157 μg/kg/16 hr[33]	
Monkey . .			1.6—19.4 μg/hr[31]	
Dog. . . .			40—120 μg/kg/24 hr[30]	
Cow . . .			3.34 ± 0.24 μg/ml[36]	

References to Table 18. [1] DAVIES et al. (1954). — [2] RODNIGHT (1956). — [3] LEMBECK and NEUHOLD (1955). — [4] KURIAKI and INOUE (1956). — [5] SJOERDSMA et al. (1959, 1960). — [6] BRUNE and HIMWICH (1961). — [7] UDENFRIEND et al. (1955), SJOERDSMA et al. (1956). — [8] MACFARLANE et al. (1956). — [9] NIKKILA (1958). — [10] PELTOLA and LEPPÄNEN (1960). — [11] OLSON et al. (1960). — [12] BARBEAU and JASMIN (1961). — [13] SCHWEMMLE et al. (1961). — [14] KOPIN (1959). — [15] FELDSTEIN et al. (1959). — [16] MILNE et al. (1960). — [17] PERMAN (1961). — [18] DEGKWITZ et al. (1962). — [19] PARE et al. (1960). — [20] ARMSTRONG et al. (1958). — [21] SPRINCE et al. (1961). — [22] FERRARI et al. (1957). — [23] BERTACCINI (1960). — [24] BERTACCINI and NOBILI (1961). — [25] BERTACCINI and ERSPAMER (1962). — [26] KIVALO et al. (1961). — [27] CASS and MARSHALL (1962). — [28] DONALDSON (1962), DONALDSON et al. (1961). — [29] HESS et al. (1959). — [30] ERSPAMER and TESTINI (1959). — [31] ANDERSON et al. (1958). — [32] SJOERDSMA et al. (1957). — [33] BARTLET (1963). — [34] KRÜGER and SMITH (1960b). — [35] GOTTFRIES and MAGNUSSON (1962). — [36] BERTACCINI and CHELI (1963).

noon, according to PELTLOLA and LEPPÄNEN (1960) between 5 p.m. and 9 p.m., according to BETTENDORF et al. (1962) between 1 p.m. and 4 p.m.

PELTOLA and LEPPÄNEN (1960) found that on the average one half of the daily amount of 5-HIAA is excreted during the night, SCHWEMMLE et al. (1961) and DEGWITZ et al. (1962, 1964) that nocturnal excretion of 5-HIAA is approximately 15% less than diurnal, finally BETTENDORF et al. (1962) that 50% of the total 5-HIAA is excreted between 10 p.m. and 7 a.m.

Administration of tap water by stomach tube or of isotonic NaCl solution orally or subcutaneously produces a conspicuous increase in the urinary excretion of 5-HIAA in the rat. The same increase can be observed after administration of water plus posterior-pituitary antidiuretic hormone. Tap water is less effective than physiological saline; the latter, in its turn, is more effective by the subcutaneous route than by mouth. Increase of 5-HIAA may be, for short periods, as high as 3 times normal. The minimum oral dose of tap water causing a significant increase in urinary 5-HIAA is 2 ml/kg, that of physiological saline 1 ml/kg. Generally excess 5-HIAA coincides with excess urine elimination, but there is no obligatory correlation of the intensity of the two phenomena (BERTACCINI and ERSPAMER 1962). The above observation have been essentially confirmed in man (BERTACCINI and co-workers, unpublished observations; DEGKWITZ et al. 1962), but the mechanism of action of water or saline remains still to be elucidated.

Removal of large segments of the intestine is followed both in the experimental animal and in man by a more or less conspicuous reduction in the urinary excretion of 5-HIAA. This is a direct consequence of the removal of an important part of the 5-HT secreting tissue (BERTACCINI 1960, HAVERBACK and DAVIDSON 1958, BERTACCINI and CHIEPPA 1960).

Administration of excess dietary tryptophan or of a tryptophan load is followed by a conspicuous increase in the urinary excretion of 5-HIAA, in all probability depending on accelerated biosynthesis of 5-HT. In the rat the minimum oral dose of L-tryptophan producing a significant increase in urinary 5-HIAA is 100 mg/kg; 200 mg/kg may cause a 300% increase for a 4-hour period (BERTACCINI and NOBILI 1961).

Conversely, in the rat the absence of tryptophan from the diet is reflected in a 50% fall of urinary 5-HIAA, within 3 days (TOWSEND et al. 1958).

Neither nicotinic acid deficiency in the dog, nor pyridoxine or riboflavine deficiency in the rat causes any significant change in the urinary excretion of 5-HIAA (FERRARI et al. 1957, HARDING-GAUDIN 1961, EDELSTEIN et al. 1962).

The statement of PIGEAUD et al. (1958) that 5-HIAA excretion increases during pregnancy was not confirmed by SCHWEMMLE et al. (1961).

The urinary excretion of 5-HIAA in the rat is increased from 157 to 250—265 μg/kg/24 hr after 2—3 weeks of exposure of the animal to cold (6°), and this increase persists as long as exposure is continued, up to 12 months. According to LEBLANC (1963) the changed excretion of 5-HIAA may not be specific to cold and may parallel the increased metabolic activity.

In the presence of a localized area of intestinal stasis produced in rats surgically by the creation of midintestinal diverticula, the excretion in the urine of 5-HT, tryptamine and 5-HIAA is not altered, whereas that of indican and IAA, free and conjugated, is significantly increased (DONALDSON et al. 1961, DONALDSON 1962).

11. Biological fluids and liquids other than urine

Mammalian semen. The statement by KATSH (1959) that human seminal plasma contains as much as 135 μg/ml 5-HT has not been confirmed. HAWKER et al. (1960) and ELIASSON (1961) could not find any 5-HT either in human or in ram semen and MANN et al. (1961) assessed by spectrofluorometric estimation the following "5-HT equivalents" in the semen of mammals: man 0.15 μg, bull 1 μg, ram 0.5 μg, boar 0.05 μg, dog 0.15 μg/ml.

Amniotic fluid. The amniotic liquid of the goat and the rabbit contains, if any, only traces of 5-HT: 0.006—0.03 and <0.05 μg/ml, respectively (PEPEU and GIARMAN 1962, BERTACCINI unpublished data).

In human amniotic liquid the 5-HT content was found by KOREN et al. (1961) to vary between 0 and 0.38 μg/ml. However, the credibility of these values is impaired by the apparent unsuitability of the chemical assay procedure employed (1-nitroso-2-naphtol reagent).

Allantoid fluid. According to PEPEU and GIARMAN (1962) the 5-HT concentration in the allantoid fluid of the goat ranges between 0.12 and 0.4 μg/ml.

III. Invertebrates

So far 5-HT has been detected in particularly large amounts in some venom apparatuses of molluscs, scorpions, insects and coelenterates (Table 19) and in much less conspicuous but important amounts in the nervous tissue of molluscs (Table 20).

Table 19. *Occurrence of 5-HT and related indole derivatives in invertebrate tissues other than nervous tissue*

Animal species and tissue	5-HT	Other indole derivatives	Reference
Molluscs			
Posterior salivary glands			
Octopus vulgaris (Bari)	300—500 μg		1
Octopus vulgaris (Bermudas)	68—72 μg		2
Octopus macropus	—0.5 μg		1
Octopus bimaculata	present		3
Eledone moschata	280—750 μg		1
Median salivary glands			
Loligo pealii	0.38 μg		2
Anterior salivary glands			
Octopus vulgaris (Bermudas)	0.48—2.4 μg		2
Hypobranchial body			
Murex trunculus	80—290 μg		4
Murex brandaris	present		4
Gills			
Mytilus edulis	0.1—1.0 μg	5-HTP	5
	1.45 μg	0.05—0.5 μg	6
Modiolus demissus	0.3 μg		6
Tissues from different molluscan species			2
Intestine	0.6—0.7 μg		
Heart	0.2—0.5 μg		
Kidney	0.3—2.0 μg		
Musculature	0.08—1.0 μg		
Connectives	2.2 μg		
Skin	0.04 μg		
Crustaceans			
Green glands	0.06—1.0 μg		2
Pericardial organ	17 μg	5,6-dihydroxy-tryptamine	2,7
Heart		6-HT	17, 19
Insects			
Acanthoscurria atrox	0.058 μg per mg dry venom		18
Acanthoscurria sternalis	0.14 μg per mg dry venom		
Pterinopelma vellutinum	0.033 μg per mg dry venom		
Lycosa erythrognatha	0.014 μg per mg venom gland		
Phoneutria fera	0.52—2.65 μg per mg dry venom		
Polybia occidentalis	0.28 μg per abdomen		
Polistes versicolor	1.04—1.2 μg per sting apparatus		
Polistes versicolor vulgatus	1.94 μg per sting apparatus		
Polistes gallica	0.7—0.8 μg per venom apparatus		10
Vespa vulgaris	0.32 μg per mg dry venom		8
Vespa crabro	7.5—19 μg per mg dry venom sac		9
Vespa maculata	1.29 μg per sting apparatus		18
Synoeca surinama	0.97—2.74 μg per sting apparatus		18
Apis mellifera	5 ng; 0.03 μg per venom apparatus		2,8,10
Luciola italica	1 μg per head, 2 μg per thorax, 1 μg per abdomen, 2 μg per pair of wings		20
Periplaneta americana ♂ utriculi majores	?	o-dihydroxy-indolealkyl-amine	11

Table 19. (Continued)

Animal species and tissue	5-HT	Other indole derivatives	Reference
corpora cardiaca glands . . .	present		11
Scorpions			
Leiurus quinquestriatus	2—4 μg per mg dry venom		12
Buthotus minax	0.03—0.04 μg per mg dry venom		12
Vejovis sp.	58—138 μg per sting segment		2
Hadrurus arizonensis	0.55 μg per sting segment		2
Parabuthus hunteri	present		12
Worms			
Dugesia tigrina whole	2 μg		2
Dugesia dorotocephala whole . .	1.5—3.4 μg		
Lineus ruber whole	0.18—0.43 μg		
Cerebratulus lacteus whole . . .	0.08—2.9 μg		
Arenicola marina body wall . .	2.3 μg		
Amphitrite ornata gills	0.26 μg		
	0.19 μg		
Fasciola hepatica	0.06—0.07 μg		13
Coelenterates			
Hydra oligactis whole	1.5 ng per animal		2,14
Sagartia luciae whole	50—100 ng per animal		2,14
Calliactis parasitica			
coelenteric tissue	500—660 μg } per g freeze-dried tissue		15
column	13—36 μg } per g freeze-dried tissue		
tentacles	6—12 μg } per g freeze-dried tissue		
Metridium senile			
whole animal	0.04—0.05 μg		2,14,16
body wall	0.02—0.09 μg		
oral disk and tentacles . . .	0.08—0.17 μg		
tentacles	0.24—0.47 μg	bufotenine, 5-HTP	
acontia	0.60—1.3 μg		
Anemonia sulcata	non detectable		15
Actinia equina	non detectable		15
Physalia	non detectable		15

Unless otherwise stated the above values are per g fresh tissue.

References to Table 19. [1] ERSPAMER (1948b, 1954b, 1954c), ERSPAMER and BORETTI (1951), ANASTASI and ERSPAMER (1962). — [2] WELSH and MOORHEAD (1959, 1960). — [3] CLARK (1960), HARTMAN et al. (1960). — [4] ERSPAMER (1948a, 1954b, 1954c). — [5] AIELLO (1962). — [6] GOSSELIN et al. (1962). — [7] CARLISLE (1956), CARLISLE and KNOWLES (1959), CARLISLE (1964), MAYNARD and WELSH (1959). — [8] JAQUES and SCHACHTER (1954). — [9] BHOOLA et al. (1960, 1961). — [10] ERSPAMER (1954c). — [11] DAVEY (1960), COLHOUN (1963, 1964), — [12] ADAM and WEISS (1956, 1959). — [13] MANSOUR et al. (1957). — [14] WELSH (1960). — [15] MATHIAS et al. (1957, 1958, 1960). — [16] PHILIPPS (1956). — [17] KERKUT and PRICE (1963). — [18] WELSH and BATTY (1963). — [19] KERKUT and PRICE (1964). — [20] BERTACCINI et al. (to be published).

It is certain that numerous other examples of indolealkylamines will be discovered in invertebrates.

Quite recently, for example, an unexpected localization of 5-HT has been described by MANN (1963) in the octopus. MANN found that the glandular portion of the spermatogenic sac of the octopus contained 120 μg 5-HT per g fresh tissue in the smallest specimens and as much as 1690 μg/g in the largest specimens. The weight of the glandular portion was 2.5—3 g per kg octopus. It is suggested that this 5-HT may play a part in the ejaculatory process. This might perhaps be envisaged as an induction of either the discharge of the spermatophores from the spermatophoric sac, or a stimulation of contractions within the male or female reproductive tract, assisting the passage of spermatozoa to the site of fertilization.

Table 20. *Occurrence of 5-HT in nervous tissue of invertebrates*

Animal species	Tissue	5-HT content (in μg base per g wet tissue)	Reference
Molluscs			
Venus mercenaria	pooled ganglia	30—40	1
Pecten magellanicus	visceral ganglia	36	
Mytilus edulis	ganglia	10—15	
Artica islandica	ganglia	20	
Spisula solidissima	ganglia	8—14.3	
Ensis directus	ganglia	21—39	
Mya arenaria	ganglia	22	
Buccinum undatum	ganglia	7.7	
Busycon canaliculatum	ganglia	8.4—9.7	
	nerves	2—2.5	
Fasciolaria tulipa	ganglia and nerves	7.6—9.4	
Polinices heros	ganglia	10.6	7
Crepidula fornicata	ganglia	5.0	
Melongena corona	ganglia	4.5	
Viviparus japonicus	ganglia	1.2	
Helix pomatia	ganglia	2—3; <1	2,3
	nerve cords	non detectable	3
Astacus leptodactylus	nerve cords	non detectable	3
Astacus fluviatilis	nerve cords	non detectable	3
Loligo pealii	"brain"	0.7	1
	optic ganglia	1.15	1
Octopus briareus	pooled ganglia	1.6	1
Octopus vulgaris	"brain"	0.8; 0.25	1,4
	optic ganglia	2.3; 2.3	1,4
	stellate ganglia	0.72	4
	nerves	1.5	4
Eledone moschata	optic ganglia	2—4	5
	nerves	1.5—2	5
Crustaceans			
Cancer irroratus, Cancer borealis, Carcinus moenas, Homarus americanus, Panulirus argus, Orconectes virilis, Palinurus vulgaris, Gecarcinus lateralis	nerve cords, ventral ganglia, leg nerves, "brain"	<0.1	1,4
Worms			
Lumbricus terrestris	nerve cords	10.4	1
Hirudo medicinalis	nerve cords	6.9	1
	nerve cords	0.2	4
Amphitrite ornata	nerve cords	5.4	1
Arenicola marina	nerve cords	3.1	1
Glycera dibranchiata	nerve cords	4.6	1
Insects			
Blaberus gigantea	nerve cords	<0.02	1
Locusta migratoria	ganglia	<0.2	4
Periplaneta americana	"brain"	present	6
	ventral nerve cord	present	6
Holothurians			
Thyone briareus	region of nerve ring	0.03—0.05	1

References to Table 20. [1] WELSH and MOORHEAD (1959, 1960). — [2] MENG (1958). — [3] JULLIEN et al. (1961), CARDOT et al. (1962, 1963). — [4] ERSPAMER, unpublished data. — [5] BERTACCINI (1961). — [6] COLHOUN (1963). — [7] MIROLLI and WELSH (1964).

The resemblance of this localization with that found in the male reproductive tract of the dogfish (MANN 1960) is evident. It would be instructive to carry out comparative studies on different octopod or cephalopod species to see whether the occurrence of 5-HT in the spermatogenic sac is a constant finding.

The 5-HT in the venom glands does not seem to have any particular significance but that of a facultative constituent of the venom. In fact, the venom of strictly related species may present, for completely unknown reasons, striking differences in 5-HT content. This is true of the posterior salivary glands and the hypobranchial body of molluscs, the venom apparatus of *Hymenoptera*, the venom apparatus of scorpions, etc. The opinion cannot be rejected that here, as in the case of amphibian skin, 5-HT may merely be a metabolite destined for external secretion.

Things are completely different with the 5-HT present in molluscan nervous tissue. All the investigators found that molluscan ganglia and peripheral nerves contain important amounts of 5-HT and that this 5-HT behaves, towards different drugs, exactly like the 5-HT occurring in the brain of mammals. Moreover, it has been demonstrated that the turnover rate of 5-HT in the ganglia of molluscs is very high, the half-life of the amine being not longer than 15 to 20 minutes (BERTACCINI 1961).

From this it may reasonably be inferred that, in sharp contrast to other localizations of 5-HT in the molluscan body, neuronal 5-HT must have a general biological significance, probably in the transmission of nervous impulses. Appropriate procedure indicates that 5-HT is stored in granules in the molluscan ganglia (WELSH 1958).

It is conceivable that a thorough study of the 5-HT in the nervous tissue of molluscs may offer a key to a better understanding of the function of the amine in the brain of vertebrates.

According to CARDOT (1963) the nerve cords of *Helix pomatia* also contain trace amounts of tryptamine.

IV. Plants

The data reported in Table 21 are intended merely to be an exemplification of the wide distribution of indolealkylamines in the vegetable kingdom. It may be anticipated that these compounds will be met with in numerous other plant tissues.

Tables 22 and 23 show the content of tryptamines and other amines in the different parts of some edible fruits and their appearance during the ripening process.

There appears to be more 5-HT in unripe pineapples (50—60 μg/g) than in the ripe fruit (19 μg/g). A trace of the amine is also detectable in the stalk (0.2 μg/g), but none in the leaves of the crown or in the base (FOY and PARRATT 1961).

It is very interesting to note that not only 5-hydroxyindoles but also 4-hydroxyindoles and 2-hydroxyindoles have been found in the vegetable kingdom. We refer to psilocin and psilocybin (see Table 21) and to 2-hydroxyindoleacetic acid, which has been detected in the shooting seeds of *Brassica rapa* and the red gooseberry as well as in the caryopsides of Indian corn (KLAMBT 1959). This means that the vegetable cells contain enzymes capable of hydroxylating the indole nucleus at the 4- and 2-positions also.

The significance of indolealkylamines in plants is not very well understood. It may be that in some cases they act as growth factors or as precursors of auxines and that in other cases they intervene in the synthesis of pigments. But a third, likely possibility is that, as in the animal kingdom, some examples of indolealkylamines in plants are to be considered mere metabolic end products possessing no particular significance.

Table 21. *Occarrence of 5-HT and related indole derivatives in the vegetable kingdom*

Species	5-HT	Other indole derivatives	Reference
Neurospora crassa		β-hydroxy-pseudo-tryptophan	1
Panaeolus campanulatus	80 μg/g	other indole derivatives	2, 25
Panaeolus foenesecii	240 μg/g		25
Panaeolus sphinctrinus	present	psilocybin 1.9 μg/g, 5-HTP	3, 28
Psilocybe (several species)		psilocybin 0.1—6 μg/g psilocin 0—2.5 μg/g	4
Stropharia cubensis		psilocybin 0.1—5 μg/g psilocin 0—2.5 μg/g	3
Amanita mappa		bufotenine	5
Piptadenia peregrina (seeds)		bufotenine 9.4 μg/, 5-HIAA	6
Piptadenia peregrina (bark)		N-methyltryptamine, 5-methoxy-N-methyltryptamine, 5-methoxy-N,N-dimethyltryptamine	7
Piptadenia colubrina (seeds)		bufotenine	8
Piptadenia macrocarpa (seeds and pods)		bufotenine, bufotenine oxide, N,N-dimethyltryptamine, N,N-dimethyltryptamine oxide	9
Gossypium hirsutum (fruit)	present		10
Symplocarpus foetidus (leaves)	present		10
Citrullus vulgaris	present		11
Dictyoloma incanescens (bark)		5-methoxy-N,N-dimethyltryptamine	8
Mimosa hostilis (roots)		N,N-dimethyltryptamine	8
Urtica dioica (stings)	3—5 ng/sting		12
Laportea moroides (hairs)	1 ng/hair		13
Mucuna pruriens (trichomes)	150 μg per g trichomes		14
Prestonia amazonica (leaves)		N,N-dimethyltryptamine	15
Acacia fluribunda (tops)		tryptamine	16
Phalaris arundinacea		5-methoxy-N-methyltryptamine	17
Acer saccharinum		gramine	8
Acer rubrum (fruit)		gramine	18
Hippophae rhamnoides	present		19
Arundo donax		gramine	20
Barley		gramine, N-methyltryptamine	21
Girgensohnia diptera		N-methyltryptamine	26
Girardinia heterophylla	present		29
Maize (chopped green)	13.7 μg/g dry matter		27
Ananas comosus			
unripe fruit	50—60 μg/g		22
ripe fruit	19 μg/g		
fresh juice	12—22 μg/ml		
canned juice	1.3—25 μg/ml		
Carica papaya (fruit)	1.1—2.1 μg/g		23
Passiflora foetida (fruit)	1.4—3.5 μg/g		23
Juglans regia (nut)	170—340 μg per g kernel		24
Eggplant (fruit)	2 μg/g	tryptamine 0.5—3 μg/g	25
Avocado	10 μg/g		25
Red plum	10 μg/g	tryptamine 0.2 μg/g	25
Blue-red plum	8 μg/g	tryptamine 2 μg/g	25
Banana Plantain Tomatoes	see Tables 22 and 23		

References to Table 21. [1] SHERWOOD (1957). — [2] TYLER (1958). — [3] DELAY et al. (1959), CERLETTI (1960), MARMO (1960). — [4] HOFMANN et al. (1958, 1963), HOFMANN and TROXLER (1959). — [5] WIELAND and MOTZEL (1953). — [6] STROMBERG (1954), FISH et al. (1955). — [7] LEGLER and TSCHESCHE (1963). — [8] PACHTER et al. (1959). — [9] FISH et al. (1955, 1956). — [10] BULARD and LEOPOLD (1958). — [11] DANNENBOURG and LIVERMAN (1957). — [12] COLLIER and CHESHER (1956). — [13] ROBERTSON et al. (1957). — [14] BOWDEN et al. (1954). — [15] HOCHSTEIN and PARADIES (1957). — [16] WHITE (1944). — [17] WILKINSON (1958). — [18] PACHTER (1959). — [19] PURKHALSKAIA and MENSHIKOV (1960). — [20] ORCHOFF and NORKINA (1935). — [21] BRANDT et al. (1935), v. EULER et al. (1936), KIRKWOOD and MARION (1950). — [22] BRUCE (1960, 1961), WEST (1960), FOY and PARRATT (1961). — [23] FOY and PARRATT (1960). — [24] KIRBERGER and BRAUN (1961). — [25] WIER and TYLER (1963). — [26] YURASHEWSKII (1941). — [27] NEUMARK (1964). — [28] TYLER and GROGER (1964). — [29] SAXENA et al. (1964).

Numerous research workers (WAALKES et al. 1958, WEST 1960, KIRBERGER and BRAUN 1961) have called attention to the possibility that ingestion of edible fruits, especially bananas, containing large amounts of 5-HT and catecholamines

Table 22. *Indolealkylamines and phenylalkylamines in bananas (µg/g wet tissue)*

	5-HT	Trypt-amine	Tyr-amine	Dop-amine	Nor-adrenaline
a) Banana					
Hard green					
outer peel	0.1[2]; 74[1]	=	=	=	=
inner peel	0.2; 13				
pulp . . .	25; 24				
Ripe					
outer peel	52; 96	0[1]	65[1]	700[1]	122[1]
inner peel	40; 38				
pulp . . .	19; 36	0	7	8	2
Over-ripe					
outer peel	39; 161	=	=	=	=
inner peel	30; 170				
pulp . . .	22; 35				
b) Plantain					
Unripe					
skin . . .	13[3]; 1[4]	0[4]	=	=	5[3]; 1.8[4]
pulp . . .	50; 16	0	=	=	2.0[4]
Ripe					
skin . . .	41[3]	=	=	=	6.2[3]
pulp . . .	57; 45[1]	=	=	=	2.5
Over-ripe					
skin . . .	6[3]	=	=	=	15[3]
pulp . . .	12	=	=	=	10

References to Table 22. [1] WAALKES et al. (1958), UDENFRIEND et al. (1959). — [2] WEST (1958). — [3] FOY and PARRATT (1960). — [4] MARSHALL (1959).

may lead to erroneous chemical diagnosis of carcinoid tumour or pheocromocytoma. In this regard the observation by FOY and PARRATT (1962) seems relevant that whereas there is no significant difference between the urinary 5-HIAA of Nigerians not on a plantain diet and Europeans living in Nigeria (5.3 and 4.5 mg/24 hr),

Table 23. *Tryptamines in tomatoes (µg/g wet tissue)* (WEST 1959a, 1959b)

	5-HT	Tryptamine	Tryptophan		5-HT	Tryptamine	Tryptophan
Young plant				Fruit			
main stems .	0	0	2.5	unripe pulp .	0.2	1.0	0.2
leaf stems .	0.3	0	2.5	ripe skin . .	1.5	1.8	0.2
leaves . . .	0.5	0	2.0	ripe pulp . .	3.4	4.0	0.8
				ripe pips . .	1.0	4.8	0.4

5-HTP and 5-HIAA are not present in detectable amounts.

Nigerian subjects on two main plantain meals present a urinary excretion of 5-HIAA as high as 28 mg/24 hr.

The possibility that 5-HT in edible fruits may constitute a contributory factor in intestinal disorders (MARSHALL 1959) has been minimized by UDENFRIEND et al. (1959) and by CROUT and SJOERDSMA (1959).

References

ADAM, K. R., and C. WEISS: 5-Hydroxytryptamine in scorpion venom. Nature (Lond.) **178**, 421—422 (1956).

— — Distribution of 5-hydroxytryptamine in scorpion venoms. Nature (Lond.) **183**, 1398—1399 (1959).

ADAMS, B. G.: Serum 5-hydroxytryptamine levels following experimental increase in gastrointestinal activity in man. Lancet **1960 I**, 207—208.

ADAMS-RAY, J., A. DAHLSTRÖM, K. FUXE, and N.-Å. HILLARP: Mast cells and monoamines. Experientia (Basel) **20**, 80—82 (1964).

AIELLO, E. L.: Identification of the cilioexcitatory substance present in the gill of the mussel *Mytilus edulis*. J. cell. comp. Physiol. **60**, 17—21 (1962).

AIRAKSINEN, M. M., and V. J. UUSPÄÄ: Is urinary 5-hydroxytryptamine formed in the kidney? Biochem. Pharmacol. 8, 46 (1961).

ALBRECHT, P., M. B. VISSCHER, J. J. BITTNER and F. HALBERG: Daily changes in 5-hydroxytryptamine concentration in mouse brain. Proc. Soc. exp. Biol. (N.Y.) **92**, 703—706 (1956).

AMIN, A. H., T. B. B. CRAWFORD and J. H. GADDUM: The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. J. Physiol. (Lond.) **126**, 596—618 (1954).

ANASTASI, A., and V. ERSPAMER: Occurrence and some properties of eledoisin in extracts of posterior salivary glands of eledone. Brit. J. Pharmacol. **19**, 326—336 (1962).

ANDERSON, E. G., and D. D. BONNYCASTLE: A study of the central depressant action of pentobarbital, phenobarbital and diethyl ether in relationship to increases in brain 5-hydroxytryptamine. J. Pharmacol. exp. Ther. **130**, 138—143 (1960).

—, and J. CUDIA: The anatomical localization of norepinephrine and 5-hydroxytryptamine in cat spinal cord. Fed. Proc. **21**, 341 (1962).

— S. D. MARKOWITZ and D. D. BONNYCASTLE: Brain 5-hydroxytryptamine and anticonvulsant activity. J. Pharmacol. exp. Ther. **136**, 179—182 (1962).

ANDERSON, J. A., M. R. ZIEGLER and D. DOEDEN: Banana feeding and urinary excretion of 5-hydroxyindoleacetic acid. Science **127**, 236—238 (1958).

ANTONELLI, A. R., G. BERTACCINI and P. MANTEGAZZINI: Relationship between mesencephalic and hypothalamic concentration of 5-hydroxytryptamine and cortical electrical activity of cats. J. Neurochem. **8**, 157—158 (1961).

APRISON, M. H., M. A. WOLF, G. L. POULOS and T. L. FOLKERTH: Neurochemical correlates of behavior. III. Variation of serotonin content in several brain areas and peripheral tissues of the pigeon following 5-hydroxytryptophan administration. J. Neurochem. **9**, 575—584 (1962).

ARMIN, J., and R. T. GRANT: Further observations on vasoconstrictor substances in blood of rabbit and man. J. Physiol. (Lond.) **138**, 401—416 (1957).

ARMSTRONG, M. D., K. N. F. SHAW, M. J. GORTAWSKI and H. SINGER: The indole acids of human urine. Paper chromatography of indole acids. J. biol. Chem. **232**, 17—30 (1958).

ASHCROFT, G. W., and D. F. SHARMAN: 5-Hydroxyindoles in human cerebrospinal fluid. Nature (Lond.) **186**, 1050—1051 (1960).

— — The effect of reserpine on the concentration of 5-OR indolyl compounds in the caudate nucleus and the cerebrospinal fluid of the dog. J. Physiol. (Lond.) **158**, 32—33 P (1961).

— — Drug-induced changes in the concentration of 5-OR indolyl compounds in cerebrospinal fluid and caudate nucleus. Brit. J. Pharmacol. **19**, 153—160 (1962).

AXELROD, J., R. J. WURTMAN, and CH. M. WINGET: Melatonin synthesis in the hen pineal gland and its control by light. Nature (Lond.) **201**, 1134 (1964).

BARAC, G.: Elimination rénale de l'acide 5-hydroxyindoleacétique chez le Chien. C. R. Soc. Biol. (Paris) **155**, 1732—1734 (1961).

BARBEAU, A., et G. JASMIN: Dosage de l'acide 5-hydroxyindoleacétique urinaire dans la maladie de Parkinson. Rev. canad. Biol. **20**, 837—838 (1961).

BARCHAS, J. D., and D. X. FREEDMAN: Brain amines: response to physiological stress. Biochem. Pharmacol. **12**, 1232—1235 (1963).

—, and A. B. LERNER: Localization of melatonin in the nervous system. J. Neurochem. **11**, 489—491 (1964).

BARTLET, A. L.: The 5-hydroxytryptamine content of mouse brain and whole mice after treatment with some drugs affecting the central nervous system. Brit. J. Pharmacol. **15**, 140—146 (1960).

— The influence of chlorpromazine on the excretion of 5-hydroxyindoleacetic acid from mice. J. Physiol. (Lond.) **165**, 25—26 P (1963).

BEAVER, M. H., and B. S. WOSTMANN: Histamine and 5-hydroxytryptamine in the intestinal tract of germ-free animals, animals harbouring one microbial species and conventional animals. Brit. J. Pharmacol. **19**, 385—393 (1962).

BENDITT, E. P.: 5-Hydroxytryptamine and 5-hydroxytryptophan decarboxylase in rat mast cells. In: G. P. LEWIS (Ed.), 5-Hydroxytryptamine, p. 31—34. London: Pergamon Press 1957.
— S. BADER and K. B. LAM: Studies of the mechanisms of acute vascular reactions to injury. Arch. Path. **60**, 104—115 (1955a).
— J. HOLCENBERG, and D. LAGUNOFF: The role of serotonin (5-hydroxytryptamine) in mast cells. Ann. N.Y. Acad. Sci. **103** (3), 179—184 (1963).
— R. L. WONG, M. ARASE and E. ROEPER: 5-Hydroxytryptamine in mast cells. Proc. Soc. exp. Biol. (N.Y.) **90**, 303—304 (1955b).
BERTACCINI, G.: Osservazioni sul contenuto in 5-idrossitriptamina di vari tessuti del ratto durante lo sviluppo postnatale. Ric. Sci. **28**, 2261—2263 (1958).
— Effect of convulsant treatment on the 5-hydroxytryptamine content of brain and other tissues of the rat. J. Neurochem. **4**, 217—222 (1959).
— Tissue 5-hydroxytryptamine and urinary 5-hydroxyindoleacetic acid after partial or total removal of the gastro-intestinal tract in the rat. J. Physiol. (Lond.) **153**, 239—249 (1960).
— Discussion. In: S. S. KETY and J. ELKES (Eds.), Regional Neurochemistry, p. 305—306. London: Pergamon Press 1961.
—, e R. CHELI: Considerazioni sulla eliminazione urinaria di acido 5-idrossiindolilacetico nel bovino. Arch. Sci. biol. (Bologna) **47**, 336—338 (1964).
—, and S. CHIEPPA: Urinary excretion of 5-hydroxyindoleacetic acid after removal of the large intestine in man. Lancet **1960 I**, 881.
—, and V. ERSPAMER: The effect of the administration of water or isotonic NaCl solution on the urinary excretion of 5-hydroxyindoleacetic acid in the rat. J. Pharm. Pharmacol. **14**, 687—697 (1962).
—, and M. B. NOBILI: Effect of L-tryptophan on diuresis and 5-hydroxyindoleacetic acid excretion in the rat. Brit. J. Pharmacol. **17**, 519—525 (1961).
BETTENDORF, G., A. P. MOJE u. H.-J. SCHMERMUND: Der Einfluß der Strahlenbehandlung auf die 5-Hydroxy-Indol-Essigsäure-Ausscheidung. Strahlentherapie **117**, 370—376 (1962).
BHATT, K. G. S., H. R. K. ARORA, H. L. DHAR and R. K. SANYAL: Changes in serotonin content in the heart following acute myocardial infarction in the dog. Med. exp. **9**, 46—48 (1963).
BHATTACHARYA, B. K., and G. P. LEWIS: The release of 5-hydroxytryptamine by histamine liberators. Brit. J. Pharmacol. **11**, 202—208 (1956).
BHOOLA, K. D., J. D. CALLE and M. SCHACHTER: The identification of acetylcholine, 5-hydroxytryptamine and other substances in hornet venom. J. Physiol. (Lond.) **151**, 35—36P (1960).
— — — Identification of acetylcholine, 5-hydroxytryptamine, histamine, and a new kinin in hornet venom *(V. crabro)*. J. Physiol. (Lond.) **159**, 167—182 (1961).
BOGDANSKI, D. F., L. BONOMI and B. B. BRODIE: Occurrence of serotonin and catecholamines in brain and peripheral organs of various vertebrate classes. Life Sciences No 1, 80—84 (1963).
— A. PLETSCHER, B. B. BRODIE and S. UDENFRIEND: Identification and assay of serotonin in brain. J. Pharmacol. exp. Ther. **117**, 82—88 (1956).
—, and S. UDENFRIEND: Serotonin and monoamine oxidase in brain. J. Pharmacol. exp. Ther. **116**, 7—8 (1956).
— H. WEISSBACH and S. UDENFRIEND: The distribution of serotonin, 5-hydroxytryptophan decarboxylase, and monoamine oxidase in brain. J. Neurochem. **1**, 272—278 (1957).
BOGGS, D. E., R. ROSENBERG and H. A. WAISMAN: Effects of phenylalanine, phenylacetic acid, tyrosine and valine on brain and liver serotonin in rats. Proc. Soc. exp. Biol. (N.Y.) **114**, 356—358 (1963).
BONNYCASTLE, D. D., M. F. BONNYCASTLE and E. G. ANDERSON: The effect of a number of central depressant drugs upon brain 5-hydroxytryptamine levels in the rat. J. Pharmacol. exp. Ther. **135**, 17—20 (1962).
— N. J. GIARMAN and M. K. PAASONEN: Anticonvulsant compounds and 5-hydroxytryptamine in rat brain. Brit. J. Pharmacol. **12**, 228—231 (1957).
BORÉUS, L. O., and B. WESTERHOLM: 5-Hydroxytryptamine in the Schultz-Dale reaction. Acta physiol. scand. **56**, 17—25 (1962).
BORGERT, H., u. K. KEITEL: Über die vasokonstriktorischen Substanzen im Blutserum. Biochem. Z. **175**, 1—7 (1962).
BORN, G. V. R., and R. E. GILLSON: Studies on the uptake of 5-hydroxytryptamine by blood platelets. J. Physiol. (Lond.) **146**, 472—491 (1959).
BOWDEN, K., B. G. BROWN and J. E. BATTY: 5-Hydroxytryptamine: its occurrence in cowhage. Nature (Lond.) **174**, 925—926 (1954).

Bowers jr., M. B.: Stimulation and sensitization of the isolated Venus heart by cerebrospinal fluid. Brit. J. Pharmacol. **19**, 295—298 (1962).
Bracco, M., e P. C. Curti: Ricerche sulla natura del fattore vasocostrittore delle piastrine. Haematologica **37**, 721—736 (1953).
— — The vasoconstrictor factor of platelets. Experientia (Basel) **10**, 71—72 (1954).
— — e V. Giuliano: Identificazione della 5-OH-triptamina nei trombociti degli uccelli. Experientia (Basel) **12**, 31—33 (1956).
Brandt, K., H. v. Euler, H. Hellström u. N. Lofgren: Gramin und zwei Begleiter desselben in Laubblättern von Gerstensorten. Hoppe-Seylers Z. physiol. Chem. **235**, 37—42 (1935).
Bridges, J. M., M. Baldini, C. Fichera and W. Dameshek: Effect of antiplatelet antibodies on the *in vitro* uptake of 5-hydroxytryptamine by blood platelets. Nature (Lond.) **197**, 364—366 (1963).
Brocklehurst, W. E., J. H. Humphrey and W. L. M. Perry: Cutaneous antigen-antibody reactions in the rat. J. Physiol. (Lond.) **150**, 489—500 (1960).
Brodie, B. A., P. A. Shore and A. Pletscher: Serotonin-releasing activity limited to Rauwolfia alkaloids with tranquilizing action. Science **123**, 992—993 (1956).
Brodie, B. B., D. F. Bogdanski, and L. Bonomi: Formation, storage and metabolism of serotonin (5-hydroxytryptamine) and catecholamines in lower vertebrates. In: D. Richter Ed., Comparative Neurochemistry, pp. 367—377. Oxford: Pergamon Press 1964.
—, S. Spector and P. A. Shore: Interaction of monoamine oxidase inhibitors with physiological and biochemical mechanisms in brain. Ann. N.Y. Acad. Sci. **30** (3), 609—616 (1959).
Bruce, D. W.: Serotonin in pineapple. Nature (Lond.) **188**, 147 (1960).
— Carcinoid tumours and pineapples. J. Pharm. Pharmacol. **13**, 256 (1961).
Brune, G., and H. E. Himwich: Effects of reserpine on urinary tryptamine and indole-3-acetic acid excretion in mental deficiency, schizophrenia and phenylpyruvic oligophrenia. In: G. Tonini (Ed.), Techniques for the study of psychotropic drugs, p. 176—184. Modena: Soc. Tip. Modenese 1961.
Bülbring, E., and A. Crema: The release of 5-hydroxytryptamine in relation to pressure exerted on the intestinal mucosa. J. Physiol. (Lond.) **146**, 18—28 (1959a).
— — The action of 5-hydroxytryptamine, 5-hydroxytryptophan and reserpine on peristalsis in anaesthetized guinea-pigs. J. Physiol. (Lond.) **146**, 29—53 (1959b).
Bulard, C., and A. C. Leopold: 5-Hydroxytryptamine chez les plantes supérieures. C. R. Acad. Sci. (Paris) **247**, 1282—1284 (1958).
Cambridge, G. W., and J. A. Holgate: 5-HT in plasma. J. Physiol. (Lond.) **142**, 53—54P (1958).
Cardot, J.: Mise en évidence de la tryptamine dans les extraits nerveux du Mollusque *Helix pomatia*. C. R. Soc. Biol. (Paris) **157**, 853—854 (1963).
—, et J. Ripplinger: Recherches sur les amines indoliques cardio-actives présentes dans le tissue nerveux du mollusque *Helix pomatia*. J. Physiol. (Paris) **55**, 217—218 (1963).
— — et M. Lonchampt: Sur la non spécificité tissulaire des acides aminés basiques et des amines chez l'Escargot (*Helix pomatia* L.) C. R. Soc. Biol. (Paris) **156**, 1433—1435 (1962).
Carlini, E. A., and J. P. Green: The subcellular distribution of histamine, slow-reacting substance and 5-hydroxytryptamine in the brain of the rat. Brit. J. Pharmacol. **20**, 264—277 (1963).
Carlisle, D. B.: An indole-alkylamine regulating heart-beat in Crustacea. Biochem. J. **63**, 32—33P (1956).
— On the venom of the lesser weeverfish, Trachinus vipera. J. mar. biol. Ass. U. Kingd. **42**, 155 (1962).
— The neurohumoral control of heart rate in crustaceans. In: D. Richter Ed., Comparative Neurochemistry, pp. 323—328. Oxford: Pergamon Press 1964.
—, and F. Knowles: Endocrine control in Crustacea, p. 72. Cambridge: Cambridge University Press 1959.
Carlsson, A., T. Magnusson and E. Rosengren: 5-Hydroxytryptamine of the spinal cord normally and after transection. Experientia (Basel) **19**, 359 (1963).
Cass, R., and P. B. Marshall: Effect of adrenocortical hormones on tissue histamine and 5-hydroxytryptamine in the rat. Arch. int. Pharmacodyn. **136**, 311—332 (1962).
Cerhová, M., A. Šidlova and A. Zelený: The effect of skin inflammation on blood content of serotonin and histamine. Physiol. bohemoslov. **11**, 136—141 (1962).
Cerletti, A.: Über Vorkommen und Bedeutung der Indolstruktur in der Medizin und Biologie. Progr. Drug Res. **2**, 227—249 (1960).
Chieco Bianchi, L., L. Fiore Donati, N. Pennelli and G. Bertaccini: Mast cell reaction and 5-hydroxytryptamine content in the skin of syrian golden hamsters painted with 9:10-dimethyl-1:2-benzanthracene. Nature (Lond.) **199**, 293—294 (1963).

CLARK, W. G.: Amine content and biosynthesis in mastocytomas and Octopus salivary glands. Fed. Proc. **19**, 9 (1960).

COLHOUN, E. H.: Synthesis of 5-hydroxytryptamine in the American cockroach. Experientia (Basel) **19**, 9—10 (1963).

— Aspects of biologically active substances in insects with particular reference to the cockroach, *Periplaneta americana*. In: D. RICHTER Ed., Comparative Neurochemistry, pp. 333—339. Oxford: Pergamon Press 1964.

CORREALE, P.: The occurrence and distribution of 5-hydroxytryptamine (enteramine) in the central nervous system of vertebrates. J. Neurochem. **1**, 22—31 (1956).

COSTA, E., and M. H. APRISON: Distribution of intracarotidly injected serotonin in the brain. Amer. J. Physiol. **192**, 95—100 (1958).

COUPLAND, R. E., and I. D. HEATH: Chromaffin cells, mast cells and melanin. II. The chromaffin cells of the liver capsule and gut in ungulates. J. Endocr. **22**, 71—76 (1961).

—, and J. F. RILEY: Mast cells and 5-hydroxytryptamine in precancerous mouse skin. Nature (Lond.) **187**, 1128—1129 (1960).

CRAWFORD, N.: Plasma free serotonin (5-hydroxytryptamine). Clin. chim. Acta **8**, 39—45 (1963).

CROUT, J. R., and A. SJOERDSMA: The clinical and laboratory significance of serotonin and catechol amines in bananas. New Engl. J. Med. **261**, 23—26 (1959).

CULLEY, W. J., R. N. SAUNDERS, E. T. MERTZ and D. H. JOLLY: Plasma tryptophan and brain serotonin levels of rats fed a tryptophan deficient diet. Fed. Proc. **22**, 203 (1963); — Proc. Soc. exp. Biol. (N.Y.) **113**, 645—648 (1963).

DALGLIESH, C. E., C. C. TOH and T. S. WORK: Fractionation of the smooth muscle stimulants present in extracts of the gastrointestinal tract. Identification of 5-hydroxytryptamine and its distinction from substance P. J. Physiol. (Lond.) **120**, 298—310 (1953).

DANNENBOURG, W. N., and J. L. LIVERMAN: Conversion of tryptophan-2-C^{14} to indoleacetic acid by watermelon tissue slices. Plant Physiol. **32**, 263—269 (1957).

DAVEY, K. G.: A pharmacologically active agent in the reproductive system of insects. Canad. J. Zool. **38**, 39—45 (1960).

DAVIES, D. F., K. M. WOLFE and H. M. PERRY: Studies on primary amines. II. Their natural occurrence in urine of normotensive and hypertensive patients. J. Lab. clin. Med. **43**, 620—632 (1954).

DAVIS, R. B., W. R. MEEKER jr. and W. L. BAILEY: Serotonin release by bacterial endotoxin. Proc. Soc. exp. Biol. (N.Y.) **108**, 774—776 (1961).

DAY, S., and J. P. GREEN: Levels of heparin, histamine and 5-hydroxytryptamine in neoplastic mast cells in vivo. Fed. Proc. **18**, 381 (1959).

DEGKWITZ, R., R. FROWEIN, E. KIRBERGER, C. KULENKAMPFF u. U. MOHS: Über Normalwerte der stündlichen 5-HIES-Ausscheidung im Urin beim Menschen und die Messungen störender Faktoren. Klin. Wschr. **40**, 285—289 (1962).

— O. SCHULENBURG u. H. SIEROSLAWSKI: Die 5-HIES-Ausscheidung im Urin beim Schlafen und Wachen. Klin. Wschr. **42**, 102—103 (1964).

DE IRALDI, A. P., and E. DE ROBERTIS: Action of reserpine on the submicroscopic morphology of the pineal gland. Experientia (Basel) **17**, 122—124 (1961).

— L. M. ZIEHER and E. DE ROBERTIS: The 5-hydroxytryptamine content and synthesis of normal and denervated pineal gland. Life Sci. **9**, 691—696 (1963).

DELAY, J., P. PICHON et T. LAMPERIÈRE: La psilocybine (Historique-Pharmacophysiologie-Clinique). Presse méd. **67**, 1731—1733 (1959).

DESPOPOULOS, A.: Renal metabolism of 5-hydroxyindole acetic acid. Fed. Proc. **15**, 48 (1956); — Amer. J. Physiol. **189**, 548—550 (1957).

DEULEFEU, V., and B. BERINZAGHI: Picrolonates of bufotenine, bufotenidine and dehydrobufotenine. J. Amer. chem. Soc. **68**, 1665—1666 (1946).

DONALDSON jr., R. M.: Excretion of tryptamine and indole-3-acetic acid in urine of rats with intestinal diverticula. Amer. J. Physiol. **202**, 289—292 (1962).

— H. A. DOLCINI and S. J. GRAY: Urinary excretion of indolic compounds in rats with intestinal pouches. Amer. J. Physiol. **200**, 794—796 (1961).

— S. MALKIEL and S. J. GRAY: Serotonin studies on mouse tissues. Proc. Soc. exper. Biol. (N.Y.) **103**, 261—263 (1960).

DUBNICK, B., G. A. LEESON, M. CHESSIN and CH. C. SCOTT: Accumulation of serotonin in the brain of reserpine-treated mice after inhibition of monoamine oxidase: effect of body temperature. Arch. int. Pharmacodyn., **126**, 194—202 (1960).

— — and G. E. PHILLIPS: An effect of monoamine-oxidase inhibitors on brain serotonin of mice in addition to that resulting from inhibition of monoamine oxidase. J. Neurochem. **9**, 299—306 (1962).

EBER, O., u. F. LEMBECK: Hydroxytryptamingehalt des Rattendarmes bei verschiedenem Tryptophangehalt der Nahrung. Pflügers Arch. ges. Physiol. **265**, 563—566 (1958).

EDELSTEIN, E. L., Y. PFEIFER, J. E. STEINER and F. G. SULMAN: Excretion of urinary 5-HIAA in dog pellagra. Proc. Soc. exp. Biol. (N.Y.) **110**, 13—16 (1962).

EHRINGER, H., O. HORNYKIEWICZ u. K. LECHNER: Die Wirkung von Methylenblau auf die Monoaminoxydase und den Katecholamin- und 5-Hydroxytryptaminstoffwechsel des Gehirnes. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **241**, 568—582 (1961).

ELIASSON, R.: Critical evaluation of the occurrence of 5-hydroxytryptamine in human semen. J. Urol. **86**, 676—678 (1961).

ENDE, N., and E. I. CHERNISS: Mast cells, histamine and serotonin. Amer. J. clin. Path. **30**, 35—36 (1958).

ENERBACK, L.: Serotonin in human mast cells. Nature (Lond.) **197**, 611 (1963).

ERSHOFF, B. H., and E. M. GAL: Effects of radiation on tissue serotonin levels in the rat. Proc. Soc. exp. Biol. (N.Y.) **108**, 160—162 (1961).

— R. HELLMERS and A. F. WELLS: Effects of a radioprotective agent on tissue serotonin levels in the X-irradiated rat. Proc. Soc. exp. Biol. (N.Y.) **110**, 536—538 (1962).

ERSPAMER, V.: Pharmakologische Studien über Enteramin. I. Über die Wirkung von Acetonextrakten der Kaninchenmagenschleimhaut auf den Blutdruck und auf isolierte überlebende Organe. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **196**, 343—365 (1940a).

— Pharmakologische Studien über Enteramin. III. Über das Vorhandensein eines enteraminähnlichen Stoffes in Milzextrakten. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **196**, 391—407 (1940b).

— Presenza di enteramina o di una sostanza enteraminosimile negli estratti gastrointestinali e splenici dei pesci e negli estratti gastroenterici delle ascidie. Experientia (Basel) **2**, 369—371 (1946).

— Ricerche chimiche e farmacologiche sugli estratti di ghiandola ipobranchiale di Murex. IV. Presenza negli estratti di enteramina o di una sostanza enteraminosimile. Arch. int. Pharmacodyn. **76**, 308—326 (1948a).

— Active substances in the posterior salivary glands of octopoda. I. Enteramine-like substance. Acta pharmacol. (Kbh.) **4**, 213—223 (1948b).

— Über den 5-Hydroxytryptamin-(Enteramin-)Gehalt des Magen-Darmtraktes bei den Wirbeltieren. Naturwissenschaften **40**, 318—319 (1953).

— Il sistema cellulare enterocromaffine e l'enteramina (5-idrossitriptamina). Rend. sci. Farmitalia **1**, 1—193 (1954a).

— Pharmacology of indolealkylamines. Pharmacol. Rev. **6**, 425—487 (1954b).

— Quantitative estimation of 5-hydroxytryptamine in gastrointestinal tract, spleen and blood of vertebrates. Ciba Foundation, Symposium on Hypertension, p. 78—84. London: Churchill 1954 c.

— Isolation of bufoviridine from the skin of *Bufo viridis* and its identification as dihydrobufothionine. Biochem. Pharmacol. **2**, 270—275 (1959a).

— Isolation of leptodactyline (*m*-hydroxyphenylethyltrimethylammonium) from extracts of *Leptodactylus* skin. Arch. Biochem. Biophys. **82**, 431—438 (1959b).

—, and B. ASERO: Isolation of enteramine from extracts of posterior salivary glands of *Octopus vulgaris* and *Discoglossus pictus* skin. J. biol. Chem. **200**, 311—318 (1953).

—, G. BERTACCINI and J. M. CEI: Occurrence of an eleidosin-like polypeptide (physalaemin) in skin extracts of *Physalaemus fuscumaculatus*. Experientia (Basel) **18**, 562—563 (1962a).

— — — Occurrence of bradykinin-like substances in the amphibian skin. Experientia (Basel) **18**, 563—564 (1962b).

—, and G. BORETTI: Identification and characterization, by paper chromatography, of enteramine, octopamine, tyramine, histamine and allied substances in extracts of posterior salivary glands of octopoda and in other tissue extracts of vertebrates and invertebrates. Arch. int. Pharmacodyn. **88**, 296—332 (1951).

—, u. R. FAUSTINI: Über den 5-Hydroxytryptamin-(Enteramin-, Serotonin-)Gehalt des Serums und des Milzgewebes bei Wirbeltieren sowie der Hämolymphe bei Octopoden. Naturwissenschaften **40**, 317—318 (1953).

—, and A. TESTINI: Observations on the release and turnover rate of 5-hydroxytryptamine in the gastrointestinal tract. J. Pharm. Pharmacol. **11**, 618—623 (1959).

—, and M. VIALLI: Presence of enteramine in the skin of amphibia. Nature (Lond.) **167**, 1033 (1951).

— — Ricerche preliminari sulle indolalchilamine e fenilalchilamine degli estratti di pelle di anfibio. Ric. sci. **22**, 1420—1425 (1952).

— T. VITALI, M. L. ROSEGHINI and J. M. CEI: Occurrence of new imidazolealkylamines (spinaceamine and 6-methylspinaceamine) in skin extracts of *Leptodactylus pentadactylus labyrinthicus*. Experientia (Basel) **19**, 346—347 (1963).

EULER, H. v., H. ERDTMAN u. H. HELLSTRÖM: Über das Alkaloid Gramin. Ber. dtsch. chem. Ges. **69**, 743—747 (1936).

FALCK, B.: Observations on the possibilities of the cellular localization of monoamines by a fluorescence method. Acta physiol. scand. **56**, Suppl. 197, 1—25 (1962).

FAUSTINI, R.: The enteric distribution of 5-hydroxytryptamine (enteramine, serotonin) in some large domestic mammals and the appearance of 5-hydroxytryptamine and the enterochromaffin cell system in the embryonic calf. Amer. J. vet. Res. **16**, 397—400 (1955).

FELDBERG, W., and C. C. TOH: Distribution of 5-hydroxytryptamine (serotonin, enteramine) in the wall of the digestive tract. J. Physiol. (Lond.) **119**, 352—362 (1953).

FELDMAN, S., G. IZAK and D. NELKEN: Blood coagulation studies and serotonin determinations in serum and cerebrospinal fluid in multiple sclerosis. Acta psychiat. scand. **32**, 37—49 (1957).

FELDSTEIN, A., H. HOAGLAND and H. FREEMAN: Blood and urinary serotonin and 5-hydroxyindole acetic acid levels in schizophrenic patients and normal subjects. J. nerv. ment. Dis. **129**, 62—68 (1959).

FERRARI, V., E. GINOULHIAC e L. T. TENCONI: Osservazioni sperimentali sui derivati 5-idrossiindolici nella carenza da piridossina. Boll. Soc. ital. Biol. sper. **33**, 1418—1421 (1957).

FEYRTER, F.: Über die peripheren endokrinen (parakrinen) Drüsen des Menschen. Wien u. Düsseldorf: Maudrich 1953.

FIORE-DONATI, L., G. DE BENEDICTIS, L. CHIECO-BIANCHI and G. BERTACCINI: Development of mast cell reaction during chemical skin carcinogenesis of mouse. Nature (Lond.) **193**, 287—288 (1962).

FISCHER, E., F. A. VAZQUES, T. A. FERNÁNDEZ and L. LISKOWSKI: Bufotenin in human urine. Lancet **1961 I**, 890—891.

FISH, M. S., and E. C. HORNING: Studies on hallucinogenetic snuffs. J. nerv. ment. Dis. **124**, 33—37 (1956).

—, N. M. JOHNSON and E. C. HORNING: Piptadenia alkaloids. Indole bases of P. peregrina (L.) Benth. and related species. J. Amer. chem. Soc. **77**, 5892—5895 (1955).

FOY, J. M., and J. R. PARRATT: A note on the presence of noradrenaline and 5-hydroxytryptamine in plantain *(Nusa sapientum* var., *paradisiaca)*. J. Pharm. Pharmacol. **12**, 360—364 (1960).

— — 5-Hydroxytryptamine in pinneaples. J. Pharm. Pharmacol. **13**, 382—383 (1961).

— — Urinary excretion of 5-hydroxyindoleacetic acid in West Africans. Lancet **1962 I**, 942—943.

FRANKLAND, M., F. KENDRICKS and M. GREIPEL: Serotonin concentration in the spleen. Amer. J. dig. Dis. **7**, 347—355 (1962).

FREEDMAN, D. X.: Effects of LSD-25 on brain serotonin. J. Pharmacol. exp. Ther. **134**, 160—166 (1961).

FREUND, H.: Über die pharmakologischen Wirkungen des defibrinierten Blutes. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **86**, 266—280 (1920).

FRYDMAN, B., and V. DEULOFEU: Isolation of 5-hydroxytryptamine from the skin of the toad Bufo arenarum Hensel. Experientia (Basel) **17**, 545—546 (1961).

FURANO, A. V., and J. P. GREEN: The uptake of biogenic amines by mast cells of the rat. J. Physiol. (Lond.) **170**, 263—271 (1964).

FURTH, J., P. HAGEN and E. I. HIRSCH: Transplantable mastocytoma in the mouse containing histamine, heparin and 5-hydroxytryptamine. Proc. Soc. exp. Biol. (N.Y.) **95**, 824—828 (1957).

GADDUM, J. H., and N. J. GIARMAN: Preliminary studies on the biosynthesis of 5-hydroxytryptamine. Brit. J. Pharmacol. **11**, 88—92 (1956).

GAL, E. M., and P. A. DREWES: Levels of serotonin during convulsion and the effect of reserpine. Nature (Lond.) **189**, 234 (1961a).

— — Studies on the metabolism of 5-hydroxytryptamine (serotonin). I. Effect of starvation and thiamine deficiency. Proc. Soc. exp. Biol. (N.Y.) **106**, 295—297 (1961b).

— — Studies on the metabolism of 5-hydroxytryptamine (serotonin). II. Effect of tryptophan deficiency in rats. Proc. Soc. exp. Biol. (N.Y.) **110**, 368—371 (1962).

— — and C. A. BARRACLOUGH: Effect of reserpine and the metabolism of serotonin in tryptophan deficient rats. Biochem. Pharmacol. **8**, 32 (1961).

GARDNER, L. I., and A. A. TYCE: Histamine and related compounds in urticaria pigmentosa: analyses of tissues having mast-cell infiltration. Pediatrics **21**, 805—812 (1958).

GARVEN, J. D.: The estimation of 5-hydroxytryptamine in the presence of adrenaline. Brit. J. Pharmacol. **11**, 66—70 (1956).

GEIGER, R. S., N. CANTOR and F. A. GIBBS: Localization of monoamines and action of hallucinogens on them in adult mammalian brain cells in long term culture. Fed. Proc. **23**, 351 (1964).

GERSCH, M., F. FISCHER, H. UNGER u. W. KABITZER: Vorkommen von Serotonin im Nervensystem von *Periplaneta americana* L. *(Insecta)*. Z. Naturforsch. B **16**, 351—352 (1961).

GERTNER, S. B., M. K. PAASONEN and N. J. GIARMAN: Studies concerning the presence of 5-hydroxytryptamine (serotonin) in the perfusate from the superior cervical ganglion. J. Pharmacol. exp. Ther. **127**, 268—275 (1959).

GIARMAN, N. J., and M. DAY: Presence of biogenic amines in the bovine pineal body. Biochem. Pharmacol. **1**, 235 (1958).

— — and G. PEPEU: Presence of neuro-humors in bovine pineal glands. Fed. Proc. **18**, 394 (1959).

—, and D. X. FREEDMAN: Serotonin content of the pineal glands of man and monkeys. Nature (Lond.) **186**, 480—481 (1960).

—, and S. L. M. SCHANBERG: The intracellular distribution of 5-hydroxytryptamine (HT, serotonin) in the rat's brain. Biochem. Pharmacol. **1**, 301—306 (1959).

GIRARD, J.-P.: Le rôle de l'adénosine triphosphorique (ATP) dans la fixation intraplaquettaire de la sérotonine. Schweiz. med. Wschr. **93**, 1456—1459 (1963).

GLUCKMAN, M. I.: Cerebral free and bound serotonin (5HT) after iproniazid (IIH) and reserpine (R). Fed. Proc. **19**, 264 (1960).

GÖRÖG, P., and L. SZPORNY: The depleting effect of vincamin on the cerebral serotonin level. Biochem. Pharmacol. **11**, 165—166 (1962).

GORDON, P.: Changes in blood serotonin during exposure to cold. Nature (Lond.) **191**, 183—184 (1961).

GOSSELIN, R. E., K. E. MOORE and A. S. MILTON: Physiological control of molluscan gill cilia by 5-hydroxytryptamine. J. gen. Physiol. **46**, 277—296 (1962).

GOTTFRIES, C. G., and T. MAGNUSSON: Excretion of tryptamine in man during treatment with MAO inhibitors. Acta psychiat. scand. **38**, 223—226 (1962).

GREEN, H., S. M. GREENBERG, R. W. ERICKSON, J. L. SAWYER and TH. ELLISON: Effect of dietary phenylalanine and tryptophan upon rat brain amine levels. J. Pharmacol. exp. Ther. **136**, 174—178 (1962a).

—, and J. L. SAWYER: Intracellular distribution of serotonin in rat brain. I. Effect of reserpine and the monoamine oxidase inhibitors, tranylcypromine and iproniazid. Arch. int. Pharmacodyn. **135**, 426—441 (1962).

— — R. W. ERICKSON and L. COOK: Effect of repeated oral administration of monoamine oxidase inhibitors on rat brain amines. Proc. Soc. exp. Biol. (N.Y.) **109**, 347—349 (1962b).

GREEN, J. P., and S. M. DAY: Heparin, 5-hydroxytryptamine, and histamine in neoplastic mast cells. Biochem. Pharmacol. **3**, 190—205 (1960b).

—, M. ROBERTS and S. M. DAY: Fractionation of heparin from a mast cell tumour of the mouse. Fed. Proc. **19**, 133 (1960a).

GRETTE, K.: Determination of 5-hydroxytryptamine with the isolated, perfused pig ear. Acta pharmacol. (Kbh.) **13**, 177—183 (1957).

GURSEY, D., and R. E. OLSON: Depression of serotonin and norepinephrine levels in brain stem of rabbit by ethanol. Proc. Soc. exp. Biol. (N.Y.) **104**, 280—281 (1960).

—, J. W. VESTER and R. E. OLSON: Effect of ethanol administration upon serotonin and norepinephrine levels in rabbit brain. J. clin. Invest. **38**, 1008—1009 (1959).

HADDOX jr., CH. H., and M. S. SASLAW: Urinary 5-methoxytryptamine in patients with rheumatic fever. J. clin. Invest. **42**, 435—441 (1963).

HAGGENDAL, J., and M. LINDQUIST: Ineffectiveness of ethanol on noradrenaline, dopamine or 5-hydroxytryptamine levels in brain. Acta pharmacol. (Kbh.) **18**, 278—280 (1961).

HAGMÜLLER, K., L. HAIDER u. H. HELLAUER: Enterochromaffine Zellen, Serotonin und Zink in der Magen-Darm-Wand des Meerschweinchens und der Maus vor und nach chronischer Zufuhr von Aethanol. Wien. klin. Wschr. **73**, 834—836 (1961).

HARDING-GAUDIN, F.: Excrétion urinaire d'acide 5-hydroxyindolylacétique chez le rat albinos carencé ou non en riboflavine. Acta vitamin. (Milano) **15**, 193—196 (1961).

HARTMAN, W. J., W. G. CLARK, S. D. CYR, A. L. JORDAN and R. A. LEIBHOLD: Pharmacologically active amines and their biogenesis in the octopus. Ann. N.Y. Acad. Sci. **90** (3), 637—666 (1960).

HARVEY, J. A., A. HELLER and R. Y. MOORE: The effect of unilateral and bilateral medial forebrain bundle lesions on brain serotonin. J. Pharmacol. exp. Ther. **140**, 103—110 (1963).

HAVERBACK, B. J., and J. D. DAVIDSON: Serotonin and the gastrointestinal tract. Gastroenterology **35**, 570—578 (1958).

— F. T. DUTSCHER, P. A. SHORE, E. G. TOMICH, L. L. TERRY and B. B. BRODIE: Serotonin changes in platelets and brain induced by small daily doses of reserpine. Lack of effect of depletion of platelet serotonin in hemostatic mechanisms. New Engl. J. Med. **256**, 343—345 (1957).

HAWKER, R. W., V. S. ROBERTS and C. F. WALMSLEY: Some properties of an oxytocic substance in extracts of semen. Endocrinology **67**, 187—193 (1960).

HESS, S. M., and W. DOEPFNER: Behavioral effects and brain amine content in rats. Arch. int. Pharmacodyn. **134**, 89—99 (1961).
— B. G. REDFIELD and S. UDENFRIEND: Tryptamine in animal tissues following administration of iproniazid. Fed. Proc. **18**, 402 (1959a).
— — — The effect of monoamine oxidase inhibitors and tryptophan on the tryptamine content of animal tissues and urine. J. Pharmacol. exp. Ther. **127**, 178—181 (1959b).
—, and S. UDENFRIEND: A fluorometric procedure for the measurement of tryptamine in tissues. J. Pharmacol. exp. Ther. **127**, 175—177 (1959).
HIROSE, K.: Relation between the platelet count of human blood and its vasoconstrictor action after clotting. Arch. int. Med. **21**, 604—612 (1918).
HOCHSTEIN, F. A., and A. M. PARADIES: Alkaloids of Banisteria caapi and Prestonia amazonicum. J. Amer. chem. Soc. **79**, 5735—5736 (1957).
HOFMANN, A., A. FREY, H. OTT, TH. PETRZILKA u. F. TROXLER: Konstitutionsaufklärung und Synthese von Psilocybin. Experientia (Basel) **14**, 397—399 (1958).
— R. HEIM et H. TSCHERTER: Présence de la psilocybine dans une espèce européenne d'Agaric, le *Psilocybe semilanceata* Fr. C. R. Acad. Sci. (Paris) **257**, 10—12 (1963).
—, and F. TROXLER: Identifizierung von Psilocin. Experientia (Basel) **15**, 101—102 (1959).
HSIA, D. Y.-Y., K. NISHIMURA and Y. BRENCHLEY: Mechanisms for the decrease of brain serotonin. Nature (Lond.) **200**, 578 (1963).
HUBER, W. G., and R. P. LINK: Relationship of serotonin and reserpine in the chicken. Proc. Soc. exp. Biol. (N.Y.) **109**, 118—120 (1962).
HUMPHREY, J. H., and R. JAQUES: The histamine and serotonin content of the platelets and polymorphonuclear leucocytes of various species. J. Physiol. (Lond.) **124**, 305—310 (1954b).
—, and C. C. TOH: Absorption of serotonin (5-hydroxytryptamine) and histamine by dog platelets. J. Physiol. (Lond.) **124**, 300—304 (1954a).
IACHELLO, R., E. RIVA SANSEVERINO e A. URBANO: Sulla presenza di 5-idrossitriptamina in estratti di ghiandola sottomascellare di cane. Boll. Soc. ital. Biol. sper. **38**, 516—518 (1962).
INOUYE, A., K. KATAOKA and J. SHINAGAWA: 5-Hydroxytryptamine in the subcellular particles of rabbit brain. Nature (Lond.) **194**, 286—287 (1962).
JACKSON, H. R., S. J. WILSON and H. E. HEATH: 5-Hydroxytryptamine-C^{14} platelet survival studies. J. Lab. clin. Med. **62**, 887 (1963).
JANEWAY, T. C., H. B. RICHARDSON and E. A. PARK: Experiments on the vasoconstrictor action of blood serum. Arch. intern. Med. **21**, 565—603 (1918).
JAQUES, R., and M. SCHACHTER: The presence of histamine, 5-hydroxytryptamine and a potent slow contracting substance in wasp venom. Brit. J. Pharmacol. **9**, 53—58 (1954).
JENSEN, H.: Chemical studies on toad poisons. *Bufo arenarum*, *Bufo regularis* and *Xenopus laevis*. J. Amer. chem. Soc. **57**, 1765—1768 (1935).
JENSEN, K.: Paper chromatography determination of indoles in human cerebrospinal fluid. Acta neurol. scand. **38**, 278—284 (1962).
JOHANSSON, S.-A.: 5-Hydroxytryptamine in burns. Acta physiol. scand. **48**, 126—132 (1960).
JOHNSEN jr., H. A., R. E. SMITH and W. SIMON: Diurnal variations in the excretion of urinary 5-hydroxyindoles. Clin. Res. **6**, 268—269 (1958).
JOYCE, D.: Changes in the 5-hydroxytryptamine content of rat, rabbit and human brain after death. Brit. J. Pharmacol. **18**, 370—380 (1962).
— 5-Hydroxytryptamine content of glioma. Experientia (Basel) **19**, 187—188 (1963).
JULLIEN, A., J. CARDOT and J. RIPPLINGER: Observations sur les substances cardioactives d'origine nerveuse chez les Crustacés Décapodes et chez les Mollusques Pulmonés. J. Physiol. (Paris) **53**, 381—382 (1961).
KÄRKI, N. T., R. KUNTZMAN and B. B. BRODIE: Norepinephrine and serotonin brain levels at various stages of ontogenetic development. Fed. Proc. **19**, 282 (1960b).
— — — Storage, synthesis, and metabolism of monoamines in the developing brain. J. Neurochem. **9**, 53—58 (1962).
—, and M. K. PAASONEN: Presence of 5-hydroxytryptamine after raunescine in blood plasma in vivo. Nature (Lond.) **185**, 109 (1960).
— — and P. PELTOLA: Factors influencing the release of 5-hydroxytryptamine from the rabbit intestine into the venous blood. Ann. Med. exp. Fenn. **38**, 231—236 (1960a).
KAKIMOTO, Y., and M. D. ARMSTRONG: On the identification of octopamine in mammals. J. biol. Chem. **237**, 422—427 (1962).
KARZEL, K.: Einfluß des Mastzellentumors P-815 der Maus auf den 5-Hydroxytryptamin-Gehalt ihrer Organe. Med. exp. **10**, 115—118 (1964).
KATAOKA, K.: Subcellular distribution of 5-hydroxytryptamine in the rabbit brain. Jap. J. Physiol. **12**, 623—638 (1962).
KATSH, S.: Serotonin and histamine in human ejaculate. J. Urol. **81**, 570—572 (1959).

KELLER, R.: Histamin und 5-Hydroxytryptamin in den Gewebemastzellen der Albinoratte. Helv. physiol. Acta **15**, 371—375 (1957).
KERKUT, G. A., and G. A. COTTRELL: Acetylcholine and 5-hydroxytryptamine in the snail brain. Comp. Biochem. Physiol. **8**, 53—63 (1963).
—, and M. A. PRICE: 6-HT in crab heart. Life Sciences No 2, 129—130 (1963).
— — Chromatographic separation of cardioaccelerators (6 HT and a mucopeptide) from *Carcinus* heart. Comp. Biochem. Physiol. **11**, 45—52 (1964).
KIND, L. S., A. BURKHALTER and R. SHERINS: Increased lung serotonin and pulmonary edema in mice injected with antiserum to EHRLICH'S ascites tumor. Proc. Soc. exp. Biol. (N. Y.) **108**, 735—737 (1961).
KINDWALL, E. P., L. O. BORÉUS and B. WESTERHOLM: Failure to show change in rat tissue histamin and serotonin after rapid decompression. Amer. J. Physiol. **203**, 389—390 (1962).
KIRBERGER, E., u. L. BRAUN: Über das Vorkommen von 5-Hydroxytryptamin in der Walnuß (Juglans regia). Biochim. biophys. Acta (Amst.) **49**, 391—393 (1961).
KIRKWOOD, S., and L. MARION: The biogenesis of alkaloids. I. The isolation of N-methyltryptamine from barley. J. Amer. chem. Soc. **57**, 1765—1768 (1950).
KISS, G., u. H. MICHL: Über das Giftsekret der Gelbbauchunke, *Bombina variegata* L. Toxicon **1**, 33—39 (1962).
KIVALO, E., U. K. RINNE and H. KARINKANTA: The effect of imipramine on the 5-hydroxytryptamine content and monoamine oxidase activity of the rat brain and on the excretion of 5-hydroxyindole acetic acid. J. Neurochem. **8**, 105—108 (1961).
KLAMBT, H.-D.: Die 2-Hydroxy-indol-3-essigsäure, ein pflanzliches Indolderivat. Naturwissenschaften **46**, 649 (1959).
KLEEBERG, J., J. BOXER and E. J. STEINER: Studies on almonds. III. The serotonin content of dried sweet almonds. Arch. int. Pharmacodyn. **144**, 432—436 (1963).
KOCH, G., u. G. ENGELHARDT: Über das argyrophile Helle-Zellen-Organ in der Harnröhrenschleimhaut des Säugetieres. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **236**, 463—473 (1959).
KOPIN, I. J.: Tryptophan loading and excretion of 5-hydroxyindoleacetic acid in normal and schizophrenic subjects. Science **129**, 835—836 (1959).
KOREN, Z., B. ECKSTEIN, A. BRZEZINSKI and F. G. SULMAN: Adrenaline, noradrenaline and serotonin estimations in urine and amniotic fluid during delivery. J. Obstet. Gynaec. Brit. Cwlth **68**, 438—440 (1961).
KUNTZMAN, R., P. A. SHORE, D. BOGDANSKI and B. B. BRODIE: Microanalytical procedures for fluorometric assay of brain DOPA-5-HTP decarboxylase, norepinephrine and serotonin, and a detailed mapping of decarboxylase activity in brain. J. Neurochem. **6**, 226—232 (1961).
KURIAKI, K., et T. INOUE: Teneur en 5-hydroxytryptamine du placenta et des urines gravides et post-partum. C. R. Soc. Biol. (Paris) **150**, 1835—1837 (1956).
LEBLANC, J.: Secretion and activity of histamine and serotonin during cold adaptation. Amer. J. Physiol. **204**, 520—522 (1963).
LEGLER, G., u. R. TSCHESCHE: Isolierung von N-Methyltryptamin, 5-Methoxy-N-methyltryptamin und 5-Methoxy-N,N-dimethyltryptamin aus der Rinde von Piptadenia peregrina Benth. Naturwissenschaften **50**, 94—95 (1963).
LERNER, A. B., and J. D. CASE: Melatonin. Fed. Proc. **19**, 590—592 (1960).
— — K. BIEMANN, R. V. HEINZELMAN, J. SZMUSZKOVICZ, W. C. ANTHONY and A. KRIVIS: Isolation of 5-methoxyindole-3-acetic acid from bovine pineal glands. J. Amer. chem. Soc. **81**, 5264 (1959a).
— — W. MORI and M. R. WRIGHT: Melatonin in peripheral nerves. Nature (Lond.) **183**, 1821 (1959b).
— — and Y. TAKAHASHI: Isolation of melatonin and 5-methoxyindole-3-acetic acid from bovine pineal glands. J. biol. Chem. **235**, 1992—1997 (1960).
LEROY, J. G.: 5-Hydroxytryptamine levels in brain of mice pretreated with α-methyl-dopa. Arch. int. Pharmacodyn. **134**, 492—496 (1961).
LEVENE, R. Z.: Mast cells and amines in normal ocular tissues. Invest Ophthal. **1**, 531—543 (1962).
LEWIS, G. P.: 5-Hydroxytryptamine in the mast cells of the rat. In: G. P. LEWIS, 5-Hydroxytryptamine, p. 26—31. London: Pergamon Press 1957.
— 5-Hydroxytryptamine. J. Pharm. Pharmacol. **10**, 529—540 (1958).
LONG, R. F.: Inhibition of 5-hydroxytryptamine uptake by platelets *in vitro* and *in vivo*. Biochem. J. **82**, 4—5 P (1962).
MAAS, J. W.: Neurochemical differences between two strains of mice. Nature (Lond.) **197**, 255—257 (1963).

MAASS, A. R., and M. J. NIMMO: A new inhibitor of serotonin metabolism. Nature (Lond.) **184**, 547—548 (1959).
MACFARLANE, P. S., C. E. DALGLIESH, R. W. DUTTON, B. LENNOX, L. M. NYHUS and A. N. SMITH: Endocrine aspects of argentaffinoma, with special reference to the use of urinary 5-hydroxyindoleacetic acid estimation in diagnosis. Scot. med. J. **1**, 148—155 (1956).
MÄRKI, F., A. V. ROBERTSON and B. WITKOP: Dehydrobufotenine, a novel type of tryciclic serotonin metabolite from *Bufo marinus*. J. Amer. chem. Soc. **83**, 3341—3342 (1961).
MAGUS, R. D., F. W. KRAUSE and B. E. RIEDEL: Release of thyroidal serotonin by reserpine, methyldopa and guanethidine. Biochem. Pharmacol. **13**, 115—117 (1964).
MANN, T.: Serotonin (5-hydroxytryptamine) in the male reproductive tract of the spiny dogfish. Nature (Lond.) **188**, 941—942 (1960).
— 5-Hydroxytryptamine in the spermatophoric sac of Octopus. Nature (Lond.) **199**, 1066—1067 (1963).
— R. F. SEAMARK and D. F. SHARMAN: On the question of the occurrence and metabolism of 5-hydroxytryptamine and related indole compounds in mammalian semen. Brit. J. Pharmacol. **17**, 208—217 (1961).
MANSOUR, T. E., A. D. LAGO and J. L. HAWKINS: Occurrence and possible role of serotonin in *Fasciola hepatica*. Fed. Proc. **16**, 319 (1957).
MARMO, E.: Psilocibina e psilocina: principi attivi dei funghi allucinogeni messicani. Clin. ter. **18**, 464—490 (1960).
MARSHALL, P. B.: Catechols and tryptamines in the "makote" banana (Musa paradisiaca). J. Pharm. Pharmacol. **11**, 639 (1959).
MATHIAS, A. P., D. M. ROSS and M. SCHACHTER: Identification and distribution of 5-hydroxytryptamine in a sea anemone. Nature (Lond.) **180**, 658—659 (1957).
— — — Distribution of histamine, 5-hydroxytryptamine, tetramethylammonium, and other substances in coelenterates possessing nematocysts. J. Physiol. (Lond.) **142**, 56—57P (1958).
— — — The distribution of 5-hydroxytryptamine, tetramethylammonium, homarine, and other substances in sea anemones. J. Physiol. (Lond.) **151**, 296—311 (1960).
MAYNARD, D. M., and J. H. WELSH: Neurohormones of the pericardial organs of brachyuran crustacea. J. Physiol. (Lond.) **149**, 215—227 (1959).
MAYNERT, E. W., G. I. KLINGMAN and H. K. KAJI: Tolerance to morphine. II. Lack of effects on brain 5-hydroxytryptamine and γ-aminobutyric acid. J. Pharmacol. exp. Ther. **135**, 296—299 (1962).
—, R. LEVI and A. J. D. DE LORENZO: The presence of norepinephrine and 5-hydroxytryptamine in vesicles from disrupted nerve-ending particles. J. Pharmacol. exp. Ther. **144**, 385—392 (1964).
— — and K. KURIYAMA: Vesicles containing norepinephrine (NE) and 5-hydroxytryptamine (5-HT) from disrupted nerve-ending particles. Fed. Proc. **23**, 350 (1964).
MEIER, H.: Serotonin (5-hydroxytryptamine) content of canine mastocytoma. Proc. Soc. exp. Biol. (N.Y.) **100**, 815—817 (1959).
MELCHING, H. J., H. ERNST u. H. RÖSSLER: Untersuchungen über einen biologischen Strahlenschutz. XXXVI. Zum Stoffwechsel des 5-Hydroxytryptamins bei der Ganzkörperbestrahlung weißer Mäuse und Ratten. Strahlentherapie **113**, 394—401 (1960).
MELMON, K., and A. SJOERDSMA: Serotonin in platelets. Lancet **1963 II**, 316—318.
MENG, K.: 5-Hydyroxytrptamin und Acetylcholin als Wirkungsantagonisten beim Helix-Herzen. Naturwissenschaften **45**, 470 (1958).
MENGEL, CH. E., and M. G. KELLY: Biochemical and morphologic changes in a mast-cell neoplasm during treatment with cyclophosphamide. Cancer Res. **21**, 1545—1550 (1961).
MICHAELSON, I. A., and V. P. WHITTAKER: The distribution of 5-hydroxytryptamine in brain fractions. Biochem. Pharmacol. **11**, 505—506 (1962).
— — The subcellular localization of 5-hydroxytryptamine in guinea-pig brain. Biochem. Pharmacol. **12**, 203—211 (1963).
MILNE, M. D., M. A. CRAWFORD, C. B. GIRÃO and L. LOUGHRIDGE: The excretion of indolylacetic acid and related indolic acids in man and the rat. Clin. Sci. **19**, 165—179 (1960).
MIROLLI, M., and J. H. WELSH: The effects of reserpine and LSD on molluscs. In: D. RICHTER Ed., Comparative Neurochemistry, pp. 433—443. Oxford: Pergamon Press 1964.
MÖRSDORF, K.: Spectrofluorometrische Bestimmung des 5-Hydroxytryptamingehaltes der Rattenpfote bei experimentellen „Entzündungen". Med. exp. (Basel) **1**, 87—90 (1959).
— Die serotoninfreisetzende Wirkung einiger zur Auslösung experimenteller „Entzündungen" verwendeter Stoffe in vitro. Med. exp. (Basel) **4**, 293—297 (1961).
MOORE, K. E., and T. M. BRODY: The effect of triethyltin on tissue amines. J. Pharmacol. exp. Ther. **132**, 6—12 (1961).
MORAN, N. C., B. UVNÄS and B. WESTERHOLM: Release of 5-hydroxytryptamine and histamine from rat mast cells. Acta physiol. scand. **56**, 26—41 (1962).

MORAN, N. C., and B. WESTERHOLM: The influence of reserpine on 5-hydroxytryptamine and histamine content of rat mast cells and of some rat tissues. Acta physiol. scand. **58**, 20—29 (1963).

NACHMIAS, V. T.: Amine oxidase and 5-hydroxytryptamine in developing rat brain. J. Neurochem. **6**, 99—104 (1960).

NAERS, K., and S. SCHANCHE: Effect of reserpine on serotonin in rabbit serum. Nature (Lond.) **117**, 1130—1131 (1956).

NEUMARK, H.: Formation of serotonin in chopped green maize. Nature (Lond.) **201**, 527—528 (1964).

NIKKILA, E. A.: Urinary excretion of the serotonin metabolite 5-hydroxyindole acetic acid in neurocirculatory asthenia. Acta med. scand. **162**, 231—235 (1958).

NIKODIJEVIĆ, B., and T. TRAJKOV: Mechanism of ulcerogenic action of 5-hydroxytryptamine in rat's stomach. Arch. int. Pharmacodyn. **143**, 442—445 (1963).

O'CONNOR, J. M.: Über den Adrenalingehalt des Blutes. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **67**, 195—232 (1912).

OLSON, R. E., D. GURSEY and J. W. VESTER: Evidence for a defect in tryptophan metabolism in chronic alcoholism. New Engl. J. Med. **263**, 1169—1174 (1960).

ONO, S., L. ZOMPETTI, P. HAGEN and J. FURTH: Relation of mastocytoma to mast cell leukemia, and of heparin, histamine and serotonin to mast cells. Blood **14**, 770—780 (1959).

ORCHOFF, A. P., u. S. S. NORKINA: Über die Alkaloide von *Arundo donax*. Ber. dtsch. chem. Ges. **68**, 436—437 (1935).

OWMAN, CH.: On the presence of 5-hydroxytryptamine in pineal nerves. Biochem. Pharmacol. **12**, Suppl., 112 (1963).

PAASONEN, M. K.: 5-Hydroxytryptamine in mammalian thyroid gland. Experientia (Basel) **14**, 95—96 (1958).

—, and N. J. GIARMAN: Brain levels of 5-hydroxytryptamine after various agents. Arch. int. Pharmacodyn. **114**, 189—200 (1958).

—, and N. T. KÄRKI: Increase of 5-hydroxytryptamine in the rat brain by raunescine. Brit. J. Pharmacol. **14**, 164—167 (1959).

— — and S. MOLKKA: Influence of iproniazid and 5-hydroxytryptophan on the 5-hydroxytryptamine content in the gastro-intestinal tract and thyroid gland of rats. Ann. Med. exp. Fenn. **39**, 405—410 (1961).

— P. D. MACLEAN and N. J. GIARMAN: 5-Hydroxytryptamine (serotonin, enteramine) content of structures of limbic system. J. Neurochem. **1**, 326—333 (1957).

—, and P. PELTOLA: The effect of methimazole and potassium thiocyanate on the 5-hydroxytryptamine content of the rat thyroid gland. Ann. Med. exp. Fenn. **38**, 228—230 (1960).

—, and M. VOGT: The effect of drugs on the amounts of substance P and 5-hydroxytryptamine in mammalian brain. J. Physiol. (Lond.) **131**, 617—626 (1956).

PACHTER, I., D. E. ZACHARIUS and O. RIBEIRO: Indole alkaloids of *Acer saccharinum* (the silver maple), *Dictyoloma incanescens*, *Piptadenia colubrina*, and *Mimosa hostilis*. J. organ. Chem. **24**, 1285—1287 (1959).

PACHTER, I. J.: A note on the occurrence of gramine in *Acer rubrum* L. J. Amer. pharm. Ass. (sci. Ed.) **48**, 670 (1959).

PARE, C. M. B., M. SANDLER and R. S. STACEY: 5-Hydroxyindoles in mental deficiency. J. Neurol. Neurosurg. Psychiat. **23**, 341—346 (1960).

PARKER-WILLIAMS, E. J., PH. COHEN, P. WALTROUSE and F. H. GARTNER: Platelet preservation studies using platelets labeled with C^{14}-5-hydroxytryptamine. J. clin. Invest. **42**, 963 (1963).

PARRATT, J. R., and G. B. WEST: Tissue histamine and 5-hydroxytryptamine. J. Physiol. (Lond.) **132**, 40—41 P (1956a).

— — Influence of age on tissue histamine and 5-hydroxytryptamine. J. Physiol. (Lond.) **133**, 71—72 P (1956b).

— — 5-Hydroxytryptamine and tissue mast cells. J. Physiol. (Lond.) **137**, 169—178 (1957a).

— — Release of 5-hydroxytryptamine and histamine from tissues of the rat. J. Physiol. (Lond.) **137**, 179—192 (1957b).

— — The relationship of 5-hydroxytryptamine to capillary permeability in the skin of the rat. J. Physiol. (Lond.) **140**, 105—112 (1958).

PELTOLA, P., and V. LEPPÄNEN: Studies on the excretion of 5-hydroxyindoleacetic acid. Ann. Med. intern. Fenn. **49**, 283—291 (1960).

PEPEU, G., and N. J. GIARMAN: Contrasting findings on serotonin (5-HT) in fetal life. Pharmacologist **2**, 91 (1960).

— — Serotonin in the developing mammal. J. gen. Physiol. **45**, 575—583 (1962).

PERMAN, E. S.: Observations on the effect of ethanol on the urinary excretion of histamine, 5-hydroxyindole acetic acid, catecholamines and 17-hydroxycorticosteroids in man. Acta physiol. scand. **51**, 62—67 (1961).

PERRY, TH. L., S. HANSEN and L. C. JENKINS: Amine content of normal human cerebrospinal fluid. J. Neurochem. **11**, 49—53 (1964).
—, N. F. SHAW and D. WALKER: Apparent absence of amines in cerebrospinal fluid of phenylketonurics. Nature (Lond.) **189**, 926—927 (1961).
PHILIPPS, J. H.: Isolation of active nematocysts of *Metridium senile* and their chemical composition. Nature (Lond.) **178**, 932 (1956).
PHILLIPS, A. W., H. R. NEWCOMB, J. E. SMITH and R. LACHAPELLE: Serotonin in the small intestine of conventional and germ-free chicks. Nature (Lond.) **192**, 380 (1961).
PIGEAUD, H., R. BURTHIAULT, R. BETHOUX et S. NELKEN: Le dosage de l'acide 5-hydroxyindole-acétique au cours de la grossesse normale et dans les suites de couches immédiates. Gynéc. et Ostét. **57**, 415—425 (1958).
PLETSCHER, A.: Beeinflussung des 5-Hydroxytryptaminstoffwechsels im Gehirn durch Isonikotinsäurehydrazide. Experientia (Basel) **12**, 479—480 (1956a).
— Wirkung von Isonicotinsäurehydraziden auf den 5-Hydroxytryptaminstoffwechsel in vivo. Helv. physiol. Acta **14**, C 76—79 (1956b).
— W. P. BURKARD, H. BRUDERER and K. F. GEY: Decrease of cerebral 5-hydroxytryptamine and 5-hydroxyindoleacetic acid by an arylalkylamine. Life Sci. No 11, 827—833 (1963).
— P. A. SHORE and B. B. BRODIE: Serotonin as a mediator of reserpine action in brain. J. Pharmacol. exp. Ther. **116**, 84—89 (1956).
PSCHEIDT, G. R.: Serotonin and norepinephrine in chicken brain: distribution, normal level and effect of reserpine and monoamine oxidase. Fed. Proc. **23**, 305 (1964).
—, and H. E. HIMWICH: Reserpine, monoamine oxidase inhibitors and distribution of biogenic amines in monkey brain. Biochem. Pharmacol. **12**, 65—72 (1963).
— C. MORPURGO and H. E. HIMWICH: Studies on norepinephrine and 5-hydroxytryptamine in various species. In: D. RICHTER Ed., Comparative Neurochemistry, pp. 401—412. Oxford: Pergamon Press 1964.
— — Chicken brain amines, with special reference to cerebellar norepinephrine. Life Sci., No 7, 524—526 (1963).
PURKHALSKAIA, E., and G. P. MENSHIKOV: 5-Hydroxytryptamine from *Hippophae rhamnoides* as antitumoral agent in animal experiments. Biul. eksp. Biol. Med. **50**, 105—110 (1960).
PUT, T. R., and L. A. H. HOGENHUIS: Brain serotonin and thyroid function. Acta physiol. pharmacol. neerl. **10**, 343—352 (1962).
QUAY, W. B.: Cytologic and metabolic parameters of pineal inhibition by continuous light in the rat (*Rattus norvegicus*). Z. Zellforsch. **60**, 479—490 (1963a).
— Effect of dietary phenylalanine and tryptophan on pineal and hypothalamic serotonin levels. Proc. Soc. exp. Biol. (N.Y.) **114**, 718—721 (1963b).
— Circadian rhythm in rat pinael serotonin and its modifications by estrous cycle and photoperiod. Gen. comp. Endocr. **3**, 473—479 (1963c).
— Circadian and estrous rhythms in pineal melatonin and 5-hydroxy-indole-3-acetic acid. Proc. Soc. exp. Biol. (N.Y.) **115**, 710—713 (1964).
—, and A. HALEVY: Experimental modification of the rat pineal's content of serotonin and related indole amines. Physiol. Zool. **35**, 1—7 (1962).
RAND, M., and G. REID: Source of "serotonin" in serum. Nature (Lond.) **168**, 385 (1951).
— — On the presence in rabbit serum of thrombotonin (thrombocytin or serotonin). Aust. J. exp. Biol. med. Sci. **30**, 153—161 (1952).
RESNICK, R. H., and S. J. GRAY: Serotonin release by hydrochloric acid. I. In vivo and in vitro demonstration. J. Lab. clin. Med. **59**, 462—468 (1962).
— G. T. SMITH and S. J. GRAY: Endocrine influences on tissue serotonin content of the rat. Amer. J. Physiol. **201**, 571—573 (1961).
RICE, W. G., and J. MITCHENER: Histochemical evidence of 5-hydroxytryptamine in a dog mast cell tumour. Nature (Lond.) **189**, 767—768 (1961).
RILEY, J. F.: Fluorescent mast cells in precancerous mouse skin. Experientia (Basel) **14**, 141 (1958).
ROBERTSON, P. A., and W. V. MACFARLANE: Pain-producing substances from the stinging bush *Laportea moroides*. Aust. J. exp. Biol. med. Sci. **35**, 381—394 (1957).
ROBILLARD, E., and Y. ALARIE: Mechanical properties and histamine and serotonin content of guinea pig lungs as influenced by microparticles inhalation. Canad. J. Biochem. **41**, 2177—2182 (1963).
ROBINSON, B., G. F. SMITH, A. H. JACKSON, D. SHAW, B. FRYDMAN and V. DEULOFEU: Dehydrobufotenin. Proc. Chem. Soc., August 1961, p. 310—311.
ROBSON, J. M., and J. B. SENIOR: The 5-hydroxytryptamine content of the placenta and foetus during pregnancy in mice. Brit. J. Pharmacol. **22**, 380—391 (1964).
RODNIGHT, R.: Separation and characterization of urinary indoles resembling 5-hydroxytryptamine and tryptamine. Biochem. J. **64**, 621—626 (1956).

ROOS, B.-E.: The effect of monoamine oxidase inhibitors on the level of 5-hydroxyindoleacetic acid in human cerebrospinal fluid. Life Sci. No 1, 1—4 (1963).

ROSENBERG, J. C., R. C. LILLEHEI, W. H. MORAN and B. ZIMMERMANN: Effect of endotoxin on plasma catechol amines and serum serotonin. Proc. Soc. exp. Biol. (N.Y.) **102**, 335—337 (1960).

RYALL, R. W.: Sub-cellular distribution of pharmacologically active substances in guinea-pig brain. Nature (Lond.) **196**, 680—681 (1962).

— The subcellular distributions of acetylcholine, substance P, 5-hydroxytryptamine, γ-aminobutyric acid and glutamic acid in brain homogenates. J. Neurochem. **11**, 131—145 (1964).

SANDERS, R., T. P. WAALKES, J. W. GILBERT jr. and L. L. TERRY: Serotonin (5-hydroxytryptamine) and pulmonary thromboembolism. Surg. Gynec. Obstet. **109**, 455—459 (1959).

SANNER, E.: Studies on the excretion mechanism of serotonin (5-hydroxytryptamine) in the chicken kidney. Acta physiol. scand. **58**, 330—341 (1963).

—, and B. WORTMAN: Tubular excretion of serotonin (5-hydroxytryptamine) in the chicken. Acta physiol. scand. **55**, 319—324 (1962).

SANYAL, R. K., and G. B. WEST: The relationship of histamine and 5-hydroxytryptamine to anaphylactic shock in different species. J. Physiol. (Lond.) **144**, 525—531 (1958).

SAXENA, P. R., K. KISHOR, M. C. PANT and K. P. BHARGAVA: Pharmacologically active constituents of *Girardinia heterophylla*. J. Pharm. Pharmacol. **16**, 361 (1964).

SCHANBERG, S. M., and N. J. GIARMAN: Drug-induced alterations in the subcellular distribution of 5-hydroxytryptamine in rat's brain. Biochem. Pharmacol. **11**, 187—194 (1962).

— C. M. MCKEAN and N. J. GIARMAN: A mechanism of the indole defect in experimental phenylketonuria. Fed. Proc. **21**, 269 (1962).

SCHINDLER, R., M. DAY and G. A. FISCHER: Culture of neoplastic mast cells and their synthesis of 5-hydroxytryptamine and histamine in vitro. Cancer Res. **19**, 47—51 (1959).

SCHONE, H.-H., u. E. LINDNER: Die Wirkung des N-[3'-Phenyl-propyl-(2')]-1,1-dipenylpropyl-(3)-amins auf den Stoffwechsel von Serotonin und Noradrenalin. Arzneimittel-Forsch. **10**, 583—585 (1960).

SCHULZ, H., H. STROBACH u. E. HIEPLER: Serotoninbestimmungen an Thrombocyten und an Fraktionen von Thrombocyten. Klin. Wschr. **42**, 232—236 (1964).

SCHWABE, U., D. HEYL, H. J. HILDEBRANDT u. T. HUKUHARA: Alkylphosphatvergiftung und 5-Hydroxytryptamin-Stoffwechsel des Zentralnervensystems. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **241**, 254—259 (1961).

SCHWEMMLE, K., E. SCHMID, F. SCHEIFFARTH, L. ZICHA u. E. SCHICHOR: Zur Frage der gegenseitigen Beziehungen zwischen adrenocorticotropem Hormon bzw. Glucocorticoiden und dem Serotonin-Stoffwechsel. Arzneimittel-Forsch. **11**, 616—619 (1961).

SHERWOOD W. K.,: Experience with "BGE", a naturally occurring indole compound. J. nerv. ment. Dis. **125**, 490—491 (1957).

SHORE, P. A., and B. B. BRODIE: LSD-like effects elicited by reserpine in rabbits pretreated with iproniazid. Proc. Soc. exp. Biol. (N.Y.) **94**, 433—435 (1957).

— A. PLETSCHER, E. G. TOMICH, R. KUNTZMAN and B. B. BRODIE: Release of blood platelet serotonin by reserpine and lack of effect on bleeding time. J. Pharmacol. exp. Ther. **117**, 232—236 (1956).

SIMON, A.: Über die Pharmakologie der gefäßverengernden Stoffe der Blutseren. I. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **190**, 273—279 (1938).

— Über die Pharmakologie der gefäßverengernden Stoffe der Blutseren. II. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. **192**, 701—707 (1939).

SIMON, S. E., K. D. CAIRNCROSS, D. G. SATCHELL, W. S. GAY and S. EDWARDS: The toxicity of *Octopus maculosus* Hoyle venom. Arch. int. Pharmacodyn. **149**, 318—329 (1964).

SJOERDSMA, A., J. A. OATES and L. GILLESPIE jr.: Quantitation of monoamineoxidase inhibition produced with various drugs in man. Proc. Soc. exp. Biol. (N.Y.) **103**, 485—487 (1960).

— — P. ZALTZMAN and S. UDENFRIEND: Identification and assay of urinary tryptamine: application as an index of monoamine oxidase inhibition in man. J. Pharmacol. exp. Ther. **126**, 217—222 (1959).

— T. P. WAALKES and H. WEISSBACH: Serotonin and histamine in mast cells. Science **125**, 1202—1203 (1957 L.).

— H. WEISSBACH, L. L. TERRY and S. UDENFRIEND: Further observations on patients with malignant carcinoid. Amer. J. Med. **23**, 5—15 (1957 b).

— — and S. UDENFRIEND: A clinical, physiologic and biochemical study of patients with malignant carcinoid. Amer. J. Med. **20**, 520—532 (1956).

SKILLEN, R. G., C. H. THIENES, J. CANGELOSI and L. STRAIN: Brain 5-hydroxytryptamine in ozone-exposed rats. Proc. Soc. exp. Biol. (N.Y.) **108**, 121—122 (1961).

SKILLEN, R. G., C. H. THIENES and L. STRAIN: 5-Hydroxytryptamine, 5-hydroxytryptophan decarboxylase and monoamine oxidase in hearts of normal, thyroid fed and propylthiouracil-fed male and female rats. Endocrinology **70**, 743—747 (1962).

SMITH, D. E., and Y. S. LEWIS: Preparation and effects of an anti-mast cell serum. J. exp. Med. **113**, 683—692 (1961).

SMITH, G., and A. N. SMITH: The role of serotonin in experimental pulmonary embolism. Surg. Gynec. Obstet. **101**, 691—700 (1955).

SMITH, S. E.: The pharmacological actions of 3,4-dihydroxyphenyl-α-methylalanine (α-methyldopa), an inhibitor of 5-hydroxytryptophan decarboxylase. Brit. J. Pharmacol. **15**, 319—327 (1960).

— R. S. STACEY and I. M. YOUNG: 5-Hydroxytryptamine and 5-hydroxytryptophan decarboxylase activity in the developing nervous system of rats and guinea-pigs. Biochem. Pharmacol. **8**, 32 (1961).

SNOW, P. J. D., J. E. LENHARD-JONES, G. CURZON and R. S. STACEY: Humoral effects of metastasing carcinoid tumours. Lancet **1955 II**, 1004—1009.

SOCHOR, F., and D. LAKATUA: Daily variations of 5-hydroxyindoleacetic acid urinary excretion. Fed. Proc. **23**, 437 (1964).

SOUTHERN, A. L.: Functioning metastatic bronchial carcinoid with elevated levels of serum and cerebrospinal fluid serotonin and pituitary adenoma. J. clin. Endocr. **20**, 298—305 (1960).

SPECTOR, S., R. KUNTZMAN, P. A. SHORE and B. B. BRODIE: Evidence for release of brain amines by reserpine in presence of monoamine oxidase inhibitors: implication of monoamineoxidase in norepinephrine metabolism in brain. J. Pharmacol. exp. Ther. **130**, 256—261 (1960).

SPRINCE, H., C. M. PARKER, D. JAMESON, J. T. DAWSON jr., M. KNOWLTON and F. C. DOHAN: Detection and isolation of indoleacetamide from human urine: results with schizophrenic and normal subjects. J. Lab. clin. Med. **57**, 763—770 (1961).

STACEY, R. S.: 5-Hydroxytryptamine and other pharmacologically active substances in the central nervous system. Acta physiol. neerl. **8**, 222—239 (1959).

— Uptake of 5-hydroxytryptamine by platelets. Brit. J. Pharmacol. **16**, 284—295 (1961).

—, and T. J. SULLIVAN: Effect of diet and antibiotics on intestinal 5-hydroxytryptamine. J. Physiol. (Lond.) **137**, 63—64 P (1957).

—, and I. M. YOUNG: Concentration of 5-hydroxytryptamine in the small intestine and platelets of the developing guinea pig. Biochem. Pharmacol. **13**, 129—134 (1964).

STOCK, K., u. E. O. WESTERMANN: Biogene Amine im Fettgewebe. Naunyn-Schmiedebergs Arch. exp. Path. Pharmak. **246**, 15—16 (1963).

— — Concentration of norepinephrine, serotonin, and histamine, and of amine-metabolizing enzymes in mammalian adipose tissue. Lipid Res. **4**, 297—304 (1963).

STOLK, A.: Mast cell reaction during chemical skin carcinogenesis of the lizard Lacerta agilis. Experientia (Basel) **19**, 20—21 (1963).

STROMBERG, V. L.: The isolation of bufotenine from *Piptadenia peregrina*. J. Amer. chem. Soc. **76**, 1707 (1954).

STURM jr., A., u. G. STÜTTGEN: Nachweis von 5-Hydroxytryptophan in menschlichen Mastzellen. Klin. Wschr. **40**, 199—201 (1962).

SULLIVAN, T. J.: The effect of diet on the 5-hydroxytryptamine content of the small intestine and of other organs in rats and mice. Brit. J. Pharmacol. **15**, 513—519 (1960).

— Effect of antibiotics on the 5-hydroxytryptamine content of the small intestine and other organs in rats and mice. Brit. J. Pharmacol. **16**, 90—98 (1961).

SUPEK, Z., M. JOVIĆ u. S. KECKES: Der 5-Hydroxytryptamin-Gehalt der Haut der Ratte bei experimenteller Entzündung. Arzneimittel-Forsch. **11**, 132—133 (1961).

TABACHNICK, I. A., and A. A. RUBIN: Some relationships between peripheral monoamine oxidase inhibition and brain 5-hydroxytryptamine levels in brain. Proc. Soc. exp. Biol. (N.Y.) **101**, 435—437 (1959).

TELFORD, J. M., and G. B. WEST: The effects of corticosteroids and related compounds on the histamine and 5-hydroxytryptamine content of rat tissues. Brit. J. Pharmacol. **15**, 532—539 (1960).

TODRICK, A., M. DICK and A. C. TAIT: Effect of reserpine in therapeutic dosage on excretion of 5-hydroxyindoleacetic acid. Brit. med. J. **1958 I**, 496—499.

TOH, C. C.: Release of 5-hydroxytryptamine (serotonin) and histamine from platelets by tissue extracts. J. Physiol. (Lond.) **133**, 402—411 (1956).

— Effect of temperature on the 5-hydroxytryptamine (serotonin) content of tissues. J. Physiol. (Lond.) **151**, 410—415 (1960).

TOWNE, J. C., E. FENSTER, J. O. SHERMAN and T. SCHAEFER: Estimation of serotonin and catechol amines in acetone solution. Fed. Proc. **21**, 420 (1962).

TOWSEND, E. E., J. G. KATIS and T. L. SOURKES: Effect of tryptophan deficiency in rat on liver tryptophan peroxidase-oxidase (TPO) and urinary 5-hydroxy-3-indoleacetic acid (HIAA). Fed. Proc. **17**, 324 (1958).

TURNER, W. J., and E. A. MAUSS: Serotonin (5-hydroxytryptamine) and acetylcholine in human ventricular and spinal fluids. Arch. gen. Psychiat. **1**, 646—650 (1959).

TWAROG, B. M.: Response of a molluscan smooth muscle to acetylcholine and to 5-hydroxytryptamine. J. cell. comp. Physiol. **44**, 141—164 (1954).

—, and I. H. PAGE: Serotonin content of some mammalian tissues and urine. Amer. J. Physiol. **175**, 157—161 (1953).

TYCE, G. M., E. V. FLOCK and CH. A. OWEN: 5-Hydroxindoles in the rat after hepatectomy. Fed. Proc. **22**, 632 (1963).

— G. H. C. STOBIE, E. V. FLOCK and J. L. BOLLMAN: 5-Hydroxytryptamine content of the brain after hepatectomy. Fed. Proc. **21**, 301 (1962).

— — — — 5-Hydroxytryptamine in the gastrointestinal tract after intestinal obstruction and hepatectomy. Proc. Soc. exp. Biol. (N.Y.) **115**, 1068—1072 (1964).

TYLER jr., V. E.: Occurrence of serotonin in a hallucinogenic mushroom. Science **128**, 718 (1958).

—, and D. GROGER: Occurrence of 5-hydroxytryptamine and 5-hydroxytryptophan in *Panaeolus sphinctrinus*. J. pharm. Sci. **53**, 462 (1964).

UDENFRIEND, S., W. LOVENBERG and A. SJOERDSMA: Physiologically active amines in common fruits and vegetables. Arch. Biochem. Biophys. **85**, 487—490 (1959).

— E. TITUS and H. WEISSBACH: The identification of 5-hydroxy-3-indoleacetic acid in normal urine and a method for its assay. J. biol. Chem. **216**, 499—505 (1955).

— H. WEISSBACH and D. F. BOGDANSKI: Biochemical findings relating to the action of serotonin. Ann. N.Y. Acad. Sci. **66** (3), 602—608 (1957).

— B. WITKOP, B. G. REDFIELD and H. WEISSBACH: Studies with reversible inhibitors of monoamine oxidase: harmaline and related compounds. Biochem. Pharmacol. **1**, 160—165 (1958).

UTLEY, J. D.: Gamma aminobutyric acid and 5-hydroxytryptamine concentrations in neurons and glial cells in the medial geniculate body of the cat. Biochem. Pharmacol. **12**, 1228—1230 (1963).

UUSPÄÄ, V. J.: The 5-hydroxytryptamine content of the brain and some other organs of the hedgehog *(Erinaceus europaeus)* during activity and hibernation. Experientia (Basel) **19**, 156—158 (1963).

—, and V. I. UUSPÄÄ: VANE's rat fundus strip method in determination of 5-hydroxytryptamine. Ann. Acad. Sci. fenn. A, IV, **60**, 1—17 (1962).

VARAGIĆ, V., M. KRSTIĆ, S. STEPANOVIĆ and S. HAJDUKOVIĆ: The effect of γ-irradiation on the amount of 5-hydroxytryptamine in the gut and spleen in the early phase after irradiation. Experientia (Basel) **19**, 647—648 (1963).

VIALLI, M., e V. ERSPAMER: Ricerche sul secreto delle cellule enterocromaffini. IX. Intorno alla natura chimica della sostanza specifica. Boll. Soc. med.-chir. Pavia **51**, 1111—1116 (1937).

WAALKES, T. PH., and H. COBURN: The role of platelets and the release of serotonin and histamine during anaphylaxis in the rabbit. J. Allergy **30**, 394—407 (1959).

— — The role of histamine and serotonin during anaphylaxis in the mouse. J. Allergy **31**, 151—161 (1960a).

— — Serotonin, histamine, and the Arthus phenomenon. J. Allergy **31**, 181—184 (1960b).

— — and L. L. TERRY: The effect of reserpine on histamine and serotonin. J. Allergy **30**, 408—414 (1959).

— A. SJOERDSMA, C. R. CREVELING, H. WEISSBACH and S. UDENFRIEND: Serotonin, norepinephrine and related compounds in bananas. Science **127**, 648—650 (1958).

WALASZEK, E. J. and L. G. ABOOD: Fixation of 5-hydroxytryptamine by brain mitochondria. Proc. Soc. exp. Biol. (N.Y.) **101**, 37—40 (1959).

WANG, H. L., V. H. HARWALKER and H. A. WAISMAN: Effect of dietary phenylalanine and triptophan on brain serotonin. Arch. Biochem. Biophys. **96**, 181—184 (1962).

— — —: Influence of dietary phenylalanine and tryptophan on tissue serotonin. Fed. Proc. **20**, 6 (1961).

WEISSBACH, H., T. PH. WAALKES and S. UDENFRIEND: Presence of serotonin in lung and its implication in the anaphylactic reaction. Science **125**, 235—236 (1957).

— — — A simplified method for measuring serotonin in tissues; simultaneous assay of both serotonin and histamine. J. biol. Chem. **230**, 865—871 (1958).

WEISSMAN, A., and K. F. FINGER: Effects of benzquinamide on avoidance behavior and brain amine levels. Biochem. Pharmacol. **11**, 871—880 (1962).

WELSH, J. H.: Neurohormones of invertebrates. I. Cardio-regulators of *Cyprina* and *Buccinum*. J. Mar. biol. Ass. U. Kingd. **35**, 193—201 (1956).

WELSH, J. H.: Serotonin as a possible neurohumoral agent: evidence obtained in lower animals. Ann. N.Y. Acad. Sci. **66** (3), 618—630 (1957).
— Evidence for 5-HT granules in molluscan ganglia. Anat. Rec. **132**, 516 (1958).
— 5-Hydroxytryptamine in coelenterates. Nature (Lond.) **186**, 811—812 (1960).
— The quantitative distribution of 5-hydroxytryptamine in the nervous system, eyes and other organs of some vertebrates. In: D. RICHTER Ed., Comparative Neurochemistry, pp. 355—366. Oxford: Pergamon Press 1964.
—, and C. S. BATTY: 5-Hydroxytryptamine content of some arthropod venoms and venom-containing parts. Toxicon **1**, 165—173 (1963).
—, and M. MOORHEAD: Identification and assay of 5-hydroxytryptamine in molluscan tissues by fluorescence method. Science **129**, 1491—1492 (1959).
— — The quantitative distribution of 5-hydroxytryptamine in the invertebrates, especially in their nervous system. J. Neurochem. **6**, 146—169 (1960).
WEST, G. B.: Tryptamines in edible fruits. J. Pharm. Pharmacol. **10**, 589—590 (1958a).
— Comparison of the release of histamine and 5-hydroxytryptamine from tissues of the rat, mouse and hamster. Int. Arch. Allergy **13**, 336—347 (1958b).
— Tryptamine in tomatoes. J. Pharm. Pharmacol. **11**, 319—320 (1959a).
— Indole derivatives in tomatoes. J. Pharm. Pharmacol. **11**, 275—277 T (1959b).
— Carcinoid tumours and pineapples. J. Pharm. Pharmacol. **12**, 768 (1960).
WHITE, E. P.: Alkaloids of the leguminosae. VIII—XIII. N. Z. J. Sci. Technol., Sect. B **25**, 137—162 (1944).
WHITTAKER, V. P.: The isolation and characterization of acetylcholine-containing particles from brain. Biochem. J. **72**, 694—706 (1959).
— The subcellular localization of transmitter substances in the central nervous system. Biochem. Pharmacol. **5**, 392—398 (1961).
— Sub-cellular distribution of 5-hydroxytryptamine in guinea pig brain. Nature (Lond.) **195**, 1100 (1962).
WIEGAND, R. G., and J. E. PERRY: Effect of L-Dopa and N-methyl-N-benzyl-2-propynylamine. HCl on dopa, dopamine, norepinephrine, epinephrine and serotonin levels in mouse brain. Biochem. Pharmacol. **7**, 181—186 (1961).
—, and E. SCHERFLING: Determination of 5-hydroxytryptophan and serotonin. J. Neurochem. **9**, 113—114 (1962).
WIELAND, TH., u. W. MOTZEL: Über das Vorkommen von Bufotenin im gelben Knollenblätterpilz. Justus Liebigs Ann. Chem. **581**, 10—16 (1953).
WIER, J. K., and V. E. TYLER jr.: Quantitative determination of serotonin in Panaeolus species. J. pharm. Sci. **52**, 419—422 (1963).
WILKINSON, S.: 5-Methoxy-N-methyltryptamine: a new indole alkaloid from *Phalaris arundinacea* L. J. chem. Soc. **2**, 2079—2081 (1958).
WURTMAN, R. J., J. AXELROD and J. E. FISCHER: Melatonin synthesis in the pineal gland: effect of light mediated by the sympathetic nervous system. Science **143**, 1328—1330 (1964).
YEH, S. D. J., J. D. SOLOMON and B. F. CHOW: Influence of vitamin B 6 on tissue serotonin levels in rats. Fed. Proc. **18**, 357 (1959).
YURASHEVSKII, M. K.: Alkaloids of *Girgensohnia diptera*, family Chenopodiaceae. J. gen. Chem. (U.S.S.R.) **10**, 1781—1783 (1940).
YUWILLER, A., and R. T. LOUTTIT: Effects of phenylalanine diet on brain serotonin in the rat. Science **134**, 831—832 (1961).
ZARAFONETIS, C. J. D., and J. P. KALAS: Serotonin, catecholamines and amine oxidase activity in the venom of certain reptiles. Amer. J. med. Sci. **240**, 764—768 (1960).
ZBINDEN, G., A. PLETSCHER u. A. STUDER: Alimentäre Beeinflussung der enterochromaffinen Zellen und des 5-Hydroxytryptamin-Gehaltes von Gehirn und Darm. Z. ges. exp. Med. **129**, 615—620 (1958).
ZIEHER, L. M., and E. DE ROBERTIS: Subcellular localization of 5-hydroxytryptamine in rat brain. Biochem. Pharmacol. **12**, 596—598 (1963).
ZUCKER, M. B., B. K. FRIEDMAN and M. M. RAPPORT: Identification and quantitative determination of serotonin (5-hydroxytryptamine) in blood platelets. Proc. Soc. exp. Biol. (N.Y.) **85**, 282—285 (1954).
— L. HELLMAN and B. ZUMOFF: Rapid disappearance of C^{14}-labeled serotonin from platelets in patients with carcinoid syndrome. J. Lab. clin. Med. **63**, 137—146 (1964).
—, and M. M. RAPPORT: Identification and quantitative determination of serotonin (5-hydroxytryptamine) in platelets, the source of serum serotonin. Fed. Proc. **13**, 170—171 (1954).