Journal of Chromatography, 466 (1989) 89–218
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 21 207

REVIEW

BIOGENIC AMINES AND THEIR METABOLITES IN BODY FLUIDS OF NORMAL, PSYCHIATRIC AND NEUROLOGICAL SUBJECTS[a]

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(Received December 14th, 1988)

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[a] *Editor's note:* This review is a unique discussion of the determination of traces of amines in biological fluids. As such it is of interest not only in the medical field but also to toxicologists, food scientists, nutritionists, etc., and was hence accepted for publication in the general section of this journal.

0021-9673/89/$03.50

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1. INTRODUCTION AND SCOPE OF THE REVIEW

The biogenic monoamines have been implicated in the neurochemistry and physiology of mental illness and neurological disorders. Because the direct assessment of the monoamines and their metabolites in the brain of living human subjects is not possible and *post-mortem* samples suffer from a number of limitations, peripheral measures of these compounds in urine, blood plasma and cerebrospinal fluid have been carried out for the purpose of assessing the presence of a dysfunction in a given condition. The results of hundreds of such investigations have been published over the last 40–50 years.

These studies have been interesting not only for purely scientific reasons, but also because they have potentially important practical applications for clinicians in the diagnosis and treatment of these disorders. Originally it was hoped that analysis of accessible body fluids of patients and normal controls would reveal statistically reliable differences in metabolite concentrations which could serve as biological "state" or "trait" markers. Despite a wealth of published papers and increasing

sophistication of biochemical and analytical methodology, however, few marker candidates have been unambiguously established. More hopeful has been some psychopharmacological work in which metabolite concentrations have been used as predictors of drug response or have been observed to respond to drug treatment in a manner which parallels clinical response.

Part of the difficulty in obtaining consistently significant differences in the metabolite concentrations of patients and controls undoubtedly reflects the complexity and heterogeneity of psychiatric disorders; it is also caused, however, as a consequence of biochemical individuality (sex, age, weight, height, ethnic origin, circadian rhythms), environmental factors (diet, drug or alcohol ingestion, cigarette smoking, physical and mental stress, posture) and for analytical reasons (sample storage conditions and the specificity and sensitivity of the analytical methods). The importance of using specific and sensitive methods for quantification becomes evident when comparing some of the earliest work with more recent results. Improvements in and the introduction of new types of chromatography and derivatives have produced ever better component resolution (and therefore greater specificity of the measurements), and new and more sensitive means of detection have permitted ever smaller amounts to be quantified.

This review is a summary of the results obtained over the last 25–30 years of investigations of the concentrations of the biogenic monoamines and their metabolites in the biological fluids of normal, psychiatric and neurological subjects. In the first section, concentration values for normal controls and the analytical methods employed are presented; in the second section, the concentrations for psychiatric and neurological patients are tabulated; in the final section the individual and environmental factors which may influence metabolite concentrations are described.

2. CONCENTRATIONS OF BIOGENIC MONOAMINES AND THEIR METABOLITES IN BODY FLUIDS OF NORMAL SUBJECTS

2.1. Explanation of the tables

The calculation of the weighted mean of the mean concentrations for each metabolite and fluid (and weighted mean of the standard errors of the mean) was carried out as follows. For each study selected for inclusion, the reported concentration (converted to common units) and standard error (converted from standard deviation where required) was multiplied by the number of subjects in the study. All the products were added to give a grand total concentration and standard error, which was then divided by the total number of subjects to give the weighted mean value ± standard error of the mean (S.E.M.) reported in the tables. For a paper to be cited in a table, it was necessary that the method of analysis, number of subjects and concentration in a biological fluid be reported. Papers in which the results clearly conflicted with those in the majority of similar papers were excluded. For those metabolites for which few analyses have been carried out, markedly different results from different studies are presented separately. In the column headed "References and methods", the abbreviations refer to the method of isolation/separation and detection/quantification. A reference number followed by an asterisk (*) indicates that the paper cited

includes full details of the procedure for the isolation and quantification of the metabolite. The abbreviations are those commonly used in the literature, as follows:

IE = ion exchange;
PC = paper chromatography;
TLC = thin-layer chromatography;
Fl = spectrophotometric detection and quantification (mostly fluorimetric);
GC = gas chromatography;
ECD = electron-capture detection;
FID = flame ionization detection;
ND = nitrogen detection;
NCI = negative chemical ionization;
MS = mass spectrometry;
HPLC = high-performance liquid chromatography;
ED = electrochemical, amperometric or coulometric detection;
REA = radioenzymatic assay;
RIA = radioimmunoassay;
n.d. = not detected.

2.2. *Creatinine as a unit of urinary concentrations*

Expression of excretion rates in units of metabolite per milligram of creatinine has been suggested as a means of correcting for incomplete urine collections. However, several investigators have concluded that this may obscure important metabolic variations in some mental patients[1–3]. For example, a high correlation between excretion rates of homovanillic acid (HVA), indoleacetic acid (IAA), 5-hydroxyindoleacetic acid (5-HIAA) and tryptamine (TRA) and the excretion rate of creatinine has been noted[2–4]. Further, daily excretion of creatinine in normals subjects[5] and schizophrenics[1–3,6] has been found to be highly variable, with unmedicated schizophrenics excreting significantly lower amounts than normal subjects[4]. Treatment of schizophrenics with sulpiride or chlorpromazine, however, increases creatinine excretion[4]. Some of the daily variation may be due to dietary factors[6], but this does not appear to be the sole cause of the variability[1,3,7]. A diurnal variation in creatinine excretion has also been reported[8]. McDonald and Weise[3] explained the difference in excretion rates of creatinine between normal subjects and schizophrenics to be due to the fact that the schizophrenics were older and heavier, a finding corroborated by Jenner *et al.*[9], who found that creatinine excretion was related to body weight. That women, who generally weigh less than men, also excrete significantly less creatinine than men lends further confirmation to these results[8,10,11]. It has also been shown that there is a high correlation between urine volume and creatinine excretion[6,12]. As the daily urine volume is extremely variable, it was concluded that the use of creatinine excretion as a correction factor for incomplete 24-h sample collection is not justified. Soliman *et al.*[13] found that urinary creatinine is stable for only 24 h when frozen, and not even for 24 h if the samples had been acidified before freezing. However, in an HPLC analysis of creatinine in CSF (at physiological pH), Swahn and Sedvall[4] observed no correlation between creatinine level and storage time. In view of the problems associated with creatinine excretion measurements, urinary excretion rates are expressed by most authors in units per 24 h, and this convention is followed in this review.

2.3. Correlations between concentrations in body fluids and the brain

In contrast to an assessment of the activity of a given neuronal system in the brain, the quantification of neurotransmitters and their metabolites in the CSF or peripheral body fluids permits the control of such factors as diet, age and sex of the subjects, medication and general physical health through experimental design. Such studies also permit the accumulation of large sample sizes, and repeated measurements in the same individual. It is necessary, however, to assess how well the concentrations of the metabolites in the biological fluids correlate with brain concentrations before it is valid to relate the results of an experiment to brain neuronal activity.

It has been suggested that lumbar CSF levels of the biogenic amine metabolites partially reflect metabolism in the spinal cord[492,884] and may have some relevance to neurotransmission in the brain[14,15]. Stanley *et al.*[16] measured HVA and 5-HIAA in 48 individuals at autopsy and determined that their concentrations in the cerebral cortex were positively correlated with their levels in the CSF for the same individual. They concluded, as did other authors[17,18], that the CSF concentrations of HVA and 5-HIAA do, in large part, reflect brain metabolism and may offer a valid means of determining the central activity of the serotonin and dopamine systems. Davis *et al.*[19] ascertained that about 50% of plasma HVA originates in the brain, and by measuring venous samples from both the internal jugular vein and the radial artery Maas *et al.*[20] were able to calculate the average production of HVA and 5-HIAA in brain. The data were related to the urinary excretion of these metabolites and indicated that approximately 33% of urinary HVA and 34% of 5-HIAA are derived from the brain.

Elevated levels of noradrenaline (NA) in the brains of schizophrenics have been shown to be correlated with elevated NA levels in the CSF[21]. Other investigations have led to the conclusion that in the CSF the major metabolite of noradrenaline, 3-methoxy-4-hydroxyphenyl glycol (MHPG), arises largely from central metabolism[22,23]. Estimates of the percentage of urinary MHPG originating in the brain range from a low of 20%[24] to as much as 60%[25]. There are considerable data showing a large peripheral contribution to MHPG levels in CSF, plasma and urine, so it may be that such measurements will not prove useful for the assessment of central noradrenergic activity[26]. Further, although as much as 60% of plasma MHPG has been claimed to be produced in the brain[27], it has been shown that plasma MHPG is oxidized to vanilmandelic acid (VMA), raising more questions about the validity of its use as an index of central NA activity[28].

A significant positive correlation between the concentrations of the catecholamines and their metabolites in plasma and in CSF[29–31] and between the concentrations of MHPG in urine and CSF[32–34,686] has been reported by several authors, although not by all[35]. As the CSF concentrations of these metabolites may reflect central nervous system metabolism, it may be permissible in some instances to conclude that plasma, and even urine, concentrations also reflect central activity. A positive correlation between plasma total MHPG and 24-h urinary MHPG in psychiatric patients has been reported[36]; an earlier study showed no correlation[37]. Low-dose administration of debrisoquin has been reported to eliminate about 80% of the peripheral contribution to plasma HVA and MHPG, resulting in a situation in which at least 75% of these metabolites in plasma originated in the brain[38]. Thus, debrisoquin potentially provides a method for studying brain catecholamines through measurement of their metabolites in plasma.

Sandler and co-workers[39,40], observing a high correlation between both free and conjugated phenylacetic acid (PAA) in plasma and CSF taken at the same time, suggested that plasma PAA measurements might justifiably be employed clinically to provide an estimate of central phenylethylamine (PE) changes.

Probenecid is a drug used to block transport of monoamine acid metabolites out of the cerebrospinal fluid. It has generally been assumed that the resultant rise in the CSF concentrations of the metabolites will reflect presynaptic turnover of the parent amine in the central nervous system. However, it has been remarked that the CSF levels of probenecid correlate with the levels of metabolites, suggesting that the blockade may be incomplete at the probenecid concentrations obtainable in human studies[41]. A review of the probenecid test, including its theoretical basis, the assumptions on which it is based and its limitations has been published[42]. It shows that the test can be extended from the measurement of dopamine and serotonin turnover to include comparisons of turnover of other monoamines, such as octopamine, *p*-tyramine and tryptamine. The differential effects of probenecid on the CSF concentrations of the monoamine metabolites in controls and the psychiatric and neurological disorders are presented in the relevant sections of this review.

2.4. Comparison of analytical methods

In order to assess the merits of the various analytical procedures, studies comparing GC, LC, mass fragmentography, radioenzymatic assay and fluorimetry have been carried out. The subject has also been reviewed for the catecholamines[43] and for the biogenic amines and their metabolites[44].

Comparisons of the results of analyses on the same samples by radioenzymatic and LC assays have shown that the former tend to produce higher values with greater scatter, but are more reliable for concentrations below 100 pg/ml[45–48]. In an interlaboratory comparison of plasma catecholamine concentrations, 34 laboratories employing radioenzymatic, HPLC and fluorimetric assay produced, in some instances, considerable differences in results when analyzing the same sample by the same method[46]. The fluorimetric assays gave unacceptable results. Tracy *et al.*[49] found that measurement of urinary 5-HIAA by a colorimetric assay gave excellent agreement with an LC assay only for high concentrations. On the other hand, a high correlation in the results of measurements of the urinary catecholamines by fluorimetry and by LC has been obtained[50]. Although some researchers have been able to obtain accurate and precise quantifications by fluorimetry, many have not. The key factor seems to be adequate purification, without which the results may be too high owing to contributions to the fluorescence from other substances[51], or too low owing to quenching of the fluorescence by other substances[52,53].

GC–MS and fluorimetry have been compared for the quantification of 5-HIAA[54,55], HVA[52,54–56] and serotonin[57]. For HVA in CSF, the values were found to be lower when measured by fluorimetry[52,54–56], but for 5-HIAA[54] good agreement between the two methods was obtained. Good agreement in the results of measurements of 5-HIAA and HVA in CSF by HPLC and GC–MS have also been reported[55]. Plasma serotonin (5-HT) levels were determined to be lower when measured by fluorimetry than by GC–MS[57]. GC using a nitrogen detector gave results comparable to those obtained by GC–MS for the determination of the isothiocyanate derivatives of biogenic amines[58].

Various aspects of the use of GC–MS with selected ion monitoring[59–62], GC–MS with negative ion chemical ionization[63] and HPLC[64,65] for the determination of biogenic amines and their metabolites have been reviewed.

2.5 Intra-individual variation

Most reported concentrations of metabolites are the result of measurements on a single sample from each subject. Large intra-individual day-to-day variations in concentrations may obscure real differences between groups of subjects, particularly if the size of the groups is small. This problem has been addressed by longitudinal studies for some metabolites in some fluids.

Urinary excretion of the biogenic amines and their metabolites is characterized, in general, by large day-to-day variations. The trace amines *m*- and *p*-tyramine (mTA and pTA), PE and TRA were quantified in urine from one subject daily for 28 days; the concentration of the unconjugated mTA and pTA remained fairly constant, but the unconjugated PE and TRA and all the conjugated amine levels were extremely variable[67]. Using the same urine samples, the excretion of the acidic metabolites of the trace amines also exhibited very large daily variations[68]. In a study on the reliability of urinary monoamine and metabolite output measurements, Linnoila *et al.*[69] showed that the urinary concentrations of normetanephrine, 5-HT, dopamine (DA), NA, PE, HVA and 5-HIAA were highly variable with time and that at the very least two measurements on different days were required for the data to be reliable. Only MHPG and VMA proved to be relatively stable from one 24-h sample to the next. Hollister *et al.*[70], however, observed that the urinary excretion of MHPG, although stable for three consecutive 24-h collections, was not stable over a period of several weeks, suggesting that excretory pattents are not traits. Large daily variations in the urinary excretion of pTA, PE, normetanephrine (NMN) and metanephrine (MN)[71], PAA[72] and 3,4-dimethoxyphenylethylamine[73] have also been noted in other studies.

In plasma, over periods of up to 3 days, MHPG concentration shows minimal variation within subjects[37,74–76], but across a 5-week study period considerable variation was reported[75]. Plasma noradrenaline concentration appears to be stable for at least a few days[76].

2.6 Determination of conjugates

Conjugates of the amines and their metabolites, mostly sulfates and glucuronides, may be determined after either acid[145,298] or enzymatic hydrolysis[239,241,242] or directly by a radioenzymatic assay[236] or by HPLC[162,191]. Techniques for the determination of phenolic amine neurotransmitter conjugates have also recently been reviewed[66].

2.7 Tables of values calculated as weighted means

In Tables 1–18 amines in urine are usually expressed as μg per 24 h, whereas in plasma and CSF the units are pg/ml. The acidic metabolites, on the other hand, are usually given in mg per 24 h in urine and ng/ml in plasma and CSF. Any other units are listed directly in the tables, as is the nature of the conjugates when this is known. If

TABLE I

UNCONJUGATED BIOGENIC AMINES IN URINE

Amine	*References and methods*[a]	*Total No. of subjects*	*Weighted mean ± S.E.M. (μg per 24 h)*
Histamine	Bioassay: 77*, 78, 79*, 80*; IE–Fl: 81*, 82*; PC-GC-Fl: 83* REA: 84*, 85*, 86, 87*; HPLC–Fl: 88*	248	19.7 ± 2.3
N^{τ}-Methylhistamine	PC–GC–Fl: 83*; HPLC–Fl: 88*	28	276 ± 26
Phenylethylamine	Fl: 89; GC–FID: 90*; GC–ECD: 91*, 92*, 93, 94*; TLC–MS: 67*, 95*, 96*, 97*; GC–MS: 98*, 99, 100, 101, 102, 103*, 104*, 105*	266	8.1 ± 1.8
m-Tyramine	GC–ECD: 94*; TLC–MS: 67*, 95*, 96*, 97*; GC–MS: 99, 102*, 103*	93	83 ± 10
p-Tyramine	IE–Fl: 106, 107, 108, 109, 110*; PC–Fl: 111; Fl: 112, 113; GC–ECD: 94*; TLC–MS: 67*, 95*, 96*, 97*; GC–MS: 99, 102, 103*, 114	189	579 ± 75
Tryptamine	IE–Fl: 115*, 116*; Fl: 111, 112, 117*, 118; GC–ECD: 94*; TLC–MS: 67*, 95*, 96*, 97*; GC–MS: 119, 120	147	103 ± 19
p-Octopamine	REA: 121, 122, TLC–MS: 123*	38	0.80 ± 0.15
p-Synephrine	TLC–MS: 123*	4	6.9 ± 0.7
Noradrenaline	Fl: 43, 112, 124; alumina–Fl: 125*, 126*, 127*, 128*, 129, 130*, 131, 132, 133, 134; IE–Fl: 50*, 135*, 136*, 137*, 138*, 139, 155; bioassay: 132; GC–ECD: 140*; GC–MS: 103*, 141; REA–TLC: 142, 143*; HPLC–ED: 144*, 145*, 146*, 147*, 148, 149, 150, 151, 160*, 161*; HPLC–Fl: 144*, 152*	981	40.1 ± 3.9

Adrenaline	Fl: 43, 112, 124; alumina–Fl: 125*, 126*, 127*, 128*, 129, 130*, 131, 132, 133, 134, 153*; IE–Fl: 50*, 126*, 135*, 136*, 137*, 138*, 139, 155*; bioassay: 132, 134; GC–ECD: 140*; GC–MS: 141; REA–TLC: 142, 143; HPLC–ED: 144*, 145*, 146*, 147*, 148, 151, 161*; HPLC–Fl: 152*	777	10.1 ± 1.2
Dopamine	Fl: 43, 112; alumina–Fl: 111, 130*, 133, 156*; IE–Fl: 50*, 138*, 139, 155*, 157; GC–ECD: 140*; GC–MS: 103*; REA: 158; REA–TLC: 142, 143*; alumina–REA–IE–TLC: 159*; HPLC–EC: 145*, 146*, 147*, 148*, 151, 160*, 161*, 162*; HPLC–Fl: 152*	719	263 ± 34
5-Hydroxytryptamine	IE–Fl: 115*, 116*, 163, 164; GC–ECD: 94*	55	120 ± 23
Normetanephrine	Alumina–Fl: 130*; PC–Fl: 165*; IE–Fl: 118, 139, 166*, 167*, 168*, 169, 170; GC–ECD: 94*, 171*; REA: 174*; GC–MS: 76, 103*, 172, 173*; HPLC–ED: 175*	326	194 ± 17
Metanephrine	Alumina–Fl: 130*; PC–Fl: 165*; IE–Fl: 118, 139, 166*, 167*, 168*, 169, 170; GC–ECD: 171*; RIA: 176*; GC–MS: 76, 172, 173*; HPLC–ED: 175*	305	95 ± 9
3-Methoxytyramine	IE–Fl: 177*, 178*; GC–ECD: 171*, 94*; GC–MS: 103*	86	83 ± 11
3,4-Dimethoxy-phenylethylamine	IE–Fl: 179*, 180*, PC–Fl: 181*; RIA: 182*; TLC–radioactivity: 183	96	0.35 range: n.d.–1.71
N,N-Dimethyltryptamine	GC–ND: 184; GC–MS: 185*	19	0.38 ± 0.12
N-Methyltryptamine	GC–ND: 184	19	0.86 ± 0.22
Bufotenin	GC–MS: 186	10	1.71
Melatonin	Bioassay: 187	5	9.6 ± 1.2
6-Hydroxymelatonin	GC–MS: 188, 189*; RIA: 190*	39	14.7 ± 1.7

[a] In all tables, reference numbers followed by an asterisk (*) indicates that the paper cited includes full details of the procedure for the isolation and quantification of the metabolite.

TABLE 2

CONJUGATED BIOGENIC AMINES IN URINE

Amine	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (μg per 24 h)*
Histamine	Bioassay: 79, 80	54	27 ± 5
Phenylethylamine	GC–FID: 90*; TLC–MS: 67*, 96*, 97*	31	19.9 ± 7.4
m-Tyramine	TLC–MS: 67*, 96*, 97*	19	90 ± 14
p-Tyramine	IE–PC–Fl: 107; TLC–MS: 67*, 96*, 97*	21	455 ± 135
Noradrenaline	REA–TLC: 142; HPLC–ED: 145*, 191*	23	139 ± 37
	HPLC–Fl: 191*	11	3-Sulfate: 124 ± 41
	HPLC–Fl: 191*	11	4-Sulfate: 21.6 ± 6.1
Adrenaline	IE–Fl: 155*; REA–TLC: 142; HPLC–ED: 145*	24	20.0 ± 3.0
	HPLC–Fl: 191*	11	3-Sulfate: 18 ± 2.1
	HPLC Fl: 191*	11	4-Sulfate: 3 ± 0.3
Dopamine	REA–TLC: 142; GC–MS: 193; HPLC–ED: 145*, 162*, 192*; HPLC–Fl: 191*, 194*	68	785 ± 167
	HPLC–ED: 162*; HPLC–Fl: 191*, 194*	20	3-Sulfate: 392 ± 72
	HPLC–ED: 162*; HPLC–Fl: 191*, 194*	20	4-Sulfate: 69 ± 10
5-Hydroxytryptamine	IE–Fl: 164	5	34 ± 9 (glucuronide)
		5	52 ± 13 (sulfate)
Normetanephrine	IE–Fl: 135*, 166*, 195*; GC–MS: 193	71	Total: 183 ± 23
Metanephrine	RIA: 176*	15	13.4 ± 2.7
6-Hydroxymelatonin	RIA: 190*	18	Sulfate: 9.7 ± 1,7

no standard error of the mean is shown, this is because none was reported in the reference cited.

3. PSYCHIATRIC DISORDERS

3.1. Depression

3.1.1. Introduction

Biogenic amine hypotheses of affective disorders have mainly been derived from pharmacological and biochemical findings in experimental animals and from animal models of depression. These hypotheses state that some depressive disorders

TABLE 3

UNCONJUGATED BIOGENIC AMINES IN PLASMA

Amine	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (pg/ml)*
Histamine	IE–Fl: 197* REA: 85*, 87, 198*, 199*, 200, 201*; REA–TLC: 202*, 203, 204*; HPLC–Fl: 205*, 206*; HPLC–ED: 207*; GC–MS: 208*, 209*	428	537 ± 49
N^{τ}-Methylhistamine	GC–MS: 87*, 210;	15	1492 ± 167
Phenylethylamine	GC–MS: 211, 212;	19	124 ± 27
m-Tyramine	GC–MS: 102	10	540 ± 150
p-Tyramine	GC–MS: 99	15	680 ± 90
Tryptamine	GC–ND: 58*	4	n. d.
p-Octopamine	REA: 213	14	400 ± 60
Noradrenaline	Alumina–Fl: 133, 214*, 215, 216*, 217*, 218*, 219, 220, 221, IE–Fl: 136*, 222*, 223*, 292*; REA–TLC: 31, 142*, 143*, 172, 224*, 225*, 226, 227, 228, 229*, 230*, 231, 232*, 233, 234, 235*, 236, 237, 238, 239, 240, 241*, 242, 243, 244*, 245, 246, 294; alumina–REA: 76, 247*, 248*, 249*, 250, 251, 252, 253, 254, 255; IE–REA: 256*; IE–REA–TLC: 257, 258, 259*; REA–HPLC: 260*, 261*, 262, 272*; PC–REA–TLC: 263; REA: 264, 265, 266, 267, 268, 269*, 270, 271, 293; GC–ECD: 273*, 274*; GC–MS: 275*; HPLC–ED: 45, 47, 276*, 277*, 278, 279, 280, 281, 282*, 283*, 284, 285, 286*, 287, 288, 289, 290, 299*; HPLC–Fl: 291*	1651	275 ± 32
Adrenaline	Alumina–Fl: 43*, 214*, 215, 216*, 217*, 218*, 219, 220; IE–Fl: 223*, 292*; REA–TLC: 31, 142, 143*, 172, 224*, 225*, 226, 228, 229*, 230*, 231, 232*, 233, 234, 235*, 236, 238, 239, 240, 241*, 242, 244*, 246, 269*, 293, 294*; IE–REA: 256*; alumina–REA: 249*; IE–REA–TLC: 257, 258, 259*;	1067	63 ± 11

(Continued on p. 100)

TABLE 3 (*continued*)

Amine	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (pg/ml)*
	REA–HPLC: 260*, 262, 272*; REA: 265, 267, 271; GC–ECD: 274*; HPLC–ED: 45, 47, 277*, 278, 280, 281, 283*, 286*, 287, 290, 299*; HPLC–Fl: 291		
Dopamine	IE–Fl: 295*; alumina–REA–IE–TLC: 159, 296*; REA–TLC: 142, 143*, 228, 229*, 230*, 232*, 233, 234, 236, 239, 240, 241*, 242, 244*, 269*, 294*, 297; REA–HPLC: 260*, 262; IE–REA–TLC: 259; REA: 158; 270, 271, 298*; GC–ECD: 274*; HPLC–ED: 47, 280, 281, 283, 286*, 287, 290, 299*	535	86 ± 15
5-Hydroxytryptamine	REA: 300*, 301*; RIA: 301*; HPLC–ED: 290, 303*, 304*, 305; HPLC–Fl: 305, 306, 307*, 308*; IE–Fl: 309*;	226	1440 ± 142 (platelet-poor)
	HPLC–Fl: 307*	7	387 ± 84 (ultrafiltrate)
Normetanephrine	IE–REA–TLC: 310*; GC–MS: 311*	12	116 ± 17
Metanephrine	GC–MS: 311*	3	118 ± 92
3-Methoxytyramine	GC–MS: 311*	3	418 ± 84
N,N-Dimethyl-tryptamine	GC–MS: 312*, 313	44	~ 500
Melatonin	GC–MS: 314*; RIA: 315, 316, 317*, 318	26	Day: 11 ± 2 Night: 47 ± 9
	GC–MS: 319*; RIA: 320*	18	24 h: 44 ± 8

TABLE 4

CONJUGATED BIOGENIC AMINES IN PLASMA

Amine	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (pg/ml)*
Noradrenaline	REA–TLC: 142, 236, 238, 239, 241*, 242, 244*, 269*, 321; REA–HPLC: 262; HPLC–ED, Fl: 283*	111	782 ± 259
	REA–TLC: 239	6	Glucuronide: 139 ± 49
	REA–TLC: 236, 238, 239, 241*, 321	46	Sulfate: 636 ± 57
Adrenaline	REA–TLC: 142, 236, 238, 239, 241*, 242, 244, 269*, 321; REA–HPLC: 262; HPLC–ED, Fl: 283*; GC–MS: 273*	116	221 ± 78
	REA–TLC: 239	6	Glucuronide: 22 ± 6
	REA–TLC: 236, 238, 239, 241*, 321	46	Sulfate: 216 ± 43
Dopamine	REA–TLC: 142, 236, 239, 241*, 242, 244*, 269*, 321, 322; REA–HPLC: 262; REA: 158, 298; HPLC–ED: 283*, 323*; HPLC–Fl: 194*, 283*; GC–ECD: 324*	183	2926 ± 696
	REA–TLC: 239	6	Glucuronide: 924 ± 121
	REA–TLC: 236, 239, 241*, 242, 321, 322	84	Sulfate: 3178 ± 343
Normetanephrine	GC–MS: 311*	3	494 ± 37
Metanephrine	GC–MS: 311*	3	335 ± 63
3-Methoxytyramine	GC–MS: 311*	3	668 ± 217

TABLE 5

UNCONJUGATED BIOGENIC AMINES IN CEREBROSPINAL FLUID

Amine	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (pg/ml)*
Histamine	REA: 87*	11	43.1 ± 5.7 ng/ml
N^{τ}-Methylhistamine	GC–MS: 325*	5	2.0 ± 0.1 ng/ml
Phenylethylamine	GC–MS: 99	15	600 ± 100
p-Tyramine	GC–MS: 99	15	790 ± 250
Tryptamine	GC–ND: 58*	4	1–6 ng/ml
Noradrenaline	IE–Fl: 326; alumina–Fl: 220; REA–TLC: 31, 143*, 229*, 243; alumina–REA: 327; PC–REA–TLC: 263; REA–HPLC: 262; REA: 21, 270, 328; HPLC–ED: 329, 330, 331*, 332, 333*, 334, 336; HPLC–Fl: 335	455	119 ± 16
Adrenaline	REA–TLC: 31, 143*, 229*; REA–HPLC: 262; REA: 270; HPLC–ED: 336	118	47 ± 23
Dopamine	REA–TLC: 143*, 263; REA: 270; REA–HPLC: 262; HPLC–ED: 329, 331*, 336	165	48 ± 14
5-Hydroxytryptamine	HPLC–ED: 303*, 337*, 338*, 339*	42	678 ± 94
Normetanephrine	GC–MS: 340*, 341*	19	1800 ± 420
Metanephrine	GC–MS: 341*	6	80 ± 20
3-Methoxytyramine	GC–MS: 341*	6	635 ± 184
Melatonin	RIA: 342; GC–MS: 319*	17	59 ± 28
N,N-Dimethyltryptamine	GC–MS: 343*, 344*	10	n.d. – 1500

TABLE 6

CONJUGATED BIOGENIC AMINES IN CEREBROSPINAL FLUID

Amine	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (pg/ml)*
Noradrenaline	REA–HPLC: 262	40	199 ± 137
Adrenaline	REA–HPLC: 262	40	30 ± 34
Dopamine	REA–HPLC: 262; HPLC–ED: 332, 345*	117	594 ± 108

TABLE 7

UNCONJUGATED ACID METABOLITES IN URINE

Acid metabolite	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (mg per 24 h)*
Imidazoleacetic	IE–REA: 346*; HPLC–Fl: 347*	20	1.6 ± 0.2
N^{τ}-Methylimidazoleacetic	GC–FID: 348*, 349, 350; HPLC–Fl: 347*	76	2.6 ± 0.2
N^{π}-Methylimidazoleacetic	GC–FID: 349, 350 HPLC–Fl: 347*	42	2.2 ± 0.3
Phenylacetic	GC–MS: 96*, 97*, 351*, 352	73	8.5 ± 1.7
o-Hydroxyphenylacetic	GC–FID: 93	27	1.0 ± 0.1
m-Hydroxyphenylacetic	GC–FID: 93; GC–MS: 96*, 97*; GC–ECD: 972*	74	6.6 ± 0.8
p-Hydroxyphenyl acetic	IE–PC–Fl: 107; GC–ECD: 102; 972*; GC–FID: 93, 108, 109; GC–MS: 96*, 97*, 103*	113	19.0 ± 2.4
Indoleacetic	IE–Fl: 116*; GC–MS: 96*, 97*, 353*, 354*	67	10.2 ± 1.3
o-Hydroxymandelic	GC–MS: 355*	10	7.3 ± 1.1 μg/g creatinine
m-Hydroxymandelic	GC–MS: 355*, 356*	7	59 ± 14 μg per 24 h
p-Hydroxymandelic	GC–FID: 93 GC–MS: 96*, 97*, 103*	50	2.8 ± 0.5
Mandelic	GC–MS: 97*	8	0.23 ± 0.01
5-Hydroxyindoleacetic	Colorimetry 131, 357, 358, 359, 360, 361, 362, 363; Sephadex–FL: 120; Bioassay: 364; IE–FL: 116*, 118, 164; Fl: 365, 366, 367; GC–ECD: 972*; GC–MS: 141, 353*, 354*; HPLC–ED: 49*, 146*, 368*, 369, 370*, 371*, 372*; HPLC–Fl: 373*	741	4.56 ± 0.38

(*Continued on p. 104*)

TABLE 7 (*continued*)

Amine	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (mg per 24 h)*
Homovanillic	IE–Fl: 139, 374*, 375*, 376, 377, 378*; silica–Fl: 379*, 380*; TLC–Fl: 381*; alumina–Fl: 130*, 156*; PC–Fl: 382*, 383*, 384*; GC–FID: 93, 385, 386*, 387*; GC–ECD: 388*, 389*, 972*; GC–MS: 97*, 103*, 141, 354*; HPLC–ED: 146*, 151*, 390, 391*, 392*	729	4.85 ± 0.36
Isohomovanillic	PC–colorimetry: 393*; GC–ECD: 388*	15	0.19 ± 0.04
Vanilmandelic	Colorimetry: 394*, 395*, 396*, 397*, 398*, 399*; PC–colorimetry: 367, 384*, 400; alumina–Fl: 130*; IE–Fl: 8*, 135*, 139, 157, 376, 378*, 401*, 402*, 403*, 404*; GC–FID: 93, 385, 386*, 405*; GC–ECD: 118, 169, 170, 388*, 406*, 407; GC–MS: 76, 97*, 103*; alumina–REA: 174*, 408*; HPLC–ED: 151*, 390, 391*, 392*, 409*; HPLC–Fl: 410	1408	4.07 ± 0.25
3.4-Dihydroxy-phenylacetic	Alumina–Fl: 156; electrophoresis–Fl: 411; IE–Fl: 138*, 377, 378*; GC–ECD: 412*; GC–MS: 103*, 193; HPLC–ED: 151*	134	1.87 ± 0.19
3,4-Dihydroxy-mandelic	IE–Fl: 135*, 378*, 413*; electrophoresis–Fl: 411*; alumina–REA: 408*; HPLC–ED: 151*	79	0.29 ± 0.03
3,4-Dimethoxy-phenylacetic	GC–tritium: 180*	8	Trace
5-Methoxyindole-acetic	GC–MS: 189*, 414*	33	5–38

TABLE 8

CONJUGATED ACID METABOLITES IN URINE

Acid metabolite	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (mg per 24 h)*
Imidazoleacetic	IE–REA: 346*	10	3.30 ± 0.22
Phenylacetic	GC–ECD: 939*; GC–FID: 72*, 93, 415*, 416, 629; GC–MS: 97*, 103*, 105*, 351*, 352, 417; HPLC–Fl: 418*	338 (includes 276 totals)	145 ± 15
m-Hydroxyphenylacetic	GC–MS: 97*	8	1.2 ± 0.7
p-Hydroxyphenylacetic	IE–Fl: 107; GC–FID: 109; GC–MS: 97*	18	6.1 ± 2.8
Mandelic	GC–MS: 97*	8	0.12 ± 0.06
5-Hydroxyindoleacetic	GC–MS: 419*	5	0.38 mg/l
Homovanillic	IE–Fl: 377; GC–MS: 419*	13	−0.6 to +5.8 mg/l
3,4-Dihydroxyphenylacetic	IE–Fl: 377; GC–ECD: 412*	20	1.05 ±0.08
3,4-Dihydroxymandelic	IE–Fl: 135*	9	0.17 ± 0.04

are associated with or may be the result of deficiencies in central catecholamine or indoleamine transmission. In man amine metabolite and pharmacological studies have tentatively identified two biochemical sub-types of depressive illness: one subtype claims an abnormality of central noradrenaline systems, and the other an abnormality in central serotonin systems. Several in-depth reviews of these theories have been published in the last few years[616–623,748]. More recently, the putative neuromodulator phenylethylamine has been implicated in the aetiology of affective disorder and this amine has been recently reviewed[624,625]. Other suggested mechanisms have involved abnormal conjugation of *p*-tyramine as a trait marker in major depression[717–722], although a recent study comparing conjugation of ingested deuterium-labelled tyramine in healthy volunteers and depressed patients showed no difference in conjugation between the two groups[970].

The weighted means (calculated as for the normal subjects) of the results of studies on depressed subjects are presented in Tables 19–28. The depressed subjects here have not been differentiated according to the various clinical sub-types of depression. These studies in aggregate indicate that depressed patients as a group show reduced 5-HIAA concentrations in plasma and CSF (but not in urine), reduced MHPG and 3,4-dihydroxyphenylglycol (DHPG) concentrations in urine, plasma and CSF and reduced homovanillic acid and 3,4-dihydroxyphenylacetic acid (DOPAC) concentrations in urine and CSF (but not in plasma) of depressed subjects. Although many of these reductions are not very substantial, the large total number of subjects suggests that these trends may be significant. The parent amines do not appear to be reduced in any of the biological fluids of depressed subjects.

An examination of each of the references cited shows that in over half of them

TABLE 9

UNCONJUGATED ACID METABOLITES IN PLASMA

Acid metabolite	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*
Imidazoleacetic	IE–REA: 346*	10	277 ± 13
N^{τ}-Methylimidazoleacetic	GC–MS: 420*, 421*	6	11.7 ± 1.6
N^{π}-Methylimidazoleacetic	GC–MS: 420*	5	10.3 ± 2.0
Phenylacetic	GC–MS: 40, 97*, 422*, 423, 424*, 425, 426, 427, 428	327	124 ± 14
m-Hydroxyphenylacetic	GC–MS: 59*, 97*, 424*, 425, 426, 427, 428	293	13.4 ± 2.2
p-Hydroxyphenylacetic	GC–MS: 59*, 97*, 424*, 425, 426, 427, 428	293	69.0 ± 8.8
Indoleacetic	GC–MS: 97*, 428; HPLC–ED: 429*; HPLC–Fl: 430*	144	293 ± 38
Mandelic	GC–MS: 431*, 432*	16	13.6; 41.0
m-Hydroxymandelic	GC–MS: 432*	10	n.d.
p-Hydroxymandelic	GC–MS: 59*, 97*, 428, 432*	106	9.7 ± 0.8
5-Hydroxyindoleacetic	GC–MS: 20, 433; HPLC–ED: 434*, 435*; HPLC–Fl: 430*	45	10.5 ± 1.1
Homovanillic	GC–MS: 20, 59*, 97*, 428, 433, 436*, 437, 438, 439*, 440, 441*, 442, 443; HPLC–ED: 444*, 445, 446, 447*, 448	311	10.0 ± 1.0
Vanilmandelic	GC–MS: 59*, 279, 428, 432*, 436*, 439*, 449*; HPLC–ED: 447*, 451*	163	7.0 ± 0.8
3,4-Dihydroxyphenylacetic	IE–REA–TLC: 259*; REA–TLC: 452*; GC–MS: 59*, 441*; HPLC–ED: 286, 453*	73	3.4 ± 0.5
3,4-Dihydroxymandelic	REA–TLC: 31, 235*, 244*, 245, 452*; IE–REA–TLC: 259*	99	1.94 ± 0.35

TABLE 10

CONJUGATED ACID METABOLITES IN PLASMA

Acid metabolite	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*
Imidazoleacetic	IE–REA: 346*	10	25 ± 3
Phenylacetic	GC–MS: 40, 97*, 422*, 423, 424*, 425, 426, 428, 454*	273	345 ± 35
m-Hydroxyphenyl-acetic	GC–MS: 97*, 424*, 425, 426, 428	219	2.1 ± 1.1
p-Hydroxyphenyl-acetic	GC–MS: 97*, 424*, 425, 426, 428	219	13.6 ± 4.3
3,4-Dihydroxy-mandelic	REA–TLC: 244*	5	7.9 ± 1.0

no comparison with normal controls was made, but in the remainder of the studies the equivocal evidence for the proposed hypotheses of depression suggests that the serotonergic and noradrenergic systems may indeed be deficient in depression, which appears also to be the case for PAA. Hence cerebrospinal fluid 5-HIAA concentrations in depressed subjects have been reported to be significantly reduced[470,471,473,474,482,496,510,626–628], to exhibit a trend to be reduced[466,478,487,498,517] and to be no different[170,330,332,463,480,488,493,494,503,505,518,531,536,630–633] than normal controls. Plasma 5-HIAA tends to be reduced[305], whereas urinary 5-HIAA mostly shows no difference between depressed and normal subjects[118,120,361,366]. Most investigators have found no significant differences between the urinary[93,103,193], plasma[440] or CSF[330,332,480,485,494,498,499,503,505,509,518] concentrations of HVA in normal and depressed subjects. In four studies a significant reduction was claimed[487,496,510,528], and a trend to decreased HVA in depression has been reported in a few others[170,493,517,536,631,633]. Urinary[103,193] and CSF[330,332,503] concentrations of DOPAC are also not significantly different between depressed and normal populations. A slight decrease in urinary dopamine (DA)[103] and non-significant increases in plasma[287,332,345] and CSF[634] dopamine levels in depression have been reported.

In the noradrenergic system, the major central metabolite, MHPG, has been found to be significantly reduced[120,169,193,557,562,564,565,568], to show a trend to be reduced[76,118,477,551,563] or to be unchanged[32,103,170,566,571,572] in the urine of depressives. In plasma[27,76,440,448,587,588,593,607] and CSF[35,170,330,332,494,498,503,505,517,518,610,612,633], however, MHPG concentrations in depressed and normal subjects have not been found to be significantly different, with one exception in which MHPG in the CSF of depressed subjects was significantly reduced[500]. The concentrations of two other noradrenergic metabolites, DHPG in plasma[603] and VMA in CSF[541], have been reported to be significantly lower in depression. Dajas and co-workers[149,150] have claimed a significant elevation of urinary noradrenaline in depression, and a trend to elevated plasma[76,284,287,288,326,723] and CSF[255] levels in depression has been reported by other investigators. Urinary VMA[76,93,103,118,169,170,193,562,637] and normetanephrine, the methylated metabolite of noradrenaline[76,103,118,169,170,193], were not significantly different in depressed and control subjects.

In a major study on a large number of severely depressed patients and healthy

TABLE 11

UNCONJUGATED ACID METABOLITES IN CEREBROSPINAL FLUID

Acid metabolite	*References and methods*[a]	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*
N^t-Methylimidazoleacetic	GC–MS: 420*, 421*	15	0.14; 3.19
N^π-Methylimidazoleacetic	GC–MS: 420*	10	11.3 ± 2.6
Phenylacetic	GC–MS: 39, 40, 422*, 785, 454*, 455*, 456; HPLC–ED: 336	125	24.0 ± 3.1
m-Hydroxyphenylacetic	GC–MS: 432*	10	~0.5
p-Hydroxyphenylacetic	GC–MS: 457; HPLC–ED: 458*	32	8.8 ± 1.4
Indoleacetic	HPLC–Fl: 270, 459, 460, 461	184	4.35 ± 0.55
p-Hydroxymandelic	GC–MS: 457	5	1.3 ± 0.4
5-Hydroxyindoleacetic	Sephadex–Fl: 18, 462*, 463, 464, 465, 466; TLC–Fl: 328, 467, 468, 469, 470, 471, 472, 473, 478, 479, 480, 481, 482; column chromatography–Fl: 15, 154, 474, 475, 476; IE–Fl: 483; Fl: 22, 131, 450, 484, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498; GC–ECD: 500*; GC–MS: 54, 419*, 433, 450, 501, 502, 503, 504*, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514;	1553	26.2 ± 2.2

	HPLC–Fl: 270; HPLC–ED: 303*, 330, 332, 333*, 334, 336, 337*, 339*, 515*, 516*, 517*, 518, 519*, 520*, 521*, 522*, 523, 524, 525, 526		
Homovanillic	Sephadex–Fl: 263, 464, 480, 481, 499, 527, 528*; IE–Fl: 328, 529, 530; column chromatography: 468, 531; Fl: 15, 18, 22, 131, 270, 467, 469, 472, 475, 476, 479, 484, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 532, 533, 534, 535, 536; GC–ECD: 498, 500* GC–MS: 54, 170, 419*, 433, 441*, 450, 457, 501, 502*, 504*, 505, 506, 507, 508, 510, 511, 512, 513, 514, 537*, 538, 539*; HPLC–ED: 330, 332, 333*, 334, 339*, 515*, 516*, 517*, 518, 519*, 520*, 521*, 522*, 524, 525, 526	1606	40.7 ± 4.3
Vanilmandelic	GC–MS: 450, 457, 501, 538, 541	44	0.98 ± 0.16
3,4-Dihydroxy-phenylacetic	GC–MS: 441*, 450, 502*, 503, 513, 540; HPLC–ED: 330, 331*, 332, 339*, 524	252	0.49 ± 0.04
3,4-Dihydroxy-mandelic	REA–TLC: 31	36	2.35 ± 0.26

TABLE 12

CONJUGATED ACID METABOLITES IN CEREBROSPINAL FLUID

Acid metabolite	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*
Phenylacetic	GC–MS: 40, 454*, 455*; HPLC–ED: 336	54	24.5 ± 4.5
Homovanillic	GC–MS: 502*	23	0.25 ± 0.58
3,4-Dihydroxy-phenylacetic	GC–MS: 502*, 503, 540	40	0.22 ± 0.01

controls, two sub-groups of depressed patients were identified, one excreting normal levels of adrenaline, metanephrine, noradrenaline and normetanephrine and the other excreting very high levels[971]. Interestingly, the HVA concentration in the CSF of subjects in the high excretion group was significantly low.

In addition to the major neurotransmitters and their metabolites, the comparisons indicate that there may also be deficiencies in PE and pTA metabolism in depression. Although the parent amine concentrations in the urine of depressives appear to be normal, PAA and *p*-hydroxyphenylacetic acid concentrations in urine, plasma and CSF are all lower in depressed than in normal subjects. A statistically significant reduction in urinary PAA has been reported and proposed as a biological "state" marker for unipolar depression[416,417,629,663], but other research groups reported no reduction at all in the urinary excretion of PAA in depression[72,352]. In a study of PE excretion in depression, DeLisi *et al.*[417] reported that those patients forming a sub-

TABLE 13

UNCONJUGATED ALCOHOL AND GLYCOL METABOLITES IN URINE

Alcohol or glycol	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (μg per 24 h)*
Phenyl glycol	GC–MS: 542*	1	22
p-Hydroxyphenyl-ethanol	GC–MS: 542*	1	n.d.
p-Hydroxyphenyl-glycol	GC–MS: 542*	1	13
3-Methoxy-4-hydroxyphenyl glycol	Fl: 543*; IE–Fl: 544; GC–ECD: 11*, 545; GC–MS: 97*, 419*, 546*, 547*; HPLC–ED: 548*	109	113 ± 17
3-Methoxy-4-hydroxyphenyl-ethanol	GC–MS: 546*	9	n.d.
3,4-Dihydroxy-phenyl glycol	REA–TLC: 549*	7	155 ± 42 μg/l

TABLE 14

CONJUGATED ALCOHOL AND GLYCOL METABOLITES IN URINE

Alcohol or glycol	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (μg per 24 h)*
p-Hydroxyphenyl-ethanol	GC–MS: 542*	1	11
p-Hydroxyphenyl-glycol	GC–MS: 542*	1	78
3-Methoxy-4-hydroxyphenyl glycol	Fl: 543*; Sephadex–Fl: 551; IE–Fl: 108, 376, 544, 552*, 553*, 554*, 555; alumina–REA: 174*; GC–FID: 385, 387*, 477; GC–ECD: 11*, 70, 118, 120, 131, 170, 407, 545, 546*, 556*, 557, 558, 559*, 560, 561*, 562, 563*, 564, 565, 566, 567*, 568, 569, 570, 571, 572, 573, 574*; GC–MS: 10, 32, 76, 103*, 141, 193, 542*, 547*; HPLC–ED: 548*, 575*, 576*, 577*; HPLC–Fl: 578*	936	1854 ± 156
	IE–Fl: 544, 555; Sephadex–Fl: 551; GC–ECD: 11*, 407, 561*, 546*; GC–MS: 547*; HPLC–ED: 548*	141	Sulfate: 1070 ± 130
	IE–Fl: 544, 555; GC–ECD: 11*, 407, 546*; GC–MS: 547*; HPLC–ED: 548*	111	Glucuronide: 1010 ± 90
3-Methoxy-4-hydroxyphenyl-ethanol	GC–MS: 546*	9	239 ± 50
3,4-Dihydroxy-phenyl glycol	REA–TLC: 549*	7	584 ± 133 μg/l
	GC–MS: 579*	7	Total: 325 ± 60 μg/g creatinine
3,4-Dihydroxy-phenylethanol	GC–MS: 579*	4	Total: 16 ± 15 μ/g creatinine

TABLE 15

UNCONJUGATED ALCOHOL AND GLYCOL METABOLITES IN PLASMA

Alcohol or glycol	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*
3-Methoxy-4-hydroxyphenyl glycol	GC–ECD: 74*, 580*; GC–MS: 26, 27, 29, 75, 76, 243, 440, 442, 449*, 581*, 583*, 584*, 585, 586, 587, 588, 589*, 590, 591, 592, 593; HPLC–ED: 447*, 448, 577*, 594*, 595*, 596*, 597, 598*, 599, 600*, 601*	402	3.55 ± 0.33
3,4-Dihydroxyphenylethanol	REA–TLC: 602*; IE–REA–TLC: 259*	22	0.17 ± 0.07
3,4-Dihydroxyphenyl glycol	REA–TLC: 31, 235*, 244*, 245, 452*, 549*, 602*, 603; IE–REA–TLC: 259*; GC–MS: 589*; HPLC–ED: 282*, 453*, 604	204	0.81 ± 0.07

TABLE 16

CONJUGATED GLYCOL METABOLITES IN PLASMA

Glycol	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*
3-Methoxy-4-hydroxyphenyl glycol	GC–ECD: 74*, 573, 580*; GC–MS: 29, 279, 437, 449*, 581*, 584*, 585, 589*, 605*; HPLC–ED: 446, 606*, 607;	251	11.3 ± 0.8
3,4-Dihydroxy-phenyl glycol	REA–TLC: 244, 549*, 603; GC–MS: 589	70	1.18 ± 0.11

group with very high PE excretion (three times the highest value found in the controls) were clinically indistinguishable from depressed patients with low PE excretion. As PE excretion is not correlated with PAA excretion, these results suggest that depression is not associated with a generalized PE deficit and that reported PAA reductions may not reflect a PE abnormality.

3.1.2. Tables of values for depressed subjects (all clinical sub-types combined)

The studies discussed above and the comparisons of the weighted means in Tables 19–28 for depressed subjects with all clinical sub-types combined suggest that there may well be a monoamine dysfunction in depression. The current view, however, is that affective disease is a heterogeneous group of disorders. Therefore, the amine and metabolite concentrations in various diagnostic sub-types of depression are compared with each other and with controls in Tables 29–36.

3.1.3. Comparison of unipolar and bipolar depressed subjects

Comparisons of unipolar and bipolar depressed subjects are given in Tables 29–31.

To summarize, bipolar patients exhibited lower CSF concentrations than did unipolar patients in five of seven studies on 5-HIAA, three of four studies on MHPG and three of seven studies on HVA. Plasma MHPG concentrations were lower in bipolar patients in three of four studies and urinary MHPG concentrations in eleven of thirteen studies. Plasma noradrenaline levels were lower in the bipolar subjects in all five studies. There would appear, therefore, to be a noradrenergic dysfunction in bipolar subjects.

Some investigators have suggested that the unipolar depressive disorders can be subdivided into two or three sub-types based on differences in pretreatment urinary MHPG levels[169,562,568,571,637,740,741] and on CSF monoamine metabolite levels[745]. A bimodal distribution of 5-HIAA in the CSF of patients with endogenous depression has been found by several investigators[531,667,678,680,745], but could not be confirmed by others[518,683,686]. For unipolar depressive patients, multiple regression analysis has revealed strong correlations which suggest that high and low HVA, MHPG and 5-HIAA syndromes should be isolated[681]. Evidence has also been reported that in both unipolar and bipolar patients high and low monoamine syndromes are characterized by different symptomatology[681]. Schildkraut *et al.*[749] have

TABLE 17

UNCONJUGATED ALCOHOL AND GLYCOL METABOLITES IN CEREBROSPINAL FLUID

Alcohol or glycol	*References and methods*[a]	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*
p-Hydroxyphenyl-ethanol	GC–MS: 457	8	12.3 ± 1.7
3-Methoxy-4-hydroxyphenyl glycol	Fl: 608; GC–ECD: 22, 35, 131, 494, 497, 498, 500*, 558, 609*, 610*, 611, 612; GC–MS: 170, 243, 419*, 433, 450, 501*, 502*, 504*, 505, 506, 507, 508, 510, 513, 538, 581*, 589*, 605*; HPLC–ED: 330, 332, 333*, 339*, 515*, 516*, 517*, 518, 520*, 522*, 526, 600*, 613*, 614*	884	10.5 ± 1.2 (mostly total MHPG)
3-Methoxy-4 hydroxyphenyl-ethanol	GC–ECD: 558	3	5.7 ± 0.9
3,4-Dihydroxy-phenylglycol	REA–TLC: 31, 549*; GC–MS: 589*	45	1.00 ± 0.07
3,4-Dihydroxy-phenylethanol	REA–TLC: 602*	8	1.62 ± 0.86
5-Hydroxytryptophol	GC–MS: 615*	24	0.78 ± 0.11

TABLE 18

CONJUGATED ALCOHOL AND GLYCOL METABOLITES IN CEREBROSPINAL FLUID

Alcohol or glycol	*References and methods*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*
3-Methoxy-4-hydroxyphenyl glycol	GC–MS: 419*, 502*, 581*, 589*; HPLC–ED: 613*, 614*	97	0.51 ± 0.10
3-Methoxy-4-hydroxyphenyl-ethanol	GC–ECD: 558	2	3.3 ± 1.0
3,4-Dihydroxy-phenyl glycol	REA–TLC: 549*; GC–MS: 589*	9	0.14 ± 0.04

developed an equation based on the concentrations of noradrenaline, MHPG, VMA, normetanephrine and metanephrine for calculating a depression score which has good predictive value. It has also been demonstrated that urinary MHPG output is highly reliable both during and between recurring depressive episodes[743], that is, low or high excreters are reliably low or high during different episodes. The concentrations of metabolites in biological fluids of bipolar patients on the depressed and manic phases are presented in Tables 32–34.

3.1.4. Comparison of bipolar-depressed and bipolar-manic subjects

To summarize the comparisons of bipolar-depressed and bipolar-manic subjects in Tables 32–34 urinary dopamine and noradrenaline are reported to be consistently higher in manic than in depressed subjects. The major metabolites of these amines, HVA in CSF and MHPG in urine and CSF, also tend to be higher in manic patients. Measurements of monoamine metabolites in CSF have shown abnormal, perhaps excessive, central noradrenergic activity in patients with mania[509]. Longitudinal studies of the switch process from depression to mania have shown highly significant correlations of high urinary[647] and plasma MHPG[585,739] and high urinary noradrenaline[642,643,645] and VMA[642,750] concentrations with the manic phase.

3.1.5. Comparison of psychotic and non-psychotic (neurotic) depressed subjects

This comparison is presented in Table 35.

3.1.6. Comparison of depressed subjects with and without melancholia

This comparison is presented in Table 36.

3.1.7. Panic disorder, agoraphobia and anxiety

Dysfunction of the central noradrenergic system has been postulated to play an important role in the neurobiology of both major depressive and panic disorders and there is evidence suggesting an overlap between these disorders[593]. In studying these disorders, plasma and urinary noradrenaline and MHPG have been used as an indirect measure of noradrenergic activity. The results, however, have been equivocal.

TABLE 19

UNCONJUGATED BIOGENIC AMINES IN URINE

Amine	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (μg per 24 h)*	
			Depressives	*Normals*[a]
Phenylethylamine	69, 93, 102, 103, 635, 638, 639	81	7.7 ± 2.1	8.1 ± 1.8
m-Tyramine	102, 103	23	49 ± 8	83 ± 10
p-Tyramine	102, 103, 114, 638, 639	60	583 ± 64	579 ± 75
Tryptamine	7, 118, 119, 120, 640	67	96 ± 19	103 ± 19
Noradrenaline	69, 103, 131, 149, 150, 637, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652	441	52 ± 6	40 ± 4
Adrenaline	637, 641, 642, 643, 644, 645, 646, 649, 650, 651, 652, 653	299	19 ± 2	10 ± 1.2
Dopamine	103, 641, 642, 643, 645, 654	39	281 ± 52	263 ± 34
5-Hydroxytryptamine	69, 163	32	168 ± 34	120 ± 23
Normetanephrine	69, 76, 103, 118, 169, 170, 196, 562, 637, 638, 639, 644, 646, 648, 649, 650, 651, 655	463	277 ± 30	194 ± 17
Metanephrine	76, 118, 169, 170, 562, 637, 644, 646, 649, 650, 651, 655	405	133 ± 11	95 ± 9
3-Methoxytyramine	103, 639	10	12.9 ± 3.9	83 ± 11
N,N-Dimethyl-tryptamine	656	14	0.80	0.38 ± 0.12
N-Methyltryptamine	656	14	0.80	0.86 ± 0.22
Melatonin	187	5	11.6 ± 1.1	9.6 ± 1.2
6-Hydroxymelatonin	657	27	7.2 ± 1.2	14.7 ± 1.7

[a] Weighted normal means taken from Table 1.

TABLE 20

CONJUGATED BIOGENIC AMINES IN URINE

Amine	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (μg per 24 h) (normals[a])*
Noradrenaline (total)	69, 149, 193, 196, 638, 639, 648	100	244 ± 36 (conjugated = 139 ± 37)
Dopamine (total)	69, 193, 639, 658	51	764 ± 148
Dopamine (conjugated)	157	13	304 (785 ± 167)
Normetanephrine (total)	193	28	195 ± 24 (total = 183 ± 23)

[a] Weighted normal means taken from Table 2.

TABLE 21

UNCONJUGATED BIOGENIC AMINES IN PLASMA

Amine	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (pg/ml)*	
			Depressives	*Normals[a]*
Phenylethylamine	211	3	120 ± 60	124 ± 27
Noradrenaline	76, 246, 255, 284, 285, 287, 288, 659	209	263 ± 59	275 ± 32
Adrenaline	287	22	87 ± 9	63 ± 11
Dopamine	287	22	93 ± 20	86 ± 15
Melatonin	660	4	188 ± 38	44 ± 8

[a] Weighted normal means taken from Table 3.

TABLE 22

UNCONJUGATED AND CONJUGATED BIOGENIC AMINES IN CEREBROSPINAL FLUID

Amine	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (pg/ml)*	
			Depressives	*Normals[a]*
Noradrenaline	28, 330, 332, 661, 662	78	128 ± 20	119 ± 16
Adrenaline	634	7	16.0 ± 3.4	47 ± 23
Dopamine	634	7	12	48 ± 14
Conjugated dopamine	332, 345, 662	196	756 ± 47	594 ± 108

[a] Weighted normal means taken from Tables 5 and 6.

TABLE 23

UNCONJUGATED (AND TOTAL) ACID METABOLITES IN URINE

Acid metabolite	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (mg per 24 h)*	
			Depressives	*Normals*[a]
Phenylacetic (total)	72, 93, 103, 352, 416, 417, 629, 663	243	119 ± 16	149 ± 15
o-Hydroxyphenylacetic	93	23	0.81 ± 0.10	1.0 ± 0.1
m-Hydroxyphenylacetic	93	23	4.45 ± 0.63	6.8 ± 0.9
p-Hydroxyphenylacetic	93, 103, 639	33	9.90 ± 1.00	18.6 ± 2.6
Indoleacetic	7, 640	29	3.60 ± 0.70	10.2 ± 1.3
p-Hydroxymandelic	93, 103	29	1.29 ± 0.20	2.8 ± 0.5
5-Hydroxyindoleacetic	7, 69, 118, 120, 131, 163, 361, 366, 639, 642, 645	147	5.10 ± 0.74	4.53 ± 0.37
Homovanillic	69, 93, 103, 193, 642, 639, 654, 658	96	4.32 ± 0.46	4.79 ± 0.32
Vanilmandelic	30, 69, 76, 93, 103, 118, 169, 170, 193, 196, 409, 562, 568, 637, 638, 639, 642, 644, 646, 648, 649, 650, 651, 664, 665	574	4.02 ± 0.31	4.07 ± 0.25
3,4-Dihydroxyphenylacetic	103, 193, 658	41	1.08 ± 0.18	1.90 ± 0.19

[a] Weighted normal means taken from Tables 7 and 8.

TABLE 24

UNCONJUGATED ACID METABOLITES IN PLASMA

Acid metabolite	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*	
			Depressives	*Normals*[a]
Phenylacetic	427	46	98 ± 5	124 ± 14
m-Hydroxyphenyl-acetic	427	46	12.9 ± 2.4	13.4 ± 2.2
p-Hydroxyphenyl-acetic	427	46	59.4 ± 5.1	69.0 ± 8.8
Homovanillic	440, 448, 694, 708, 712	98	14.8 ± 2.0	9.7 ± 0.9
5-Hydroxyindole-acetic	305, 708	26	7.2 ± 2.6	11.4 ± 1.5

[a] Weighted normal means taken from Table 9.

TABLE 25

UNCONJUGATED AND CONJUGATED ACID METABOLITES IN CEREBROSPINAL FLUID

Acid metabolite	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*	
			Depressives	*Normals*[a]
Phenylacetic	39, 456	30	19.6 ± 2.0	24.0 ± 3.1
p-Hydroxyphenyl-acetic	458	4	4.0 ± 0.5	8.8 ± 1.4
Indoleacetic	461, 666, 667, 668	143	5.7 + 0.7	4.35 ± 0.55
5-Hydroxyindole-acetic	131, 170, 330, 332, 463, 466, 470, 471, 473, 474, 478, 480, 487, 488, 493, 494, 496, 498, 503, 505, 510, 517, 518, 531, 536, 616, 626, 627, 628, 629, 630, 631, 632, 633, 636, 649, 653, 662, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694	1892	24.0 ± 2.1	26.2 ± 2.2
Homovanillic	131, 170, 330, 332, 480, 485, 487, 493, 494, 496, 498, 499, 503, 505, 509, 510, 517, 518, 528, 536, 616, 631, 633, 649, 653, 662, 668, 670, 671, 673, 674, 675, 676, 677, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 693, 694	1547	32.1 ± 3.4	40.7 ± 4.3
Conjugated Homovanillic	503	10	2.2 ± 1.7	0.25 ± 0.06
Vanilmandelic	541	19	0.70 ± 0.17	0.98 ± 0.16
3,4-Dihydroxy-phenylacetic	330, 332, 503, 662	59	0.34 ± 0.22	0.49 ± 0.04
Conjugated 3,4-dihydroxyphenylacetic	503, 662	37	0.46 ± 0.10	0.22 ± 0.10

[a] Weighted normal means taken from Tables 11 and 12.

TABLE 26

UNCONJUGATED AND CONJUGATED GLYCOL METABOLITES IN URINE

Glycol metabolite	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (μg per 24 h)*	
			Depressives	*Normals*[a]
3-Methoxy-4-hydroxyphenyl glycol	555	36	64	113 ± 17
Conjugated 3-methoxy-4-hydroxyphenyl glycol	10, 25, 27, 28, 30, 32, 33, 35, 69, 76, 103, 118, 120, 169, 170, 193, 196, 477, 551, 555, 557, 562, 563, 564, 565, 566, 568, 571, 572, 616, 635, 637, 638, 639, 644, 645, 646, 647, 648, 650, 651, 683, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706	1373	1582 ± 138	1866 ± 165
3,4-Dihydroxyphenyl glycol (total)	706	20		352 ± 38 584 ± 133 μg/l

[a] Weighted normal means taken from Tables 13 and 14.

TABLE 27

UNCONJUGATED AND CONJUGATED GLYCOL METABOLITES IN PLASMA

Glycol metabolite	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*	
			Depressives	*Normals*[a]
3-Methoxy-4-hydroxyphenyl glycol	26, 28, 37, 76, 440, 448, 587, 588, 593, 707, 708, 709, 710, 711, 712	225	3.84 ± 0.34	3.55 ± 0.31
Conjugated 3-methoxy-4-hydroxyphenyl glycol	37, 585, 607 (total), 711	13	8.33 ± 0.66	11.3 ± 0.8
3,4-Dihydroxy-phenyl glycol	603, 711, 713	124	0.79 ± 0.07	0.82 ± 0.07
Conjugated 3,4-dihydroxyphenyl glycol	603, 713	101	0.81 ± 0.07	1.18 ± 0.11

[a] Weighted normal means taken from Tables 15 and 16.

TABLE 28

UNCONJUGATED AND CONJUGATED GLYCOL METABOLITES IN CEREBROSPINAL FLUID

Glycol metabolite	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*	
			Depressives	*Normals*[a]
3-Methoxy-4-hydroxyphenyl glycol	30, 35, 131, 170, 330, 332, 494, 498, 500, 503, 505, 509, 510, 517, 518, 610, 612, 616, 633, 649, 653, 662, 668, 679, 680, 681, 682, 683, 685, 686, 688, 690, 693, 694, 703, 714, 715, 716	897	9.68 ± 0.56	10.6 ± 1.2
Conjugated 3-methoxy-4-hydroxyphenyl glycol	494, 503, 714	41	2.2 ± 0.5	0.51 ± 0.10

[a] Weighted normal means taken from Tables 17 and 18.

TABLE 29

SEROTONIN SYSTEM

The significance tests reported in this and subsequent tables were performed by the authors of the papers cited, not by the author of this review.

Metabolite	*Reference*	*Biological fluid*	*Concentrations*		
			Unipolar	*Bipolar*	*Control*
5-Hydroxy-indoleacetic	120	Urine	–	4.13 ± 0.51 mg per 24 h	3.83 ± 0.25 mg per 24 h
	674	CSF	10 ± 2 ng/ml		18 ± 3
	496	CSF	16.4 ± 0.9[a]	14.6 ± 1.7[a] ng/ml	27.5 ± 1.2 ng/ml
	498	CSF	32.0 ± 3.2	23.0 ± 2.9	28 ± 6
	681	CSF	21.0 ± 1.8[b]	17.8 ± 10.5[b]	26.7 ± 13.4 (S.D.)
	687	CSF	29.4 ± 2.2	22.0 ± 3.4	
	170	CSF (male)	19.7 ± 0.9	20.4 ± 1.4	20.6 ± 0.8
	170	CSF (female)	25.4 ± 1.2	23.3 ± 1.7	21.8 ± 1.3
	330	CSF	–	17.6 ± 2.5	14.3 ± 0.9
		CSF weighted means ± S.E.M.	21.1 ± 1.4 (n = 175)	19.3 ± 2.1 (n = 97)	22.8 ± 1.9 (n = 132)

[a] $p < 0.001$ *vs.* control.
[b] $p < 0.01$ *vs.* control.

TABLE 30

NORADRENALINE SYSTEM

Amine or metabolite	*Reference*	*Biological fluid*	*Concentrations*		
			Unipolar	*Bipolar*	*Control*
Noradrenaline	637	Urine	45 ± 4 μg per 24 h	27 ± 4 μg per 24 h	
	650	Urine	46.2 ± 3.6	23.4 ± 3.1	
	723	Plasma	550* pg/ml	400* pg/ml	280 pg/ml
	284	Plasma	220 ± 41*	122 ± 15*	147 ± 10
	285	Plasma	233 ± 10†	161 ± 7*	264 ± 10
	76	Plasma	351 ± 81††	268 ± 30	232 ± 25
	288	Plasma	318 ± 49**	123 ± 17	142 ± 10
		Plasma weighted mean ± S.E.M.	346 ± 45 (n=65)	300 ± 15 (n=62)	191 ± 13 (n=135)
	330	CSF		57 ± 11 pg/ml	54 ± 8 pg/ml
	332	CSF		76 ± 13	67 ± 7
Adrenaline	637	Urine	9.8 ± 1.0 μg per 24 h	8.2 ± 1.2 μg per 24 h	
	650	Urine	25.8 ± 2.1	17.7 ± 1.8	
Normetanephrine	169	Urine	207 ± 25 μg per 24 h	187 ± 30 μg per 24 h	
	637	Urine	323 ± 43	225 ± 26	
	76	Urine	293 ± 23	275 ± 46	293 ± 24
	650	Urine	310 ± 22	227 ± 31	
		Urine weighted mean ± S.E.M.	296 ± 26 (n=102)	226 ± 31 (n=50)	
Metanephrine	637	Urine	144 ± 11	161 ± 19	
	169	Urine	92 ± 7	85 ± 16	75 ± 6
	76	Urine	138 ± 19	138 ± 49	130 ± 15
	650	Urine	141 ± 7	133 ± 10	
		Urine weighted mean ± S.E.M.	134 ± 9 (n=102)	135 ± 16 (n=50)	
Vanilmandelic acid	637	Urine	3.78 ± 0.25 mg per 24 h	4.04 ± 0.21 mg per 24 h	
	169	Urine	4.68 ± 0.51	3.93 ± 0.78	4.63 ± 0.44
	568	Urine	3.93 ± 0.17	4.04 ± 0.16	
	76	Urine	4.65 ± 0.28	4.30 ± 0.27	3.96 ± 0.22
	650	Urine	3.61 ± 0.49	3.44 ± 0.22	
		Urine weighted mean ± S.E.M.	3.91 ± 0.34 (n=145)	3.82 ± 0.25 (n=66)	
	330	CSF		386 ± 48 pg/ml	437 ± 34 pg/ml

(*Continued on p. 126*)

TABLE 30 (*continued*)

Amine or metabolite	*Reference*	*Biological fluid*	*Concentrations*		
			Unipolar	*Bipolar*	*Control*
3-Methoxy-4-hydroxyphenyl glycol[a]	25	Urine	1860 ± 170 μg per 24 h	1590 ± 250 μg per 24 h	
	25	Urine	1860 ± 170†††	830 ± 75[b]	
	169	Urine	1161 ± 142*	916 ± 153*	1348 ± 65
	120	Urine		1320 ± 190	1600 ± 80
	637	Urine	1590 ± 177	1209 ± 89	
	477	Urine	1580 ± 120		1680 ± 120
	701	Urine	904 ± 126	676 ± 115	
	566	Urine	1820 ± 120***	1090 ± 120 (group I)	1330 ± 120
	566	Urine	1820 ± 120	1440 ± 200 (group II)	1330 ± 120
	32	Urine (male)	3606 ± 241	3772 ± 631	3478 ± 280
	32	Urine (female)	3054 ± 222	2502 ± 205	2558 ± 280
	568	Urine (male)	2378 ± 133	1410 ± 186***	2021 ± 133
	568	Urine (female)	1853 ± 146	1336 ± 127***	1820 ± 157
	704	Urine	856 ± 136	1496 ± 266	
	571	Urine	2081 ± 143		1767 ± 117
	572	Urine	1790 ± 110	1440 ± 100	1850 ± 20
	572	Urine (male)	1890 ± 150	1600 ± 140	1890 ± 130
	572	Urine (female)	1670 ± 150	1370 ± 130	1830 ± 170
	76	Urine	2521 ± 245	2429 ± 359	2760 ± 190
	650	Urine	2155 ± 131	2123 ± 131	
	551	Urine	1480 ± 96	1037 ± 191	1451 ± 103
		Urine weighted mean ± S.E.M.	2038 ± 149 (n = 332)	1668 ± 180 (n = 151)	1856 ± 119 (n = 203)

3-Methoxy-4-hydroxyphenyl glycol[c]	27	Plasma	4.3 ± 0.6††† ng/ml	2.7 ± 0.4[d] ng/ml	
	27	Plasma	3.6 ± 0.3	3.0 ± 0.4	
	76	Plasma	3.2 ± 0.4	3.4 ± 0.3	3.0 ± 0.1
	448	Plasma	3.69 ± 0.62	2.89 ± 0.28	
		Plasma weighted mean ± S.E.M.	3.55 ± 0.36 ($n=51$)	3.16 ± 0.33 ($n=18$)	
	610	CSF	11.9 ± 0.6 (total)	6.1 ng/ml (total)	
	35	CSF	11.9 ± 0.6 (total)		10.8 ± 0.8 (total)
	498	CSF	14 ± 1.1***	15 ± 2.0	10 ± 0.9†
	681	CSF	10.7 ± 0.4	10.5 ± 0.5	11.0 ± 2.8 (S.D.)
	170	CSF	8.9 ± 0.3**	8.5 ± 0.3	8.0 ± 0.2
	330	CSF		8.1 ± 0.4	8.3 ± 1.8
		CSF weighted mean ± S.E.M.	10.4 ± 0.5 ($n=117$)	10.5 ± 0.5 ($n=67$)	8.7 ± 0.7 ($n=115$)

* $p < 0.05$ *vs.* control.
** $p < 0.001$ *vs.* control.
*** $p < 0.01$ *vs.* control.
† $p < 0.02$ *vs.* bipolar.
†† $p < 0.01$ *vs* bipolar.
††† $p < 0.001$ *vs.* bipolar.
[a] Conjugated or total.
[b] With history of mania.
[c] Unconjugated.
[d] With melancholia.

TABLE 31

DOPAMINE SYSTEM

Amine or metabolite	*Reference*	*Biological fluid*	*Concentrations*		
			Unipolar	*Bipolar*	*Control*
Dopamine	654	Urine	210 ± 30 μg per 24 h	170 ± 40 μg per 24 h	
Homovanillic acid	654	Urine	5.82 ± 0.71 mg per 24 h	4.97 ± 0.67 mg per 24 h	
	448	Plasma	10.7 ± 2.6 ng/ml	11.2 ± 3.8	
	674	CSF	20 ± 2	34 ± 4	
	498	CSF	88 ± 10***	78 ± 22*	45 ± 5 ng/ml
	681	CSF	37.0 ± 4.5**	33.3 ± 4.6***	54.6 ± 27.3 (S.D.)
	528	CSF	19.6 ± 13.2** (S.D.)	34.4 ± 14.2 (S.D.)	41.8 ± 4.2 (S.D.)
	687	CSF	27.7 ± 5.7	34.4 ± 8.3	
	170	CSF (female)	31.8 ± 2.1**	33.1 ± 1.9**	43.7 ± 26
	170	CSF (male)	38.4 ± 2.6**	36.9 ± 3.8**	40.0 ± 2.3
	330	CSF		32.4 ± 4.1	32.8 ± 2.2
	332	CSF		36.0 ± 5.5	32.0 ± 2.0
		CSF weighted mean ± S.E.M.	39.3 ± 4.1 (n=121)	37.1 ± 5.3 (n=89)	39.3 ± 2.9 (n=149)

* $p < 0.05$ *vs.* control.
** $p < 0.01$ *vs.* control.
*** $p < 0.001$ *vs.* control.

TABLE 32

SEROTONIN SYSTEM

Metabolite	*Reference*	*Biological fluid*	*Bipolar–depressed*	*Bipolar–manic*	*Control*
5-Hydroxy-indoleacetic acid	361	Urine	4.07 ± 1.56 mg per 24 h	2.91 ± 0.42 mg per 24 h	2.70 ± 0.48 mg per 24 h
	645	Urine	4.40 ± 0.80	7.60 ± 1.3	
	627	CSF	19.8 ± 1.5* ng/ml	19.7 ± 1.6* ng/ml	42.3 ± 3.2 ng/ml
	673	CSF	15.8 ± 2.7	8.8 ± 1.8	
	674	CSF	18 ± 3	15 ± 2	
	724	CSF	25	28	27
	496	CSF	14.6 ± 1.7*	13.9 ± 2.9*	27.5 ± 1.2
	170	CSF (male)[a]	20.1 ± 0.8	22.5 ± 2.8	20.6 ± 0.8
	170	CSF (female)[a]	24.8 ± 1.0	30.8 ± 3.5**	21.8 ± 1.3
	518	CSF	22.7 ± 1.5	22.8 ± 2.9	22.2 ± 1.8
		CSF weighted mean ± S.E.M.	22.1 ± 1.3 ($n = 269$)	21.4 ± 2.4 ($n = 90$)	25.8 ± 1.6 ($n = 157$)

* $p < 0.001$ *vs.* control.

** $p < 0.01$ *vs.* control.

[a] These values are also reported in refs. 509 and 633.

TABLE 33

NORADRENALINE SYSTEM

Amine or metabolite	*Reference*	*Biological fluid*	*Bipolar–depressed*	*Bipolar–manic*	*Control*
Noradrenaline	641	Urine	27.9 ± 3.7†† μg per 24 h	93.9 ± 7.9 μg per 24 h	
	725	Urine	41.1	67.8	
	643	Urine	20.7 ± 2.1	56.2 ± 11.6	
	644	Urine	53 ± 12	102 ± 15	
	645	Urine	36.7 ± 7.1	61.1 ± 13.3	
	647	Urine	13.6 ± 1.8[a]††	36.0 ± 3.4[a]	
		Urine weighted mean ± S.E.M.	38.3 ± 2.1 (*n* = 58)	72.9 ± 11.2 (*n* = 25)	
	723	Plasma	315 ± 70 pg/ml	376 ± 65 pg/ml	280 pg/ml
	723	Plasma	400***	590***	280
	326	CSF	700	500	200 ± 80
	726	CSF	210††	460	225
Adrenaline	641	Urine	9.6 ± 1.1†† μg per 24 h	19.5 ± 1.8 μg per 24 h	
	725	Urine	26.9	35.9	
	643	Urine	5.6 ± 0.8	8.3 ± 1.4	
	645	Urine	10.6 ± 1.6	18.6 ± 6.5	
		Urine weighted mean ± S.E.M.	22.0 ± 1.2 (n = 54)	23.1 ± 3.7 (n = 21)	
Normetanephrine	727	Urine	99 ± 11[b]	206 ± 22[b]	
	170	Urine	279 ± 16	299 ± 35	192 ± 8 μg per 24 h
Metanephrine	170(M)	Urine	149 ± 8	157 ± 23	107 ± 7
	170(F)	Urine	122 ± 7	91 ± 11	88 ± 5
Vanilmandelic acid	728	Urine	2.34 ± 0.16†† mg/g creatinine	8.16 ± 0.51 mg/g creatinine	
	157	Urine	1.5 mg per 24 h	1.8 mg per 24 h	
	170	Urine	3.56 ± 0.20	3.55 ± 0.38	2.72 ± 0.16 mg per 24 h
	541	CSF	0.60 ± 0.20*** ng/ml	0.80 ± 0.15 ng/ml	1.05 ± 0.15 ng/ml

3-Methoxy-4-hydroxyphenyl glycol	696	Urine	1180 ± 90 μg per 24 h	2750 ± 150 μg per 24 h	
	645	Urine	2230 ± 220	2500 ± 340	
	727	Urine	805	1182	
	647	Urine[c]	1030††	1190	
	170(M)	Urine	2273 ± 144	2740 ± 512	2267 ± 143 μg per 24 h
	170(F)	Urine	1968 ± 136	1909 ± 751	1660 ± 121
	704	Urine	1496 ± 266	1647 ± 538	
	572	Urine	1440 ± 100	2110 ± 190	1850 ± 20
		Urine weighted mean ± S.E.M.	2001 ± 138 ($n=146$)	2266 ± 382 ($n=42$)	1933 ± 101 ($n=99$)
	585	Plasma[d]	13.7 ± 0.6 ng/ml	21.1 ± 1.3 ng/ml	
	611	CSF[d]	8.9 ± 1.1†*	15.5 ± 3.0	14 ± 1.5
	612	CSF	18.0	27.8*	16 ± 0.9
	729	CSF	15.8	23.0***	15.9
	724	CSF	10.5	15.5	16.0
	170	CSF	8.8 ± 0.2**	11.0 ± 1.0††**	8.0 ± 0.2
	518	CSF	8.0 ± 0.4	8.4 ± 0.4***	7.7 ± 0.4
		CSF weighted mean ± S.E.M.	9.3 ± 0.4 ($n=205$)	15.3 ± 1.3 ($n=69$)	11.4 ± 0.5 ($n=180$)

* $p < 0.01$ *vs.* control.
** $p < 0.001$ *vs.* control.
*** $p < 0.05$ *vs.* control.
† $p < 0.05$ *vs.* manic.
†† $p < 0.001$ *vs.* manic.
[a] Longitudinal study of 45 days.
[b] Longitudinal study of 20 days.
[c] Longitudinal study of 84 days.
[d] Unconjugated + conjugated MHPG.

TABLE 34

DOPAMINE SYSTEM

Amine or metabolite	*Reference*	*Biological fluid*	*Bipolar–depressed*	*Bipolar–manic*	*Control*
Dopamine	641	Urine	324 ± 88 μg per 24 h	423 ± 46 μg per 24 h	
	725	Urine	185	344	
	643	Urine	153 ± 31	276 ± 81	
	645	Urine	193 ± 20	218 ± 19	
	157	Urine	520	710	
	157	Urine[a]	180	410	
		Urine weighted mean ± S.E.M.	232 ± 41 ($n=60$)	415 ± 42 ($n=28$)	
Homovanillic acid	485	CSF	22.7 ± 5.0 ng/ml	22.2 ± 6.2 ng/ml	
	673	CSF	26.5 ± 12.1	44.2	
	496	CSF	15.9 ± 2.0*	44.4 ± 3.8*	33.4 ± 1.0 ng/ml
	170[b](M)	CSF	32.4 ± 1.6	43.7 ± 5.4	43.7 ± 2.6
	170[b](F)	CSF	38.0 ± 2.1	59.0 ± 10.4**	40.0 ± 2.3
	518	CSF	31.8 ± 2.9	38.0 ± 5.0	28.6 ± 2.5
		CSF weighted mean ± S.E.M.	31.4 ± 2.6 ($n=160$)	40.6 ± 5.5 ($n=45$)	36.1 ± 2.1 ($n=13$)

* $p < 0.01$ *vs.* control.

** $p < 0.02$ vs. control.

[a] Conjugated dopamine (values not included in weighted mean).

[b] These values are also reported in refs. 509 and 633.

TABLE 35

COMPARISON OF PSYCHOTIC AND NON-PSYCHOTIC (NEUROTIC) DEPRESSED SUBJECTS

Amine or metabolite	*Reference*	*Biological fluid*	*Psychotic depressed*	*Non-psychotic*
Noradrenaline	149	Urine	195 ± 58 μg per 24 h	133 ± 16 μg per 24 h
	287	Plasma	366 ± 119 pg/ml	438 ± 49 pg/ml
Adrenaline	730	Urine	15.7 μg per 24 h*	6.6 μg per 24 h
	287	Plasma	97 ± 12 pg/ml	85 ± 10 pg/ml
Dopamine	730	Urine	280 μg per 24 h	212 μg per 24 h
	287	Plasma	282 ± 12 pg/ml**	51 ± 4 pg/ml
Normetanephrine	730	Urine	49.6 μg per 24 h	40.5 μg per 24 h
5-Hydroxy-indoleacetic acid	7	Urine	6.0 ± 1.2 mg per 24 h	6.0 ± 0.9 mg per 24 h
	746	Urine	3.0 ± 0.2 mg/g creatinine[a]	3.3 ± 0.2 mg/g creatinine[b]
	673	CSF	12.8 ± 5.0 ng/ml	15.9 ± 2.0 ng/ml
Homovanillic acid	746	Urine	3.3 ± 0.3 mg/g creatinime[a]	3.0 ± 0.3 mg/g creatinime[b]
	440	Plasma(M)	10.8 ± 1.0 ng/ml	12.3 ± 1.6 ng/ml
	440	Plasma(F)	21.1 ± 3.2	16.2 ± 2.1
	448	Plasma	11.4 ± 2.5	10.8 ± 3.1
	673	CSF	28.6 ± 7.5	27.3 ± 9.1
Vanilmandelic acid	730	Urine	3.52 mg per 24 h*	2.18 mg per 24 h
3,4-Dihydroxy-phenylacetic acid	730	Urine	1.56	1.02
3,4-Dihydroxy-mandelic acid	730	Urine	0.74	0.39
3-Methoxy-4-hydroxyphenyl glycol	746	Urine	2006 ± 216 μg/g creatinine[a]	1472 ± 145 μg/g creatinine[b]
	448	Plasma	3.36 ± 0.74 ng/ml	3.53 ± 0.65 ng/ml

* $p < 0.01$ *vs.* non-psychotic depressed.
** $p < 0.001$ *vs.* non-psychotic depressed.
[a] Delusional depressed.
[b] Non-delusional depressed.

TABLE 36

COMPARISON OF DEPRESSED SUBJECTS WITH AND WITHOUT MELANCHOLIA

Amine or metabolite	*Reference*	*Biological fluid*	*With melancholia*	*Without melancholia*
Noradrenaline	193	Urine	331 ± 54 μg per 24 h	211 ± 29 μg per 24 h
	284	Plasma	370 ± 39 ng/ml	
	662	CSF	123 ± 15	
Dopamine	193	Urine (total)	662 ± 118 μg per 24 h	716 ± 136 μg per 24 h
	662	CSF (sulfate)	679 ± 98 ng/ml	
5-Hydroxytryptamine	305	Plasma	0.85	
Normetanephrine	193	Urine	227 ± 21 μg per 24 h	145 ± 24 μg per 24 h
5-Hydroxy-	510	CSF	17.8 ± 0.8 ng/ml	
indoleacetic	466	CSF	15.0 ± 1.7	
acid	662	CSF	16.6 ± 1.5	19.3 ± 2.6 ng/ml
	736	CSF	25.8	
Homovanillic	193	Urine	3.89 ± 0.37 mg per 24 h	5.41 ± 0.65 mg per 24 h
acid	712	Plasma	18.9 ± 2.4 ng/ml	
	510	CSF	36.3 ± 2.0	
	662	CSF	20.1 ± 2.7*	33.1 ± 6.4 ng/ml
Vanilmandelic acid	193	Urine	5.84 ± 0.85 mg per 24 h	5.27 ± 0.55 mg per 24 h
3,4-Dihydroxy-	193	Urine	1100 ± 250 μg per 24 h	1475 ± 220 μg per 24 h
phenylacetic acid	662	CSF (unconjugated)	230 ± 29 pg/ml*	319 ± 45 pg/ml
	662	CSF (conjugated)	390 ± 48*	538 ± 65
3-Methoxy-4-	193	Urine (total)	1240 ± 172 mg per 24 h	929 ± 176 mg per 24 h
hydroxyphenyl	440	Plasma(M)	3.3 ± 0.2 ng/ml	
glycol	440	Plasma(F)	4.1 ± 0.4	
	27	Plasma	3.9 ± 0.5	
	712	Plasma	5.1 ± 0.6	
	510	CSF	9.4 ± 0.3	
	662	CSF	9.0 ± 0.8	8.1 ± 0.4 ng/ml
Phenylacetic acid	629	Urine	103 ± 16 mg per 24 h	98.5 ± 10.2 mg per 24 h

* $p < 0.05$ *vs.* subjects without melancholia.

TABLE 37

NORADRENALINE AND METABOLITES IN PANIC DISORDER

Amine or metabolite	*Reference*	*Biological fluid*	*Without panic disorder*	*With panic disorder*
Noradrenaline	150	Urine	12.3 ± 1.4 ng/min	38.3 ± 6.9* ng/min
	246	Plasma	288 ± 22 ng/ml	161 ± 14 ng/ml
Adrenaline	246	Plasma	13 ± 2.5 ng/ml	16 ± 3.2 ng/ml
3-Methoxy-4-hydroxyphenyl glycol	569	Urine	1607 ± 181 μg per 24 h	727 ± 59* μg per 24 h
	705	Urine	1871 ± 171 μg per 24 h	2439 ± 235** μg per 24 h
	591	Plasma	3.6 ± 0.3 ng/ml	3.9 ± 0.2 ng/ml
	599	Plasma	4.4 ± 0.3	3.3 ± 0.2*
	592	Plasma	3.6 ± 0.5	3.3 ± 0.3
	593	Plasma	3.7 ± 0.3	3.6 ± 0.2

* $p < 0.01$; subjects with panic disorder *vs.* those without panic disorder.
** $p < 0.05$; subjects with panic disorder *vs.* those without panic disorder.

Some authors have claimed a reduction in noradrenergic activity in panic disorder and related phobias based on findings of lower plasma MHPG levels[599] and lower urinary excretion of MHPG[569] and noradrenaline[246]. Other workers have reported an elevation of urinary MHPG[705], plasma MHPG[894] and noradrenaline excretion[150] in panic disorder, suggesting that it may be associated with increased noradrenergic activity, and still other investigators found no significant differences in plasma MHPG between subjects with panic disorder and those without[591–593]. A survey of the results of these studies is presented in Table 37.

Yu *et al.*[427] measured the plasma concentrations of the acidic metabolites of the trace amines and found significantly lower *p*-hydroxyphenylacetic acid (PHPA) in agoraphobic patients if compared with healthy controls, but not if compared with depressed controls.

Anxiety has been reported to be correlated with plasma[26,709,894] and urinary[570,731] MHPG and with 5-HIAA[531] and HVA[732] in CSF.

3.1.8. Suicide

A positive correlation has often been found between strong suicidal thoughts, suicide attempts and self-aggressivity and low concentrations of 5-HIAA in the CSF[466,505,506,531,733–735]. Those attempting suicide by violent means show significantly lower 5-HIAA in CSF than non-violent suicide attempters[465], and violent offenders who have a history of suicide attempts have been reported to have a significantly lower level of 5-HIAA in their CSF than those who have no such history[636]. It has been claimed that the distribution of concentrations of 5-HIAA in CSF is bimodal[531,667,678,680,745]; Åsberg *et al.*[678] found that subjects with the lower concentrations are more likely to commit suicide. Furthermore, patients with low 5-HIAA concentrations in the CSF had significantly higher scores in easily evoked anxiety, general anxiety, hostility and depressive inhibition[738]. However, in contrast to the above, a number of studies have shown that subjects who had made a suicide attempt were no more likely to have low concentrations of 5-HIAA in their CSF than non-suicidal subjects[498,736,737]. A trend to low HVA concentrations in the CSF of suicidal subjects has been noted[465,505,506,733]. No statistically significant differences in MHPG concentrations in the CSF of non-suicidal and suicidal patients have been observed[505,506,733], but the item "Suicidal Tendencies Worst Week" score from the *Schedule for Affective Disorders and Schizophrenia* (SADS) was highly significantly and negatively correlated with the MHPG level in CSF and only to a slight extent with 5-HIAA levels[747]. The score on the item "Seriousness of Intent of Worse Suicide Attempt" earlier in life correlated significantly and negatively with both MHPG and 5-HIAA[747]. Studies of 5-HIAA in CSF in depression and suicidal behaviour have been reviewed[620].

3.1.9. Correlation of metabolite concentrations with severity of depression

On the basis of the amine hypotheses of affective disorders, one would predict that there would be a correlation between the severity of the disorder as measured by psychometric rating scales and the concentrations of the amine metabolites in biological fluids, particularly in CSF. In fact, the CSF concentrations of 5-HIAA and HVA (but not MHPG) have been reported by some groups to be significantly negatively correlated with scores on the Hamilton Depression Rating Scale (HDRS)[662,742],

whereas others found MHPG levels to be correlated with symptom ratings but HVA and 5-HIAA levels were not[509,518], and some other groups found no correlation for any of the CSF metabolites with the severity of the depression[33,633,671,689]. An explanation for these contradictory results may be found in another study in which the authors observed no correlation of CSF metabolite concentration with global depression severity, but did observe correlations with some symptoms of depression[531,633]. The urinary excretion of MHPG has not shown any correlation with ratings on the HDRS[120,700,702,743,744], except in one study[582]. Monoamine metabolite concentrations predicted from the SADS symptom items compared well with the true CSF values[681] and various symptoms and descriptive variables on the SADS were correlated univariately with urinary MHPG[32]. Using a computer program based on these relationships, it was possible to classify 20 out of 21 unipolar and all bipolar subjects correctly[681]. Using the Bech–Rafaelson Melancholia Scale, a modification of the HDRS, no significant correlation with any CSF metabolite was found[736].

Some anxiety symptoms are correlated with the plasma concentration of MHPG, but measures of global and state anxiety were not[593]. Within individuals, MHPG excretion and state anxiety have been observed to co-vary highly significantly[731]. However, in a population of depressed individuals, state anxiety and urinary MHPG do not co-vary significantly, so it is not possible to predict that an individual with a high baseline state anxiety will have a high baseline urinary MHPG excretion, or *vice versa*[731]. Easily evoked and general anxiety scores were found to be negatively correlated with the 5-HIAA concentration in CSF[738], whereas the HVA concentration has been reported to be positively correlated with anxiety[732]. Patients scoring high on anxiety and hostility in the Rorschach test had low CSF concentrations of 5-HIAA[510].

Phenylacetic acid excretion, which has been reported to be low in unipolar depression by some workers[416,417,629,663], but not by others[72,352], does not correlate with either the HDRS or the Carroll Rating Scale[72].

Probenecid, which inhibits the active transport of amine metabolites from the CSF to the blood, has been used to assess the central turnover of the monoamines in depression. Probenecid-induced accumulations of 5-HIAA[470,471,480,482,493] and HVA[480,493,499] in the CSF of depressed subjects have been shown to be significantly smaller than the accumulations in control subjects. The differences appeared to correlate with the depressive state[471]. A significant increase in MHPG concentrations can be attained only at very high doses of probenecid, and even at high probenecid doses MHPG sulfate concentration does not increase, suggesting that a probenecid-sensitive transport mechanism for MHPG sulfate does not occur[494]. At the usual doses of probenecid, MHPG accumulation is too meagre to be used for the assessment of noradrenaline turnover[493]. Mania and high levels of anxiety have been associated with a greater accumulation of noradrenaline after probenecid administration than either controls or depressed subjects, indicating that alterations in mood may be associated with changes in central noradrenaline metabolism[726]. In depressed patients suffering from severe motor retardation, central dopamine turnover is diminished, as evidenced by a sub-normal accumulation of HVA in the CSF after probenecid administration[499,759].

In the dexamethasone suppression test, induction by dexamethasone of plasma MHPG concentration increases have been directly correlated with the severity of

depressive symptoms[446,448,710,711,760]. Dexamethasone-resistant depressed patients showed elevated plasma noradrenaline and adrenaline levels[761] and urinary 3,4-dihydroxyphenyl glycol excretion[711]. No difference in MHPG concentrations in urine[744] or CSF[653] between dexamethasone suppressors and non-suppressors has been reported.

3.1.10. Effects of drugs and treatments

3.1.10.1. Effects of anti-depressant drugs on metabolite concentrations. These effects are shown in Table 38.

In addition to the studies on anti-depressant drugs, a study on anti-anxiolytic drugs demonstrated that urinary MHPG declined significantly ($p < 0.01$) after long-term use of chlordiazepoxide, clobazam, diazepam, nitrazepam, and oxazepam[570]. After withdrawal of treatment, urinary MHPG increases.

3.1.10.2. Metabolite values as predictor of response to drugs. For clinicians, a biochemical test predictive of a patient's therapeutic response to a drug would be a very useful treatment tool. Several investigators have demonstrated that pretreatment concentrations of MHPG or 5-HIAA in urine or CSF may be used as a basis for selection of anti-depressant drug therapy for depressed patients, and that this method of drug selection produces better clinical results than traditional selection methods. The differential responses of depressed patients to drug treatments permitted their classification as responders or non-responders. Statistically significant differences in the concentrations of some monoamines and their metabolites between the two groups were noted.

Low baseline urinary excretion of MHPG has been observed in patients who respond well to imipramine[686], L-deprenyl[635], D-amphetamine[560,698], nortriptyline[582,741] and desipramine[741], whereas subjects excreting large amounts of MHPG did not respond to treatment with these drugs. On the other hand, patients with high initial urinary MHPG levels responded well to alprazolam[751] and amitriptyline[700,741], whereas those with low concentrations did not. Other groups of workers, however, have reported that pretreatment urinary MHPG levels were not a predictor of response to amitriptyline[477,686,702]. The results of studies on the predictive value of pretreatment MHPG concentrations in CSF have been contradictory. High[716] and low[649] pretreatment values of MHPG in CSF have been claimed to predict which patients will respond to imipramine[649,716] and amitriptyline[649], and other groups have reported that MHPG in CSF is not a predictor of response to imipramine[688], amitriptyline[686,688], desimipramine[685] or femoxetine[685]. High urinary noradrenaline excretion may be a predictor of a positive response to alprazolam[651], whereas low excretion is a predictor of response to moclobemide[149].

A positive response to iproniazid[366,756], isocarboxazid[366] and *p*-chloro-N-methylamphetamine[163] has been predicted on the basis of low pretreatment concentrations of urinary 5-HIAA. Similarly, low pretreatment levels of 5-HIAA in CSF have been reported to be useful in predicting a positive response to treatment with imipramine[686] and zimelidine[682], and higher CSF concentrations of 5-HIAA predict a positive response to nortriptyline[667]. Some investigators have reported that 5-HIAA and HVA in CSF are not useful as predictors of response to desimipramine[682], amitriptyline[631,686,688] or imipramine[631,688] treatment. For depressed patients treated with a variety of anti-depressant drugs and grouped according to their responses, it

TABLE 38

EFFECTS OF ANTI-DEPRESSANT DRUGS ON METABOLITE CONCENTRATIONS

Drug	*Reference*	*Biological fluid*	*Category of depressive disorder*	*Effect on amines or metabolite*[a]
Alprazolam	751	Urine	Endogenous	MHPG (effect not stated)
	752	Plasma	Healthy normals	MHPG↓ ($p < 0.001$)
	651	Urine	Not classified	NA↓ ($p < 0.01$); A↓ ($p < 0.002$); NMN↓ ($p < 0.05$); VMA↓ ($p < 0.05$); MHPG↓ ($p < 0.05$)
	755	Plasma	Panic	MHPG↓
Amitriptyline	485	CSF	Not classified	5-HIAA↓ ($p < 0.02$); HVA↓ (N.S.)
	631	CSF	Unipolar + bipolar	5-HIAA↓ ($p < 0.05$); HVA↓ (N.S.)
	741	Urine	Unipolar + bipolar	MHPG↑ (low excreters); ↓ (high excreters)
	700	Urine	Bipolar	MHPG↑ ($p < 0.05$)
	659	Plasma	Severe depression	NA↓ ($p < 0.01$)
	707	Plasma	Endogenous	MHPG↓ ($p < 0.05$)
	688	CSF	Unipolar + bipolar	MHPG↓ ($p < 0.001$); 5-HIAA↓ ($p < 0.001$); HVA (N.S.)
	650	Urine	Unipolar	NA (N.S.); A (N.S.); VMA (N.S.); MHPG↓ ($p < 0.001$); NMN↓ ($p < 0.001$); MN ($p < 0.001$)
	650	Urine	Bipolar	NA (N.S.); A (N.S.); NMN (N.S.); MHPG↓ ($p < 0.001$); VMA↓ ($p < 0.001$); MN↓ ($p < 0.001$)
	736	CSF	Endogenous	MHPG (N.S.); 5-HIAA (N.S.); HVA (N.S)
D-Amphetamine	560	Urine	Endogenous	MHPG↑ (significant) (responders); ↓(N.S.) (non-responders)
	698	Urine	Endogenous	MHPG↓ ($p < 0.05$)
Bupropion	753	CSF	Not classified	HVA (N.S.); 5-HIAA (N.S.)
	694	CSF	Unipolar + bipolar	MHPG↓ (N.S.); HVA↓ (N.S.)
	694	Plasma	Unipolar + bipolar	HVA↑ (good responders); N.S. (poor responders)

(*Continued on p. 140*)

TABLE 38 (*continued*)

Drug	*Reference*	*Biological fluid*	*Category of depressive disorder*	*Effect on amines or metabolite*[a]
Chlorimipramine	679	CSF	Endogenous	5-HIAA↓ ($p < 0.001$); MHPG↓ ($p < 0.001$); HVA (N.S.)
	305	Plasma	Melancholia	5-HIAA↓ (N.S.); 5-HT↓ (N.S.); IAA (N.S.)
p-Chloro-N-methylamphetamine	163	Urine	Vital	5-HT↑ ($p < 0.01$); 5-HIAA↑ ($p < 0.05$)
Clonidine	587	Plasma	Endogenous	MHPG↓ ($p < 0.05$)
	894	Plasma	Panic, anxiety	MHPG↓ ($p < 0.002$)
	255	Plasma	Unipolar	NA↓ (N.S.); MHPG↓ ($p < 0.05$)
	255	Plasma	Bipolar	NA ↓ (N.S.); MHPG↓ (N.S.)
	604	Plasma	Not classified	DHPG↓ (N.S.)
Clorgyline	450	CSF	Not classified	HVA↓ ($p < 0.02$); MHPG↓ ($p < 0.001$); 5-HIAA↓ ($p < 0.02$); VMA (N.S.); DOPAC (N.S.)
	639	Urine	Bipolar	NA (N.S.); NMN↑ ($p < 0.01$); VMA↓ ($p<0.05$); MHPG↓ ($p < 0.05$); DA (N.S.); 3-MT↑ ($p < 0.05$); HVA↓ ($p < 0.05$); 5-HIAA↓ (N.S.); PE↓ (N.S.); pTA↑ ($p < 0.05$); pHPA↓ (N.S.)
	658	Urine	Unipolar + bipolar	DA↓ (N.S.); HVA↓ ($p < 0.01$); DOPAC↓ (N.S.);
	753	CSF	Not classified	5-HIAA↓ (significant); HVA↓ (significant)
	690	CSF	Not classified	MHPG↓ ($p < 0.001$); HVA↓ ($p < 0.01$); 5-HIAA↓ ($p < 0.01$)
L-Deprenyl	635	Urine	Atypical	PE↑ ($p < 0.05$); MHPG↓ ($p < 0.05$)
	753	CSF	Not classified	HVA↓ ($p < 0.005$); 5-HIAA↓
Desimipramine	741	Urine	Unipolar + bipolar	MHPG↑
	703	CSF	Unipolar + bipolar	MHPG↓ ($p < 0.05$)
	703	Urine	Unipolar + bipolar	MHPG↓ ($p < 0.01$)
	28	Plasma	Endogenous	MHPG↓ ($p < 0.002$)
	28	Urine	Endogenous	MHPG (N.S.)
	690	CSF	Not classified	MHPG↓ ($p < 0.001$); HVA↓ (N.S.); 5-HIAA↓ ($p < 0.01$)

	658	Urine	Unipolar + bipolar	DA↓ (N.S.); HVA↓ (N.S.); DOPAC↓ (N.S.)
	685	CSF	Not classified	5-HIAA↑ ($p < 0.02$); MHPG (N.S.); HVA (N.S.)
	753	CSF	Not classified	5-HIAA↓ (significant); HVA (N.S.)
Femoxetine	685	CSF	Not classified	5-HIAA↑ ($p < 0.05$); MHPG (N.S.); HVA (N.S.)
Fluvoxamine	318	Plasma	Healthy normals	Melatonin↑ ($p < 0.05$)
Imipramine	665	Urine	Endogenous	VMA↓ ($p < 0.01$); NMN↑ ($p < 0.05$)
	754	Urine	Endogenous	NMN↑
	664	Urine	Endogenous	VMA↓ ($p < 0.05$)
	118	Urine	Primary depression	MHPG↓ ($p < 0.05$); VMA (N.S.); NMN (N.S.); MN (N.S.); TRA↑ ($p < 0.025$); 5-HIAA (N.S.)
	631	CSF	Unipolar + bipolar	5-HIAA↓ ($p < 0.05$)
	676	CSF	Psychotic depression	HVA↑ (N.S.); 5-HIAA↑ (N.S.)
	741	Urine	Unipolar + bipolar	MHPG↑
	716	CSF	Endogenous	MHPG↓ (N.S.)
	688	CSF	Unipolar + bipolar	MHPG↓; 5-HIAA↓; HVA (N.S.)
	709	Plasma	Agoraphobia	MHPG↓ ($p < 0.001$)
	301	Plasma	Not classified	5-HT↑ ($p < 0.02$)
	650	Urine	Unipolar	NA↓ (N.S.); A↓ (N.S.); VMA↓ ($p < 0.01$); NMN↓ ($p < 0.001$); MN↓ ($p < 0.001$); MHPG↓ ($p < 0.001$)
	650	Urine	Bipolar	NA↑ (N.S.); A↑ (N.S.); VMA↓ ($p < 0.01$); NMN↑ (N.S.); MN↑ (N.S.); MHPG (N.S.)
Iproniazid	756	Urine	Not classified	5-HIAA↓ (N.S.)
	366	Urine	Melancholia, neurotic	5-HIAA↑ ($p < 0.001$)
Isocarboxazide	366	Urine	Melancholia, neurotic	5-HIAA↑ ($p < 0.001$)
	736	CSF	Endogenous	5-HIAA↓ (N.S.); MHPG↓ ($p < 0.01$); HVA↓ ($p < 0.001$)
Lithium carbonate	485	CSF	Manic	5-HIAA↓ (N.S.); HVA↓ (N.S.)
	157	Urine	Manic	DA↓ ($p < 0.01$); conjugated DA↓ ($p < 0.01$); VMA (N.S.)
	157	Urine	Depressed	DA↓ (N.S.); conjugated DA↑ (N.S.); VMA (N.S.)

(*Continued on p. 142*)

TABLE 38 (*continued*)

Drug	*Reference*	*Biological fluid*	*Category of depressive disorder*	*Effect on amines or metabolite*[a]
	25	Urine	Unipolar + bipolar	MHPG (acute, N.S.) MHPG↑ (chronic, N.S.)
	675	CSF	Manic	5-HIAA↑ ($p < 0.001$); HVA↑ ($p < 0.05$)
	698	Urine	Unipolar + bipolar	MHPG↑ (N.S.)
	659	Plasma	Bipolar, neurotic, melancholic	NA↑ ($p < 0.05$)
	658	Urine	Unipolar + bipolar	DA↓ (N.S.); DOPAC↓ (N.S.); HVA↓ ($p < 0.001$)
	332	CSF	Euthymic bipolar	5-HIAA↑ ($p < 0.05$); DOPAC↑ (N.S.); HVA↑ (N.S.); NA↑ (N.S.); DA·SO_4↓ (N.S.); MHPG↑ (N.S.)
Moclobemide	149	Urine	Unipolar	NA↓ (significant); A↓ (N.S.); DA↓ (N.S.)
Nortriptyline	667	CSF	Endogenous	5-HIAA↓ ($p < 0.005$); IAA↓ ($p < 0.05$)
	741	Urine	Unipolar + bipolar	MHPG↑
	27	Urine	Unipolar + bipolar	MHPG↓ (N.S.)
Pargyline	450	CSF	Not classified	HVA↓ ($p < 0.01$); MHPG↓ ($p < 0.01$); VMA↓ (N.S.); DOPAC↓ (N.S.); 5-HIAA↓ ($p < 0.05$)
Phenelzine	664	Urine	Endogenous	VMA↓ ($p < 0.01$)
	672	CSF	Not classified	HVA↓ ($p < 0.001$); 5-HIAA↓ (N.S.)
	646	Urine	Not classified	TRA↑ ($p < 0.01$); NA↑ (N.S.); A↑ (N.S.); NMN↑ ($p < 0.05$); MHPG↓ ($p < 0.05$); VMA↓ ($p < 0.05$)
	757	Plasma	Dysthymic	PE↑
	757	Urine	Dysthymic	PE↑
Timolol	271	Plasma	Healthy normal	NA↑ (basal, $p < 0.05$); ↓ (exercize, p, < 0.05); DA (N.S.)
Tranyl	211	Plasma	Not classified	PE↑ (significant)
cypromine	211	Urine	Not classified	PE↑ (N.S.)

Yohimbine	591	Plasma	Healthy normal	MHPG↑ ($p < 0.001$)
	591	Plasma	Agoraphobia	MHPG↑ ($p < 0.001$)
	752	Plasma	Healthy normal	MHPG↑ ($p < 0.05$)
	604	Plasma	Not classified	DHPG↑; (+ desimipramine: DHPG↓)
	755	Plasma	Panic	MHPG↑
Zimelidine	668	CSF	Not classified	5-HIAA↓ ($p < 0.05$); IAA↑ ($p < 0.05$); MHPG↓ ($p < 0.05$); HVA↓ (N.S.)
	703	CSF	Unipolar + bipolar	MHPG↑ (N.S.)
	703	Urine	Unipolar + bipolar	MHPG↓ ($p < 0.01$)
	648	Urine	Unipolar + bipolar	MHPG↓ ($p < 0.05$); NA↓ (N.S.); NMN↓ (N.S.); VMA↓ (N.S.)
	658	Urine	Unipolar + bipolar	HVA↓ (N.S.); DA↑ (N.S.)
	753	CSF	Not classified	HVA↑ (N.S.); 5-HIAA↓ (significant)
	690	CSF	Not classified	MHPG↓ ($p < 0.02$); 5-HIAA↓ ($p < 0.01$); HVA (N.S.)
Electroconvulsive therapy	671	CSF	Endogenous	5-HIAA (N.S.); HVA (N.S.)
	676	CSF	Psychotic depression	5-HIAA↑ ($p < 0.01$); HVA ↑($p < 0.01$)
	677	CSF	Endogenous	5-HIAA↑ (N.S.); HVA↑ (N.S.);
	758	CSF	Psychotic depression	MHPG↓ (significant); 5-HIAA (N.S.); HVA (N.S.)
	658	Urine	Unipolar + bipolar	DA↓ ($p < 0.05$); DOPAC↑ (N.S.); HVA↓ (N.S.)
	708	Plasma	Not classified	MHPG↑ (N.S.); HVA↓ (N.S.); 5-HIAA↓ (N.S.)
	689	CSF	Unipolar + bipolar	5-HIAA↑ (N.S.); HVA↑ (N.S.)
	736	CSF	Endogenous	5-HIAA↑ (N.S.); HVA↑ (N.S.); MHPG↑ (N.S.)

[a] For abbreviations, see text; also: A = adrenaline; 3MT = 3-methoxytyramine. N.S. = not significant. ↑, Concentration increases during drug treatment; ↓, concentration decreases during drug treatment.

was observed that CSF monoaminergic metabolite concentrations in responders correlated well with each other, but did not correlate in non-responders[693]. This suggests that interactions between monoamine systems in non-responders may be disrupted.

3.1.10.3. Correlation of changes in metabolite levels with therapeutic response. If a dysfunction in noradrenergic (or other monoaminergic) activity is associated with depression, as has been postulated, a clinical recovery after drug treatment might be expected to be correlated with changes in amine metabolite concentrations. Several studies have been devoted to establishing such correlations, but most have not demonstrated significant correlations. In CSF, after ECT[671,677] or treatment with lithium[485], amitriptyline[630,688], desimipramine[685], femoxetine[685] or imipramine[688], changes in 5-HIAA concentrations were found not to be correlated with clinical improvement. Similarly for HVA in CSF, no correlation of changes in concentration with changes in psychometric ratings were reported after treatment of depressed patients with ECT[671,677], amitriptyline[630,688], desimipramine[685], femoxetine[685] or imipramine[688]. Changes in the MHPG concentration in CSF after imipramine[688], amitriptyline[688], desimipramine[685] or femoxetine[685] treatment also did not reflect improvements in clinical condition. However, manic scores have been reported to increase after lithium treatment of manic patients in a manner which parallels the increase in the CSF concentrations of 5-HIAA and HVA[675]. Changes in the plasma concentrations of MHPG[28,708] after treatment with desimipramine[28] or ECT[708] and of noradrenaline and serotonin after amitriptyline or lithium carbonate[659] do not correspond with clinical improvement. Plasma HVA and 5-HIAA concentrations also do not change in accord with clinical improvement following ECT[708], and patients improved after treatment with bupropion do not show any comparable change in plasma HVA levels[694]. However, in subjects suffering from panic attacks, a reduction in the frequency and severity of the attacks following clonidine or imipramine treatment is reflected in a corresponding reduction in plasma MHPG[894], whereas treatment with yohimbine, an adrenergic receptor antagonist which increases noradrenergic function, produces an increase in the frequency of panic attacks and a corresponding increase in plasma MHPG[591]. Changes in urinary MHPG excretion have been shown to be correlated with clinical response after treatment with imipramine[118], but not after treatment with desimipramine[648], zimelidine[648], L-deprenyl[635] and D-amphetamine[698]. However, Beckmann *et al.*[698] have shown that patients on amphetamine who exibited markedly increased psychomotor activity and behaviourally rated hypomania also exhibited elevations of MHPG excretion, whereas those without such responses exhibited reductions of MHPG. Acute lithium treatment was not associated with a change in urinary MHPG excretion which correlated with psychometric ratings, but chronic treatment was so correlated[25]. It was concluded that change in the clinical state is the most important variable contributing to MHPG changes. In a study of the effects of amitriptyline and imipramine on the noradrenergic system, a differential effect between responders and non-responders and between unipolar and bipolar patients on changes in the urinary concentrations of the metabolites of noradrenaline was noted[650]. Other workers have reported changes in urinary VMA concentration which are correlated with depression rating scale score changes following treatment with imipramine[118,665] or which are not correlated when treatment is with desimipramine[648]. Normetanephrine excretion behaves similarly to VMA in response to treatment with imipramine[665,754] and desipramine[648].

Noradrenaline excretion does not change with changes in clinical condition after alprazolam treatment[651]. Treatment with iproniazid has been claimed to produce a clinical recovery which is synchronous with an elevation of 5-HIAA excretion[366]. After administration of L-deprenyl, the improved clinical condition is not correlated with a corresponding change in phenylethylamine excretion[635].

3.2. Schizophrenia

3.2.1. Introduction

A hypothesis claiming hyperactivity of dopaminergic pathways in schizophrenia has been postulated in recent years and is supported by evidence that high doses of dopamine-releasing drugs may precipitate a schizophrenia-like psychosis even in normal subjects, and that neuroleptics which ameliorate schizophrenic symptoms are known to block dopamine receptors with a potency that parallels their therapeutic efficacy[762,870]. In contradiction, a recent report has claimed low dopamine activity in chronic schizophrenia[893].

Noradrenaline and serotonin[881] hypotheses of schizophrenia have been presented, but in a review Rodnight[762] has demonstrated that in the research carried out up to 1983 no consistent abnormalities have emerged. One of the earliest models of schizophrenia concerned the indoleamines and a transmethylation hypothesis in which the product would be the psychedelic N,N-dimethyltryptamine[763–765] of bufotenin[969]. Inadequate specificity and sensitivity of the isolation and quantification procedures initially seemed to lend support to this theory, but more recent work using more sophisticated methodology has shown at best only a trend to elevated urinary dimethyltryptamine excretion in schizophrenics[343,763–765]. However, a highly significant elevation in the urinary excretion of bufotenin in psychotics has recently been reported, although there was no correlation between the level of bufotenin excretion and severity of the disorder[969]. Another methylated product, 3,4-dimethoxyphenylethylamine, has been claimed to be found in greater amounts in schizophrenics than in normal controls[180,183,771], but the incidence has proved to be low and excretion inconsistent[179,180]. A third hypothesis stems from the close structural similarity between phenylethylamine and amphetamine, the similar behavior in rats induced by both compounds and the similarity with paranoid schizophrenic symptoms exhibited by drug abusers overdosed on amphetamine[624,625]. The weighted means of the results of studies on schizophrenia are presented in Tables 39–46. The subjects have not been differentiated according to clinical sub-type of schizophrenia.

3.2.2. Tables of values for schizophrenic subjects (all sub-types combined)

In aggregate, the studies reported in Tables 39–46 do not provide firm support for any of the amine hypotheses of schizophrenia. Dopamine concentration, although apparently markedly higher in the urine of schizophrenics, is lower in plasma and in CSF is no different from controls. HVA is higher in schizophrenic plasma, but not different from controls in urine or CSF. The noradrenaline concentration is elevated in the plasma and CSF of schizophrenics, as is the MHPG concentration in plasma, but this may not be of aetiological significance as it has been suggested that the high state of arousal often observed in schizophrenics may account for noradrenergic abnormalities in plasma and CSF[143,762]. No serotonergic abnormality is apparent

TABLE 39

UNCONJUGATED BIOGENIC AMINES IN URINE

Amine	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (μg per 24 h)*	
			Schizophrenics	*Normals*[a]
Phenylethylalmine	89, 100, 101, 102, 105	157	11.3 ± 2.6	8.1 ± 1.8
m-Tyramine	102	23	44 ± 11	83 ± 10
p-Tyramine	102, 113	51	481 ± 97	579 ± 75
Tryptamine	117, 766, 767	59	115 ± 7	103 ± 19
Noradrenaline	131, 143, 148, 652, 768	113	46 ± 6	40 ± 4
Adrenaline	131, 143, 148, 652	128	13.2 ± 2.6	10.1 ± 1.2
Dopamine	143, 148, 768, 893	58	446 ± 61	263 ± 34
5-Hydroxytryptamine	769	22	51	120 ± 23
Normetanephrine	770, 893	42	242, 110	194 ± 17
Metanephrine	770	22	9.6	95 ± 9
3,4-Dimethoxy-phenylethylamine	179, 180, 183, 771	41	1.6 ± 0.4	0.35
N,N-Dimethyl-tryptamine	656	26	1.2	0.38 ± 0.12
N-Methyltryptamine	656	26	0.7	0.86 ± 0.22
Bufotenin	186	26	1.1	1.71
	969	75	1.88 μg/g creatinine	0.37 μg/g creatinine

[a] Weighted normal means taken from Table 1.

TABLE 40

CONJUGATED BIOGENIC AMINES IN URINE

Amine	*Reference*	*Total No. of subjects*	*Weighted mean ± S.E.M. (μg per 24 h)*	
			Schizophrenics	*Normals*[a]
Noradrenaline	770	22	6.5	139 ± 37
Dopamine	770	22	446	785 ± 167
Normetanephrine	770	22	154	183 ± 23
Metanephrine	770	22	55	13.4 ± 2.7

[a] Weighted normal means taken from Table 2.

from these tables. Although phenylethylamine excretion is higher in schizophrenics, its concentration in plasma appears to be lower. No consistent trends for the major metabolite, phenylacetic acid, are observed.

A study of each of the references cited in the tables for comparisons of metabolite levels in controls and schizophrenics reveals no consistent differences, except for an elevation of noradrenaline in urine, plasma and CSF. As schizophrenia is not a single disease entity but a biologically heterogeneous collection of possibly distinct sub-types, this may explain some of the discrepancies reported for metabolite concentrations. Tables 47–50 summarize data obtained from several laboratories for different clinical types of schizophrenia.

3.2.3. Comparison of chronic and acute schizophrenic subjects

Comparisons of chronic and acute schizophrenic subjects are presented in Tables 47 and 48.

3.2.4. Comparison of paranoid and non-paranoid schizophrenic subjects

Comparisons of paranoid and non-paranoid schizophrenic subjects are presented in Tables 49 and 50.

3.2.5. Metabolite values as predictor of severity of disorder

Although an early study on the relationship between metabolite concentrations in the CSF of schizophrenic patients and diagnostic assessment of the severity of the disorder found no correlation[724], recent investigations have revealed a high positive correlation of plasma HVA (before treatment) with the global severity of the illness in schizophrenic patients[19,443,445,784,799,801]. However, it has also been claimed that plasma MHPG gives a better correlation with rated psychosis than does plasma HVA[802]. A positive correlation between the CSF concentration of 5-HIAA and the score on the Brief Psychiatric Rating Scale for schizophrenic behaviour has been reported[515]. MHPG excretion is not related to the severity of an acutely schizophrenic illness[807], but the sulfate conjugate has been reported to be strongly negative-

TABLE 41

UNCONJUGATED BIOGENIC AMINES IN PLASMA

Amine	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (pg/ml)*	
			Schizophrenics	*Normals*[a]
Phenylethylamine	212	14	74 ± 24	124 ± 27
Noradrenaline	143, 148, 254, 280, 772, 773, 774	223	458 ± 56	275 ± 32
Adrenaline	143, 280	74	55 ± 4	63 ± 11
Dopamine	143, 280	74	49 ± 5	86 ± 15
5-Hydroxytryptamine	364, 359	200	74 ± 5[b] (ng/ml)	387 ± 84[c] (pg/ml)

[a] Weighted normal means taken from Table 3.
[b] Whole blood.
[c] Ultrafiltrate.

TABLE 42

UNCONJUGATED AND CONJUGATED BIOGENIC AMINES IN CEREBROSPINAL FLUID

Amine	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (pg/ml)*	
			Schizophrenics	*Normals*[a]
Phenylethylamine	455	15	45 ± 2	600 ± 100
Noradrenaline	21, 143, 326, 327, 328, 329, 331, 334, 345, 661, 734, 775, 777	327	162 ± 17	119 ± 16
Adrenaline	143	8	14.2 ± 1.8	47 ± 23
Dopamine	143	8	55 ± 1.4	48 ± 14
Dopamine (conjugated)	345	46	673 ± 47	594 ± 108
Normetanephrine	775	13	360 ± 200	1800 ± 420
3-Methoxytyramine	775	13	n.d.	635 ± 184

[a] Weighted normal means taken from Tables 5 and 6.

TABLE 43

UNCONJUGATED AND CONJUGATED ACID METABOLITES IN URINE

Acid metabolite	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (mg per 24 h)*	
			Schizophrenics	*Normals*[a]
Phenylacetic	352	23	11.0 ± 2.8	8.5 ± 1.7
Phenylacetic (conjugated)	105, 352	62	113 ± 16	143 ± 16
Indoleacetic	354, 766, 767	26	8.6 ± 0.8	10.2 ± 1.3
5-Hydroxyindole-acetic	131, 354, 358, 359, 360, 364 365, 767, 778, 779, 893	370	5.4 ± 0.7	4.5 ± 0.4
Homovanillic	354, 778, 779, 780, 893	64	3.9 ± 0.4	4.8 ± 0.3
Vanilmandelic	131, 407, 768, 778, 779, 780, 893	168	3.7 ± 0.3	4.1 ± 0.2
3,4-Dihydroxyphenylacetic	893	20	0.9 ± 0.1	1.9 ± 0.2
3,4-Dimethoxyphenylacetic	180, 781	23	0–27 μg/g creatinine	(trace)

[a] Weighted normal means taken from Tables 7 and 8.

TABLE 44

UNCONJUGATED AND CONJUGATED ACID METABOLITES IN PLASMA

Acid metabolite	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*	
			Schizophrenics	*Normals*[a]
Phenylacetic	425	42	149 ± 17	124 ± 14
Phenylacetic (conjugated)	425	42	423 ± 46	345 ± 35
m-Hydroxyphenylacetic	425	42	7.7 ± 1.2	13.4 ± 2.2
m-Hydroxyphenyl-acetic (conjugated)	425	42	0.9 ± 0.4	2.1 ± 1.1
p-Hydroxyphenylacetic	425	42	57.0 ± 6.8	69.0 ± 8.8
p-Hydroxyphenyl-acetic (conjugated)	425	42	37.6 ± 8.0	13.6 ± 4.3
Homovanillic	438, 442, 443, 445, 782, 783, 784, 801, 802, 803, 804, 805	198	13.2 ± 1.3	9.7 ± 0.9
3,4-Dihydroxyphenylacetic	801	15	2.4 ± 0.4	3.5 ± 0.5

[a] Weighted normal means taken from Tables 9 and 10.

TABLE 45

UNCONJUGATED AND CONJUGATED ACID METABOLITES IN CEREBROSPINAL FLUID

Acid metabolite	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (ng/ml)*	
			Schizophrenics	*Normals*[a]
Phenylacetic	336, 455, 456, 785	59	18.4 ± 2.6	24.0 ± 3.1
Phenylacetic (conjugated)	336, 455	26	20.2 ± 5.6	24.5 ± 4.5
p-Hydroxyphenylacetic	458,786	22	5.8 ± 0.7	8.8 ± 1.4
Indoleacetic	461	17	4.1 ± 0.1	4.4 ± 0.6
p-Hydroxymandelic	786	12	3.0 ± 0.4	1.3 ± 0.4
5-Hydroxyindoleacetic	18, 131, 328, 334, 345, 485, 503, 507, 508, 512, 515, 518, 626, 661, 669, 676, 687, 732, 758, 776, 777, 787, 788, 789, 790, 791, 791,792	619	24.5 ± 2.8	26.2 ± 2.2
Homovanillic	18, 131, 328, 345, 485, 503, 507, 508, 512, 515, 518, 534, 661, 676, 687, 695, 732, 758, 773, 775, 776, 777, 786, 787, 788, 789, 790, 791, 794, 795, 796, 797, 798, 799, 801	803	39.1 ± 4.2	40.7 ± 4.3
Homovanillic (conjugated)	503	7	0.20 ± 0.40	0.25 ± 0.58
Vanilmandelic	541, 775, 786	37	1.64 ± 0.37	0.98 ± 0.16
3,4-Dihydroxy-phenylacetic	331, 345, 503, 513, 775, 777, 786 (see also 801)	132	0.49 ± 0.06	0.49 ± 0.04
3,4-Dihydroxyphenylacetic (conjugated)	503	7	0.10 ± 0.10	0.22 ± 0.10

[a] Weighted normal means taken from Tables 11 and 12.

TABLE 46

UNCONJUGATED AND CONJUGATED ALCOHOL AND GLYCOL METABOLITES IN URINE, PLASMA AND CEREBROSPINAL FLUID

Glycol or alcohol	*References*	*Total No. of subjects*	*Weighted mean ± S.E.M. (normals[a])*
3-Methoxy-4-hydroxyphenyl glycol (unconjugated)	442, 588, 782, 801, 802, 803	207	4.18 ± 0.26 (ng/ml plasma) (3.55 ± 0.31)
3-Methoxy-4-hydroxyphenyl glycol (conjugated)	10, 131, 407, 565, 704, 893	179	1448 ± 315 (μg per 24 h urine) (1866 ± 165)
3-Methoxy-4-hydroxy-phenylethanol	775	13	340 ± 230 (pg/ml CSF) (5.7 ± 0.9) (ng/ml)
3-Methoxy-4-hydroxyphenyl glycol (unconjugated)	131, 345, 503, 507, 508, 515, 518, 538, 661, 758, 773, 775, 776, 789, 790, 791, 797, 800, 801	464	9.91 ± 1.04 (ng/ml CSF) (10.6 ± 1.2)
3-Methoxy-4-hydroxyphenyl glycol (conjugated)	503, 800	26	2.3 ± 0.4 (ng/ml CSF) (0.51 ± 0.10)

[a] Weighted normal means in parentheses taken from Tables 14, 15, 17 and 18.

TABLE 47

BIOGENIC AMINES

Amine	*Reference*	*Biological fluid*	*Chronic*	*Acute*	*Control*
Noradrenaline	143	Urine	38.7 ± 3.0 μg per 24 h	35.4 ± 1.4 μg per 24 h	37.2 ± 0.7 μg per 24 h
	143	Plasma	260 ± 18 pg/ml	265 ± 14* pg/ml	230 ± 10 pg/ml
	143	CSF	147 ± 9	159 ± 18	125 ± 6
	328	CSF	259 ± 148*	216 ± 16**	207 ± 11
Adrenaline	143	Urine	12.5 ± 1.0 μg per 24 h	11.7 ± 0.5 μg per 24 h	11.2 ± 0.5 μg per 24 h
	143	Plasma	38.1 ± 3.2 pg/ml	35.9 ± 1.9 pg/ml	37.0 ± 2.0 pg/ml
	143	CSF	15.4 ± 2.8	12.1 ± 0.6	12.2 ± 0.8
Dopamine	143	Urine	320 ± 16 μg per 24 h	292 ± 7 μg per 24 h	292 ± 11 μg per 24 h
	143	Plasma	59.3 ± 6.1 pg/ml	50.2 ± 3.3 pg/ml	55.2 ± 3.7 pg/ml
	143	CSF	54.3 ± 1.8	55.9 ± 2.6	53.5 ± 2.0

* $p < 0.05$ *vs.* control.
** $p < 0.05$ *vs.* chronic.

TABLE 48

ACID AND GLYCOL METABOLITES

Acid or glycol metabolite	*Reference*	*Biological fluid*	*Chronic*	*Acute*	*Control*
5-Hydroxy-indoleacetic acid	358	Urine	5.3 ± 0.4 mg per 24 h	5.5 ± 0.9 mg per 24 h	5.2 ± 0.3 mg per 24 h
	131	Urine	3.8 ± 0.4	2.6 ± 0.4	4.4 ± 0.9
	328	CSF	34.8 ± 3.1 ng/ml	31.4 ± 1.6 ng/ml	35.5 ± 2.1 ng/ml
	131	CSF	28.4 ± 2.2	20.6 ± 2.8	40.6 ± 4.2
	626	CSF	16.4 ± 1.1	10.9 ± 0.9*	17.4 ± 2.0
Homovanillic acid	131	CSF	42.4 ± 4.8 ng/ml	41.4 ± 4.2 ng/ml	42.4 ± 3.8 ng/ml
	328	CSF	33.4 ± 3.0	28.8 ± 2.8	33.1 ± 2.3
Vanilmandelic acid	131	Urine	4.2 ± 0.4 mg per 24 h	3.6 ± 0.4 mg per 24 h	4.8 ± 0.8 mg per 24 h
3-Methoxy-4-hydroxyphenyl glycol	10	Urine	1530 ± 252 μg per 24 h	1097 ± 110 μg per 24 h	1352 ± 164 μg per 24 h
	131	Urine	1400 ± 400	1100 ± 400	2090 ± 300
	131	CSF	15.2 ± 3.6 ng/ml	12.6 ± 1.2 ng/ml	21.4 ± 3.2 ng/ml

* $p < 0.01$ *vs.* control.

ly correlated with severity in chronically ill subjects[407]. Repeated sampling in schizophrenics demonstrated that plasma MHPG appeared to be altered by changes in clinical state and may reflect psychosis-related changes in norepinephrine function in schizophrenia[892]. In addition, patients with idiosyncratic behaviour exhibit elevated MHPG excretion[704]. High levels of normetanephrine and metanephrine excretion have been associated with agitated behavior in both schizophrenic and depressed patients, with lower levels being reported during periods of calm[808]. An elevation in the excretion of the catecholamines and their metabolites during periods of catatonia returns nearly to normal during remission[809]. Conjugated phenylacetic acid concentrations in CSF have been shown to be highly correlated with hallucinatory behavior and unusual thought content[455]. Patients with the highest phenylethylamine concentration in CSF also had the highest scores on the Brief Psychiatric Rating Scale[455]. Urinary tryptamine excretion has been claimed to be positively correlated with the severity of psychotic activity and with changes in the severity of psychotic activity[767,810,821], as has urinary indoleacetic acid[821]. High urinary tryptamine, which corresponds to marked psychotic activity, has been shown to be associated with low platelet monoamine oxidase activity[117]. Platelet monoamine oxidase has been demonstrated to be significantly lower in chronic schizophrenics and lower in chronic paranoid schizophrenics than in chronic non-paranoid schizophrenics[824]. On this basis it has been suggested that chronic paranoid schizophrenia may be a different disorder from other chronic forms of schizophrenia.

Computed tomography scans of chronic schizophrenics revealed significantly larger ventricular brain ratios and structural changes consistent with cortical atrophy, and these results were significantly correlated inversely with the CSF concentration of HVA[508,798,799,812] and with 5-HIAA[508,811]. The results for MHPG also showed a negative correlation, but this was not statistically significant[508]. These results suggest that enlargements of the brain ventricles found in some schizophrenic patients may be associated with deficiencies in central monoamine transmission mechanisms. During measurements of regional cerebral blood flow in schizophrenic patients, the levels of HVA and 5-HIAA (but not MHPG) in the CSF were found to be correlated with blood flow during the Wisconsin Card Sorting Test but not during number-matching tests or at rest[813]. These results have been claimed to indicate a reduction in dopaminergic and serotonergic projections to the pre-frontal cortex as a possible neurochemical mechanism for pre-frontal dysfunction in schizophrenics[813].

3.2.6. Effects of drugs on metabolite concentrations

3.2.6.1. Effects on anti-psychotic drugs on metabolite concentrations. The subjects participating in the studies reported in Table 51 had been drug-free for at least 1 week and in most cases more than 2 weeks.

3.2.6.2. Metabolite values as predictor of response to drugs. High pretreatment excretion rates of the catecholamines and MHPG have been observed to be associated with a positive therapeutic response to propranolol, whereas low rates were associated with no improvement[818]. Early neuroleptic response has been reported to be significantly correlated to pretreatment plasma HVA in both sexes and to plasma MHPG in women[802,825]. Subjects who responded well to haloperidol treatment were found to exhibit significantly higher pretreatment plasma HVA and a trend to higher MHPG concentrations than those who did not respond[782]. No relationship between

TABLE 49

BIOGENIC AMINES

Amine	*Reference*	*Biological fluid*	*Paranoid*	*Non-paranoid*	*Control*
Phenylethylamine	100	Urine	19.0 ± 4.0* μg per 24 h	7.0 ± 1.5† μg per 24 h	8.0 ± 2.0 μg per 24 h
	102	Urine	17.4 ± 5.5*	7.9 ± 2.4†	5.3 ± 0.5
	101	Urine	8.3 ± 1.4**	5.0 ± 1.5†	4.1 ± 0.5
	105	Urine	16.6 ± 18.4*	10.2 ± 12.9†	6.5 ± 3.7
	806	Urine	18.1*	8.6	5.6
	212	Plasma	65 ± 5* pg/ml	–	99 ± 10 pg/ml
m-Tyramine	102	Urine	37.8 ± 11.6 μg per 24 h	49.8 ± 9.6 μg per 24 h	54.2 ± 6.3 μg per 24 h
p-Tyramine	102	Urine	603 ± 287	310 ± 68	377 ± 56
Noradrenaline	148	Urine	105 ± 19** ng/min	–	19 ± 3 ng/min
	143	Urine	35.0 ± 1.2 μg per 24 h	38.6 ± 4.8[a] μg per 24 h	37.2 ± 0.7 μg per 24 h
	143	Plasma	265 ± 13* pg/ml	249 ± 14[a] pg/ml	230 ± 11 pg/ml

	280	Plasma	426 ± 55	302 ± 65[a]	210 ± 6
	254	Plasma	238 ± 42	197 ± 20	201 ± 24
	329	CSF	163 ± 12	–	133 ± 10
	143	CSF	160 ± 11*	138 ± 7[a]	125 ± 6
Adrenaline	148	Urine	27.9 ± 8.6 ng/min	–	9.4 ± 4.1 ng/min
	143	Urine	11.9 ± 0.5 μg per 24 h	12.5 ± 1.7 μg per 24 h	11.2 ± 0.5 μg per 24 h
	280	Plasma	90 ± 72 pg/ml	59 ± 49[a] pg/ml	70 ± 40 pg/ml
	143	Plasma	36.6 ± 1.9	37.7 ± 4.3[a]	37.0 ± 2.0
	143	CSF	13.3 ± 1.1	15.6 ± 5.0	12.2 ± 0.8
Dopamine	143	Urine	283 ± 10 μg per 24 h	318 ± 25 μg per 24 h	292 ± 11 μg per 24 h
	148	Urine	524 ± 49** ng/min	–	210 ± 36 ng/min
	143	Plasma	54 ± 4 pg/ml	54 ± 7 pg/ml	55 ± 4 pg/ml
	280	Plasma	42 ± 10	24 ± 2	18 ± 9
	143	CSF	56 ± 2	54 ± 2	54 ± 2
N,N-Dimethyl-tryptamine	656	Urine	1223* ng per 24 h	–	87 386 ng per 24 h
N-Methyl-tryptamine	656	Urine	678	–	856

* $p < 0.05$ *vs.* control.
** $p < 0.01$ *vs.* control.
† $p < 0.05$ *vs.* paranoid.
[a] Hebephrenic patients.

TABLE 50

ACID METABOLITES

Acid metabolite	*Reference*	*Biological fluid*	*Paranoid*	*Non-paranoid*	*Control*
Phenylacetic (unconjugated)	352	Urine	14 ± 5** mg per 24 h	8.2 ± 3* mg per 24 h	9.8 ± 1.5 mg per 24 h
	336	CSF	11.5 ± 1.6 ng/ml	–	22.2 ± 3.0 ng/ml
	455	CSF	11.6 ± 1.4	–	21.6 ± 3.1
Phenylacetic (total or conjugated)	105	Urine	125 ± 23 mg per 24 h	150 ± 19 mg per 24 h	141 ± 16 mg per 24 h
	806	Urine	90*	69*	156
	352	Urine	83 ± 11*	64 ± 18*	150 ± 19
	455	CSF	20.0 ± 5.5 ng/ml	–	22.6 ± 5.4 ng/ml
	336	CSF	20.4 ± 5.5	–	23.6 ± 5.2
5-Hydroxy-indoleacetic	18	CSF	32.2 ± 3.3 ng/ml	29.3 ± 3.0 ng/ml	–
Homovanillic	18	CSF	30.1 ± 2.8	22.7 ± 2.7†	–

* $p < 0.05$ *vs.* control.
** $p < 0.01$ *vs.* control.
† $p < 0.01$ *vs.* paranoid.

pretreatment CSF concentrations of HVA or MHPG and clinical response was observed for treatment with chlorpromazine, thiothixene, melperone, sulpiride or clozapine[797]. Also, pretreatment excretion rates of 5-HIAA or HVA proved to be unsuitable in predicting clinical response to reserpine treatment[778,779].

3.2.6.3. Correlation of changes in metabolite levels with therapeutic response. The changes in metabolite concentrations produced by treatment of schizophrenics with anti-psychotic drugs mostly did not correlate with clinical improvement. Thus, changes in urinary 5-HIAA concentration following chlorpromazine or reserpine treatment were not related to therapeutic response[778,779]. Changes in urinary HVA concentration after treatment with chlorpromazine or reserpine[778,779] and flupenthixol[807], in plasma HVA after treatment with apomorphine[820], chlorpromazine[815], fluphenazine[815], haloperidol[815], perphenazine[815], thioridazine[815] and thiothixene[807], trifluoroperazine[815] and verapamil[819] and in CSF HVA after treatment with chlorpromazine[695,797], haloperidol[695], melperone[797], thioridazine[695] and thiothixene[797] could not be demonstrated to be correlated with improvements in clinical condition. However, the acute effect of neuroleptics may be reflected by changes in plasma HVA concentration[804,805]. Decreases in plasma HVA following treatment with fluphenazine[445,784] and in CSF noradrenaline after treatment with pimozide proved to be significantly correlated with therapeutic response. Decreases in urinary MHPG after treatment with flupenthixol[807], in plasma MHPG after treatment with verapamil[819] and in CSF MHPG after treatment with chlorpromazine[797], melperone[797], thiothixene[797] and verapamil[819] were likewise not correlated with therapeutic response. It has been claimed that a decline in the excretion of 3,4-dimethoxyphenylethylamine during long-term treatment with chlorpromazine is highly significantly correlated with clinical improvement[183].

3.2.6.4. Tardive dyskinesia. Until recently, it has been thought that tardive dyskinesia was caused by excessive dopaminergic activity in nigrostriatal pathways secondary to chronic neuroleptic treatment. A statistically significant positive correlation between plasma HVA[816] and CSF HVA[334] and the severity of the dyskinesia has been reported. However, recent investigations have demonstrated no significant differences in either plasma HVA[822] or CSF HVA[790,513] between normals or control schizophrenics and subjects suffering from tardive dyskinesia. The CSF concentrations of MHPG[513,790], 5-HIAA[334,513,790] and DOPAC[513] are also not significantly different in tardive dyskinesia compared with controls. However, urinary MHPG may be lower in schizophrenics with tardive dyskinesia than in those free from the disorder[823]. Serum[772] and CSF[334] concentrations of noradrenaline have been reported to be elevated in schizophrenic subjects with tardive dyskinesia. The measurement of HVA and 5-HIAA in the CSF of tardive dyskinesic patients before and after treatment with probenecid gave no indication of reduced function of the dopaminergic and serotonergic systems[826].

TABLE 51

EFFECTS OF ANTI-PSYCHOTIC DRUGS ON METABOLITE CONCENTRATIONS

Drug	*Reference*	*Biological fluid*	*Category schizophrenia*	*Effect on amine or metabolite*[a]
Apomorphine	820	Serum	Chronic	HVA↓ ($p < 0.01$)
Chlorpromazine	778	Urine	Not classified	5-HIAA↑ (N.S.); HVA↑ ($p < 0.01$); VMA↓ ($p < 0.02$))
	779	Urine	Not classified	5-HIAA↑; HVA↑; VMA↓
	814	CSF	Acute	5-HIAA (N.S.); HVA↑ ($p < 0.005$)
	795	CSF	Acute	HVA↑ ($p < 0.001$)
	695	CSF	Acute	HVA↑ ($p < 0.01$)
	807	Urine	Acute	MHPG (N.S.)
	183	Urine	Acute	DMPEA↓ ($p < 0.05$)
	797	CSF	Not classified	HVA↑ ($p < 0.01$); MHPG↓ (< 0.001)
	815	Plasma	Psychotic	HVA↑ (longitudinal study; ↓ long-term)
	777	CSF	Chronic	DA↓ ($p < 0.05$); DOPAC↓ ($p < 0.01$); HVA↓ ($p < 0.05$); NA↓ (< 0.05) (effect of withdrawal of drug after long-term use)
Debrisoquin sulfate	801	Urine	Acute	MHPG↓ ($p < 0.01$); HVA↓ ($p < 0.001$); DOPAC↓ ($p < 0.005$)
	801	Plasma	Acute	MHPG↓ ($p < 0.001$); HVA↓ ($p < 0.001$); DOPAC↓ ($p < 0.001$)
	801	CSF	Acute	MHPG↓ ($p < 0.001$); HVA↓ (N.S.); DOPAC↓ (N.S.)
β-Flupenthixol	807	Urine	Acute	MHPG↓ ($p < 0.025$)
Fluphenazine	815	Plasma	Not classified	HVA↑ (longitudinal study; ↓ long-term)
	445	Plasma	Chronic	HVA↓ ($p < 0.01$)
	784	Plasma	Not classified	HVA↓ ($p < 0.001$)
	803	Plasma	Chronic	MHPG (N.S. with alprazolam augmentation)
Haloperidol	780	Urine	Acute	HVA↑ ($p < 0.02$); DA↑ (N.S.); VMA↑ (N.S.)
	695	CSF	Acute	HVA↑ ($p < 0.01$)
	515	CSF	Paranoid	MHPG↓ (N.S.); HVA↑ (N.S.); 5-HIAA↓ (N.S.)
	329	CSF	Paranoid	DA↑ ($p < 0.01$); NA↑ ($p < 0.01$)
	782	Plasma	Acute	HVA↑ (longer term↓); MHPG↑ (longer term↓);

	815	Plasma	Psychotic	HVA↑ (longitudinal: long-term↓)
	777	CSF	Chronic	DA↓ ($p < 0.05$); DOPAC↓ ($p < 0.01$); HVA↓ ($p < 0.05$); NA↓ ($p < 0.05$) (effect of withdrawal of drug after long-term use)
	19	Plasma	Not classified	HVA (N.S.)
	817	Plasma	Not classified	HVA↑
	804	Plasma	Not classified	HVA↑ ($p < 0.001$)
Melperone	789	CSF	Acute	HVA↑ ($p < 0.001$); (↓ $p < 0.025$ after 4 weeks); 5-HIAA (N.S.); MHPG (N.S.) (↓ $p < 0.001$ after 4 weeks)
	797	CSF	Not classified	HVA↑ ($p < 0.001$); MHPG↓ ($p < 0.001$)
α-Methyldopa	767	Urine	Chronic	5-HIAA↓ ($p < 0.01$); TRA (N.S.); IAA↓ (N.S.)
Oxypertine	139	Urine	Chronic	NA↑ ($p < 0.01$); MN↑ ($p < 0.02$); NMN↑ ($p < 0.01$); VMA↑ ($p < 0.02$) (after chronic chlorpromazine use)
Perphenazine	815	Plasma	Psychotic	HVA↑ (longitudinal study: ↓ long-term)
Pimozide	327	CSF	Undifferentiated, paranoid, schizoaffective	NA↓ ($p < 0.01$)
Reserpine	778	Urine	Not classified	5-HIAA↑ ($p < 0.05$); HVA↑ ($p < 0.001$); VMA↓ ($p < 0.001$)
	779	Urine	Not classified	5-HIAA↑ ($p < 0.05$); HVA↑ ($p < 0.001$); VMA↓ ($p < 0.001$)
	821	Urine	Not classified	IAA (N.S.); TRA (N.S.)
Sulpiride	797	CSF	Psychotic	HVA↑ ($p < 0.01$); MHPG (N.S.)
Thioridazine	695	CSF	Acute	HVA↑ ($p < 0.05$)
	815	Plasma	Psychotic	HVA↑ (longitudinal study: ↓ longer-term)
	777	CSF	Chronic	DA↓ ($p < 0.05$); DOPAC↓ ($p < 0.01$); HVA↓ ($p < 0.05$); NA↓ ($p < 0.05$); 5-HIAA (N.S.) (effect of withdrawal of drug after long-term use)
Thiothixene	789	CSF	Acute	HVA↑; 5-HIAA (N.S); MHPG (N.S.)
	797	CSF	Not classified	HVA↑ ($p < 0.001$); MHPG (N.S.)
	815	Plasma	Psychotic	HVA↑ (longitudinal study: ↓ longer-term)
Trifluoperazine	815	Plasma	Psychotic	HVA↑ (longitudinal study: ↓ longer-term)
	814	CSF	Acute	HVA↑ ($p < 0.005$); 5-HIAA (N.S.)
Verapamil	819	Plasma	Chronic	HVA↑ ($p < 0.01$); MHPG↓ ($p < 0.05$)
	819	CSF	Chronic	HVA↑ ($p < 0.01$); MHPG↓ (N.S.); 5-HIAA (N.S.)

[a] For abbreviations, see text and Table 38. MN = metanephrine; DMPEA = 3,4-dimethoxyphenylethylamine. ↑, Concentration increases during treatment; ↓, concentration decreases during treatment

TABLE 52

DOPAMINERGIC SYSTEM

Amine or metabolite	*Reference*	*Biological fluid*	*Parkinson's disease*	*Control*
Dopamine	156	Urine	67.5 ± 3.2** μg per 24 h (unconjugated)	126 ± 9 μg per 24 h
	156	Urine	230 ± 12 (conjugated)	246 ± 23
	111	Urine	150 ± 8* μg/g creatinine	127 ± 8 μg/g creatinine
	43	Urine	241 ± 22 μg per 24 h	316 ± 15 μg per 24 h
3,4-Dimethoxy-phenylethylamine	827	Urine	4.4 ± 0.3	6.8 ± 1.2
Homovanillic acid	828	Urine	4.31 mg/g creatinine	3.72 mg/g creatinine
	156	Urine	2.53 ± 0.16 mg per 24 h	2.17 ± 0.17 mg per 24 h
	497	CSF	20 ± 3.5 ng/ml	38 ± 8.5 ng/ml
	527	CSF	17 ± 2	47 ± 8
	472	CSF	12 ± 2	40 ± 7
	495	CSF	15.8 ± 1.1**	34.4 ± 1.9
	491	CSF	14.4 ± 0.8**	34.6 ± 1.9
	490	CSF	15 ± 7	53 ± 6
	529	CSF	82.1 ± 7.6 (low clinical score)	87.2 ± 9.2
	529	CSF	30.5 ± 8.6** (high clinical score)	87.2 ± 9.2
	535	CSF	15 ± 3.9	28 ± 6.8
	469	CSF	12 ± 9**	39 ± 13
	468	CSF	16 ± 5***	45 ± 5
	829	CSF	< 10 ± 1	23 ± 2
	486	CSF	19 ± 2***	53 ± 11
	533	CSF	8.5 ± 1.7**	31 ± 5
	476	CSF	20 ± 7	60 ± 8
	475	CSF	20 ± 2 ng/ml	50 ± 5 ng/ml
	532	CSF	54.6 ± 6.5***	85.9 ± 7.7
	830	CSF	63 ± 15	93 ± 7
	831	CSF (ventricular)	154 ± 19	216
3,4-Dihydroxy-phenylacetic acid	156	Urine	1.27 ± 0.08*** mg per 24 h	1.80 ± 0.18 mg per 24 h
	486	CSF	6 ± 1*** ng/ml	9 ± 1 ng/ml

* $p < 0.05$ *vs.* control
** $p < 0.001$ *vs.* control.
*** $p < 0.01$ *vs.* control.

4. NEUROLOGICAL DISORDERS

4.1. Parkinson's disease

4.1.1. Introduction

A central dopamine deficiency is considered to be an important factor responsible for the pathogenesis of Parkinson's disease. A discussion of dopamine and serotonin disturbances in Parkinsonism can be found in a review by Mendlewicz *et al.*[684]. *Post-mortem* examination of the brain of a Parkinsonian patient revealed reduced concentrations of dopamine and its metabolites in the striatum, putamen and caudate nucleus[333]. Serotonin and 5-HIAA were also lower in some regions. That the brains of patients suffering from Parkinson's disease synthesize less dopamine than normal subjects has also been shown by significantly decreased dopamine excretion and lower CSF concentrations of HVA (Table 52).

No correlation between the HVA concentration in the CSF of Parkinsonian patients and the presence or absence or rigidity or akinesia could be demonstrated[831], nor could a correlation between pretreatment severity and pretreatment HVA or 5-HIAA concentration be demonstrated[469,535,829,830,836–838].

Alterations in central serotonin metabolism have been reported to attend Parkinson's disease (Table 53), although it appears that this may be a secondary derangement having no effect on the severity of the extrapyramidal signs characteristic of the disorder[535,829,839]. Pretreatment concentrations of 5-HIAA in the CSF are generally lower in Parkinsonism (Table 53) than in control subjects but the differences have not been consistently statistically significant. The noradrenergic system appears to be normal in Parkinsonism (Table 54).

4.1.2. Metabolite concentrations in Parkinsonian patients and controls

Metabolite concentrations in Parkinsonian patients and controls are given in Tables 52–55. All concentrations given are for medication-free subjects.

4.1.3. Effect of L-*DOPA treatment*

Although the concentration of HVA in the CSF of Parkinsonian patients increases roughly in proportion to the dose of L-DOPA[468,486,495,497,529,533,828,829,836,837,840], this increase has generally not been found to correlate with clinical improvement[468,486,495,497,529,533,829,836,838]. The single exception to this finding has not been explained[830]. The DOPAC concentration in CSF also increases after ingestion of L-DOPA, but the increase is also not correlated with clinical improvement[486,840]. Furthermore, pretreatment values for HVA in CSF do not correlate with the responsiveness of the subject to L-DOPA treatment[472,535,829,838]. Some investigators have reported that those patients most responsive to L-DOPA therapy start treatment with much lower concentrations of HVA[529], whereas others have found that patients with high pretreatment HVA do as well on L-DOPA as those with low levels[838]. It has also been suggested that the change in the HVA concentration in CSF during L-DOPA treatment might be of value in predicting the response to L-DOPA[468].

A high baseline concentration of 5-HIAA in CSF has been reported to predict a good response to L-DOPA therapy[497]. Agreement on the effect of L-DOPA on the

TABLE 53

SEROTONERGIC SYSTEM

Amine or metabolite	*Reference*	*Biological fluid*	*Parkinson's disease*	*Control*
5-Hydroxytryptamine	523	CSF	7.75 ± 2.3 ng/ml	12.7 ± 2.6 ng/ml
5-Hydroxy-	832	Urine	8.73 ± 4.1 mg/g creatinine	6.6 ± 2.0 mg/g creatinine
indoleacetic	523	CSF	21.6 ± 3.6 ng/ml	25.5 ± 2.4 ng/ml
acid	475	CSF	20 ± 12	40 ± 1.5
	476	CSF	10 ± 2*	40 ± 2
	533	CSF	29 ± 3	30 ± 3
	486	CSF	13 ± 1**	19 ± 1
	829	CSF	20 ± 2	30 ± 2
	468	CSF	21 ± 2.6	27 ± 3
	469	CSF	17 ± 3.5	23 ± 3
	535	CSF	24 ± 3	28 ± 3
	490	CSF	24 ± 9	31 ± 3
	491	CSF	26.3 ± 1.5*	36.7 ± 3.8
	495	CSF	24.0 ± 1.3**	33.9 ± 3.3
	472	CSF	15 ± 3	27 ± 4
	497	CSF	14 ± 1	20 ± 2
	830	CSF	75 ± 12	57 ± 4

* $p < 0.05$ *vs.* control.
** $p < 0.01$ *vs.* control.

TABLE 54

NORADRENERGIC SYSTEM

Amine or metabolite	*Reference*	*Biological fluid*	*Parkinson's disease*	*Control*
Noradrenaline	43	Urine	40 ± 5 μg per 24 h	42 ± 3 μg per 24 h
Adrenaline	43	Urine	15 ± 0.4	17 ± 1.1
3-Methoxy-4-hydroxyphenol glycol	500	CSF	12.5 ± 1.3 ng/ml	15.1 ± 2.6 ng/ml
	833	CSF	18	16
	558	CSF	12.8 ± 1.5 (unconjugated)	11.0 ± 1.0 (unconjugated)
	558	CSF	32.0 ± 2.0 (total)	26.4 ± 3.5 (total)
	497	CSF	8 ± 1	7 ± 2
3-Methoxy-4-hydroxyethanol	558	CSF	2.8 ± 0.8 (unconjugated)	5.7 ± 0.9 (unconjugated)
	558	CSF	8.5 ± 0.5 (total)	9.0 ± 1.0 (total)

TABLE 55

OTHER AMINES AND METABOLITES

Amine or metabolite	*Reference*	*Biological fluid*	*Parkinson's disease*	*Control*
p-Tyramine	111	Urine	505 ± 33* μg/g creatinine	400 ± 34 μg/g creatinine
	834	Urine	500 ± 137	312 ± 29
Tryptamine	111	Urine	80 ± 8*	60 ± 5
	834		72 ± 5	83 ± 9
p-Hydroxyphenylacetic acid	102	Urine	7.4 ± 1.5 mg per 24 h	13.7 ± 3.5 mg per 24 h
m-Hydroxyphenyl acetic acid	102	Urine	1.7 ± 0.5 mg per 24 h	< 1 mg per 24 h
Phenylacetic acid	40	Plasma (U)[a]	105.7 ± 34.5 ng/ml	161.8 ± 22.2 ng/ml
	40	Plasma (C)[a]	425.5 ± 138.5	412.5 ± 68.7
	40	CSF (U)	25.6 ± 6.1	31.6 ± 6.5
	40	CSF (C)	20.2 ± 2.7	29.7 ± 4.0

* $p < 0.05$ *vs.* control.

[a] U = unconjugated; C = conjugated.

concentration of 5-HIAA in CSF has been poor, some workers claiming it to be reduced[495,793,829] and others finding no change[497]. No change in the CSF or urinary concentrations of MHPG[833,840] or the urinary excretion of VMA[840] was observed after L-DOPA administration.

p-Tyramine has been reported to be reduced in Parkinsonian patients on L-DOPA[103,834], but to be near normal in untreated subjects[107,111]. Tryptamine and indoleacetic acid are not affected by L-DOPA ingestion[793,834].

Although no pretreatment clinical distinction between Parkinsonian patients with low or high concentrations of HVA in CSF could be made, those with low pretreatment values responded well to treatment with amantidine[469]. With probenecid pretreated Parkinsonian patients, the administration of L-tyrosine results in a statistically significant increase in the CSF concentration of HVA, indicating an increase in dopamine turnover in these patients[846].

4.1.4. Effect of probenecid

As L-DOPA therapy can have serious side effects and because treatment should be continued for several months prior to a final assessment, it would be useful to be able to predict the results of therapy in advance. It has been suggested that the determination of HVA and 5-HIAA in CSF after treatment with probenecid may be a better diagnostic tool for Parkinson's disease than the pre-treatment values[475]. A significant ($p < 0.03$) negative correlation between the post-probenecid HVA concentration in CSF and clinical improvement scores after L-DOPA therapy, and a significant negative correlation between HVA accumulation and degree of improvement, have been demonstrated[835]. Thus, a single lumbar puncture and HVA determination after probenecid administration permits the prediction of the results of L-DOPA therapy. Several studies have shown that Parkinsonian patients treated with probenecid exhibit a significantly smaller increase in the CSF HVA concentration than normal or neurological controls, indicating a decreased dopamine turnover for the Parkinsonian patients[475,491,495,527,841]. Parkinsonian patients with markedly decreased dopamine metabolism as shown by the probenecid test seem to benefit more from L-DOPA therapy[835]. The ratio of the CSF concentrations of 5-HIAA and HVA is significantly greater in Parkinson's disease than in controls after probenecid administration, again indicating a lower dopamine turnover in Parkinsonism[830]. A substantial diminution in the response of CSF 5-HIAA to probenecid administration in Parkinson's disesase compared with controls has been reported, indicating that central serotonin turnover may also be deficient[475,495,535]. However, unlike the CSF HVA concentrations, no correlation of 5-HIAA concentrations or changes in 5-HIAA concentrations after probenecid treatment with the degree of clinical improvement after L-DOPA administration could be demonstrated[835].

4.2. Alzheimer's disease

A *post-mortem* analysis of the putamen and caudate nucleus from patients with dementia of the Alzheimer type revealed reduced concentrations of noradrenaline, serotonin and their metabolites[333]. Some differences and similarities in the pattern of reduced concentrations between patients with Alzheimer's and Parkinson's diseases were noted. The data summarized in Table 56 for metabolite concentrations

TABLE 56

METABOLITE CONCENTRATIONS IN ALZHEIMER PATIENTS AND CONTROLS

Metabolite	*Reference*	*Biological fluid*	*Alzheimer's disease*	*Control*
Homovanillic acid	526	CSF	41.7 ± 4.0 ng/ml	41.5 ± 3.8 ng/ml
	775	CSF	33.7 ± 5.1*	70.4 ± 7.4 (schizophrenic)
	333	CSF	32 ± 32	35 ± 21
	522	CSF	29.1 ± 5.9**	42.3 ± 3.4
	521	CSF	26.9 ± 0.4	26.3 ± 0.7
	507	CSF	46.4 ± 7.6	52.1 ± 4.7
	17	CSF	27.5 ± 4.2*	67.5 ± 3.7
	464	CSF	52 ± 6***	78 ± 7
	845	CSF	29 ± 5.4	33 ± 4.6
	472	CSF	38 ± 6	40 ± 6
	844	CSF	28 ± 5.4**	51 ± 7.3
	479	CSF	23 ± 4.1***	60 ± 7.2
	476	CSF	30 ± 6.3	60 ± 7.8
	339	CSF	14.8 ± 2.4*	42.2 ± 4.5
3,4-Dihydroxy-phenylacetic acid	339	CSF	0.41 ± 0.04**	0.74 ± 0.10
Noradrenaline	333	CSF	340 ± 90 pg/ml	580 ± 20 pg/ml
	243	CSF	411 ± 25**	245 ± 33
	243	Plasma	677 ± 64***	253 ± 37
3-Methoxy-4-hydroxyphenyl glycol	526	CSF	9.6 ± 0.8 ng/ml	10.1 ± 0.9 ng/ml
	775	CSF	8.5 ± 0.5	9.4 ± 0.7 (schizophrenic)
	333	CSF	5.5 ± 1.7	5.9 ± 0.4
	522	CSF	8.3 ± 0.4	7.2 ± 0.5
	507	CSF	8.8 ± 1.1	7.2 ± 0.6
	610	CSF	10.6 ± 0.1	9.8 ± 0.1
	339	CSF	9.9 ± 0.8	8.2 ± 0.4
	243	CSF	10.8 ± 0.9	7.6 ± 0.8
	243	Plasma	5.4 ± 0.6	3.4 ± 0.3
5-Hydroxy-tryptamine	337	CSF	110 ± 10 pg/ml**	400 ± 140 pg/ml (caudal)
	523	CSF	12.1 ± 3.9 ng/ml	12.7 ± 2.6 ng/ml
	339	CSF	470 ± 90 pg/ml	370 ± 100 pg/ml
5-Hydroxy indoleacetic acid	476	CSF	20 ± 3*** ng/ml	40 ± 2 ng/ml
	479	CSF	35 ± 3.4	40 ± 2.4
	844	CSF	20 ± 2.5***	29 ± 2.4
	472	CSF	31 ± 3	27 ± 4
	464	CSF	35 ± 2***	42 ± 3
	17	CSF	29.5 ± 4.5	32.5 ± 2.0
	507	CSF	22.9 ± 2.3	22.5 ± 2.7
	521	CSF	14.4 ± 0.2	10.8 ± 0.4
	522	CSF	16.0 ± 1.5**	21.4 ± 1.8
	333	CSF	17 ± 2	23 ± 3
	337	CSF	12.9 ± 1.3**	20.2 ± 1.8
	523	CSF	27.9 ± 2.9	25.5 ± 2.4
	775	CSF	22.0 ± 1.5	28.7 ± 2.3 (schizophrenic)
	526	CSF	20.6 ± 1.9	20.8 ± 2.1
	339	CSF	8.1 ± 1.9**	14.3 ± 1.3

* $p < 0.001$ vs. control.
** $p < 0.05$ vs. control.
*** $p < 0.01$ vs. control.

in CSF and in some reviews[684,842,843], although partly contradictory, indicate reduced levels of HVA and 5-HIAA in Alzheimer's disease. Significantly higher levels of noradrenaline in both plasma and CSF have been interpreted to be compatible with an increased turnover of noradrenaline in Alzheimer's disease, although the MHPG concentrations generally fall in the normal range[243]. Pre-senile dementia has been associated with lower CSF concentrations of both 5-HIAA and HVA than senile dementia[476,522,844], whereas the MHPG concentrations are not different. The more severe symptoms of the disorder are associated with lower concentrations of 5-HIAA and HVA in CSF[17,464,841], and with higher concentrations of plasma[243] and CSF[243,841] MHPG and noradrenaline. In Alzheimer patients, serotonin and 5-HIAA are negatively correlated, whereas in the same CSF fraction from Parkinsonian patients they are positively correlated, indicating a differential involvement of the serotonergic system in the two disorders[523]. Various anti-depressant drugs have been tested in Alzheimer patients and the effects on the CSF concentrations of HVA and 5-HIAA determined[526,753]. The HVA/5-HIAA ratio was able to discriminate more powerfully between the effects of different drugs than either metabolite separately.

5. OTHER DISORDERS

5.1. Aggression and violence

5.1.1. Introduction

The concentrations of 5-HIAA in the CSF of violent individuals have been consistently reported to be lower than those in non-violent persons. Brown *et al.*[636] have shown that more impulsive aggressive individuals exhibit significantly reduced 5-HIAA concentrations in their CSF compared with less compulsive individuals having a significantly lower aggression score. The MHPG and HVA concentrations did not differ between the two groups. Similarly, the 5-HIAA concentration in the CSF of murderers who have committed more than one violent crime is significantly less than that in murderers who have committed only one violent crime[734]. Both homicidal and suicidal killers have lower 5-HIAA levels in CSF than normal controls[733]. A negative correlation of the 5-HIAA concentration in CSF with the incidence of criminal acts has been demonstrated[847]. These results suggest that low levels of 5-HIAA in CSF reflect a disorder of serotonin turnover which can make an individual more prone to violence in states of emotional turmoil. Support for this hypothesis has been provided by a study of subjects exhibiting the 47, XYY syndrome[481,848] in which probenecid tests showed a much smaller CSF accumulation of 5-HIAA for the aggressive subjects than for controls, indicating a decreased serotonin turnover in the former. A dramatic increase in the CSF levels of 5-HIAA was observed for these subjects following treatment with L-tryptophan[848]. The clinical improvement in these patients was equivalent to that obtained by treatment with conventional neuroleptics.

Sandler *et al.*[423] have proposed that phenylethylamine overproduction may represent a compensatory response to curb aggressive tendencies arising as a result of some unknown functional derangement. In support of this theory they found significantly elevated levels of total and unconjugated phenylacetic acid in the plasma of aggressive prison inmates. More recently, the results of investigations by Boulton *et al.*[426] and Yu *et al.*[428] failed to confirm this finding, demonstrating a trend to a

reduced plasma concentration of phenylacetic acid in aggressive subjects. These contradictions may reflect inadequate definitions of aggression and violence, and also confusion between violent and agressive behaviour which may not be synonymous.

5.1.2. Metabolite concentrations in aggressive subjects and controls

The metabolite concentrations obtained in experiments on violent and aggressive subjects are summarized in Table 57.

5.2. Hyperkinesis and attention deficit disorder

5.2.1. Introduction

The data indicate that a dysfunction of the noradrenergic system may be involved in the aetiology of hyperkinesis and attention deficit disorder. The other monoaminergic systems do not appear to be involved, although a trend to elevated plasma indoleacetic acid in hyperkinetic children has been reported[428]. Behavioural changes in boys with attention deficit disorder with hyperactivity treated with methylphenidate were not correlated with the urinary excretion of noradrenaline or its metabolites[849]. However, treatment with D-amphetamine produced a decrease in urinary MHPG[850,851] that was related to the response to the drug. Subjects with low pretreatment urinary HVA tended to respond better to D-amphetamine than did those with normal HVA levels, and their clinical improvement corresponded with an increase in HVA excretion[851,852]. D-Amphetamine caused a reduction in the CSF concentration of HVA which was closely correlated with clinical improvement[853]. It was suggested that these results support the view that an alteration in central dopamine-mediated synaptic function may occur in hyperactive children[853].

5.2.2. Metabolite concentrations in hyperkinetic children and controls

Metabolite concentrations in hyperkinetic children and controls are given in Table 58.

5.3. Migraine

Dysfunctions of the serotonin, dopamine, noradrenaline and tyramine systems have all been implicated in migraine aetiology. A conjugation defect in dietary and tyramine-sensitive migraine has been postulated; support for this theory has been obtained by challenging patients and controls with oral tyramine and observing significantly less excretion of conjugated tyramine in the migraine patients[108,109]. However, in a more recent study in which the migraine sufferers were challenged with deuterium-labelled tyramine, these findings could not be confirmed, although a conjugating enzyme, phenolsulfotransferase, proved to be significantly less active in the migraine subjects[97].

Significant changes in serotonin and dopamine metabolism during different stages of migraine attacks have been reported[489]. Urinary 5-HIAA[367,489,859] and VMA[367] excretion have been shown to increase during a migraine attack, although some studies have shown no change in VMA excretion during an attack[489,859]. Significantly higher plasma VMA and urinary MHPG have been found in migraine patients even in the absence of an attack[97]. The relationship between the serotonergic system and migraine has been reviewed[860].

TABLE 57

METABOLITE CONCENTRATIONS IN AGGRESSIVE SUBJECTS AND CONTROLS

Metabolite		*Reference*	*Biological fluid*	*Aggression-violence*	*Control*
5-Hydroxyindoleacetic acid		481	CSF	21.6 ± 1.9 ng/ml	21 ± 3 ng/ml
		733	CSF	17.4 ± 1.4	17.4 ± 0.9
Homovanillic acid		428	Plasma	9.0 ± 0.8[c]*	5.3 ± 0.6[d]
		481	CSF	29.5 ± 11.4	47 ± 8
		733	CSF	47.3 ± 1.1	42.0 ± 0.5
3-Methoxy-4-hydroxyphenyl glycol		733	CSF	8.8 ± 0.5	9.7 ± 0.3
Vanilmandelic acid		428	Plasma	4.9 ± 0.2[a]	5.7 ± 0.6[b]
		428	Plasma	4.8 ± 0.3[c]	4.9 ± 0.6[d]
Phenylacetic acid	-U[e]	423	Plasma	214.7 ± 40.8**	107.2 ± 10.7
	-T[e]	423	Plasma	661.4 ± 113.1**	386.0 ± 50.7
	-U[e]	426	Plasma	135.5 ± 12.1[g]	125.9 ± 9.7[f]
	-U[e]	426	Plasma	136.1 ± 18.0[g]	126.9 ± 9.5[f]
	-U[e]	426	Plasma	136.1 ± 18.0[g]	79.5 ± 9.9[h]
	-C[e]	426	Plasma	308.8 ± 24.8[g]	362.6 ± 32.3[f]
	-C[e]	426	Plasma	270.4 ± 18.3[g]	361.3 ± 32.4[f]
	-C[e]	426	Plasma	270.4 ± 18.3[g]	296.4 ± 30.9[h]
	-U	428	Plasma	102.2 ± 10.0[g]	94.9 ± 9.7[f]
	-U	428	Plasma	70.6 ± 5.6[a]**	116.9 ± 13.1[b]
	-U	428	Plasma	77.9 ± 9.6[c]**	126.5 ± 21.1[d]
	-C	428	Plasma	246.4 ± 17.5[g]	263.5 ± 26.3[f]
	-C	428	Plasma	212.8 ± 19.6[a]**	275.5 ± 21.5[b]
	-C	428	Plasma	214.3 ± 29.0[c]**	325.5 ± 35.0[d]
	-T[e]	428	Plasma	343.7 ± 24.8[g]	363.5 ± 35.7[f]

-T[e]	428	Plasma	283.1 ± 23.7[a**]	391.2 ± 31.4[b]
-T[e]	428	Plasma	282.2 ± 33.7[c*]	452.0 ± 55.1[d]
p-Hydroxyphenylacetic acid	426	Plasma	65.9 ± 6.6[g**]	99.4 ± 13.1[f]
	426	Plasma	64.5 ± 6.8[g**]	99.5 ± 17.9[f]
	426	Plasma	64.5 ± 6.8[g]	66.6 ± 15.9[h]
	428	Plasma	44.5 ± 4.1[a]	65.6 ± 8.7[b]
	428	Plasma	47.0 ± 7.3[c]	44.9 ± 11.0[d]
m-Hydroxyphenylacetic acid	426	Plasma	10.3 ± 2.4[g]	7.8 ± 1.3[f]
	426	Plasma	9.6 ± 1.8[g]	9.5 ± 1.6[f]
	426	Plasma	9.6 ± 1.8[g]	16.6 ± 2.7[h]
	428	Plasma	4.6 ± 0.8[c]	6.2 ± 1.2[d]
	428	Plasma	6.2 ± 1.1[a]	6.1 ± 0.6[b]
Indoleacetic acid	428	Plasma	220 ± 14[a]	369 ± 62[b]
	428	Plasma	230 ± 24[c]	213 ± 45[d]
p-Hydroxymandelic acid	428	Plasma	9.5 ± 1.2[a]	8.7 ± 0.4[b]
	428	Plasma	8.3 ± 0.8[c]	7.0 ± 1.7[d]

* $p < 0.01$ *vs.* controls.
** $p < 0.05$ *vs.* controls.
[a] = Aggressive.
[b] = Non-aggressive.
[c] = Violent-aggressive.
[d] = non-violent, non-agressive institutional control
[e] = U = unconjugated; C = conjugated; T = total.
[f] = Non-violent institutional control.
[g] = Violent.
[h] = Non-institutional control.

TABLE 58

METABOLITE CONCENTRATIONS IN HYPERKINETIC CHILDREN AND CONTROLS

Metabolite	*Reference*	*Biological fluid*	*Hyperkinesis*	*Control*
Noradrenaline	854	Urine	31.2 μg per 24h***	17.2 μg per 24 h
Adrenaline	854	Urine	14.5	12.2
Normetanephrine	855	Urine	125 ± 15*	94 ± 7
	850	Urine	113 ± 8	93 ± 6
	856	Urine	157.7	109.9
Metanephrine	855	Urine	85 ± 9.4	74 ± 5.5
	850	Urine	73 ± 4.6	74 ± 5.0
	856	Urine	101	68
3-Methoxy-4-hydroxyphenyl glycol[a]	855	Urine	806 ± 58*	1044 ± 76
	854	Urine	1180	960
	857	Urine	761*	1078
	850	Urine	740 ± 64**	1042 ± 67
	856	Urine	830*	649
	851	Urine	666 ± 85	872 ± 95
	852	Urine	658 ± 81 (non responders)[b]	929 ± 53 μg/m^2 per 24 h
	852	Urine	723 ± 69 (responders)[b]	929 ± 53

	858	Urine(M)	810 ± 29* μg per 24 h (sulfate)	1029 ± 38 μg per 24 h (sulfate)
	858	Urine(F)	680 ± 57* (sulfate)	848 ± 37 (sulfate)
Dopamine	854	Urine	211.7	151.9
Homovanillic acid	855	Urine	2.83 ± 0.18 mg per 24 h	3.21 ± 0.22 mg per 24 h
	854	Urine	4.17	3.73
	851	Urine	2.34 ± 0.24	2.88 ± 0.21
	852	Urine	3.32 ± 0.22 $\mu g/m^2$ per 24 h (non-responders)[b]	3.07 ± 0.13 $\mu g/m^2$ per 24 h
	852	Urine	2.50 ± 0.16 (responders)[b]	3.07 ± 0.13
	853	CSF	78 ± 11 ng/ml	62 ± 7.8 ng/ml
	511	CSF	36.5 ± 3.4[c]	37.1 ± 3.3[c]
5-Hydroxy-indoleacetic acid	853	CSF	37.0 ± 6.8	37.0 ± 2.8
	511	CSF	23.2 ± 3.1[c]	24.0 ± 3.9[c]

* $p < 0.05$ *vs.* controls.
** $p < 0.01$ *vs.* controls.
*** $p < 0.003$ *vs.* controls.
[a] Total or conjugated MHPG.
[b] Responders or non-responders to amphetamine.
[c] Adults.

TABLE 59

EFFECTS OF AGE ON THE CONCENTRATIONS OF BIOGENIC AMINES AND METABOLITES

↑, Concentrations increase with increasing age; ↓, concentrations decrease with increasing age; N.C., concentrations not correlated with age; ▼, concentrations increase with age to middle age, then decrease; ▲, concentrations decrease with age to middle age, then increase.

Amine or metabolite	*Urine*	*Plasma*	*CSF*
Noradrenaline	▼: 124[a] ↑: 861[a] ($p < 0.02$); 9[a] (N.S.); 864[f]	↑: 263[a](F); 659[b](F); 228[a]; 248[a]; 251[a]; 862[a] ($p < 0.05$); 253[a]; 863[a]; 250[a,f]	N.C.: 327[d]; 634[b]; 329[d]
Adrenaline	▼: 124[a]; 861[a] N.C.: 9[a] ↑: 864[f]	↓: 228[a]	N.C.: 634[b]
Dopamine			N.C.: 329[d]
Histamine	↓: 80[a] (N.S.)		
Phenylethylamine	N.C.: 101[d]		
Phenylacetic acid	N.C.: 72[a,b]	↑: 424[a] (N.S.)	▲: 456[a] ($p < 0.01$)
Indoleacetic acid	↑: 865[a,d]		↑: 461[a] ($p < 0.02$) N.C.: 667[b]; 460[a]
p-Hydroxyphenylacetic acid	↓: 866[a]		
5-Hydroxyindoleacetic acid			↑: 534[a]; 667[b]; 170[b](F) ($p < 0.01$); 691[b](F); 867[a] ($p < 0.05$); 736[b]; 518[a,b]; 692[a] ($p < 0.01$), 170[c] (F) ($p < 0.03$); 510[b] ($p < 0.001$) ↓: 170[c](F); 524[a] (N.S.) ▲: 868[a] ($p < 0.01$) N.C.: 736[a]; 488[a]; 497[a]; 632[a,b]; 683[a,b]; 525[a]; 627[a]; 742[b]; 689[b]; 682[b]

Homovanillic acid	↑: 387[f]; 389[a,f] ↓: 869[a]	↑: 822[d] ($p < 0.01$); 822[a] (N.S.); 712[b] ($p < 0.004$) N.C.: 440[a](F); 816[d]; 784[d]	↑: 534[a]; 497[a]; 170[a]; 513[a]; 682[b]; 691[b](F); 518[b]; 525[a] ($p < 0.05$); 510[b] ($p < 0.05$) ↓: 170[c]; 524[a] (N.S.); 518[a]; ▼: 868[a] N.C.: 867[a]; 488[a]; 683[a,b]; 742[b]; 689[b];
3-Methoxy-4-hydroxyphenyl glycol	↑: 572[b] ($p < 0.05$); 713[b] ($p < 0.01$); 744[b] ($p < 0.01$); 32[b](F); 566[b]; 683[a,b] N.C.: 702[b]; 544[a]; 704[b,c,d]; 28[b]; 572[a]; 706[b]	↑: 607[a,b]; 28[b]; 712[b] ($p < 0.004$) N.C.: 26[b]; 599[b]	↑: 736[b]; 526[e](N.S.) 170[a,b]; 518[a,b] ↓: 682[b] ($p < 0.05$) N.C.: 608[a]; 742[b]; 736[a]; 683[a,b]
3,4-Dihydroxyphenyl glycol	N.C.: 706[b]	↑: 603[b](U, N.S.) ↓: 603[a](C) N.C.: 713[b]	
Vanilmandelic acid 3,4-Dihydroxyphenylacetic acid	↓: 869[a]		N.C.: 608[a] ↓: 524[a] (N.S.)

[a] Controls.
[b] Depressed.
[c] Manic.
[d] Schizophrenic.
[e] Alzheimer's disease.
[f] Children.

6. FACTORS AFFECTING THE CONCENTRATIONS OF THE BIOGENIC MONOAMINES AND THEIR METABOLITES IN BIOLOGICAL FLUIDS

6.1. Subjects variables

6.1.1. Age

That the concentrations of some biogenic amines and their metabolites may be age-dependent was established more than 30 years ago by Karki[124]. The results of numerous studies on metabolite concentration–age correlations are summarized in Table 59.

Some inconsistencies are evident, but a trend to higher concentrations with increasing age appears to occur.

6.1.2. Sex

In general, male urinary excretion of biogenic amines and their metabolites is greater than female excretion, although these differences often disappear if the results are expressed in μg/g creatinine rather than in μg per 24 h[11,126,557,563]. As women, on average, weigh less than men and also excrete less creatinine than men[9], differences in the total daily excretion of amine metabolites may be related, at least in part, to weight differences between the sexes which will be corrected for if the excretion is expressed in μg/g creatinine. Tables 60–63 also show that metabolite concentrations in the CSF of women are generally higher than those for men. As men, on average, are taller than women this difference may be at least partially accounted for by an inverse correlation between body height and CSF metabolite concentrations[882].

6.1.3. Weight

In human CSF, 5-HIAA levels in women have been reported to be affected by body size whereas those of men are not[691]. In mixed populations 5-HIAA, HVA[170,526,632] and IAA[461] concentrations in CSF appear to be independent of body weight. No correlation between the urinary catecholamines and their metabolites with weight have been found[9,170], although a trend to increasing noradrenaline excretion with increasing weight has been noted[9].

6.1.4. Height

The concentrations of HVA and 5-HIAA in CSF are widely reported to be negatively correlated with height[170,510,512,518,524,525,632,691,736,882,883], although in some instances this has been true only for female subjects[170,691]. MHPG concentrations show no correlation with height[170,736,882], except in depressed populations in which there is a modest negative correlation[170,882]. Indoleacetic acid levels in CSF are independent of subject height[461]. It has been suggested that because 5-HIAA and HVA appear in higher concentrations in the cisternal than in the lumbar CSF and show a decrease as the fluid travels towards the lumbar sac, it is not surprising that some investigators have reported a negative correlation of these metabolites with height[524].

6.1.5. CSF gradients

Because of the pronounced cisternal–lumbar and lumbar–ventricular metabo-

lite concentration gradients, it is exceedingly important that the site of puncture be standardized within a given study and also preferably between studies if meaningful comparisons are to be made[345,501,504,524,883,886,887]. The gradients for DOPAC, HVA, 5-HIAA and MHPG have been shown to be statistically significant[345]. Considerable intra-individual variations in the concentrations of noradrenaline, 5-HIAA, MHPG and HVA in the CSF from one lumbar puncture to the next have been indicated, although the mean concentrations were similar[661]. The results of spinal cord transection and spinal fluid block suggest that the spinal cord contributes to the concentration of MHPG, possibly to 5-HIAA but little to HVA[884].

A marked increase in the concentrations of amine metabolites, particurlarly HVA and 5-HIAA, as more and more CSF is removed has been demonstrated[463,501,504,530,786,886,887,889,890]. However, there is disagreement on whether a gradient is present in both recumbent and sitting subjects[886,890]. 5-HIAA and HVA, but not MHPG, were found to be significantly lower in caudal than in rostral samples[890,891] and the lumbar concentrations of several metabolites have been demonstrated to be substantially lower than in cisternal[460] or ventricular[457,473,500,581] samples. No correlation between the differences in ventricular and lumbar metabolite concentrations and body height was found, suggesting that body height may not be an accurate measure of the rostrocaudal gradient[736].

The concentrations of HVA and 5-HIAA are significantly reduced where there is evidence of a restricted flow of CSF from the ventricles to the lumbar sac[467], a fact which should be remembered when interpreting low concentrations of metabolites in the CSF. CSF sampling by air encephalography was shown to be inferior to lumbar puncture in that the former produced much higher values for metabolite concentrations[626].

6.1.6. Genetics and race

Studies of schizophrenia in twin cohorts have indicated that there is probably a genetically controlled biological mechanism that predisposes one to the illness. Data for monozygotic twins suggest that some abnormality of catecholamine metabolism may be related to this genetic predisposition[895]. The urinary excretion levels of the catecholamines were higher than normal in both members of discordant pairs and showed significant intra-class correlations, which strongly suggested the possibility of genetic control[895]. However, within families, the urinary concentrations of the catecholamine metabolites did not demonstrate any changes that could be related to psychopathology[34]. For those subjects reporting increased psychiatric morbidity among relatives, there has been found an increased variance in MHPG excretion compared with those without such a history, suggesting that urinary MHPG may be a predictor of family vulnerability for psychiatric morbidity in healthy subjects[34]. In healthy monozygotic twins, a high concordance for both free and conjugated plasma MHPG suggests that plasma levels may reflect a heritable biological trait[585].

Studies on the family histories of schizophrenic subjects have shown higher concentrations of 5-HIAA and HVA in the CSF of those patients with a family history of schizophrenia than in those without such a history[512,791,896,897]. On the other hand, low 5-HIAA and HVA concentrations are related to an increased risk of depressive disorders in family members[897]. In a study of twins and unrelated individuals, only the MHPG concentration in CSF was found to be under any major genetic influence[898].

TABLE 60

MALE–FEMALE COMPARISON OF NORADRENERGIC METABOLITE CONCENTRATIONS

Amine or metabolite	*References*	*Biological fluid*	*Control disorder*	*Male*	*Female*
Noradrenaline	124	Urine	Normal	25.2 ± 1.6 μg per 24 h	24.9 ± 1.8 μg per 24 h
	126	Urine	Normal	32.9 ± 5.5	23.6 ± 1.5
	141	Urine	Normal	8.1 ± 0.5	6.9 ± 0.5
	217	Urine	Normal	Not significantly different[a]	
	193	Urine	Depressed	330 ± 64* (total)	240 ± 22 (total)
	862	Plasma	Normal	258 pg/ml	238 pg/ml
	250	Plasma	Normal	270 ± 42	307 ± 31
	265	Plasma	Normal	444 ± 39	550 ± 33
	263	Plasma	Normal	230 ± 20	300 ± 30
	253	Plasma	Normal	390 ± 40*	530 ± 50
	772	Plasma	Schizophrenic	770 ± 80	900 ± 80
	263	CSF	Normal	160 ± 30	166 ± 10
	661	CSF	Schizophrenic	123 ± 8	125 ± 16
	327	CSF	Schizophrenic	Not significantly different[a]	
Adrenaline	126	Urine	Normal	8.9 ± 0.8* μg per 24 h	6.5 ± 0.6 μg per 24 h
	141	Urine	Normal	3.0 ± 0.3*	2.1 ± 0.2
	124, 217	Urine	Normal	Not significantly different[a]	
	862	Plasma	Normal	45 pg/ml	58 pg/ml
	265	Plasma	Normal	124 ± 23	130 ± 27
	871	Plasma	Normal	1180 ± 44**	1460 ± 82
Normetanephrine	562	Urine	Normal	196 ± 17 μg per 24 h	233 ± 33 μg per 24 h
	170	Urine	Normal	195 ± 11	189 ± 11
	557	Urine	Normal	Not significantly different[a]	
	562	Urine	Depressed	172 ± 17	214 ± 17
	170	Urine	Depressed	280 ± 23	278 ± 22
	170	Urine	Manic	329 ± 49	246 ± 34
	557	Urine	Depressed	Not significantly different[a]	
Metanephrine	562	Urine	Normal	86 ± 9 μg per 24 h	83 ± 9 μg per 24 h
	170	Urine	Normal	107 ± 7	88 ± 5
	557	Urine	Normal	Not significantly different[a]	
	562	Urine	Depressed	114 ± 22	97 ± 6
	170	Urine	Depressed	149 ± 8**	122 ± 7
	170	Urine	Manic	157 ± 23	91 ± 11
	557	Urine	Depressed	Not significantly different[a]	

Vanilmandelic acid	8	Urine	Normal	3.7 ± 0.2** mg per 24 h	2.9 ± 0.2 mg per 24 h
	562	Urine	Normal	4.16 ± 0.65	4.61 ± 0.41
	384	Urine	Normal	3.3 ± 0.10	3.3 ± 0.14
	93	Urine	Normal	4.55 ± 0.40	4.65 ± 0.32
	170	Urine	Normal	2.72 ± 0.24	2.72 ± 0.22
	608	Urine	Normal	Not significantly different[a]	
	872	Urine	Normal	4.67* mg per 24 h	3.07 mg per 24 h
	562	Urine	Depressed	4.60 ± 0.32	4.38 ± 0.26
	93	Urine	Depressed	5.37 ± 0.57*	3.68 ± 0.36
	170	Urine	Depressed	3.54 ± 0.25	3.58 ± 0.34
	170	Urine	Manic	3.88 ± 0.50	2.99 ± 0.56
3,4-Dihydroxy-phenyl glycol	603	Plasma	Normal	784 ± 52 pg/ml(U)[b]	839 ± 73 pg/ml (U)[b]
	603	Plasma	Normal	1119 ± 140 (C)[c]	1161 ± 175 (C)[c]
	549	Plasma	Normal	1184 ± 346	1091 ± 163
	603	Plasma	Depressed	560 ± 48 (U)	546 ± 50 (U)
	603	Plasma	Depressed	807 ± 94 (C)	789 ± 88 (C)
	713	Plasma	Depressed	596 ± 51 (U)	556 ± 36 (U)
	713	Plasma	Depressed	966 ± 161 (C)	707 ± 75 (C)
	706	Plasma	Depressed	Not significantly different[a]	
3-Methoxy-4-hydroxyphenyl glycol (unconjugated) (conjugated or total)	11	Urine	Normal	150 ± 23 μg per 24 h	190 ± 45 μg per 24 h
	548	Urine	Normal	112 ± 11**	140 ± 45
	544	Urine	Normal	128 ± 11	139 ± 21
	545	Urine	Normal	110 ± 30	90 ± 30
	557	Urine	Normal	1660 ± 85*	1397 ± 63
	545	Urine	Normal	1490 ± 350	1230 ± 330
	554	Urine	Normal	923 ± 142	637 ± 200
	561	Urine	Normal	2084 ± 272 (sulfate)	1664 ± 146 (sulfate)
	11	Urine	Normal	1360 ± 165 (sulfate)	1260 ± 190 (sulfate)
	11	Urine	Normal	910 ± 50 (glucuronide)	1000 ± 115 (glucuronide)
	562	Urine	Normal	1674 ± 117	1348 ± 65
	563	Urine	Normal	2105 ± 255**	1618 ± 212
	70	Urine	Normal	2253 ± 296	1591 ± 71
	477	Urine	Normal	2190 ± 230**	1370 ± 80
	566	Urine	Normal	1440 ± 210	1230 ± 120
	576	Urine	Normal	2750	2200
	32	Urine	Normal	3478 ± 280*	2558 ± 280
	548	Urine	Normal	1340 ± 105 (sulfate)	809 ± 117 (sulfate)

(*Continued on p. 180*)

TABLE 60 (*continued*)

Amine or metabolite	*References*	*Biological fluid*	*Control disorder*	*Male*	*Female*
	548	Urine	Normal	1470 ± 150 (glucuronide)	751 ± 117 (glucuronide)
	544	Urine	Normal	776 ± 80 (sulfate)	662 ± 64 (sulfate)
	544	Urine	Normal	1031 ± 122 (glucuronide)	853 ± 84 (glucuronide)
	568	Urine	Normal	2021 ± 176	1820 ± 157
	170	Urine	Normal	2267 ± 143**	1660 ± 121
	873	Urine	Normal	600 ± 50 μg/g creatinine	690 ± 52 μg/g creatinine (sulfate)
	574	Urine	Normal	1945 ± 304 μg per 24 h	1626 ± 175 μg per 24 h
	141	Urine	Normal	2200 ± 185**	1510 ± 105
	578	Urine	Normal	2040 ± 88	1410 ± 59
	557	Urine	Depressed	1337 ± 106*	892 ± 146
	562	Urine	Depressed	1394 ± 89	1155 ± 58
	563	Urine	Depressed	2019 ± 168**	1357 ± 147
	477	Urine	Depressed	1730 ± 220	1480 ± 130
	566	Urine	Depressed	1680 ± 200	1500 ± 100
	683	Urine	Unipolar	2282 ± 202	2208 ± 221
	32	Urine	Unipolar	3606 ± 241*	3054 ± 222
	32	Urine	Bipolar	3772 ± 631*	2502 ± 205
	568	Urine	Unipolar	2378 ± 133	1853 ± 146
	568	Urine	Bipolar	1410 ± 186	1336 ± 127
	170	Urine	Depressed	2273 ± 144	1968 ± 136
	170	Urine	Manic	2740 ± 512	1909 ± 751
	572	Urine	Unipolar	1890 ± 150*	1670 ± 150
	572	Urine	Depressed	1600 ± 140*	1370 ± 130
	572	Urine	Manic	2510 ± 200*	1630 ± 240
	193	Urine	Depressed	1748 ± 140**	1049 ± 92
	743	Urine	Depressed	1725***	1282
	713	Urine	Depressed	1080 ± 133 μg/g creatinine	1070 ± 97 μg/g creatinine
	744	Urine	Depressed	1100 ± 124 μg/g creatinine	1040 ± 89 μg/g creatinine

	701, 704, 706	Urine	Depressed	Not significantly different	
	807	Urine	Schizophrenic	2140 ± 170 μg/g creatinine	3610 ± 360 μg/g creatinine
(unconjugated)	442	Plasma	Normal	3.4 ± 0.9 ng/ml	3.3 ± 1.1 ng/ml
	440	Plasma	Normal	3.2 ± 0.5	3.5 ± 0.9
	597	Plasma	Normal	3.6 ± 0.2	3.4 ± 0.2
	26	Plasma	Normal	Not significantly different	
	442	Plasma	Depressed	4.0 ± 1.3	4.4 ± 1.7
	440	Plasma	Depressed	3.3 ± 0.2	4.1 ± 0.4
	26, 593	Plasma	Panic Depressed	Not significantly different	
3-Methoxy-4-hydroxyphenyl glycol (total)	874	Plasma	Normal	18.8 ± 4.5 ng/ml	15.6 ± 3.1 ng/ml
	607	Plasma	Normal	14.9 ± 0.9	13.8 ± 0.9
	606	Plasma	Normal	16.3 ± 1.4	12.6 ± 1.4
	607	Plasma	Depressed	16.9 ± 1.8	16.6 ± 1.5
(unconjugated)	509	CSF	Normal	7.8 ± 0.3	8.1 ± 0.3
	505	CSF	Normal	8.8 ± 0.3	9.7 ± 0.6
	614	CSF	Normal	7.3 ± 0.4	8.1 ± 0.6
	170	CSF	Normal	7.8 ± 0.3	8.1 ± 0.3
	608, 524	CSF	Normal	Not significantly different	
	683	CSF	Depressed	8.0 ± 0.3***	9.4 ± 0.5
	505	CSF	Depressed	8.9 ± 0.7	9.7 ± 0.5
	505	CSF	Suicidal	7.9 ± 0.5	8.4 ± 0.6
	685	CSF	Depressed	10.7 ± 0.9	11.6 ± 1.1
	686	CSF	Depressed	8.1 ± 0.3*	9.2 ± 0.4
	170	CSF	Depressed	8.5 ± 0.3	9.1 ± 0.3
	170	CSF	Manic	10.6 ± 1.3	11.7 ± 1.5
	688	CSF	Depressed	8.5 ± 0.4	9.1 ± 0.4
	509	CSF	Manic	10.6 ± 1.3	11.7 ± 1.5
	661	CSF	Schizophrenic	5.6 ± 0.5*	8.0 ± 1.0
(conjugated)	614	CSF	Normal	0.43 ± 0.03	0.40 ± 0.03

* $p < 0.05$ *vs.* females.
** $p < 0.01$ *vs.* females.
*** $p < 0.001$ *vs.* females.
[a] Separate values for males and females are not reported.
[b] Unconjugated.
[c] Conjugated

TABLE 61

MALE–FEMALE COMPARISON OF SEROTONERGIC METABOLITE CONCENTRATIONS

Amine or metabolite	*References*	*Biological fluid*	*Control disorder*	*Male*	*Female*
5-Hydroxy-tryptamine	769	Urine	Normal	72 μg per 24 h	55 μg per 24 h
	769	Urine	Depressed	40	54
	769	Urine	Schizophrenic	54	47
	359	Blood	Normal	190 ± 20 ng/ml	150 ± 10 ng/ml
	304	Plasma	Normal	2.7 ± 0.2	1.830 ± 0.3
	302	Serum	Normal	91.5 ± 5.2*	122.3 ± 6.1
	359	Blood	Schizophrenic	130 ± 20	70 ± 20
Melatonin	342	Plasma	Normal	70 ± 5 pg/ml (day)	45 ± 5 pg/ml (day)
	342	Plasma	Normal	140 ± 11 (night)	130 ± 7 (night)
	342	CSF	Normal	59 ± 33	57 ± 28
6-Hydroxy-melatonin sulfate	875	Urine	Normal	21 μg per 24 h	16 μg per 24 h
	190	Urine	Normal	9.1 ± 0.8	10.2 ± 2.7
	876	Urine	Normal	12.4 (total)	11.9 (total)
5-Hydroxy-indoleacetic acid	359	Urine	Normal	4.87 ± 0.31 mg per 24 h	5.14 ± 1.37 mg per 24 h
	141	Urine	Normal	5.31 ± 0.69*	3.11 ± 0.36
	872	Urine	Normal	4.41	4.34
	359	Urine	Schizophrenic	8.0 ± 2.1	6.6 ± 3.4
	627	CSF	Normal	42.7 ± 3.8 ng/ml	41.0 ± 6.4 ng/ml
	460	CSF	Normal	19.2 ± 1.2**	25.3 ± 2.3
	460	CSF (cisternal)	Normal	25.7 ± 1.5**	32.4 ± 2.4
	170	CSF	Normal	20.6 ± 0.8	21.8 ± 1.3
	505	CSF	Normal	17.0 ± 1.1	23.1 ± 1.9
	511	CSF	Normal	15.7 ± 3.4**	33.8 ± 5.3
	525	CSF	Normal	19.3 ± 1.2**	22.8 ± 1.0
	518	CSF	Normal	20.6 ± 2.9	23.8 ± 2.1

488, 524, 534, 868	CSF	Normal	Not significantly different	
491	CSF	Normal	M > F ($p < 0.01$)	
627	CSF	Depressed	21.4 ± 2.0 ng/ml	18.5 ± 2.3 mg/ml
627	CSF	Manic	20.3 ± 2.3	18.7 ± 2.3
667	CSF	Depressed	15.8 ± 2.1	21.0 ± 1.4
675	CSF	Manic	19.7 ± 2.1	20.2 ± 2.9
683	CSF	Depressed	18.7 ± 0.7***	24.1 ± 1.0
505	CSF	Depressed	16.9 ± 1.8	20.0 ± 1.9
505	CSF	Suicidal	10.1 ± 1.8	15.4 ± 1.3
685	CSF	Depressed	18.7 ± 2.7	16.8 ± 1.6
686	CSF	Depressed	19.3 ± 1.0***	25.3 ± 1.3
170	CSF	Unipolar	19.7 ± 0.9***	25.4 ± 1.2
170	CSF	Bipolar	20.4 ± 1.4	23.3 ± 1.7
170	CSF	Manic	22.5 ± 2.8	30.8 ± 3.5
170	CSF	Depressed	20.1 ± 0.8	24.8 ± 1.0
688	CSF	Depressed	19.7 ± 1.0**	25.2 ± 1.4
518	CSF	Depressed	19.2 ± 1.8**	25.8 ± 2.2
509	CSF	Manic	22.5 ± 2.8	30.8 ± 3.5
691	CSF	Depressed	16.0 ± 1.3	17.0 ± 1.1
661	CSF	Schizophrenic	23.9 ± 2.1	25.4 ± 3.1
511	CSF	Attention deficit	15.7 ± 9.0 (S.D.)**	33.8 ± 13.0 (S.D.)
491	CSF	Parkinson's disease	25.3 ± 2.6	26.8 ± 1.9
486	CSF	Parkinson's disease	Not significantly different	

* $p < 0.01$ *vs.* females.
** $p < 0.05$ *vs.* females.
*** $p < 0.001$ *vs.* females.

TABLE 62

MALE–FEMALE COMPARISON OF DOPAMINERGIC METABOLITE CONCENTRATIONS

Amine or metabolite	*References*	*Biological fluid*	*Control disorder*	*Male*	*Female*
Dopamine	156	Urine	Normal	161 ± 15* μg per 24 h	115 ± 14 μg per 24 h
	156	Urine	Normal	275 ± 46 (conjugated)	250 ± 79 (conjugated)
	335	CSF	Normal	1440 ± 85* pg/ml	1180 ± 96 pg/ml
	263	CSF	Normal	2920 ± 390	2810 ± 230
	156	Urine	Parkinson's disease	97.8 ± 7.0** μg per 24 h	73.3 ± 5.5 μg per 24 h
	156	Urine	Parkinson's disease	281 ± 20 (conjugated)	299 ± 38 (conjugated)
3,4-Dihydroxy-phenylacetic acid	156	Urine	Normal	2300 ± 340 μg per 24 h	1830 ± 391 μg per 24 h
	872	Urine	Normal	1210	1310
	263	CSF	Normal	3120 ± 680 pg/ml	1910 ± 140 pg/ml
	524	CSF	Normal	Not significantly different	
	156	Urine	Parkinson's disease	1586 ± 145	1813 ± 200
	486	CSF	Parkinson's disease	Not significantly different	
Homovanillic acid	156	Urine	Normal	3.53 ± 0.28*** mg per 24 h	1.36 ± 0.23 mg per 24 h
	877	Urine	Normal	3.26 ± 0.26 mg/g creatinine	3.33 ± 0.39 mg/g creatinine
	384	Urine	Normal	4.9 ± 0.1 mg per 24 h	4.9 ± 0.1 mg per 24 h
	93	Urine	Normal	4.59 ± 0.40	3.75 ± 0.25
	141	Urine	Normal	5.53 ± 0.55**	3.51 ± 0.24
	872	Urine	Normal	5.19**	3.73
	93	Urine	Depressed	3.93 ± 0.47	3.28 ± 0.18
	156	Urine	Parkinson's disease	2.4 ± 0.2	3.4 ± 0.5
	442	Plasma	Normal	13.3 ± 0.6 ng/ml	14.0 ± 0.5 ng/ml
	438	Plasma	Normal	13.2 ± 0.8	12.5 ± 1.7
	822	Plasma	Normal	12.5	14.1
	440	Plasma	Normal	13.1 ± 1.1	12.3 ± 0.7
	440	Plasma	Depressed	11.7 ± 1.0*	17.9 ± 1.8
	442	Plasma	Psychotic	14.3 ± 0.7	19.2 ± 8.7

438	Plasma	Psychotic	11.7 ± 1.2*	20.9 ± 3.4
822	Plasma	Schizophrenic	12.3	16.3
816	Plasma	Schizophrenic	14.1	14.6
783	Plasma	Schizophrenic	7.1 ± 1.2	8.4 ± 1.1
784	Plasma	Schizophrenic	Not significantly different	
505	CSF	Normal	39.1 ± 3.8 ng/ml	47.8 ± 3.5 ng/ml
263	CSF	Normal	22.9 ± 4.1	19.9 ± 1.3
170	CSF	Normal	40.0 ± 2.3	43.7 ± 2.3
525	CSF	Normal	35.3 ± 2.5	39.8 ± 2.9
509	CSF	Normal	40.0 ± 1.2	43.7 ± 2.6
486, 488, 491, 511 524, 534, 868	CSF	Normal	Not significantly different	
675	CSF	Manic	45.7 ± 6.7	43.0 ± 4.6
683	CSF	Depressed	28.6 ± 2.4	34.4 ± 2.5
505	CSF	Depressed	35.0 ± 4.4	39.8 ± 3.5
505	CSF	Suicidal	27.5 ± 3.4	36.6 ± 4.2
685	CSF	Depressed	40.2 ± 6.2	40.8 ± 4.6
686	CSF	Depressed	30.3 ± 1.7*	37.1 ± 2.6
170	CSF	Depressed	33.1 ± 1.9	36.9 ± 3.8
170, 509	CSF	Manic	43.7 ± 5.4	59.0 ± 10.4
688	CSF	Depressed	30.1 ± 1.7*	35.9 ± 2.7
691	CSF	Depressed	28.0 ± 3.0	33.6 ± 2.5
488	CSF	Depressed	Not significantly different	
795	CSF	Schizophrenic	26.0 ± 5.8*	44.2 ± 3.5
695	CSF	Schizophrenic	26.2 ± 3.1**	38.8 ± 3.1
661	CSF	Schizophrenic	32.4 ± 2.5	37.9 ± 5.3
534	CSF	Schizophrenic	Not significantly different	
491	CSF	Parkinson's disease	13.7 ± 1.1	15.0 ± 1.2
486	CSF	Parkinson's disease	Not significantly different	
511	CSF	Attention deficit	Not significantly different	

* $p < 0.05$ *vs.* females.
** $p < 0.01$ *vs.* females.
*** $p < 0.001$ *vs.* females.

TABLE 63

MALE–FEMALE COMPARISON OF TRACE AMINE METABOLITE CONCENTRATIONS

Amine or metabolite	*Reference*	*Biological fluid*	*Control disorder*	*Male*	*Female*
Phenylethyl-	93	Urine	Normal	4.7 ± 0.7 μg per 24 h	5.0 ± 0.8 μg per 24 h
amine	878	Urine	Normal	7.3 ± 2.9 μg/g creatinine	14.5 ± 3.1 μg/g creatinine
	101	Urine	Normal	Not significantly different	
	93	Urine	Depressed	6.24 ± 1.58 μg per 24 h	4.74 ± 0.94 μg per 24 h
	101	Urine	Schizophrenic	Not significantly different	
	878	Plasma	Normal	4.3 ± 0.4 ng/ml	5.6 ± 0.8 ng/ml
Phenylacetic	93	Urine	Normal	121.9 ± 18.0 mg per 24 h	119.8 ± 20.9 mg per 24 h
acid (total)	105	Urine	Normal	138.1 ± 10.4	160.9 ± 26.3
	72	Urine	Normal	129.0 ± 74.2 (S.D.)	156.6 ± 18.0 (S.D.)
	418	Urine	Normal	Not significantly different	
	93	Urine	Depressed	123.9 ± 9.0	109.9 ± 19.0
	72	Urine	Depressed	164.4 ± 14 (S.D.)	132.0 ± 102.0 (S.D.)
(unconjugated)	424	Plasma	Normal	79.5 ± 13.5* ng/ml	119.5 ± 19.1 ng/ml
(conjugated)	424	Plasma	Normal	296.4 ± 42.9**	365.6 ± 59.2
(unconjugated)	39	CSF[a]	Normal	26.7 ± 2.7	30.8 ± 5.2
	39	CSF	Depressed	13.8 ± 1.9**	23.6 ± 2.3
o-Hydroxy-	93	Urine	Normal	1.3 ± 0.2 mg per 24 h	0.8 ± 0.1 mg per 24 h
phenylacetic acid	93	Urine	Depressed	0.9 ± 0.1	0.8 ± 0.1

m-Hydroxy-	93	Urine	Normal	5.3 ± 1.3	6.2 ± 0.9
phenylacetic	93	Urine	Depressed	4.1 ± 0.9	4.7 ± 0.9
acid	424	Plasma	Normal	16.6 ± 3.7	22.6 ± 8.3
p-Hydroxy-	93	Urine	Normal	19.6 ± 3.6	22.3 ± 2.4
phenylacetic	93	Urine	Depressed	12.2 ± 2.2	13.8 ± 1.5
acid	424	Plasma	Normal	66.6 ± 22.0 ng/ml	59.6 ± 13.0 ng/ml
p-Hydroxy-	93	Urine	Normal	2.03 ± 0.32 mg per 24 h	1.59 ± 0.22 mg per 24 h
mandelic acid	93	Urine	Depressed	1.47 ± 0.31	0.96 ± 0.15
Tryptamine	769	Urine	Normal	64 μg per 24 h	56 μg per 24 h
	769	Urine	Depressed	39	30
	769	Urine	Schizophrenic	52	72
Indoleacetic	460	CSF[a]	Epileptic	3.4 ± 0.4 ng/ml	4.3 ± 0.6 ng/ml
acid	460	CSF[b]	Epileptic	2.8 ± 0.4***	4.2 ± 0.5
	667	CSF	Depressed	6.4 ± 1.4	6.4 ± 0.8
	461	CSF	Depressed	4.46 ± 0.30	4.95 ± 0.44
Histamine	879	Urine	Normal	42 μg per 24 h	49 μg per 24 h
	880	Urine	Normal	33.3 μg/l	44.4 μg/l
	80	Urine	Normal	11.5 ± 1.0 μg per 24 h	14.3 ± 1.7 μg per 24 h
	199	Plasma	Normal	790 ± 180 pg/ml	760 ± 82 pg/ml
N-Methylhistamine	880	Urine	Normal	250 μg per 24 h	163 μg per 24 h

* $p < 0.05$ *vs.* females.
** $p < 0.01$ *vs.* females.
*** $p < 0.001$ *vs.* females.
[a] Lumbar CSF.
[b] Cisternal CSF.

There was no evidence of cultural or environmental contributions to MHPG levels, but for HVA and 5-HIAA a familial influence was found where cultural heritability was higher than the genetic[898]. Urinary phenylethylamine excretion is lower in both schizophrenic and non-schizophrenic East Indian subjects than in similar North American subjects[101]. Whether this is due to dietary, cultural or other environmental factors or to genetics was not established. White males have been shown to exhibit higher plasma noradrenaline levels than black males, although females were not different[253].

6.1.7. Physical-organic diseases

Highly significant increases in the urinary excretion of VMA[387,394,401,900–904], HVA[381,387,904], MHPG conjugates[11,387,575], normetanephrine[902,905] and 5-HIAA[370,906,907] have been observed in cancer patients, particularly those suffering from pheochromocytoma. 5-HIAA and serotonin urinary excretions[907] and plasma[908] levels are elevated in patients with functioning carcinoid tumors but not in those with non-functioning or non-carcinoid tumors.

Plasma[220,228,264] and urinary[861] catecholamines and plasma[586] and urinary[151,566] MHPG have been shown to be positively correlated with blood pressure. Further, the CSF[220] and plasma[158,228,909] concentrations of noradrenaline, adrenaline and dopamine have been reported to be significantly elevated in subjects with essential hypertension, although these results were not confirmed by other investigators[252,253]. Urinary HVA and VMA excretion are also elevated in hypertensive patients[392].

In poorly controlled diabetics, increases in plasma noradrenaline have been demonstrated[258]. In Huntington's chorea, both the CSF concentration and turnover of HVA have been shown to be significantly reduced[513]; in an early study, however, the urinary excretion of HVA was normal[382]. Phenylethylamine excretion in phenylketonuria is highly significantly elevated[899]. A dysfunction of the blood–CSF barrier has been reported to cause significantly increased CSF concentrations of noradrenaline and adrenaline[262].

6.2. Environmental variables

6.2.1. Diet

Fasting has been employed as a means of determining the degree to which diet contributes to biogenic amine and metabolite levels in plasma and urine. Plasma HVA[783], phenylethylamine and *p*-tyramine[99,102] and urinary HVA[390], 3,4-dimethoxyphenylethylamine[73], VMA[390,406,409] and MHPG[70,563] have been reported to be unaffected by fasting. However, contradictory results have shown that fasting does eliminate dietary effects on plasma HVA[550,913] and urinary VMA[911]. Fasting or a diet restricted in foods known to contain caffeine[910] or protein[156] reduces the excretion of catecholamines[156,910] and their metabolites, free and conjugated histamine and its metabolites[78,912] and free plasma phenylacetic acid[424].

The ingestion of bananas, pineapple and some other foods such as plums, tomatoes and walnuts produces markedly elevated levels of urinary 5-HIAA[116,362,369,872,915]. Bananas have also been reported to result in increased urinary excretion of VMA, DOPAC and HVA[872] and plasma dopamine[240,322,916] and

noradrenaline[240,916], particularly the sulfate conjugates. Eating oranges has been reported to increase the excretion of *p*-hydroxymandelic acid[355]. Caffeine intake appears to affect primarily the noradrenergic system, increasing plasma noradrenaline and adrenaline concentrations[172,590], plasma MHPG[590] and urinary normetanephrine and metanephrine[173,910]. The ingestion of chocolate, which contains phenylethylamine, *p*-tyramine and other biogenic amines, produced no significant changes in the urinary excretion of these amines[99,100], whereas the ingestion of cheese, which also contains some biogenic amines, has been shown to produce a small increase in the excretion of conjugated *p*-tyramine and unconjugated *p*-hydroxyphenylacetic acid[107]. Urinary excretion rates of phenylethylamine[806,914] and phenylacetic acid[806] exhibited no dietary influences.

6.2.2. Smoking

Cryer *et al.*[293] have reported significantly elevated plasma noradrenaline and adrenaline concentrations in smokers. Other investigators have found an increase in the urinary excretion of adrenaline[132,350] and 1,4- and 1,5-methylimidazoleacetic acid[350,888] in smokers. No effect of smoking on VMA, 5-HIAA or histamine excretion was observed, however. It was concluded[350] that regular smokers metabolize certain endogenous amines differently from non-smokers and that this difference may be at least partly responsible for the withdrawal symptoms sometimes seen on stopping smoking. Davidson *et al.*[550] have demonstrated that smoking two cigarettes has no effect on the HVA concentration in plasma. Cyanide and formaldehyde in the saliva of cigarette smokers has been shown to react with phenylethylamine and *p*-tyramine to produce N-cyanomethyl derivatives[917].

6.2.3. Alcohol consumption

The catecholamines have been reported to be elevated in the urine[918,919] and plasma[920,921] of intoxicated subjects, although delay in the increase in plasma noradrenaline concentration following alcohol consumption has been observed[921]. An increase in plasma levels of normetanephrine and metanephrine, a significant decline in VMA excretion and a concomitant elevation in MHPG excretion have been reported to occur while subjects were drinking[920,922]. The MHPG concentration in CSF was found to be correlated with blood alcohol and to be significantly elevated during intoxication of alcoholic patients and also in healthy volunteers after ingesting 80 g of alcohol[923]. These data indicate that alcohol ingestion stimulates noradrenaline and adrenaline metabolism in the central nervous system and may be associated with an alteration in the pathways of catecholamine metabolism. Stress-induced adrenaline release (as measured by urinary excretion) has been found to be lower in non-alcoholic adoptees with alcoholic biologic relatives than in similar controls with no alcoholic relatives, suggesting that familial alcoholism may be associated with a trait of globally decreased adrenaline responsiveness[919].

The HVA concentrations in the CSF of alcoholics do not seem to differ significantly from those of controls[733,867,923], although there may be a sub-group of alcoholics who are non-suppressors in the dexamethasone suppression test and exhibit a low CSF HVA concentration[687]. 5-HIAA concentrations in the CSF of alcoholics, although tending to be lower, are not significantly different from the concentrations in non-alcoholics[463,923]. However, after 4–9 weeks of abstinence or in the immediate

post-intoxication phase, a significant decline in the CSF concentration of 5-HIAA has been reported[867]. However, alcoholic murderers proved to have significantly more 5-HIAA in their CSF than did non-alcoholic murderers[733]. Serum indoleacetic acid in alcoholics is not different from that in controls[429].

6.2.4. Stress and posture

Plasma and urinary noradrenaline can be altered by posture changes, exercize, emotional stress, various environmental factors and the method of blood sampling. Mild physical stress, as in changing posture from recumbent to standing, produces a statistically significant increase in plasma free noradrenaline (Table 64) but not in conjugated noradrenaline or free or conjugated adrenaline. However, the urinary excretion of both catecholamines has been reported to be significantly elevated in standing compared with supine subjects[129,924]. Both schizophrenic[254] and depressive[285,288,723] subjects exhibited a greater increase in plasma noradrenaline levels during stress than did controls. Furthermore, dexamethasone-resistant depressed patients showed higher noradrenaline and adrenaline plasma levels in both the lying and standing positions than did non-resistant depressed subjects, suggesting that an inefficient hyperactivity to physiological stress characterizes a noradrenergic dysregulation in depression[761]. Posture appears to have no influence on the CSF concentrations of amine metabolites[890].

More vigorous physical stress, such as walking, bicycling, handgrip contractions and knee-bends, increases urinary[124] and plasma noradrenaline concentrations (Table 65); the increases in plasma concentrations have been found to be correlated with oxygen consumption[929]. Increases in plasma adrenaline[234,299] and dopamine[234] levels in response to physical activity have also been reported. Depending on the type and duration of the exercize, MHPG excretion may be either increased[924,930] or unchanged[544,931]. Similarly, plasma MHPG[931] and DHPG[235,244,289,604] may be increased[244,289] or unchanged[235,604,931], depending on the stressor. Plasma HVA has been reported to be unchanged during exercize[550,783], although Kendler *et al.*[913] claimed an increase in plasma HVA during moderate exercise. Plasma histamine[932] and urinary phenylacetic acid[351] are unaffected by physical stressors.

Exposure to cold is mainly associated with increases in urinary[134,925] and plasma[231,238,239,288,299,927] concentrations of noradrenaline, although urinary[134] and plasma[239,299] adrenaline, plasma dopamine[239] and urinary MHPG[23] have also been reported to be increased by cold stress. The effect of cold immersion on noradrenaline is significantly greater in depressed than in normal subjects[288], showing that the noradrenergic system is dysregulated in depression.

Mental stress involving exhilarating or aggressive reactions has been associated with elevated noradrenaline excretion, whereas emotional stress involving apprehension, anxiety, pain or general discomfort is regularly accompanied by an increase in adrenaline excretion[925,933]. MHPG excretion has been reported to be significantly increased in aviators during carrier landings[934], as has phenylethylamine excretion in parachutists[914]. On the other hand, trainee pilots showed no significant changes in phenylethylamine or phenylacetic acid excretion after training flights[96]. Venipuncture generally results in an increase in plasma noradrenaline[229,251,926], although Kopin *et al.*[266] found a decrease in such stressful situations as venipuncture and hospitalization. Hospitalization has been claimed to result in increased CSF concen-

TABLE 64

PLASMA FREE CATECHOLAMINES IN NORMAL RECUMBENT AND STANDING SUBJECTS

Reference	*Noradrenaline*[a]		*Adrenaline*[a]		*Dopamine*[a]	
	Recumbent	*Standing*	*Recumbent*	*Standing*	*Recumbent*	*Standing*
248	292 ± 16	538 ± 44				
227	160 ± 20	270 ± 40	160 ± 50	210 ± 80		
228	248 ± 56	559 ± 126	41 ± 5	52 ± 9	46 ± 6	50 ± 9
265	444 ± 39	2210 ± 473				
260	182 ± 53	403 ± 87	87 ± 25	115 ± 41	33 ± 11	51 ± 18
251	279 ± 20	659 ± 83				
252	403 ± 61	639 ± 81				
274	200 ± 40	323 ± 33	58 ± 12	54 ± 13	48 ± 10	48 ± 8
235	215 ± 28	400 ± 36	83 ± 12	126 ± 11		
236	196 ± 17	336 ± 22	36 ± 4	59 ± 7	62 ± 5	56 ± 6
237	217 ± 58	351 ± 21				
275	297 ± 30	500 ± 40				
277	166 ± 14	372 ± 35	59 ± 11	51 ± 9		
254	201 ± 24	365 ± 40				
238	252 ± 34	461 ± 41	48 ± 11	57 ± 11		
245	208 ± 45	440 ± 65				
284	147 ± 10	291 ± 18				
289	149 ± 25	450 ± 18				
Weighted mean:	235 ± 26	502 ± 61	71 ± 15	89 ± 20	49 ± 8	51 ± 9
Total no. of subjects:	360	323	76	72	36	36

[a] Mean ± standard error of the mean, pg/ml.

TABLE 65

EFFECT OF PHYSICAL EXERCIZE ON PLASMA CATECHOLAMINE CONCENTRATIONS

Reference	*Noradrenaline*[a]			*Adrenaline*[a]		
	Resting	*Exercize*	*Type of exercize*	*Resting*	*Exercize*	*Type of exercize*
216	155 ± 13	373 ± 39		48 ± 3	51 ± 22	
936	–	2200 ± 100	Heavy			
219	200 ± 30	1010 ± 70	Heavy	60 ± 10	150 ± 20	Heavy
928	140	240		40	60	
937	950 ± 8	2400	Handgrip	420 ± 9	1000	Handgrip
221	108 ± 9	1000 ± 78		329 ± 21	359 ± 28	
248	292 ± 16	778 ± 80	Handgrip			
938	740 ± 160	1070 ± 200		690 ± 150	710 ± 120	
232	210 ± 11	443 ± 47	Walking	29 ± 9	42 ± 12	Walking
235	215 ± 28	259 ± 35	Handgrip	83 ± 12	152 ± 30	Handgrip
267	583 ± 39	1726 ± 264		117 ± 17	164 ± 13	
268	426 ± 81	2000 ± 380	Bicycling			
277	166 ± 44	1285 ± 425	Bicycling	59 ± 11	445 ± 137	Bicycling
144	365 ± 41	1740 ± 99		< 100	230 ± 100	
238	252 ± 34	1624 ± 316	Bicycling	48 ± 11	210 ± 70	Bicycling
244	265 ± 18	620 ± 70				
271	355 ± 58	4235 ± 1031	Maximal	71 ± 17	821 ± 235	Maximal

[a] Mean ± standard error of the mean, pg/ml.

trations of 5-HIAA and HVA[524], but another study showed no effect[170]. Plasma adrenaline shows a greater increase to cognitive stressors than to other stressors[926]. A combination of submaximal work and mental tasks induced a significant increase in the excretion of adrenaline, metanephrine and MHPG[924]. Examination stress, public speaking and mental arithmetic have been shown to increase plasma adrenaline[231,267,299,935], noradrenaline[279] or both[289,926] with the noradrenaline increase being less pronounced than that of adrenaline. Urinary MHPG and HVA (but not 5-HIAA) increased significantly during mental stress[141]. Stress and anxiety have been associated with elevated MHPG excretion, but it proved not to be possible to predict that an individual with high state anxiety will necessarily have a high urinary MHPG excretion or *vice versa*[731]. Alleviation of mental stress by transcendental meditation did not result in a lowering of plasma catecholamine levels[226].

6.2.5. Circadian, seasonal and menstrual cycles

Many physiological variables display circadian rhythms – a waxing and waning apparent only if frequent measurements are taken across the 24-h day[885]. Because the rhythms may not be synchronized in all individuals, a single measurement, even if taken at the same time for all subjects, may produce misleading results. The most dramatic day–night cycle is that of melatonin in plasma or serum[314,315,317–319,342,660,940], CSF[319,342] and urine[187,316,317], in which the night-time values are significantly higher than during the day. The male and female cycles appear to be the same[342,941]. During depression, the circadian rhythm of melatonin is disturbed but returns to normal on recovery[660]. 6-Hydroxymelatonin and its sulfate conjugate also exhibit a marked (up to 10-fold) diurnal variation in urinary excretion[188,317,876,940], which can be abolished by treatment with atenolol[317].

Noradrenaline and adrenaline excretion peaks during the day and declines at night[124,129,942–945], although the diurnal variation is lost during excercize. In contrast, dopamine excretion tends to increase during sleep[943,944,946]. Normetanephrine and metanephrine excretion show no diurnal variation[195]. Plasma noradrenaline and adrenaline have been reported to be significantly elevated during the day[947,948], although a later study revealed no diurnal variation[863]. These contradictions may be explained by another study which demonstrated that recumbent subjects exhibited a fluctuation in plasma noradrenaline levels with a median period of 107 min regardless of the time of day. The amplitude of the fluctuations was at times greater than that due to postural change[949]. Unconjugated urinary histamine is significantly higher during the day[79]. Urinary phenylethylamine excretion does not appear to show a diurnal variation[91,806,914]; however, one study has demonstrated phenylethylamine excretion to be highest between 4 and 12 p.m.[89].

Plasma MHPG[37,38,573,950] and HVA[950] exhibit a circadian rhythm with peak levels occuring during the day. In subjects who follow a constant routine, the MHPG, but not the HVA, variation is abolished[950]. It was concluded that diurnal variations for MHPG are evoked by changes in physical activity, posture and related factors, whereas the major component of HVA diurnal variation is regulated by a circadian oscillator independent of sleep or activity. In depressed patients the circadian rhythms of MHPG[573,951] and VMA[951] become desynchronized. Daily fluctuations in urinary MHPG excretion peak during the day, necessitating 24-h collections[36,70,563,952]. However, it has been demonstrated that afternoon plasma MHPG

values correlate well with 24-h excretion values[607]. In depressed patients, the urinary MHPG excretion cycle is about 3 h earlier than in normal subjects[952]. During cold exposure, the circadian rhythm of MHPG excretion, but not of VMA excretion, is abolished[23]. VMA excretion may be as much as twice as high during the day as at night[12,23,378,403]. Neither free nor conjugated plasma 3,4-dihydroxyphenyl glycol exhibit a circadian rhythm[953], although the sulfate showed a slight elevation in the afternoon. Both urinary[378] and plasma[297] 3,4-dihydroxyphenylacetic acid exhibit a marked daily periodicity, with the low point occuring at night. Urinary HVA and 3,4-dihydroxymandelic acid show a small diurnal variation[378,403]. The concentration of 5-HIAA in CSF increases progressively during the day, reaching its highest value around midnight and then decreasing by half by morning[954]. No diurnal variation in the urinary[806] or CSF[39] concentrations of phenylacetic acid were observed.

Cycles longer than the circadian rhythms are more difficult to measure. A trend towards elevated dopamine and serotonin metabolite levels in CSF in the late autumn have been reported, with the lowest levels occuring in late spring[883,955], but this could not be confirmed in later studies[524,736]. CSF samples from schizophrenic and Alzheimer patients during October to March had significantly higher concentrations of HVA and 5-HIAA (but not MHPG) than samples taken during April to September[956]. Urinary MHPG excretion is reported to be above normal in winter and below normal in summer[951].

The menstrual cycle has been reported to be the cause of variations in the excretion of histamine and its metabolites, the levels depending on the place in the cycle at the time of sampling[888]. Plasma HVA has been reported to decline after ovulation[783].

6.2.6. Sample stability and storage conditions

It has been claimed that catecholamines in plasma[959] or urine[960] are stable for periods of up to 240 days if they are frozen with antioxidants; however, other investigators have shown that storage of plasma samples with antioxidants at low temperatures was not sufficient to prevent the decomposition of unconjugated catecholamines[961,962]. Autoxidation appears to be particularly rapid when the catecholamines are placed in buffer solutions[962]. Some workers have reported that small delays in freezing samples of plasma catecholamines result in major losses[244,961], whereas others claimed that specimens stored at room temperature for periods of up to 3 weeks show no significant decline in catecholamine concentrations[963]. The contradictory nature of these results clearly indicates that caution should prevail and that the catecholamines should be analyzed as soon as possible after sample collection.

For serotonin, the best results are obtained if samples are stored at pH 6.5 and -20°C[964,965]; at acidic pH and room temperature appreciable degradation occurs[958,965,966]. Degradation of both 5-HIAA and serotonin has been reported to accelerate in the summer months, suggesting sensitivity to light[958]. In quantifying plasma serotonin, the plasma fraction must not only be platelet- and cell-free, but should also be subjected to ultrafiltration to remove protein-bound serotonin before a true plasma serotonin value can be obtained[306,307]. An albumin–sucrose "cushion" has been demonstrated to prevent platelet damage during differential centrifugation[301]. In addition, the use of prostacyclin during blood collection minimizes platelet aggregation during which platelets may be activated and release serotonin. These

procedural modifications resulted in consistent values for serotonin which were much smaller than previously published results[301]. Sulfatoxymelatonin in plasma or urine has been shown to be stable without preservative for at least 2 years at −20°C and for 5 days at +20°C[190], suggesting that the instability of the serotonin moiety resides at the free hydroxyl group. Like serotonin, 5-HIAA is stable for up to 1 month if stored at pH 6.5 and −20°C[520,957,965]. Decomposition is facilitated by light[520,958,965–967], high or room temperature[966,967] and acidic conditions[957,958,965,966].

MHPG in urine[564,567,610] and CSF[520,610,957] is stable if stored at neutral pH and −20°C (or colder) for periods of at least 2 months and for up to 30 months[564]. At acidic pH, urinary conjugated MHPG has been reported to hydrolyze almost completely within 2 weeks even at −14°C[546]. Homovanillic acid in CSF appears to be stable for long periods of storage[520,957]. 3,4-Dihydroxyphenyl glycol and 3,4-dihydroxyphenylethanol concentrations in plasma and CSF have been reported to increase after freeze–thaw cycles, although this does not appear to be due to a breakdown of the sulfate conjugate[602].

A recent study of the effect of long-term (up to 9 months) storage of untreated frozen (*i.e.*, at physiological pH and −20°C) plasma and urine samples on the concentrations of several biogenic amine metabolites demonstrated significant declines in the urinary concentrations of *m*-hydroxyphenylacetic acid, *p*-hydroxymandelic acid IAA, 5-HIAA, HVA, 3,4-dihydroxyphenylacetic acid and 3-methoxy-4-hydroxyphenyl glycol; only the phenylacetic acid, mandelic acid and VMA concentrations remained unchanged[968]. The concentration of *p*-hydroxyphenylacetic acid appeared to increase over the 9-month period, possibly owing to breakdown of the sulfate conjugate. On the other hand, the plasma concentrations remained stable except for 5-HIAA acid and *m*-hydroxyphenylacetic acid, which declined significantly.

Clearly, failure to standardize storage time and conditions within and between studies may invalidate the results and could account, in part, for many of the inconsistencies in the results reported in the literature.

7. CONCLUDING REMARKS

A generation of scientists have devoted their efforts to finding biological markers for psychiatric and neurological disorders among the biogenic amines and their metabolites, partly in the hope of opening a window on the underlying mechanisms of the disorders and partly, from the practical side, in anticipation of providing useful tools for diagnosis and treatment. Overall, the results have been disappointing, inconsistent and often contradictory. In the early studies problems with the specificity and sensitivity of the analytical procedures were responsible for the lack of agreement in the results of different groups. With modern, sensitive methodology such as GC–MS and HPLC, however, these worries are behind us and new difficulties have become apparent. The fact that, in spite of sophisticated analytical methods, no single variable or group of variables have yet been unequivocally identified as markers may lie in the multifactorial nature of psychiatric disorders and, importantly, in persisting differences in the diagnostic criteria employed by different groups of researchers. In addition, because factors such as age, sex, height and weight of the subject, together with environmental factors such as diet, smoking, drinking and drug therapy, are now known to affect the concentrations of the biogenic amines and their metabolites,

it is clear that it is imperative that controls be matched with patients for these variables, difficult as this may be. Further, the small numbers of subjects in most previous studies has undermined the potential statistical power of even the best research designs.

Clearly, future studies in the field of markers for psychiatric disorders will prove to be no more consistent than past studies unless age-, sex- and height-matched groups of large numbers of subjects and widely accepted, well defined diagnostic criteria are employed.

8. ACKNOWLEDGEMENTS

I thank R. James for typing the manuscript, A.A. Boulton for his encouragement and constructive comments and Saskatchewan Health for continuing financial support.

9. SUMMARY

The biogenic monoamines and their metabolites have been isolated, identified and quantified in human body fluids over the past forty years using a wide variety of chromatographic separation and detection techniques. This review summarizes the results of those studies on normal, psychiatric and neurological subjects. Tables of normal values and the methods used to obtain them should prove to be useful as a reference source for benchmark amine and metabolite concentrations and for successful analytical procedures for their chromatographic separation, detection and quantification. Summaries of the often contradictory results of the application of these methods to psychiatric and neurological problems are presented and may assist in the assessment of the validity of the results of experiments in this field. Finally, the individual, environmental and the methodological factors affecting the concentrations of the amines and their metabolites are discussed.

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