Abstract: One purpose of clinical neurochemistry has been to indicate "activities" of catecholamine systems, by assaying levels of the effector compounds or their metabolites in body fluids such as plasma, cerebrospinal fluid, urine, or microdialysate. This review discusses a new purpose: relating specific catecholaminergic phenotypes to neurogenetic disorders. Distinctive catecholamine patterns in several neurogenetic conditions reflect enzyme deficiencies as direct or indirect effects of gene mutations. These neurochemical patterns can provide potentially important clues to the diagnosis, treatment, and pathophysiology of neurogenetic disorders. Linking genetic abnormalities with molecular mechanisms and clinical manifestations of disease represents a useful new direction in clinical neurochemistry. Key Words: Neurochemistry—Catecholamines—Norepinephrine—Dopamine—DOPA—Phenotype—Neurogenetics. J. Neurochem. 67, 1781-1790 (1996).

Until recently, clinical catecholamine neurochemistry has been used mainly to examine release of catecholamines as effector chemicals in the brain and periphery, in order to indicate "activities" of central or peripheral neuronal systems. The development of assay techniques for simultaneous measurements of concentrations of catecholamines, the catecholamine precursor DOPA, and catecholamine metabolites, such as dihydroxyphenylglycol (DHPG), dihydroxyphenylacetic acid (DOPAC), methoxyhydroxyphenylglycol (MHPG), homovanillic acid (HVA), metanephrine (MN), and normetanephrine (NMN), has enabled detailed and comprehensive assessments of specific aspects of catecholaminergic function, including release, neuronal and extraneuronal uptake and metabolism, turnover, and synthesis (Eisenhofer et al., 1992).

The availability of these simultaneous assays has led to a novel application of clinical catecholamine neurochemistry: the delineation of neurochemical patterns associated with specific genetic abnormalities. These patterns can provide potentially important clues to the diagnosis, treatment, and pathophysiology of neurogenetic disorders. This brief review summarizes what has been learned so far from this new approach.

Understanding the clinical significance of catecholamine phenotypic changes requires detailed knowledge about the sources and meanings of levels of DOPA, catecholamines, and catecholamine metabolites in human physiological fluids, such as plasma (Figs. 1 and 2, Table 1), and knowledge about the chromosomal sites of genes encoding proteins participating in the synthesis, storage, release, metabolism, and recycling of catecholamines (Table 2).

GENETIC DISEASES WITH SPECIFIC CATECHOLAMINERGIC PHENOTYPES: SYNTHESIS

In mammals, catecholamine biosynthesis stems from a single enzymatic step—conversion of the amino acid tyrosine to the catechol amino acid L-DOPA by tyrosine hydroxylase (TH; EC 1.14.13.41; Fig. 1). Circulating catecholamines seem crucial for normal neurodevelopment, because genetic disorders of catecholamine biosynthesis typically produce severe neurological defects or fetal wastage. Thus, of mice with knockout of the TH gene, ~90% die in utero (Zhou et al., 1995).
Tyrosine hydroxylation requires tetrahydrobiopterin (BH₄) as a cofactor. In humans, genetic deficiencies of BH₄ synthesis or recycling, although compatible with survival to birth, obviate normal postnatal neurological development if not recognized and treated appropriately from early infancy.

**Dihydropteridine reductase (DHPR) deficiency**

DHPR (EC 1.6.99.7) catalyzes the conversion of dihydrobiopterin to BH₄. BH₄ is a required cofactor for hydroxylation not only of tyrosine but also of phenylalanine and tryptophan. BH₄ also appears to play a role in maintaining the bioactive (tetrahydro) form of folic acid (Pollock and Kaufman, 1978). Because of impaired phenylalanine hydroxylation, patients with DHPR deficiency have a variant of phenylketonuria. In contrast to classical phenylketonuria (caused by specific mutations in the phenylalanine hydroxylase gene), where dietary restriction of phenylalanine beginning in infancy protects against mental retardation, patients with DHPR deficiency develop seizures and serious neurodevelopmental delays even with good dietary control of phenylalanine intake (Kaufman et al., 1975a,b).

These clinical problems presumably arise from deficient activities of TH and tryptophan hydroxylase and from defective folate metabolism. Corresponding biochemical consequences include the following: low CSF levels of the serotonin metabolite 5-hydroxytryptophan (5-HTP) and 5-hydroxyindoleacetic acid; and low CSF levels of tetrahydrofolate (Niederwieser et al., 1985; Goldstein et al., 1995). Therapy combining phenylalanine restriction with oral administration of L-DOPA, 5-hydroxytryptophan (precursor of serotonin), and folinic acid appears to improve neurodevelopmental outcomes in DHPR-deficient patients (Irons et al., 1987; Goldstein et al., 1995; Smooker et al., 1995).

At least 14 different mutations have been described at the DHPR locus (Matsubara et al., 1992; Dianzani et al., 1993; Smooker et al., 1993, 1995) on chromosome 4 (Sumi et al., 1990). Combinations of neurochemical assessments with mutation detection or functional characterization of abnormal DHPR alleles should help elucidate relationships between genotype and clinical phenotype in DHPR deficiency. Moreover, in a patient we studied (Goldstein et al., 1995), the pretreatment neurochemical findings (low but detectable plasma levels of DOPA and normal levels of NE, despite absent DHPR activity in erythrocytes and fibroblasts) led to the suggestion of a DHPR-independent mechanism for recycling BH₄, illustrating how neurochemical analyses in patients with rare disorders can also enhance general understanding of catecholamine metabolism.

As suggested by the pathways in Fig. 2, defects in GTP-cyclohydrolase I (EC 3.5.4.16) or 6-pyruvoyl tetrahydropterin synthase (no EC number listed) can also

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**TABLE 1. Sources and physiological meanings of concentrations of l-DOPA, catecholamines, and catecholamine metabolites**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>l-DOPA</td>
<td>Sympathetic nerves and unknown</td>
<td>Altersations may reflect changes in TH activity and catecholamine biosynthesis</td>
</tr>
<tr>
<td>DA</td>
<td>Sympathetic nerves and unknown</td>
<td>Altersations may reflect large increases in exocytotic release</td>
</tr>
<tr>
<td>NE</td>
<td>Sympathetic nerves and (to a much smaller extent) adrenal medulla</td>
<td>Altersations indirectly reflect exocytotic release, modulated by reuptake and presynaptic adrenoceptors</td>
</tr>
<tr>
<td>EPI</td>
<td>Adrenal medulla</td>
<td>Index of adrenomedullary secretion</td>
</tr>
<tr>
<td>DOPAC</td>
<td>Enzymatic actions of MAO and AD on DA</td>
<td>Reflects MAO and AD activities, indirectly reflects TH, DBH, vesicular and transmembrane transporters, and extraneuronal COMT activity</td>
</tr>
<tr>
<td>DHPG</td>
<td>Enzymatic actions of MAO-A and AR on axoplasmic NE</td>
<td>Reflects MAO-A and AR activities, indirectly reflects DBH, vesicular and transmembrane transporters, extraneuronal COMT activity, and vesicular NE stores</td>
</tr>
<tr>
<td>NMN</td>
<td>Enzymatic actions of COMT on NE</td>
<td>Reflects extraneuronal uptake and COMT activity in nonneuronal cells</td>
</tr>
<tr>
<td>MN</td>
<td>Enzymatic actions of COMT on adrenomedullary EPI mainly before entry of EPI into the circulation</td>
<td>Reflects extraneuronal uptake and COMT activity in nonneuronal cells</td>
</tr>
<tr>
<td>MHPG</td>
<td>Enzymatic actions of COMT on DHPG and of COMT and MAO on NE</td>
<td>Reflects extraneuronal uptake and COMT activity in nonneuronal cells</td>
</tr>
<tr>
<td>VMA</td>
<td>Enzymatic actions of AD on MHPG in liver</td>
<td>Reflects hepatic metabolism of circulating and locally generated MHPG</td>
</tr>
<tr>
<td>HVA</td>
<td>Enzymatic actions of COMT on DOPAC</td>
<td>Reflects extraneuronal uptake and COMT activity in nonneuronal cells</td>
</tr>
<tr>
<td>DA sulfate</td>
<td>Conjugation of DA, mainly in gut</td>
<td>Possibly reflects inactivation of autocrine/paracrine DA</td>
</tr>
</tbody>
</table>

For abbreviations, see legend to Fig. 1.
FIG. 1. Overview of catecholamine synthetic and metabolic pathways. Note single pathway of catecholamine synthesis, via hydroxylation of tyrosine and decarboxylation of L-DOPA, compared with multiple pathways of catecholamine metabolism. Abbreviations used: 5-CH3-H4-folate, 5-methyltetrahydrofolate; THF, tetrahydrofolate; q-BH2, quinonoid dihydrobiopterin; MTHFR, methyltetrahydrofolate reductase; DHPR, dihydropyridine reductase; BH4, tetrahydrobiopterin; Tyr, tyrosine; TH, tyrosine hydroxylase; COMT, catechol-O-methyltransferase; PST, phenylsulfotransferase; 3-MTyrosine, 3-methoxytyrosine; LAAAD, L-aromatic amino acid decarboxylase; DOPA-SO4, L-DOPA sulfate; DA, dopamine; DA-SO4, dopamine sulfate; MAO, monoamine oxidase; AD, aldehyde dehydrogenase; AR, aldehyde reductase; DBH, dopamine-beta-hydroxylase; NE, norepinephrine; 3-MT, 3-methoxytyramine; 3-MT-SO4, 3-methoxytyramine sulfate; PNMT, phenylethanolamine-N-methyltransferase; NMN, normetanephrine; EPI, epinephrine; MN, metanephrine; DHPG, dihydroxyphenylglycol; MHPG, methoxyhydroxyphenylglycol; EPI-SO4, epinephrine sulfate; NMN-SO4, normetanephrine sulfate; MN-SO4, metanephrine sulfate; DHPG-SO4, dihydroxyphenylglycol sulfate; MHPG-SO4, methoxyhydroxyphenylglycol sulfate; VMA, vanillylmandelic acid; DOPAC, dihydroxyphenylacetic acid; HVA, homovanillic acid.

produce atypical phenylketonuria due to defective BH4 synthesis (Scrivener et al., 1996). Complete deficiency of either enzyme leads to about the same clinical syndrome, with seizures, limb hypertonia, intermittent hyperthermia (Scrivener et al., 1996), and predictable associated neurotransmitter abnormalities (Dhondt, 1984; Niederwieser et al., 1984). Heterozygosity for mutation at the GTP-cyclohydrolase I locus produces DOPA-responsive dystonia, as discussed later.

Deficiency of sepiapterin reductase (EC 1.1.1.153) or of carbinolamine dehydratase (no EC number listed), other enzymes in BH4 synthesis and recycling (Fig. 1) should also produce predictable clinical and neurochemical abnormalities. As carbinolamine dehydratase catalyzes a reaction that can also occur nonenzymatically, however, individuals with complete absence of this enzyme have mild clinical findings and only transient biochemical changes (Citron et al., 1993). Examples of sepiapterin reductase deficiency have not been reported to date.
Vitiligo

Progressive depigmentation in vitiligo reflects neither a neurological nor a clearly inherited condition. This disorder, nevertheless, merits inclusion in this review, because vitiligo patients may have localized, cell type-specific abnormalities of catecholamine biosynthesis (Schallreuter et al., 1994). Affected individuals have three- to fivefold increases in epidermal GTP-cyclohydrolase I activity and decreased activity of carbinolamine dehydratase (Schallreuter et al., 1994). This combination increases formation of 7-BH$_4$ (Fig. 2), a by-product that potently inhibits phenylalanine hydroxylase (Adler et al., 1992; Davis et al., 1992). The genetic factors related to these alterations remain unknown.

Vitiligo patients have been reported to have increased rates of urinary excretion of HVA and VMA, especially during the onset and in progressive active phases (Morrone et al., 1992). Increased urinary excretion of norepinephrine has been noted in some affected individuals (Schallreuter et al., 1994). Data concerning plasma catecholamine levels have been inconsistent (Orecchia et al., 1994; Schallreuter et al., 1994), possibly due to a localized catecholaminergic abnormality. Additional genetic and neurochemical studies of patients with this disorder would be useful.

L-DOPA-responsive dystonia

L-DOPA-responsive dystonia, which is inherited as an autosomal dominant trait, includes childhood-onset dystonia, abnormal gait, marked diurnal fluctuation (symptoms aggravated in the evening and alleviated in the morning after rest), concurrent or later development of parkinsonism, and normal cognitive function. Oral L-DOPA treatment dramatically improves the neurologic symptoms.

It was the pattern of biochemical abnormalities in L-DOPA-responsive dystonia—low brain and CSF levels of DA, HVA, and BH$_4$ (Nygaard, 1993; Nygaard et al., 1994; Rajput et al., 1994; Takahashi et al., 1994)—that led initially to the prediction that the disorder would be found to arise from deficient DA synthesis due to decreased tyrosine hydroxylation. Genetic linkage analysis localized the putative mutant gene to chromosome 14q (Nygaard et al., 1993), but no candidate genes emerged from the genetic maps, until Ichinose and co-workers mapped the human GTP-cyclohydrolase gene to the L-DOPA-responsive dystonia critical region (Ichinose et al., 1994). The same workers demonstrated GTP-cyclohydrolase mutations in L-DOPA-responsive dystonia patients and documented severely reduced enzyme activity in affected patients. Numerous other GTP-cyclohydrolase mutations have since been reported in L-DOPA-responsive dystonia patients (Hirano et al., 1995; Furukawa et al., 1996), including a splice junction defect that produces skipping of exon 2 and predicts a truncated protein (Hirano et al., 1995). Thus, the neurochemical abnormalities in L-DOPA-responsive dystonia not only fit the genetic.

**FIG. 2.** Pathways of de novo synthesis and recycling of BH$_4$. Abbreviations are as in the legend to Fig. 1.
abnormalities identified so far but also predicted the

type of genetic defect.

Whether an individual possesses one or two mutant
GTP-cyclohydrolase alleles profoundly influences the
resultant neurological phenotype. Comparisons of neu­
rochemical phenotypes in patients with autosomal re­
cessive GTP-cyclohydrolase deficiency (atypical phen­
yketonuria) or autosomal dominant GTP-cyclohydrol­
ase deficiency (l-DOPA-responsive dystonia) would
be informative and potentially could provide insights
about treatment possibilities.

L-Aromatic amino acid decarboxylase (LAAAD)
deficiency

LAAAD (EC 4.1.1.28) catalyzes the conversion of
L-DOPA to DA (Fig. 1) and of 5-hydroxytryptophan
to serotonin. The enzyme requires pyridoxal-5'-phos­
phate (vitamin B_{6}). A case report describing twins
resultant neurological phenotype. Comparisons of neu­
rochemical phenotypes in patients with autosomal re­
cessive GTP-cyclohydrolase deficiency (atypical phen­
yketonuria) or autosomal dominant GTP-cyclohydrol­
ase deficiency (l-DOPA-responsive dystonia) would
be informative and potentially could provide insights
about treatment possibilities.

Menkes disease

Menkes disease is an X-linked recessive cause of
infantile neurodegeneration that results from mutations
in a gene encoding a copper-transporting ATPase
(Chelly et al., 1993; Mercer et al., 1993; Vulpe et
al., 1993). Clinical features include seizures, severe developmental delay, failure to thrive,
connective tissue abnormalities, such as bladder diver­
ticula and skin laxity, hair abnormalities (“pili torti”),
and death in infancy or early childhood (Kaler, 1994).
Other syndromes with less severe neurological pheno­
types (e.g., occipital horn syndrome) have also been
associated with mutations at this locus (Kaler et al.,
1994). The clinical findings in Menkes disease and
its variants result from reduced activities of copper­
containing proteins, such as ceruloplasmin, cyto­
chrome c oxidase, superoxide dismutase, lysyl oxidase,
and DBH. Because the patients have impaired intesti­
nal copper absorption, serum copper levels are low
after the first 2 months of life.

Decreased DBH activity in patients with Menkes
disease causes a distinctive, abnormal pattern of
plasma and CSF catechols (Kaler et al., 1993b), with
high concentrations of DOPA, DOPAC, and DA, low
concentrations of DHPG (an index of intraneuronal NE
turnover), and approximately normal concentrations of
NE itself, consistent with compensatory increases in
sympathetic nerve traffic and tyrosine hydroxylation.
The neurochemical pattern (in particular, elevated ra­
tios of DOPA/DHPG and DOPAC/DHPG) provides
an excellent biochemical marker for this condition
(Kaler et al., 1993b). Thus, analyses of plasma levels
of catechols can diagnose or exclude Menkes disease
in at-risk infants during the newborn period, when clin­
cal signs are extremely subtle (Gunn et al., 1984)
and other biochemical markers unreliable (Kaler et al.,
1993a; Kaler, 1994). The abnormal pattern can also
be detected in umbilical cord blood of affected patients,
indicating DBH deficiency in utero and suggesting that
analysis of catechol levels in cord blood may constitute
a rapid, noninvasive test for Menkes disease in at-risk
newborns (Kaler et al., 1993a, 1996).

Early treatment with parenteral copper improves the
clinical outcome in some patients with Menkes disease
(Kalar et al., 1996; Tumer et al., 1996). The success
of such therapy, however, appears to depend on the
particular gene mutation (Kaler et al., 1995, 1996;
Kaler, 1996). Further analyses of clinical, biochemi­
cal, and molecular features should clarify the relative importance of mutation type and other factors in determining the likelihood of response to treatment, and improved understanding of the copper transport process mediated by the gene product and its homologues may facilitate development of novel therapies for this disorder. Correction of the abnormal neurochemical pattern could predict treatment efficacy.

Familial dysautonomia

Familial dysautonomia, inherited as an autosomal recessive trait, produces a constellation of clinical findings that suggest deficient activities of multiple peripheral neurotransmitter systems, including catecholaminergic systems. Affected patients have neurogenic orthostatic hypotension, absent lingual papillae, no histamine-induced flare or overflow tears, and episodic paroxysmal hypertension, nausea, and vomiting. All familial dysautonomia patients identified to date have shared an Ashkenazic Jewish background, suggesting that one or a few mutations account for the majority of cases. The responsible gene has not yet been reported but has been localized to chromosome 9q35 (Blumenfeld et al., 1993), a region close to the map location of the DBH gene (9q34).

Familial dysautonomia patients have high rates of excretion of HVA and low rates of excretion of VMA (Smith et al., 1963). Although this pattern might suggest deficient DBH activity, most of the patients have normal plasma DA and DOPAC levels. Familial dysautonomia patients have high plasma DOPA/DHPG ratios (although less elevated than in Menkes disease patients), a failure to increase plasma NE levels during orthostasis [analogous to patients with acquired dysautonomias (Ziegler et al., 1976, 1977)], and low plasma EPI levels (Axelrod et al., 1996).

The plasma neurochemical pattern in familial dysautonomia does not appear to fit any single abnormality of catecholamine synthesis, storage, reuptake, or metabolism. Instead, the findings suggest more global abnormalities of peripheral catecholamine systems during embryological development. Studies of nerve growth factor and its receptors have not been rewarding so far (Breakefield et al., 1984; Slaugenhaupt et al., 1995). The phenotypic pattern, nevertheless, points to deficient innervation of the adrenal medulla and other organs. Mechanisms by which the bound nerve growth factor receptor signals the cell bodies remain poorly understood; from the neurochemical phenotype, one may speculate that the genetic abnormality involves a protein participating in these mechanisms. The DBH locus should be formally excluded.

GENETIC DISEASES WITH SPECIFIC CATECHOLAMINERGIC PHENOTYPES: METABOLISM

Whereas catecholamine biosynthesis occurs mainly, if not exclusively, by a single pathway (tyrosine hydroxylation), catecholamine inactivation occurs by several alternative pathways that include at least three different intracellular enzymes (Fig. 1). From this, and from the absolute requirement of BH₄ for tyrosine hydroxylation, one might predict that, compared with the potentially devastating effect of mutations either in the TH gene itself or in genes encoding enzymes participating in synthesis or recycling of BH₄, defects in genes encoding catecholamine-metabolizing enzymes would have less serious clinical consequences.

Mutations in genes that encode membrane catecholamine transporters or vesicular amine transporters (VATs) have not been reported, despite cloning of the genes and identification of their chromosomal locations (Table 2). A recent report described successful generation of mice with a knockout of the membrane DA transporter (Giros et al., 1996). The animals had hyperlocomotion, decreased food intake, abnormal maternal behavior, and an increased likelihood of premature death. Neurochemically, the animals had decreased electrical stimulus-induced DA release and decreased tyrosine hydroxylation in dopaminergic neurons. To our knowledge, no report to date has reported knockout or transgenic animals for the membrane NE transporter or for a VAT.

Monoamine oxidase (MAO) deficiency

MAO (EC 1.4.3.4) isoenzymes inactivate catecholamines and their O-methylated metabolites (Fig. 1) and also deaminate other biogenic amines, such as serotonin. The genes encoding the two subtypes of MAO (MAO-A and MAO-B) lie adjacent to each other on the X chromosome. Oxidative deamination of serotonin depends on MAO-A; in vitro, both subtypes deaminate DOPA, DA, and NE.

Several inherited disorders involving MAO deficiency have been described. A kindred of Dutch men with impulsivity, aggressiveness, and antisocial behavior had isolated deficiency of MAO-A (Brummer et al., 1993b), with a point mutation in exon 8 of the MAO-A gene (Brummer et al., 1993a). The patients had increased urinary excretion of NMN, HVA, and VMA.

Patients with Norrie disease, inherited as an X-linked recessive trait, have blindness, deafness, and variable mental retardation. The Norrie disease gene is contiguous with the two MAO loci at Xp11.4-p11.3 (3,094,3,075), the order from centromere to telomere being Norrie disease/MAO-B/MAO-A. Norrie disease patients can have deletions that include the Norrie disease locus and either the MAO-B locus or both MAO loci (Lenders et al., 1996). Two brothers with Norrie disease and selective MAO-B deficiency had minimal neurochemical alterations and no behavioral or psychomotor abnormalities. In contrast, a patient with deletion of all three loci had markedly increased levels of O-methylated amine metabolites and low levels of deaminated catecholamines, with severe mental deficiency, autistic-like behavior, atonic seizures, and altered peripheral autonomic function (Collins et al., 1992).
TABLE 2. Chromosomal locations of catecholamine-synthesizing, metabolizing, and inactivating genes

<table>
<thead>
<tr>
<th>Protein</th>
<th>Location</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>12q-24.1</td>
<td>BH₄ cofactor; phenylketonuria</td>
</tr>
<tr>
<td>GTP-cyclohydrolase I</td>
<td>14q21-q22</td>
<td>1-DOPA-responsive dystonia</td>
</tr>
<tr>
<td>DHPR</td>
<td>4p15.31</td>
<td>Atypical phenylketonuria</td>
</tr>
<tr>
<td>Carbinolamine dehydratase</td>
<td>10q22</td>
<td>Mild phenylketonuria</td>
</tr>
<tr>
<td>TH</td>
<td>11 (short arm)</td>
<td>Fe enzyme; BH₄ cofactor</td>
</tr>
<tr>
<td>Tyrosinase</td>
<td>11q14-q21</td>
<td>Cu enzyme; albinism</td>
</tr>
<tr>
<td>LAAAAD</td>
<td>7p13-p11</td>
<td>Pyridoxine cofactor; neonatal seizures, hypotonia</td>
</tr>
<tr>
<td>Copper ATPase</td>
<td>Xq13</td>
<td>Menkes disease</td>
</tr>
<tr>
<td>DBH</td>
<td>9q34</td>
<td>Cu enzyme; ascorbate cofactor; orthostatic hypotension</td>
</tr>
<tr>
<td>PNMT</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>MAO-A</td>
<td>Xp11.23</td>
<td>Impulsivity, aggressive behavior</td>
</tr>
<tr>
<td>MAO-B</td>
<td>Xp11.4</td>
<td>Norrie disease (contiguous gene syndrome)</td>
</tr>
<tr>
<td>COMT</td>
<td>22q11.1-11.2</td>
<td></td>
</tr>
<tr>
<td>PST</td>
<td>16p11.2</td>
<td></td>
</tr>
<tr>
<td>NE transporter</td>
<td>16q12.2</td>
<td>Na⁺-dependent</td>
</tr>
<tr>
<td>DA transporter</td>
<td>5p15.3</td>
<td>Na⁺-dependent</td>
</tr>
<tr>
<td>VAT-1 (adrenal)</td>
<td>8p21.3</td>
<td></td>
</tr>
<tr>
<td>VAT-2 (brain)</td>
<td>10q25</td>
<td></td>
</tr>
<tr>
<td>AR</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>1q32-q42, 3p12, 7q31-q35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9q22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11p14-p15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13q14-q21</td>
<td></td>
</tr>
</tbody>
</table>

PH, phenylalanine hydroxylase; VAT, vesicular amine transporter. For other abbreviations, see legend to Fig. 1.

These findings imply that MAO-A deficiency produces far more serious clinical consequences than does MAO-B deficiency. Some of these differences could depend on the importance of MAO-A in serotonin metabolism, because mice exposed to MAO inhibitors in utero have increased aggressive behavior (Cases et al., 1995) mitigated by blockade of serotonin synthesis.

Pseudopheochromocytoma

Pheochromocytomas are adrenal tumors that synthesize and secrete catecholamines. The tumor, which usually is benign, typically presents as difficult-to-control hypertension, with paroxysms of severe high blood pressure, tachycardia, pallor, sweating, and headache. Because the tumor constitutes a rare, but curable, form of hypertension, hypertensive patients with these symptoms or signs often undergo diagnostic testing for pheochromocytoma. Kuchel and co-workers described a syndrome termed 'pseudopheochromocytoma' (Kuchel et al., 1981), in which the patients have clinical findings consistent with pheochromocytoma, but instead of harboring the tumor, the patients have decreased plasma levels of conjugated catecholamines. Because sulfconjugation figures prominently in the inactivation of circulating catecholamines [especially DA (Kuchel et al., 1978; Ratge et al., 1991)], these patients might have a deficiency of phenolsulfotransferase (PST; EC 2.8.2.1). Plasma levels of DA sulfate vary widely across individuals and species (Toth et al., 1986; Dousa and Tyce, 1988), consistent with polymorphisms in the PST gene (Aksoy and Weinshilboum, 1995). Patients with complete deficiency of PST have not been described to date; the gene encoding PST was cloned recently (Aksoy et al., 1994; Aksoy and Weinshilboum, 1995). The location is near the gene responsible for Batten disease, an autosomal recessive disorder of lipofuscin metabolism (Taschner et al., 1995).

Velo-cardio-facial syndrome and DiGeorge syndrome

Velo-cardio-facial syndrome includes cleft palate, craniofacial abnormalities, learning disorders, cardiac defects, and psychiatric illness in adolescence and adulthood. DiGeorge syndrome includes immunodeficiency, facial dysmorphism, mental disorders, and cardiac defects. Both syndromes have been associated with interstitial deletions of chromosome 22q11 (Scambler et al., 1992; Franke et al., 1994). A study of nine families with recurrent cardiac outflow tract defects found that five had transmitted deletions of chromosome 22q11 (Wilson et al., 1992). Chromosome 22q11 includes the locus of the gene encoding catechol-O-methyltransferase (COMT; EC 2.1.1.6). Thus, one may hypothesize that some patients with the velo-cardio-facial or DiGeorge syndrome may have only one functional COMT allele and decreased COMT activity (Dunham et al., 1992). Abnormal ratios of O-methylated to deaminated metabolites of catecholamines in plasma or urine could detect this. The relationship between COMT activity and clinical features of either syndrome remains unknown.
von Hippel–Lindau disease and pheochromocytoma

von Hippel–Lindau disease is an autosomal dominant disorder featuring hemangioblastomas, cystic tumors, renal cell carcinomas, pancreatic cysts and tumors, epididymal cystadenomas, and pheochromocytomas (Choyke et al., 1995). von Hippel–Lindau disease patients with pheochromocytoma can have false negative results of screening tests based on plasma levels or urinary excretion of catecholamines or catecholamine metabolites, and measurement of plasma- or urinary excretion of catecholamines or catecholamine metabolites, and measurement of plasma-levels or urinary excretion of catecholamines or catecho-

mors, renal cell carcinomas, pancreatic cysts and tu-

cholamine metabolites, and measurement of plasma-

ease patients with pheochromocytoma can have false

mors, epididymal cystadenomas, and pheochromocy-
pheochromocytoma (Choyke et al., 1995). von Hippel-Lindau dis-
tumors (Choyke et al., 1995). The von Hippel–Lindau disease gene, located

of this new application of clinical neurochemistry. The

...sensitive biochemical marker (Lenders et al., 1995). The von Hippel–Lindau disease gene, located on chromosome 3 (3p25), encodes a tumor suppressor gene (Latif et al., 1993; Herman et al., 1994; Linehan et al., 1995). Many mutations at different loci in this gene have been documented in individuals with the classic von Hippel–Lindau disease phenotype; however, familial pheochromocytoma seems to be associated with mutations at a specific locus (Crossey et al., 1995; Gross et al., 1996; Neumann et al., 1996).

CONCLUSIONS

The wealth of knowledge regarding the synthesis and fate of catecholamines, the availability of sensitive and specific assays for L-DOPA, catecholamines, and most of their metabolites, and recent advances in molecular genetics afford the opportunity to glean new understanding of neurogenetic disorders that involve catecholamine metabolism. This review has presented several examples rather than a comprehensive picture of this new application of clinical neurochemistry. The pathways outlined in Figs. 1 and 2 suggest the existence of several other genetic defects, as yet undiscovered, with predictable neurochemical and clinical consequences.

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