THE BIOCHEMICAL-IMMUNOLOGY WINDOW: A MOLECULAR VIEW OF PSYCHIATRIC CASE MANAGEMENT

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Abstract: Molecular regulation of brain metabolism and function can now be measured selectively. Patients with mood and thought disorders can often be classified based on this information. Clinical management can often be improved by therapeutic interventions based on advanced chemical and immunologic testing techniques. The relevant information is distributed over various medical, laboratory, and research disciplines and, thus, not easily accessible by practicing psychiatrists. This article seeks to bridge this gap. This article focuses on a molecular and cell biology look at the diagnosis and clinical management of the depressions and the schizophrenias.

INTRODUCTION

This review article develops two related sets of facts that can improve your clinical management of people with various depressions and with the schizophrenias.

First, measurement of brain regulating neurotransmitters and certain factors, which in turn regulate neurotransmitter production and function, can be routinely measured in clinical practice.

Second, the bi-directional interaction between the immune defense and repair system and the nervous system allows for clinically useful measurements of cell function that can be of value in clinical practice.

A brief explanation of our current understanding of neurotransmitters and their metabolites will be followed by an interpretive algorithm for use in their interpretation. In addition, suggestions will be made for clinical responses based on these laboratory findings.

Each neurotransmitter is identified (*) and is followed by a principle metabolite (●). It is now clear that platelets serve as a suitable model for nerve vesicle neurotransmitter status. Quantitative determination of neurotransmitter pools in platelets are a reasonable determinant of that neurotransmitter in the nervous system.

Overall *neurotransmitter turnover and metabolism*—how much neurotransmitter is being turned over each day—can be reasonably assessed by 24-hour urinary neurotransmitter and metabolite excretion quantification.

This provides three clinically useful sets of information:

1. how much neurotransmitter is present in storage vesicles, and,
2. how much neurotransmitter is produced and metabolized daily, and,
3. the relative proportions of each of the major neurotransmitters.

Neurotransmitter Pools, as measured in platelet storage vesicles which are models of nerve vesicles, give information about the amount of neurotransmitter available for release on stimulation. The relative saturation of neurotransmitter storage vesicles reflects the likelihood that free neurotransmitter will become available for nonspecific or generalized activation of neural or cellular networks.

Additionally, information is available about the relative proportion of activating and damping neurotransmitters from platelet neurotransmitter quantitative assays.

Neurotransmitter turnover and metabolism gives relative information about overall production, utilization, and degradation of the neurotransmitter throughout the day studies. These quantitative studies can lead to therapeutic interventions by providing neurotransmitter precursor amino acids or regulating enzyme activation factors as discussed below.

Laboratory values for clearly aberrant results, those usually reported by labs where the control population was not selected for elimination of depressive or schizophrenia dispositions and a proposed healthy reference range.

Measurement of neurotransmitters thus provides useful clinical information about which pathway may be functioning in proportionate excess or deficiency. Since we now are learning about both the precursor sources for and the enzyme systems that regulate neurotransmitter production and metabolism, clinical intervention at the biochemical level is becoming possible.

The clinical biochemistry and general medical literature has many references to psychopathologic and behavioral dysfunction that derives from neurotransmitter precursor excess or deficiency and where modulation of neurotransmitter precursor reduces psychopathology. In other patients the defect is in the regulation of neurotransmitters.

In such cases administration of cofactors known to activate the regulating mechanisms may be clinically beneficial. We are at the beginning of biochemical immunology in psychiatry.

Table I. Neurotransmitter studies suitable for diagnostic differentiation among depressions and the schizophrenias.

Neurotransmitters{specimen}	Laboratory Results Ranges			Test Units
	Abnormal	Usual	Healthy	
✡Acetylcholine {serum}	<40 or >80	40-80	60-70	mg./dl serum
●Histamine {whole blood}	<25 or >70	25-70	40-50	nag/ml whole blood
✡Epinephrine {platelets}	<3 or >27	3-27	8-16	ng/10^8 platelets
●Metanephrine {platelets}	<4 or >40	4-40	10-20	ng/10^8 platelets
✡Vanilmandilic acid {VMA, urine}	>9or<3	<9	3-6	mg./24^8 urine
●Norepinephrine{platelets}	<3 or >11	3-11	5-9	ng/10^8 platelets
✡Normetanephrine {platelets}	<4 or >40	4-40	10-20	ng/10^8 platelets
●Dopamine {platelets}	<1 or >11	1-11	4-6	ng/10^8 platelets
✡Homovanilic acid {HVA, urine}	>8or <2	<8	2-5	ng/24 urine
●Serotonin {platelets}	<15 or >300	15-300	70-130	ng/10^8 platelets
✡Hydroxyindole acetic acid {HIAA, urine}	>6 or < 2	<6	2-4	mg./24 urine
●Gamma-Amino Butyric Acid {GABA, plasma}	<0.5 or >3	0.5-3	1-2	μmold/dl plasma
✡Glycine {plasma}	<17 or > 31	17-31	22-26	μmold/dl plasma

Legend: ✡=neurotransmitter, ●=neurotransmitter metabolite or regulator

It is likely that the coming decades will see rapid advances in this molecular characterization of the depressions and the schizophrenias.

These approaches are low risk and potentially high gain. The low risk derives from the use of endogenous materials such as amino acids, amines, minerals, and enzyme-activating vitamins.

While it is widely believed that dietary deficiency is rare, in fact, it is common among patients with both depressions and among the schizophrenias. Biochemical individuality has been shown to exist. This means that some individuals need more than typical amounts of essential factors for their biochemical pathways to function effectively.

Table II shows the common neurotransmitter sources and metabolites.

Where deficiency of a neurotransmitter is found, administration of its source, typically 250 mg. to 1500 mg. twice daily, not at meal time to obtain best absorption, is a worthwhile clinical trial. Alternatively, encouraging a diet that is rich in the neurotransmitter source may be useful

assuming the patient has both efficient digestion and does not have absorption uptake block or enteropathy in the intestine.

Table II: Neurotransmitter: sources and major metabolites

Precursor Amino Acid/chemical	Neurotransmitter	Metabolite	
		Primary	Secondary
Serine/choline	Acetylcholine	CO_2 bile acids	
Histidine/Histamine	Imidazole		
Tyrosine/tyramine	Epinephrine	Metanephrines	VMA
Phenylalanine	Norepinephrine	Normetanephrines	VMA
Phenylalanine	Dopamine	HVA	
Tryptophan	Serotonin	HIAA	Kyneurenate
Glutamate	Gamma-Amino Butyrate	Succinate	
Glycine	Glycine	Acetate	

Legend: VMA = Vanilmandilic acid; HVA = Homovanilic acid: HIAA = Hydroxyindolacetic acid

The pharmaceutical cornucopia of antipsychotic, antidepressant, and tranquilizing drugs and sedatives act specifically by modifying the uptake, release, or metabolism of neurotransmitters. This approach overrides the physiologic regulation of neurotransmitters as derived from diet. Often, modulation of neurotransmitters through therapeutic supplementation of their precursors or cofactor requirements is clinically useful. Medication dosages may be reduced and their side-effects can often thereby be minimized as well.

Neurotransmitter modulation *via* dietary sources includes:

1) lecithin from eggs and soy that provides choline in a form that can enter the CNS through the blood brain barrier to increase acetylcholine pool and in some cases improve memory,
2) cheddar and similar cheeses whose tyramine is an adrenergic agonist and can be metabolized to norepinephrine,
3) protein-derived histidine which can become histamine,
4) wheat germ and fowl which are enriched in tyrosine, a precursor to the neurotransmitters epinephrine, norepinephrine, and dopamine,
5) wild game, ricotta cheese, and granola which are enriched in glutamate/glutamine, neurotransmitters, and energetic sources for cells, and,
(6) yogurt and duck which are enriched in sulfur amino acids needed for methylation reactions.

Table III: Neurotransmitters: Regulating cofactors and enzymes

Neurotransmitters	Regulating Cofactor(s)	Regulating Enzymes(s)
Acetylcholine	CoA, Choline	ACS
Histamine	Cu, ZN, Mn, B6	MAO
Epinephrine	Cu, Mg, B3, B6, AA, FA	COMT, MAO
Norepinephrine	Cu, Mg, B3, B6, AA, FA	COMT, MAO
Dopamine	Fe, B6, Biotin	DD, MAO
Serotonin	F3, B3, B6	TH, MAO
Gamma-Amino Butyric Acid	B6, Biotin	GD
Glycine	Lipoate	MAO

Legend: ACS = acetylcholine synthetase; COMT= catechol-O-methyl transferase; MAO=monoamine oxidase; DD = dopamine decarboxylase; TH= tryptophan hydroxylase; GD = glutamine decarcaboxylase; FA = Folic Acid.

Where excess of a neurotransmitter is found, restriction of protein intake to 50-60 grams per day is indicated along with an increase in fiber-rich complex carbohydrates rather than the up to 1150 grams protein consumption per day that is common for many people eating a Western industrialized diet.

Neurotransmitter regulation is controlled by catalysts that are dependent upon specific essential nutrient cofactors. These cofactors and the regulating enzymes responsible for neurotransmitter synthesis and metabolism are shown in **Table III.** Modulation of regulating cofactors can improve the functional performance of regulating enzymes.

Therapeutic trial with appropriate regulating factors in therapeutic doses is indicated when production or metabolism of a neurotransmitter is dysfunctional. **Table IV** suggests common therapeutic forms and dosage range that is most likely to be clinically effective. It is recommended that dosage forms be used that specify their bioavailability.

The simplicity of daily or BID dosage facilitates compliance. Time of day can vary with patient preference or convenience. Since absorption uptake blocks is quite common, you may need to give enough of these essential factors to compensate for the enteropathy (intestinal atrophy) associated uptake block.

Table IV: Regulating cofactors and therapeutic dosages

Cofactor	Effective Form	Dosage Range	Frequency
CoA	pantothenate, thioctic	100 –300 mg.	QID
Choline	choline citrate	1000- 4000 mg.	BID
Copper (Cu)	sebecate or citrate	1 – 5 mg.	QD
Zinc (Zn)	picolinate, citrate, gluconate	25 – 100 mg.	QD
Manganese (Mn)	gluconate, citrate, ascorbate	25 – 100 mg.	QD
Pyridoxine (B6)	HCI or Pyridoxyl-5-Phosphate	100-1500 mg.	BID
Magnesium (Mg)	aspartate, citrate, ascorbate	200 – 1000 mg.	BID
Niacin (B3)	sustained release or niacinamide	25 – 1500 mg.	BID
Ascorbate (AA)	mineral buffered salt	100-> 5000 mg.	QID
Folate (FA)	folate	0.4 – 50 mg.	BID[1]
Iron (Fe)	ferrous gluconate or citrate	25 – 50 mg.	QD
Biotin	biotin	500 – 5000 mcg.	BID

[1]Enough Folate and B12 to normalize the neutrophilic segmentation index (NSI) or plasma omocysteine and methylmalonic acid levels.

CLINICAL SUMMARY OF THE BIOLOGIC CATEGORIES OF THE SCHIZOPHRENIAS

Example 1: Low Histamine—The Histapenic Type {40% of Schizophrenics}
Clinically, such people are characterized by irritability, easy fatigue and frustration, tendency to easy, cyclical depressions, low libido, excessive weight on hips and thighs, great fatiguability, particularly with distress, and low tolerance for medications so that antihistamines and other medications have prominent side-effects at usual doses and are best given at the lowest effective dose. Normalization of histamine (see treatment plan below) may be helpful in these people.

Clinically it has been observed that low histamine people, when they use recreational drugs, are binge users. Paranoia and thought disorders of ten complicated their condition, particularly when alcohol or other recreational drugs are involved. Similarly, their eating may be of a binge type. When obese, the distribution is usually steatopygous or pear shape. Pain threshold is usually high. Cyclical depression is common.

Abraham Lincoln, Winston Churchill, and Eleanor Roosevelt may be among the rare histapenic types to overcome their profound self-doubt and depressions and become prominent community leaders. Perhaps they represent less severe or “form fruste” expressions of the syndrome since ability to persevere is often lacking in histapenics. Many histapenics are unable to complete projects initiated.

Physical findings are often remarkably scant although they can include rheumatoid arthritis, Parkinsonian tremors, and obsessional or hyperkinetic movements.

Laboratory findings typically include low blood histamine, low absolute basophil count, low folate, high ceruloplasmin saturation, elevated copper, and CPK elevation (or easy provocation of CPK release with exercise). Accurate histamine determinations required methods that exclude other amines and polyamines, a frequent limitation of many routinely offered histamine assays. Metabolic acidosis with total body potassium and magnesium deficiency is common.

Treatment usually includes a high protein (>100 grams/day), low fat (35 grams/day), and low carbohydrate (60 grams/day)intake. Biochemical recommendations are:

1) beta carotene (25,000 IU = 15 mg./day),
2) buffered ascorbate (to keep urinary excretion above 100 mg./dl),
3) B complex (50-100 mg./day of each component + 1 mg. Each of folate and B12{parenterally if uptake block or intrinsic factor deficiency is present}), niacin (or niacinamide, although reversible depression can be provoked by niacinamide) gradually increased to 500+ mg. BID as needed,
4) histidine (250-1000 mg. BID to raise histamine into the usual range),
5) quercetin for its anti-inflammatory effects (1,000 mg. BID),
6) GLA fatty acid (120-240 mg./day),
7) Sufficient iron, zinc, molybdenum and manganese are recommended to normalize tissue levels of these minerals and reduce body copper burden, if elevated,
8) Phenytoin (Dilantin™) usually worsens symptoms. Lithium or antipsychotic medications may help. The Alcoholics Anonymous "12 steps" model support group is suitable for this person when they are at or near their perceived "bottom" so that personal recognition of the essential need for social support assistance is present.

Example 2: High Histamine—The Histadelic Type {15% of Schizophrenics}

Family history typically includes episodic or chronic depression, suicidal ideation, alcoholism, peptic ulcer disposition, headaches, insomnia, hives, and atopic history. Women who bear all male offspring are usually histadelic. In the mixed type (see Figure1), food and chemical sensitivities and acquired nutrient deficiencies can lead to a refractory obesity until the deficiencies are corrected.

Thomas Jefferson, Benjamin Franklin, James Monroe, George Washington, and John Kennedy share a histadelic profile, as do many political and business leaders.

Physically, long fingers and toes plus prominent incisor are common. In addition, hands, feet, ears, and nose are often large. Body hair and subcutaneous fate are often scant. Veins are usually

prominent. Such people often have copious saliva excretion, few dental caries and easy, profuse sweating.

Biochemically these people often exhibit rapid metabolism with a high tolerance for carbohydrate and alcohol, which may lead to compulsive eating disorders. Medications may be rapidly metabolized hence larger than usual doses may be needed to achieve therapeutic effects.

Uncontrolled histadelics who receive folate and B12 may have intensification of their symptoms because of their effect on methylation reactions.

Clinically, it has been observed that high histamine people are disposed to recreational drug excess (five times as common in histadelic as histapenic patients), ulcer disease (twice as common in histadelics as histapenics), high sexual drive, low sleep need and obsession behavior which often moderates or disappears when their histadelic trait is treated. Pain threshold is usually low.

Asthma, atopic (allergic) history, and other autoimmune disorders are common, especially when overlapping immunopathy is present (see clinical example 5, below). Histadelics are three times as likely to show side effects to medication or immunotherapy. Hypertension and cardiovascular disease are three times more common in histadelic as histapenic people. Migraine headaches are seven times more common in this group.

Laboratory findings often include blood histamine >90 ng/ml; absolute basophil count 100/μl; serum copper and ceroplastic saturation are low; manganese is often low. If the person has a high body copper burden as marked by a high ceruloplasmin saturation, histamine may be within the usual range. When the copper overload is reduced, the histadelic disposition usual reemerges.

Treatment usually includes a high complex carbohydrate diet (150 – 200 grams/day), moderate fat (50 grams/day), and moderate protein (60 grams/day) intake. Therapy typically includes:

1) L-methionine (500 mg. QID),
2) 25 mg. Each of zinc and manganese plus 500 mcg. molybdenum (if allergies are prominent or elevated sulfite is found in the urine),
3) sufficient buffered ascorbate to maintain the urine concentration above 100 mg./dl, and,
4) essential fatty acids (120-240 mg. GLA BID) plus L-carnitine, 250 mg. BID.
5) Down regulation of immune responses through low immunoreactivity diet is often helpful. Phenytoin (Dilantin™) may help, at least in part because of its anti-folate effect. Increasing depleted acetylcholine pools and stabilizing membranes through phosphatidylcholine by recommending choline citrate (1,000 – 4,000 mg. BID) may improve or stabilize mood.

Example 3: Mauve Factor—The Pyrroluric Type {15% of Schizophrenics}
Family history typically includes difficulty with dream recall (responsive to B6 stimulation), susceptibility to nausea, cluster headaches, labile emotional responses, depression, cold sensitivity, fatigue, and anemia.

Emily Dickinson, Elizabeth Barret, and Charles Darwin may have been pyrrolurics based on their need for rigorous control of their environment, intermittent depressions, exquisite sensitivity to criticism, easy fatigue, and cluster headaches.

Physical signs usually noted are treatment-resistant constipation, an aldehydic "sweet" breath, cutaneous striae (stretch marks), difficulty tanning, photosensitivity, horizontal white "clouds" on fingernails indicating disordered protein synthesis, and menstrual irregularities.

Biochemical observations often include a B6 responsive anemia refractory to iron, B12 and folate) and disordered amine (with low spermine)/neurotransmitter metabolism that responds to B6, zinc, and manganese.

Clinical disposition includes labile emotions, easy fatiguability, tendency to withdrawal or isolation, loss of appetite, motion sickness and low stress tolerance.

Lab findings usually observed include a functional zinc deficiency as detected by zinc tolerance test; a low functional B6 activity as detected with erythrocyte glutamate-oxalate transaminase (EGOT) enzyme activity differences ±pyridoxine stimulation.

Treatment most often includes supplementation with zinc in the picolinate or citrate form (25-100 mg. every other day with 1-2 mg. Copper on the alternating days after 6 months of treatment to make sure copper deficiency does not occur due to competition between zinc and copper for absorption); adequate pyridoxine to stimulate dream recall or normalize EGOT activity; and manganese, 50 mg. every other day, is often helpful.

Example 4: Nutrient Deficient Type {15% of Schizophrenics}
Family history includes problems of pregnancy, atopic history often in childhood, digestive disorders, labile moods, and recurrent symptoms for which antibiotics, estrogens, or steroids were prescribed.

Physical signs vary with the specific deficient cofactor(s). **Table V** highlights some of the signs and symptoms associated with essential cofactor excess or deficiency.

Clinical dispositions are diverse yet deserve primary inclusion in the differential evaluation of a psychiatric patient, particularly the schizophrenic or depressed individual. Much synergy can exist between improved biochemical function and clinical psychiatric case management.

The most sensitive lab findings usually observed depend upon detection of functional deficits in enzymes that depend upon the essential cofactor. For example, erythrocyte enzymes can be sensitive indicators of the need for pyridoxine (EGOT) or thiamine (ETK). Microbial assays can also be used to detect certain vitamin deficiencies. Earlier tests of blood serum levels have often not revealed the functional deficit thus obscuring the problem from clinical awareness.

Even functional cofactor assays may miss a specific genetically dysfunctional enzyme deficit if the index assay (enzyme) system is intact. Thus, therapeutic trials based on a knowledge of intermediary metabolism are essential to optimum individual patient management.

Table V: Essential enzyme cofactors in mental health practice: syndromes/symptoms linked to excess or deficiency state

Essential Enzyme Cofactors:	Syndrome/Symptoms Associated With… Excess	Deficiency
Thiamine (B1)	NR	BeriBeri; Korsakoff's psychosis, Wernicke's encephalopathy, neuronal degeneration, anti-acid induced achlorhydria
Riboflavin (B2)	NR	hyperlipidemia, cheilosis, fatigue / photophobial, glossitis/seborrheic dermatitis
Niacin (B3)	gout, chemical hepatitis, acanthosis	Pellagra, dermatitis / diarrhea / dementia
Pyridoxine (B6)	NR[1]	depression, eczema, carbohydrate intolerance, immunopathy, stormatitis, hyperirritability, microcytic anemia
Cobalamin (B12)	NR	macrocytic anemia, fatigue, neuropathy, mania, paranoia
Pantothenate	diarrhea	nausea, headache, insomnia
Biotin[2]	feminization	alopecia, lethargy, irritability, muscle pain, organic aciduria
Folate	NR	macrocytic anemia, celiac disease, nausea, vascular fragility
Ascorbate	NR	scurvy, vascular fragility
Potassium (K)	hyperreflexis, asystole	weakness, hyperreflexis, polyuris, cardiac arrhythmias
Lithium (Li)	nausea, diarrhea, ataxis, diabetes insipidus, hypothyroidism	mood swings
Calcium (Ca)	depression, drowsiness	hyperreflexia, tetany, convulsions, disorientation, polyuris, depression
Magnesium (Mg)	depression, drowsiness	hyperreflexia, tetany, convulsions, disorientation, arrhythmias (AF, SVT)
Zinc (Zn)	anemia[3], growth disorder[4], nausea, diarrhea	immunopathy/enteropathy, carbohydrate intolerance, loss of taste, smell, appetite, growth retardation
Iron (Fe)	hemosiderosis, hemochromatosis, "gray skin"	microcytic anemia, cirrhosis, nephrosis
Copper (Cu)	Wilson's Disease, tremor	anemia (copper responsive), leukopenia
Manganese (Mn)	rigidity, dystonia, hypokinesis	weight loss, sterility, hypocholestorlemia, diabetes, seizures, lupus
Molybdenum (Mo)	gout, copper deficit	atopy, asthma
Chromium (Cr)	NR	diabetes (Type II)
Gamma Linoleic Acid (GLA)	platelets disaggregate	pseudopellagra

[1] B6 is associated with an idiosyncratic neuropathy which, in over 3,000 consecutive cases have not observed perhaps because we recognize and correct zinc deficiency and use B6 in pure form that lacks the usual chemical congeners that may be competitive inhibitiors. In addition, we frequently use the fully activated (pyridoxyl-5-phosphate, P5P) to "prime" the B6 synthetic pathways.

[2] Biotin, in pyrroluric people (who are usually B6 and zinc deficient), may increase pyrrole excretion when biotin is used in therapeutic amounts. Therapeutic doses (5-15 mg. daily) are reported to improve carbohydrate metabolism in pre-diabetic and diabetic individuals.

[3] Zinc-related anemia is most likely a relative copper deficiency.

[4] Very high zinc/copper ratios (>200) are associated with fetal developmental anomalies.

Legend: NR: not reported; AF = Atrial fibrillations; SVT= Supraventricular tachycardia; GLA = Gamma Linolenic acid

Table VI: Enzyme cofactors laboratory studies of mood disorders

Essential Enzyme Cofactors (by functional measurement, where known)	**Laboratory Results Ranges**		
	Usual	**Healthy**	**Units**
Thiamine (B1) [ETK]	100±10%	100±5%	Comparative Activity
Riboflavin (B2) [EGR]	100±10%	100±5%	Comparative Activity
Niacin (B3)	3-17	8-12	mg./D Urin. Excretion
Pyridoxine (B6)	<125%	<110%	Comparative Activity
Cobalamin (B12)	>60%	>80%	% saturation
Biotin[2]	200-500	300-400	pg/ml plasma
Ascorbate	20-55	30-40	μg per 10^6 WBCs
Folate	3-7.5	0-3	mg./D Urin. Excretion
Potassium (K)	3.5-5.3	4.2-4.8	meq/L
Lithium (Li)	0.5-1.3	0.8-1.0	meq/L serum
Calcium (Ca)	4.6-5.3	4.8-5.1	mg./dl serum
Magnesium (Mg) [loading test]	<75%	>90%	urine
Zinc (Zn) [loading test]	<75%	>90%	urine
Iron (Fe)	25-55	30-40	% saturation
Copper (Cu) [loading test]	<75%	>90%	urine
Manganese (Mn) [loading test]	<75%	>90%	urine
Molybdenum (Mo) [loading test]	<75%	>90%	urine
Gamma Linoleic Acid (GLA)	17-48	25-35	μmol/g creatinine [U]

NB: healthy ranges are inferred from best currently available information. Molybdenum deficiency is associated with inhibition of sulfite oxidase leading to increase blood sulfite (a potentiator of neuroimmunologic toxicity and muscular irriability); increased urinary sulfite and decreased urinary sulfate excretion are functional measures of molybdenum deficiency.

Legend: mg. = milligram; μlg=microgram; ng=nanogram; pg=picogram; %= percent; meq=milliequivalent; g= gram; μl= microliter, μmol= micromole; D=day; Urin. =Urinary; Rx = prescribed ; ETK = erythrocyte transketolase, a thiamine dependent enzyme; EGR = erythrocyte glutathione reductase, a riboflavin dependent enzyme; EGOT= erythrocyte glutarnate/oxalate transaminase, a pyridoxine dependent enzyme; WBC= white lbood cell; FIGLU = formiminoglutamate, a histidine metabolite whose excess indicates folate deficiency folate deficiency; TIBC= total iron binding capacity.

Abnormalities of digestion are common and can be routinely detected through comprehensive microbial and chemical analysis of stool. An increase in intestinal permeability can also often be detected.

Deficiencies may be provoked or exacerbated by elevated body burdens of lead, mercury, cadmium, arsenic, nickel, and/or aluminum. Tissue burdens of these elements can be detected by provoking excretion into the urine (24-hour collection) with the oral chelator D-Penicillamine (500 mg. QID).

A variety of sources of toxic minerals exist for people predisposed by cofactor or enzyme defiencies. Common sources include urban water supplies (lead and aluminum), tobacco smoke (cadmium, pesticides, immunoreactive peptides, carbon monoxide, and particulate irritants), occupational exposures (any) and the food supply (mercury, arsenic, and cadmium) account for most of the sources of the above six minerals. If excess is observed on provocative testing, treatment can include D-Penicillamine treatment (500 mg.BID) every *other* day (to avoid the interference with connective tissue cross-linking and other adverse effects) and sufficient buffered ascorbate to keep the urinary ascorbate level above 100 mg./dl. Alternatively, tissue competition between supplemental zinc and mercury or cadmium can be used to reduce cellular burdens of toxic minerals, especially if the zinc effect is potentiated with supplemental ascorbate.

Treatment most often includes supplementation of the deficient element, preferably with its biologic transporter to facilitate uptake and utilization. Metabolic acidosis disposes to metabolic activity. Thus, it is important to correct metabolic acidosis through a mineral rich, metabolically alkaline, low immunoreactivity diet.

Table VII: Neuroimmune function laboratory studies for mood disorders

WBC and LYMPHOCYTE REPONSES	**Laboratory Results Range**		
	Usual	**Healthy**	**Units**
Absolute Basophil Count (ABC)	30-80	40-50	/μL whole blood
Interleukin 1	80-2500	200-500	pg/ml serum
Interleukin 2	1-200	50-100	pg/ml serum
ELISA/ACT (lymphocyte subset response)	5-20%	<1%	of substaces tested

Notes and Legend: Please see footnotes to Table VI.

Example 5: Immunoreactive Type [15% of Schizophrenics; overlaps with 50+%]
Occasionally, a histadelic type will show very low blood histamine levels yielding a histapenic initial appearance. This can derive from histamine pools being chronically over used and thereby becoming depleted. This is most likely when chronic, delayed food and chemical immunologic hypersensitivities are concurrent. Labile pulse rate is common in such patients after exposure to reactive foods or chemicals, perhaps indicating immune complex formation and marginal vascular volume reserve. Accurate testing for late-phase immune responses is essential to clinical management.

Gluten (Gliadin) sensitivity is the prototype for immunopathy. In the full expression of this syndrome, atrophy of the intestinal lining occurs, and we call this condition, Sprue. Less clinically florid expressions, however, can be associated with enteropathy absorption uptake blocks that impair assimilation of essential cofactors. This can result in depleted or embalanced neurotransmitter pools or in reduced activity in regulating enzyme pathways. Milk lactalbumin is another common offender although any sensitized substance can mimic this pattern. Cerebral responses, perhaps in patients with permeable blood-brain barriers, are not uncommon.

Laboratory findings often include aberrant helper: suppressor lymphocyte profiles; metabolic acidosis with total body potassium; and magnesium deficiency is common. Chronic immunologic reactivity leads to disorder of systemic control systems including those which regulate carbohydrate metabolism, amino acid metabolism, and lipid metabolism.

Any person whose effect disorder or depression persists after usual measures have been implemented is a candidate for detailed immunologic evaluation by a technique that measure all delayed or late-phase pathways such as the ELISA/ACT test (**see Table VII).** Reduction in immunologic “load’ is specifically and generaly helpful in the management of chronic psychiatric conditions, particularly schizophrenia and depression. This benefit may be from altering the neuroimmunologic response/set point and/or from reducing the mmunologic load on the nervous system as discussed below.

Nutrient deficient and immunologic types overlap with more than half of all schizophrenic and mood disordered patients we evaluate. A current differentiation among the schizophrenias is shown in Figure 1. We now appreciate more overlap between biochemical types than had previously been identified. This provides more specific therapeutic differentiation and treatment. Adequacy, deficiency or excess of essential biochemical compounds can occasionally be a pure cause of mental illness. More often biochemical imbalance potentiates another disposition, such as histadelia, histapenia, pyrroluria, or immunopathy.

RECENT ADVANCES IN BIOLOGIC PSYCHIATRY

Among the important advances of the last twenty years is our unfolding appreciation of the bidirectional interaction between the CNS and immune system. Indeed the immune and nervous systems are different aspects of the same functional unit. The artificial differentiation between immune and nervous system derives from our reductionist research paradigm that assumes it is best to isolate each variable which we study.

Figure 1: Relative proportion of each biologic type among the schizophrenias

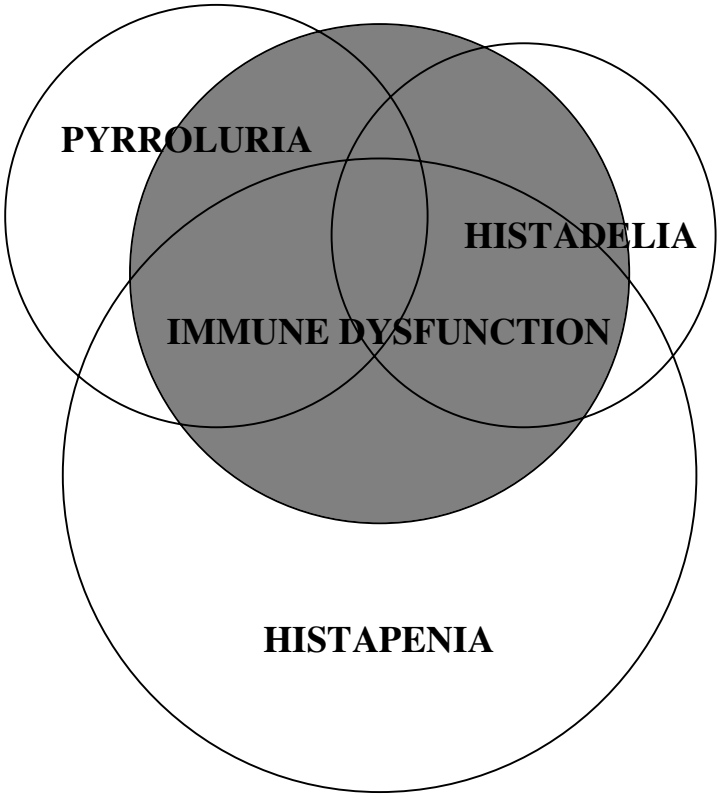

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TABLE VIII: Neurotransmitter-associated symptoms and signs

Neurotransmitters	Syndrome/Symptoms Associated With… Excess	Deficiency
Acetylcholine	hypervigilance, hypermotility, seizures, REM sleep enhancement, synchronization, excess salivation, asthma	memory deficits, flaccidity hypoarousa, REM sleep deficit, desynchronization, xerostomia/ dry mouth
Histamine	<6° hrs sleep needed, high stamina, low pain threshold, asthma, atopy, allergies, obsessions, compulsions/ phobias, drug resistant, anesthetic resistant, ruminate/"blank mind," high libido	>8° hrs sleep needed, easy fatigue high pain threshold, lethargic, hallucinations/paranoia, carefree, drug reactive, anesthetic sensitive, thoughts overlap, suicidal thoughts, flights of ideas, low libido
Epinephrine/Norepinephrine [adrenalines]	insomnia, mania, hypertension hyperphagia, migraine	narcolepsy,depression,hypotension satiety, caffeinism
Dopamine	chorea, anticholinergic, schizophrenia, sexual arousal	Parkinsonism, cholinergic, agitation, sexual disinterest
Seratonin	narcolepsy	insomnia/anxiety, impulsiveness
Glutamine/Glutamate	endurance, hypotension, agitation, eschizophrenia, mania	fatigue, hypertension, depression, seizures

Inhibitory or Antagonist Neurotransmitters

Gamma-Amino Butyric Acid [GABA]	withdrawn serenity, flaccidity, Excitoneurotoxin, satiety	excitation, action tremors, multiple sclerosis, hyperphagia
Glycine/taurine/alanine	sedation, acetylcholine agonist	agitation, acetylcholine antagonist

Legend: REM= Rapid eye movement

Cerebral immune responses can be triggered by partially digested food remnants that gain access to the systemic circulation after exceeding the trapping capacity of the small and large intestines. This is thought to derive from both increased intestinal permeability and blood brain barrier permeability.

Changes in blood/brain permeability leads to influx of whole blood platelets, monocytes, and lymphocytes plus plasma antibodies, kinins, and other factors that alter brain feedback regulation, rhythms, neurotransmitter pools, and cellular energetics.

This can result in an autoimmune attack on the CNS in susceptible, cofactor deficient patients. People with marginal or deficient antioxidant cofactor reserves secondary to nutrient poor dietary patterns or to larger individuals requirements than are provided in the diet are more susceptible to CNS immunologic involvement than are "average" people.

Use of psychotropic medications, tobacco, recreational drugs including alcohol disposes people to these deficiencies. Cerebral immune attack leads to focal, intermittent cerebral swellings and other membrane potential changes in the brain that can have focal and/or systemic, symptomatic effects.

The relative proportion of each biologic type among the schizophrenias is presented in **Figure 1.** The types may overlap. Thus, a given patient may have one or more of the specific types. In complex cases, for example, a histadelic (by history and responses to treatment) may be in a biochemical depleted or "exhausted" state and present with a usual or low histamine This can lead to confusion if laboratory results are not carefully matched to clinical history and responses to therapeutic trial.

SIGNS, SYMPTOMS, AND SYMPTOMS ASSOCIATED WITH NEUROTRANSMITTER OR ESSENTIAL COFACTOR EXCESS or DEFICIENCY are listed in **Table VIII** to highlight the range of effects currently known about neurotransmitter imbalance.

Psychiatric treatment has made great strides, particularly in the past several decades. Perhaps no advance is more clinicallly useful than our understanding of the determining role of nerotransmitter amines and the modulating role of immunology and eznyme metabolism on perception, mood, behavior, and mental health. The insight and clinical studies of histamine metabolism and pyrrole metabolites by Carl C. Pfeiffer, Ph.D., MD represent fundamental threads of the unfolding biologic psychiatry tapestry.

Much clinical overlap exists among the biologic dispositions to the schizophrenias. Yet the fundamental insight that Pfeiffer pioneered of a biologic trigger for many schizophrenics remains a landmark advance in diagnosis and clinical management.

A clinician's view, with emphasis on management of schizophrenia and other mood disorders is presented. The role of advanced diagnostic tests in clarifying patient needs and monitoring therapy is emphasized. Special attention is paid to what such tests mean for individual patients and how to improve therapy based on test results.

The Schizophrenias can be differentiated based on:
1) histamine chemistry (high, e.g., histadelia, and low, e.g., histapenia),

2) mauve factor (urinary pyrrole metabolites),
3) functional essential cofactor deficiencies or excesss, and,
4) immunology, particularly gluten, lactalbumin or other CNS-active immunogens.

The depressions can be differentiated based on the pattern of neurotransmitters in platelets and urine as well as the status of regulating enzymes.

Since various drugs, both prescription and recreational, can induce thought disorders, a careful history is essential to management of these disorders. A therapeutic trial discontinuing any suspect medicine is in order along with any other therapy.

PATIENT-CENTERED PSYCHIATRY

Health – mental and physical – depends upon proper feedback and balanced function in our cells. The major known regulators of cell function are:

- neurotransmitters,
- endorphins and related peptides,
- interleukins/cytokines
- prostaglandins,
- hormones,
- cations (Mg^{2+}, $Ca^{2+,}$, Na^{+}, K^{+})

These depend upon amino and fatty acids and sterol dietary sources and proper enzyme function which itself depends upon adequate balance of essential biochemical cofactors. We are fortunate to now have dynamic, functional, biochemical tools available in psychiatry. Proper diagnostic testing and therapeutic follow-up can improve patient prognosis in gratifying and cost-effective ways.

Your attention is called to our evolving understanding of biochemical/immunologic therapies. Our understanding is rapidly evolving. **Clinically useful studies or "We don't call medicine a 'practice' for nothing."**

The most important studies in differentiating among the schizophrenias and mood disorders such as depression are those of neurotransmitters (histamine being a useful representative), essential enzyme activators (cofactors), and lymphocyte (immune) responses.

Neurotransmitters regulate nerve information transmission which, in turn, is essential for brain function. Laboratory procedures that give clinically useful information about brain and CNS function from easily obtained blood and urine platelet or platelet and urine neurotransmitters and

their metabolites provides insight into brain and CNS chemical function based on easily obtainable samples.

Neurotransmiiter imbalance occurs when amino acid precursor supply is inadequate. Precursor deficit can occur either from a primary lack of amino acid substrate or a secondary lack due to a cofactor deficiency or inhibitor (toxicant) leading to enzyme inhibition in a step required for synthesis or degradation of the neurotransmitter. A defect in the storage and release of neurotransmitters can lead to consumption of the compound in excess of physiologic ability to replace the chemical.

Essential cofactors convert inert protein or glycoprotein structures (proenzymes). Brain and CNS function depend upon adequacy of neuroelectric function. Dysfunction can occur through:

1) absolute or proportionate deficiency of essential cofactors,
2) the presence of competitors or inhibitors that uncouple interrelated cell energetic systems,
3) reduced cell energy pools that lead to inefeficient use of essential cofactors.

Lymphocyte responses are representative of immune system function. Our humoral (antibody/opsonin) and cellular (granulocyte, lymphocyte, monocyte) immune system is responsible for defense against foreign invasion, routine repair, and interorgan communication. Especially when a hyperpermeable blood to brain barrier exists, there can be cerebral responses to neuroimmunologic stimulation.

Disordered responses of the immune system can impair neuropsychiatric function through alterations in cell electrical resting membrane potential, through complement-mediated tissue swelling altering the fine architecture of susceptible brain neural networks, and through alterations in the blood to brain permeability (barrier) itself.

This can occur through:

1) antibody attack of myelin or other nerve structure,
2) immune complex damage to nerves,
3) immunologically triggered release of neuroregulating chemicals,
4) invasion of the brain by lymphocytes and peripheral monocytes when the blood-brain barrier becomes permeable or leaky.

CONCLUSIONS

1) Some brain function, perception, and mood states are now known to depend upon essential biochemical factors from which neurotransmitters derive and immunologic modulation is regulated.
2) Laboratory tests now exist for evaluating individual patient status of essential control chemicals and immune system response. Properly interpreted results have clinical and therapeutic relevance in some cases.
3) Therapeutic use of essential biochemicals is different from avoiding deficiency disease. Individual requirements can be monitored either clinically or based on laboratory assays, examples of which are given above.
4) The patient's best biochemical function is a primary step in psychiatric management of the depressions and the schizophrenias.
5) Substantial benefit for many people can be had through advanced biochemical/immunologic management of schizophrenics and mood disorders such as depression.
6) This approach is low risk and potentially high gain for both physician and patient.
7) This approach is cost-effective and appropriately utilizes scarce resources.
8) Abnormalities in essential biochemicals and immune responses may be clinically important, amenable to treatment and identifiable based on recent advances in laboratory techniques.

Biochemical immunology provides a molecular biologist's view of the matrix from which the schizophrenias and other mood disorders such as depression express themselves.