Kryptopyrroles

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Several years ago my attention focused on kryptopyrroles and I soon found that in my clinical practice kryptopyrroles occurred as part of a quintet of signs and symptoms that emerged from treating nervous diseases.

Kryptopyrroles were first discussed as a mauve factor occurring in urine of nervous patients in the writings of Abram Hoffer, M.D., Ph.D. and Humphry Osmond, M.R.C.S., D.P.M. in their studies and theories of schizophrenia over two decades ago. They noted that the mauve factor occurred frequently in the urine of schizophrenic patients. This led them to doing a controlled study of 920 patients who suffered from a number of neuropsychiatric disorders.

Since that time Carl C. Pfeiffer, Ph.D., M.D. has found the mauve factor of kryptopyrrole to occur in five percent of normal persons that he tested. Dr. Pfeiffer modified and simplified the testing for the mauve factor and I shall refer to this method as the long method. Subsequently a more convenient qualitative determination of urinary kryptopyrroles was reported by Bauer, Ackerman and Toro with the use of an ultraviolet lamp. This method I shall refer to as the short method. In either method it is important that the urine is free of or negative for urobilinogen and any other factor that would interfere with the colorimetric findings that are qualitatively determined. To use the short method the urine must be tested immediately because kryptopyrroles are readily oxidized or degraded.

A few years ago I decided to make a comparative evaluation between the long and short methods of determining urinary kryptopyrroles (Appendix A). The patients were selected from both my psychiatric and general practices. I determined the long and short levels of urinary kryptopyrroles on 172 patients and found in 165 that the findings by the two methods correlated by both methods giving positive findings. Of the remaining six cases five were negative by the short method while the long method showed either a trace, +1, or +2 reaction and in one instance there was a +2 reaction by the short method while the long method was negative; therefore, the accuracy of detecting a positive mauve factor or kryptopyrrole in the urine by the short method as compared to the long method was 96 percent effective; so I stopped using the long method and have

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Table 1
Causes of Schizophrenia

Diagnosis	No. Examined	% who have factor
a. Normal subjects	60	0
b. Subjects physically ill		
1. Adults	100	10
2. Children	100	10
c. Neurotic subjects	200	20
d. Alcoholics	40	40
e. Schizophrenics		
1. No treatment at any time and illness present less than 1 yr.	100	75
2. Treated successfully	40	0
3. Treated unsuccessfully (mostly chronic patients from mental hospital)	200	50
f. Mental retardation		
1. Physically normal	20	50
2. Physically abnormal	20	0
g. Alcoholics after LSD	40	35

From *How To Live With Schizophrenia,* A. Hoffer, M.D., Ph.D. and H. Osmond, M.R.C.S., D.P.M. University Books 1974.

only used the short method since. Since then I have found positive kryptopyrroles in over 350 patients' urine, so I would say that porphorinuria is not uncommon. Donald Irvine et al. and later Arthur Sohler identified the mauve factor or kryptopyrrole as 2, 4-dimethyl-3-ethylpyrrole, a coproporphy-rin. Coproporphyrin is a tetrapyrrole and the quantity excreted in the urine is normally minute but increased in the porphyrinuria diseases.

In doing physical examinations on these patients with positive urinary kryptopyrroles, I found tenderness to pain over the suprarenal area when I palpated the abdomen. I found that in order to elicit this sign the patient must be relaxed and lying in a supine position with the legs flexed and the feet on the examining table. The abdomen must be approached with more than a superficial or moderate dexterity of palpation if the deep tissues are to be appreciated. This finding is in the absence of renal disease which would confuse the issue.

The reference that gave me a clue to this finding was found in the book An Endocrine Interpretation of Chapman's Reflexes. Dr. Chapman described a tender reflex area for the adrenal gland as occurring one to two and a half inches above and on either side of the umbilicus. With some patients the tenderness or pain is noted more superficially in the abdominal muscles, but all of the patients have deep visceral tenderness to pain. It should not be surprising that a swollen gland is tender to painful on palpation.

Selye demonstrated that the adrenal glands become swollen when activated by stress. In observing this phenomenon I have noted that the left adrenal appears to become more sensitive than the right and sometimes it is only tender over the left suprarenal. Sometimes in palpating these tender areas there is a dramatic defense or response of the patient because they have never been aware of this painful organ in the deep visceral area. Another correlating physical sign is the congestion and contracture of the myofascial tissues of the lower dorsal area of the spine with restriction of motion of the musculoskeletal system. This may be easily appreciated or understood by remembering about the viscerosomatic reflexes. The adrenals have splanchnic en-nervation originating from the lower thoracic and upper lumbar spinal cord segments. The sympathetic preganglionic fibers are

from the intermediolateral columns of T-10, 11, 12 and L-l and communicate to the homolateral sympathetic trunks and traverse by the greater, lesser, least and first lumbar splanchnic nerves and then to the celiac ganglions and on to the adrenal gland. The parasympathetic supply may be by the posterior nerve fibers that follow similarly. Some fibers may come from the vagus via the celiac plexus of nerves.

In looking over the list of symptoms of the patients with adrenal soreness and krypto-pyrroles in the urine, I found the following signs and symptoms: progressive loss of ambition, decreased school grades, poor concentration, poor memory, fatigue, hyperactivity, anxiety, depression, psychosis, musculoskeletal pains, headaches, migraine, dizziness, insomnia, vasomotor reactions, allergies, decreased libido and potency, digestive and bowel dysfunction. In doing laboratory work-ups on these patients I noted that frequently they had glucose intolerance and allergies. Most of the allergies involved food and air borne substances.

Diagnostic classifications of these patients included schizophrenia, minimal brain dys-function, chronic myofascitis, arthritis, depression, anxiety, stress reaction, alcoholism, allergies, epilepsy, hypoglycemia, cirrhosis or liver dysfunction.

In reviewing a group of 67 patients, krypto-pyrrole was paired with hypoglycemia 31 percent of the time and when paired with allergy it was 36 percent of the time. Fifty percent of the group showed both hypoglycemia, adrenal soreness, and kryptopyrroles in the urine. This information is from an early study before I had been particularly observant and careful in palpating for adrenal soreness. In a more recent survey of 35 cases with relevance of kryptopyrroles, adrenal soreness, glucose intolerance, allergies and nervous disorder, 97 percent showed abdominal adrenal soreness with positive kryptopyrroles, 88 percent showed glucose intolerance, 80 percent showed allergies, and 94 percent showed some degree of psychological decompensation ranging from personality change to frank anxiety, depression or psychosis (Table 2).

Table 2

Pt. Chief Complaint	**Symptoms**	G	Kp	**Abd**	**Al**	Nv
# 1 allergies, chest pains, headaches, dizziness	faintness, aches and pains, nasal congestion, chills, subnormal temperature, fatigue, abdominal pains	+	+	+	+	+
# 2 obesity	fatigue, nervousness, depression, irritability, forgetfulness, brown skin spots, headaches, insomnia, indecis-iveness, sweet craving, alcohol	+	+	+		+
# 3 dizziness, headaches	altered vision, chills, allergic rhinitis, hoarseness, tinnitis, nausea, belching, hot flashes, aches, pains, chills, feverishness, fatigue	+	+	+	+	+
# 4 depression, weakness	abdominal pains, insomnia, altered bowel function, impotency, poor concentration	+		+		+
# 5 arthritis, lower and upper back pains	tension, fatigue, weakness, abdominal pains	+	+	+	+	+
# 6 asthma, arthritis, nervousness	wheezing, difficulty breathing, aches, pain, stiffness, abdominal pains	+	+	+	+	+
# 7 skin trouble, hives	allergy, fatigue, pain, aches, pruritis, nervousness	+	+	+	+	+
# 8 dizziness, insomnia, nervousness	anxiety, poor concentration, allergy, hay fever	+	+	+	+	+

		KRYPTOPYRROLES					
Pt. Chief Complaint	**Symptoms**	G		Kp	**Abd**	Al	Nv
# 9 decrease in school work, poor attention (MBS)	irritability, fatigue	+	+	+	+	+	
#10 nervousness, depression	insomnia, abdominal pains, flatulence, fatigue, poor concentration	+	+	+	+	+	
#11 epilepsy, mental retardation	hyperactive, irritability, rages, inability to walk	+	+		+		+
#12 fainting, fatigue, headaches	irritability, weakness, depression, abdominal pains	+	+	+	+		+
#13 mental retardation, nervousness, asthma	poor attention span, lack of concentration, nasal congestion, headaches, wheezing	+	+	+	+		+
#14 dizziness, headaches, lower and upper back aches	backaches, nasal congestion, allergies, nervousness, tension	+	+	+	+		+
#15 nervousness, allergies	nasal congestion, fatigue, chronic tiredness, irritability	+	+	+	+		+
#16 mental illness	confusion, lassitude, poor concentration, withdrawn, pains, chills	+	+	+	+		+
#17 moodiness, just don't feel good, can't control feelings, feelings of despondency	allergies, arthralgias, nervous breakdown 76, itchiness, photophobia, headaches, voice change, depression, crying, fears, personality change, nausea, poor bowel function	+	+	+	+		+
#18 pressure in my head, sore neck, lower back aches	allergy, altered vision, stiffness, belching, moodiness, myalgia	+	+	+			+
#19 allergies	nausea, sneezing, asthma, abdominal pains	+	+	+	+		
#20 shoulder and backache	abdominal pains, fatigue, stiffness pruritis, insomnia	+	+	+	+		
#21 depression, can't function	insomnia, irritability, moodiness withdrawn, alcohol		+	+			+
#22 muscular aches, stiffness, arthritis	dermatitis, allergies, abdominal pains, indigestion, chills, cough, asthma, nervousness	+	+	+	+		+
#23 memory loss	poor concentration, poor memory and attention, school failure		+	+			+
#24 lower back pains, leg pains	allergies, glucose intolerance, insomnia, headaches, myalgias, pruritis, tinnitis, hoarseness, asthmatic dyspnea, nausea, gas, abdominal pains, fatigue, moodiness, crying, depression, fear, stiffness	+	+	+	+		.+
#25 headaches	arthritis, insomnia, migraine, sinusitis, chest & abdominal pains, otitis, fatigue, myalgias, leg cramps, cold hands & feet, fears, depression, crying, alcohol, moodiness	+	+	+			+
#26 weakness	allergies, asthma, high blood pressure, edema, fatigue, obesity, indigestion, sinusitis, nervousness	+	+	+	+		+
#27 pains in the back and in the kidney area	obesity, stiffness, migraine, hoarseness, chest pains, nausea, depression	+	+	+	+	+	

Pt. Chief Complaint	Symptoms	G	Kp	Abd	Al	Nv
#28 general malaise, headaches, arthritis	high blood pressure, obesity, migraine, eye troubles, dizziness, hoarseness, abdominal & chest pains, nausea, sinusitis, gas, myalgia, moodiness, depression, feverishness, chills, urinary frequency, decreased potency, fatigue	+	+	+	+	+
#29 pains and aches, miserable	photophobia, headache, dizziness, hay fever, myalgias, stiffness, cold feet, edema, fear crying spells, depression, fatigue, poor appetite, diarrhea	+	+	+	+	+
#30 headaches, lassitude, weakness	abdominal & chest pains, lack of concentration, hypotension, dizziness, moodiness, withdrawn	+	+	+		+
#31 Backache for several years	poor concentration, nervousness, insomnia, chest pains, myalgia, nausea, alcohol	?	+	+	+	+
#32 fat	tinnitis, headaches, depression, sinus disease, moodiness, gas, dyspepsia, feverishness, chills, myalgias, weight change	+	+	+	+	+
#33 backaches	fatigue, hay fever		+	+	+	
#34 lassitude, repeated "virus infections"	weakness, loss of ambition, allergies	+	+	+	+	+
#35 hypoglycemia, generally not feeling well and feeling weird, nervousness	poor circulation, abdominal pains, nausea, myalgias, digestive disturbance	+	+	+	+	+
		31	34	34	28	33

Symbols

G - glucose intolerance Kp - kryptopyrrole Abd - adrenal soreness Al - allergies Nv - nervous

Just how to understand these mutually occurring signs and symptoms remained to be answered. My inquisitiveness led me to look more closely at the porphyrins and associated physiology.

The patients who showed kryptopyrroles in their urine are considered to be suffering from porphyrinuria, which brings us to the consideration of porphyrin diseases. It is here that I started to synthesize an understanding of the pathophysiology that might account for the signs and symptoms that I have been seeing clinically. Current literature on the porphyrin diseases offered little, and essentially stated only that these diseases are a disorder of the heme metabolism (Fig. 1). There is no mention of adrenal dysfunction which appears to me to be part of the picture in the light of my physical findings. Thirty years ago very little was mentioned in the medical literature on porphyrin disorders, except that porphyrin was made by union of pyrrole groups and that it was a result of disturbance of heme metabolism (Fig. 2). In 1964 Thompson and King reported that there are, aside from acute and congenital forms, constitutional forms of porphyrinuria. Etiologies are given as chemical, (such as heavy metal and other intoxicants) idiopathic (essentially unknown causes), and systemic disease. Ten years ago Best and Taylor reported more by stating that porphyria may be characterized by abdominal, nervous and mental symptoms and that allows for a broad scope of symptomatology. Recently in

Scientific American Medicine porphyrias are discussed and defined as a diverse group of syndromes caused by defects in the synthesis of iron-porphyrin heme complex. Porphyrinurias are seen with a multitude of signs and symptoms in the patient that include photosensitivity, skin lesions, acute attacks of pain of various types and often abdominal, psychotic states or episodes, neurological signs, gastrointestinal disturbances, liver disease, and excretion of pigment precursors in the stool and urine. Generally there are two groups: erytho-poietic and hepatic. Under the heading of less rare forms, the hepatic group, there are sub-groups. All are believed to be involved in the heme metabolism and the biochemical basis for the symptomatology has not been understood.

In acute porphyrinuria there are increased amounts of coproporphyrin produced. The metabolic abnormality does not appear usually until early adulthood and the primary defect is assumed to be in the central nervous system. The condition is genetically determined and could be due to an enzyme deficiency, either causing a blockage in the conversion of porphobilinogen to porphyrins and hemes in the liver or associated with an excessive availability of d-aminolevulinic acid and of porphobilinogen in the body. Normally two molecules of ALA condense to form PBG that is polymerized to form two 4-pyrroles which leads to heme and uroporphyrinogens. ALA synthetase is the regulatory enzyme along with the heme feedback control. This may be interfered with by heavy metals and toxins. Some of the components are activated by the complement system, which may account for the allergic connection. If for some reason the rate of production of acetyl co-enzyme A were limited, the resulting deficiency of acetylcholine could interfere with the transmission of nerve impulses, and larger quantities of succinyl co-enzyme A might react with glycine to form ALA (d-aminolevulinic acid). The precise mechanism and reasons for variations is not known but as there are various symptoms manifested in these diseases, it must be assumed that there are types of deficiencies and treatment is symptomatic (Fig. 3).

Figure 1.

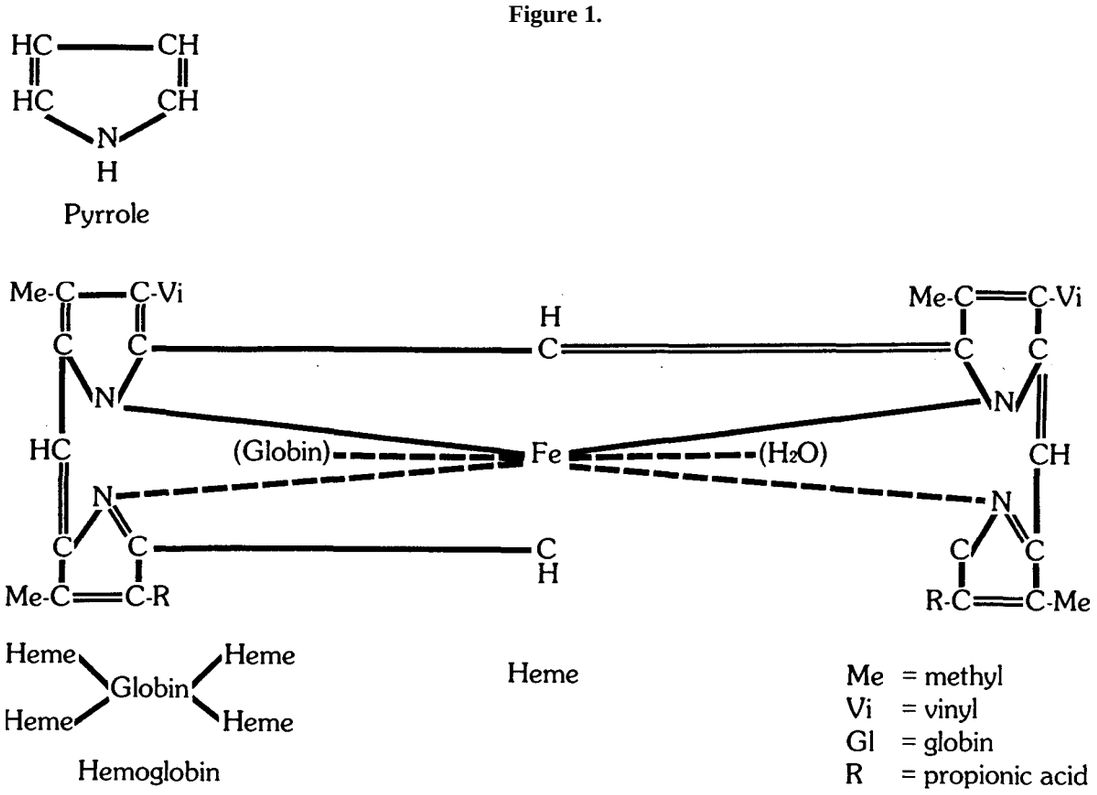


Figure 2.

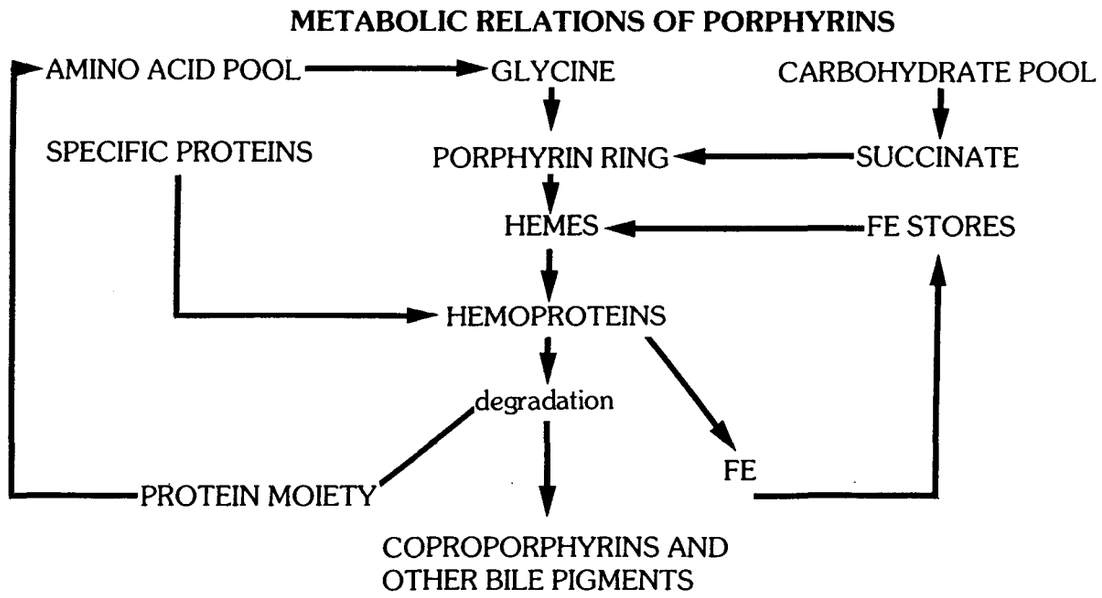
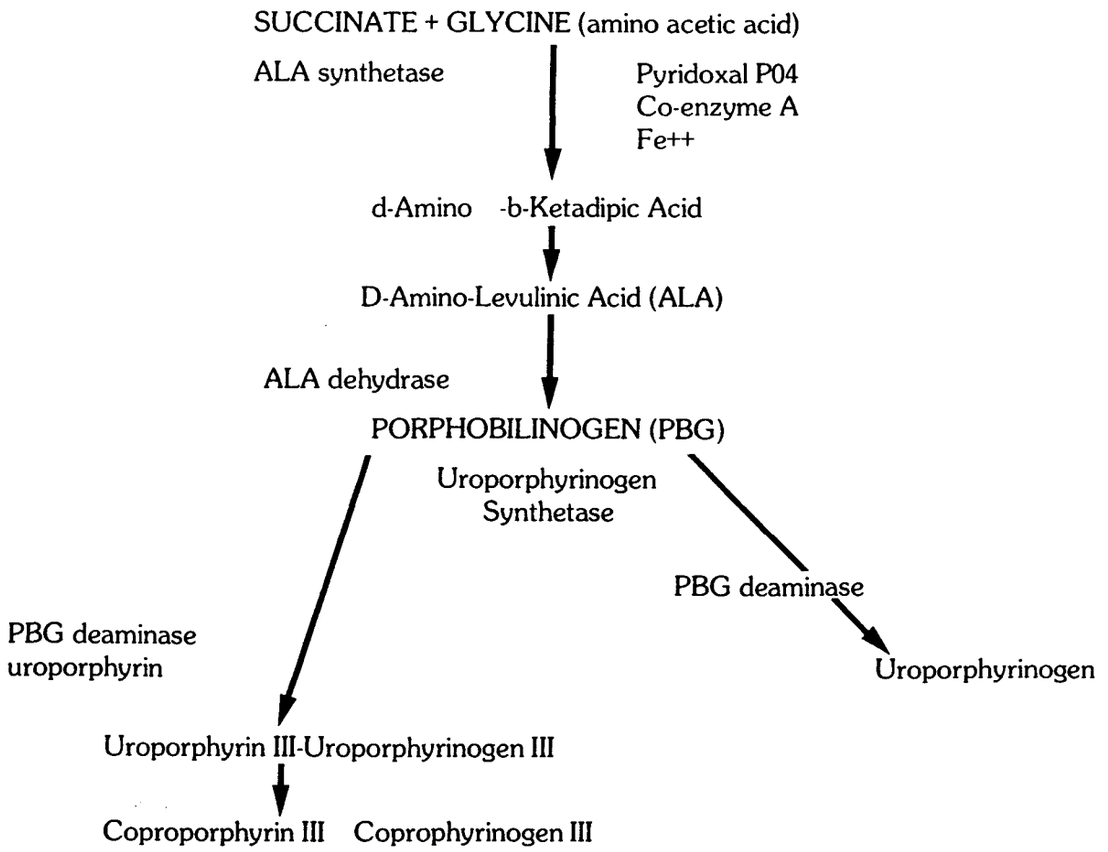


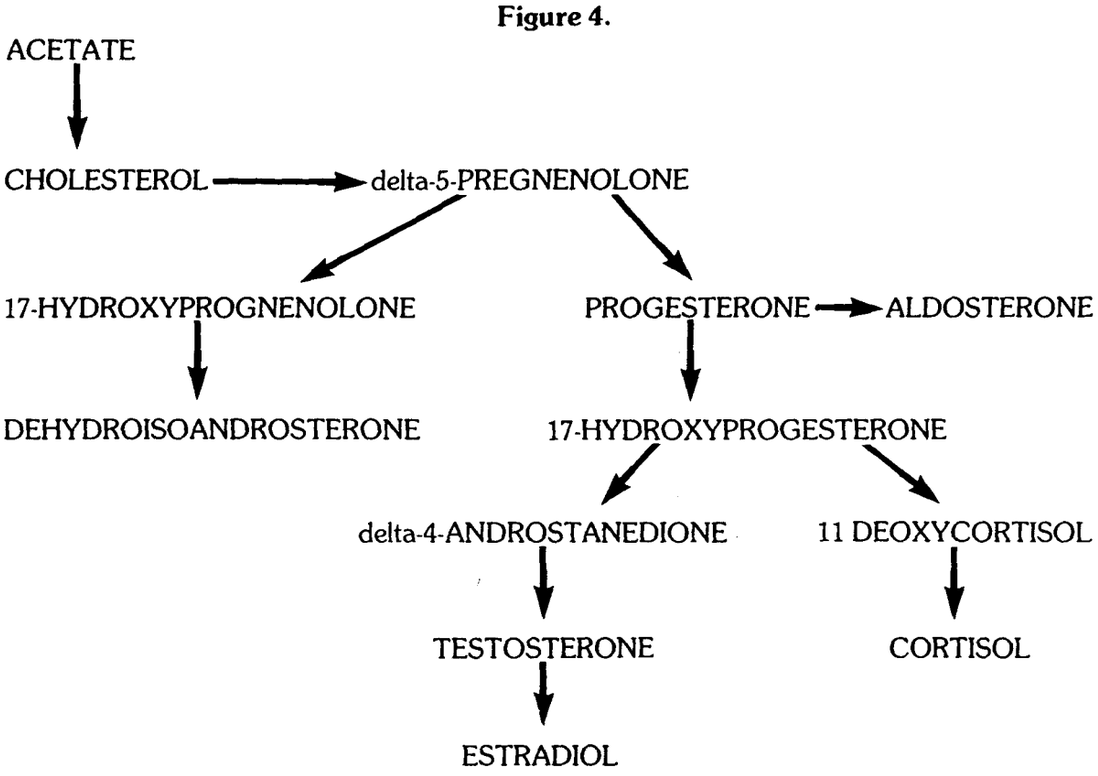
Figure 3



In an effort to better understand the occurrence of the mauve factor or krypto-pyrroles in the urine and in respect to adrenal function, I turned to the work of Abram Hoffer and Humphry Osmond who did considerable work on catecholamine metabolism in respect to Psychopathology. From their studies the adrenochrome-adrenolutin theory of psychiatric disorders evolved. If the catecholamine theory is to be pursued, it is reasonable to look into the production of the biochemicals involved.

The adrenals have a broad scope of influence on the endocrine system in addition to the metabolic processes of the medulla and cortex by effectively influencing the immune reactivity, blood cell formation,

Figure 4.



CORTEX BIOSYNTHESIS OF STEROIDS

cerebral functions, protein synthesis, liver metabolism, and other processes (Fig. 4).

From acetate and cholesterol a number of steroids are produced by the influence from the hypothalamic-pituitary axis on the adrenals. The catecholamines biosynthesis takes place in the adrenal medulla. The process starts with phenylalanine which is oxidized to tyrosine enzymatically (Fig. 5). Tyrosine is converted into dihydroxyphen-ylalanine (DOPA) by tyrosinase and then into hydroxytyramine (Dopamine) that is converted by a hydroxylase to norepinephrine. The latter is transformed to epinephrine by a methylating enzyme. These flow through the cortex into the blood stream. Norepinephrine predominates in all extra-medullary catecholamine tissues. The three major catecholamine neurotransmitters are: dopamine, norepinephrine, and serotonin. These are monoamines. Serotonin, an indolamine, is formed from tryptophan being decarboxylated into 5-hydroxytryptamine (Serotonin) (Fig. 6). Norepinephrine is found in high concentration in the ventro-medial nucleus of the hypothalamus; dopamine is high in concentration in the median eminence.

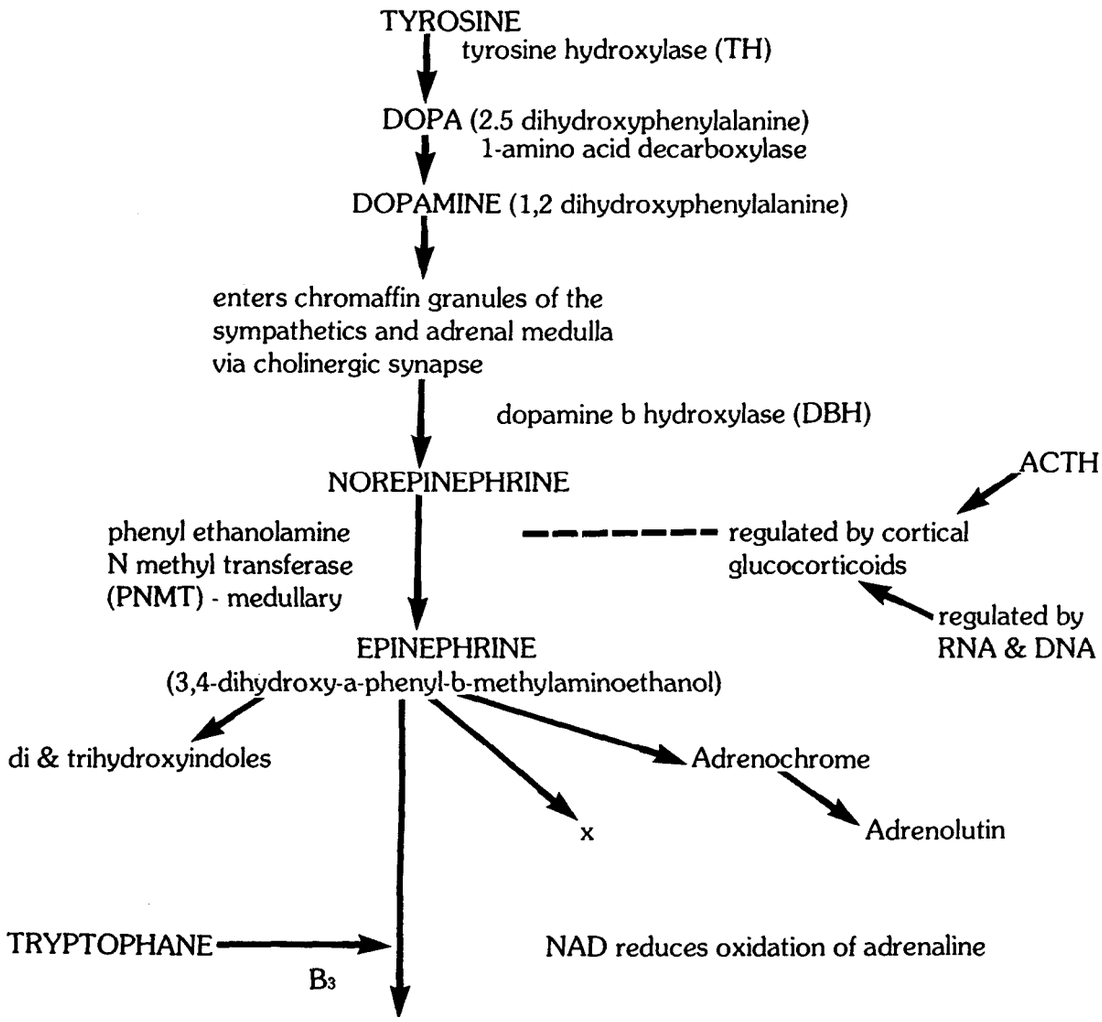
Adrenaline may become a toxic substance adrenochrome which can be converted into 5,6 dihydroxy-N-methylindole (leucoadrenochrome). Vitamin C exerts effective influence on this to block toxic adrenolutin.

Since excess adrenaline can be prevented from being converted into norepinephrine by nicotinic acid, B3 can help prevent high levels of adrenochrome and adrenolutin from forming. Vitamin C and glutathione also block the methylation of adrenaline into these toxic substances i.e., adrenochrome and adrenolutin.

Norepinephrine represents 10 percent to 30 percent of the total catecholamines. Norepinephrine is oc 3-4-dihydroxy-phenyl-B-aminoethanol and the levo form is more effective or active than the dextro form. Adrenaline is 3,4-dihydroxy-oc-phenyl-B-methylaminoethanol and the levo form or isomer is 15 times more potent than the dextro form. If noreadrenaline is methylated it becomes adrenaline.

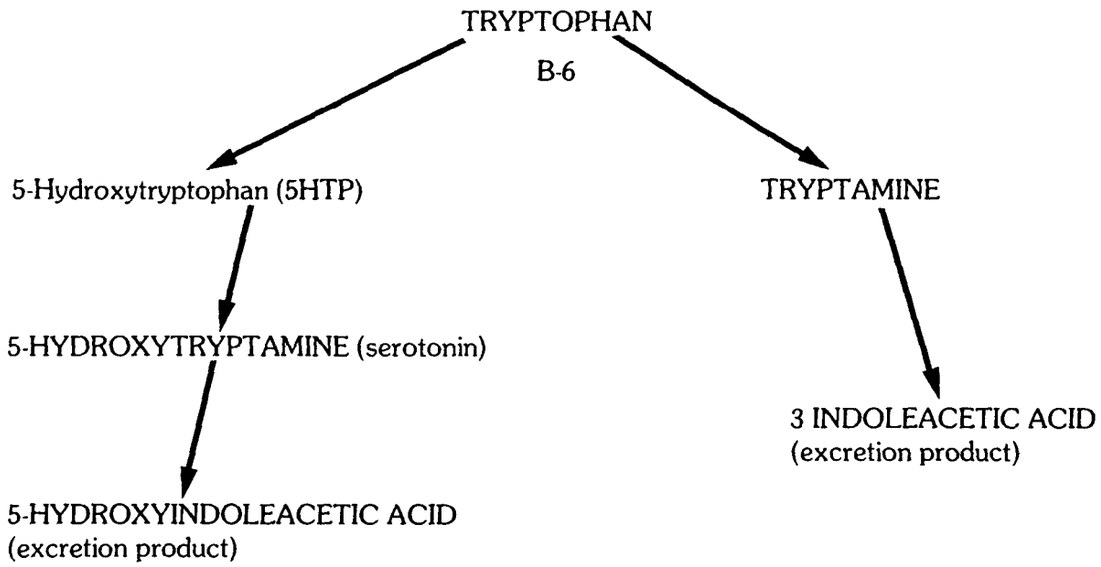
Funkenstein did considerable work with adrenaline and nonadrenaline in respect to psychiatric patients and concluded that the emotionally disturbed continued to have high levels of catecholamines even when not under stress. He showed that an increase in psychomotor activity occurred with a relative increase of catecholamines and a decrease in activity with a decrease in catecholamine levels.

Figure 5.



KRYPTOPYRROLES

Figure 6.



Metabolic pathways of Indoleamines

OTHER NEUROTRANSMITTERS: ACETYLCHOLINE
GABA (a-amino butyric acid)
HISTAMINE
PEPTIDERGICS
enkephalins
beta endorphins
neurotensin

SEROTONIN

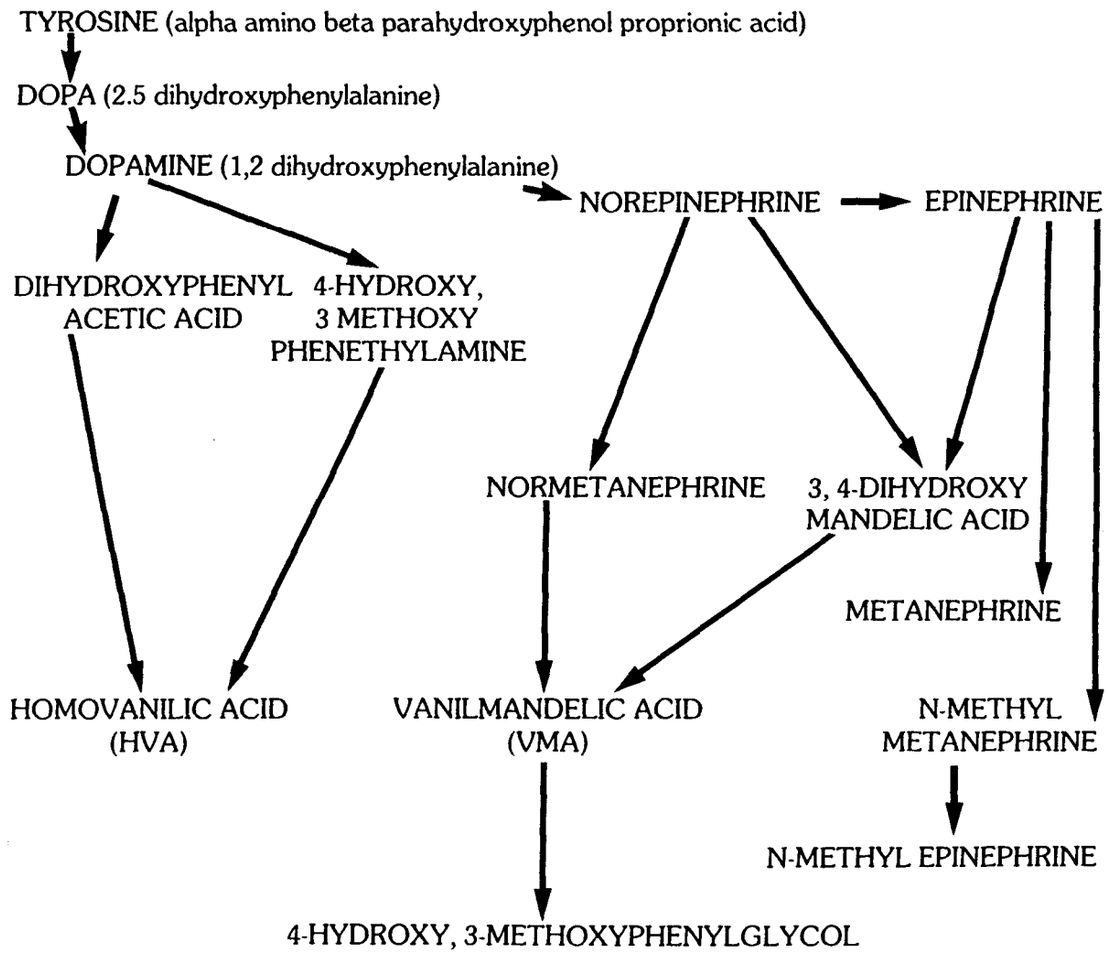
To bring together, or tie together, the heme, catecholamine, and methylation theories so as to shed understanding on the involvement of the adrenals attention is given to the works of Cannon, Selye, Funkenstein, Osmond and Hoffer, and others on their considerations on neuroendocrine and enzymic studies.

Hoffer and Osmond postulated the adrenochrome-adrenolutin theory when they found that adrenaline is oxidized to adrenochrome and then to adrenolutin. Adrenolutin is toxic and has been shown to produce psychotic reactions in people. Normally adrenochrome is transformed into leuco-adrenochrome (5, 6 dihydroxy-N-methyl-indole) which breaks down into pyrroles. Normally there is only a small amount of coproporphyrin in the urine, but in porphyrinuria or porphyria the amount is increased. This may be explained by the marked increase in adrenaline under stress. Cannon demonstrated epinephrine (adrenaline) is elaborated in response to stress years ago in his fight-flight theories on adaptation to stress. The human stress reaction evokes corticosteroid excretions. The stress may be by psychological, biochemical or physical means. It has been found that some patients undergoing stress have high Cortisol levels or production rates, particularly being noted in acute psychosis

and some depressive conditions where the defense mechanisms have not been effective. It has also been noted that stress lowers the testosterone levels. In stress the adrenals may double or quadruple the production of adrenaline.

Cannon demonstrated physical and emotional disturbances triggered the same stress response and as the adaptive mechanisms occur, especially by repeated exposure to stress, it takes a marked toll on the sympathetic neuroendocrine system. It is at this point that Selye's theories can be appreciated in the alarm reaction with the triad of lymphatic involution, gastrointestinal ulceration, and a loss of adrenal cortical lipoids and chromaffin biochemicals. In Selye's second stage of resistance, the adrenals enlarge regaining the lipoids while the medulla shows cellular vaculozation. With prolonged stress the exhaustion stage occurs with symptoms seen in the first stage. The adrenal medulla is actively involved in the catecholamine metabolism. These amines are formed from the amino acids l-phenyl-alamine or 1-tyrosine to form dopamine, noradrenaline and adrenaline. The inactivation of adrenaline results in the urinary metabolite 3-methoxy 4 hydroxy-mandelic acid (vanillylmandelic acid, VMA) (Fig. 7). The biological inactivation of adrenaline occurs by amine oxidation and catechol-O-methyl transferase. Noradrenaline is metabolized by the transformation to met-

Figure 7.



METABOLIC PATHWAYS OF THE CATECHOLAMINE NEUROTRANSMITTERS

anephrine and subsequently to VMA in the urine, which normally occurs in small amounts in the urine. A great deal of epinephrine is found in red blood cells — not in plasma or serum — and this can be readily catalyzed (methylated) to adrenochrome.

In respect to carbohydrate metabolism, adrenaline causes hyperglycemia and is antagonistic to insulin. This effect also occurs with noradrenaline but to a lesser degree. With this mobilization of glucose from the liver the glycogen stores are reduced. The muscle glycogen is also reduced and follows the Cori Cycle. Under stress or stimulation of the splanchnic nerves, the pressor output of amines is greatly increased, which may partly account for tissue protein decrease with stress. As stress continues the adaptation may be inadequate with fatigue ensuing. Stimulation of areas of the hypothalamus, mid-brain, and medulla cause signs and symptoms of adrenal medullary stimulation. Emotional excitement is a strong stimulus to the sympathetics and adrenal medullary activity. The pressor effect of this splanchnic stimulation requires the synergistic activation of acetylcholine, the mediator of impulses at all autonomic ganglia, all parasympathetic postganglionic terminations, sympathetic postganglionic endings at sweat glands and motor nerve endings in striated muscle.

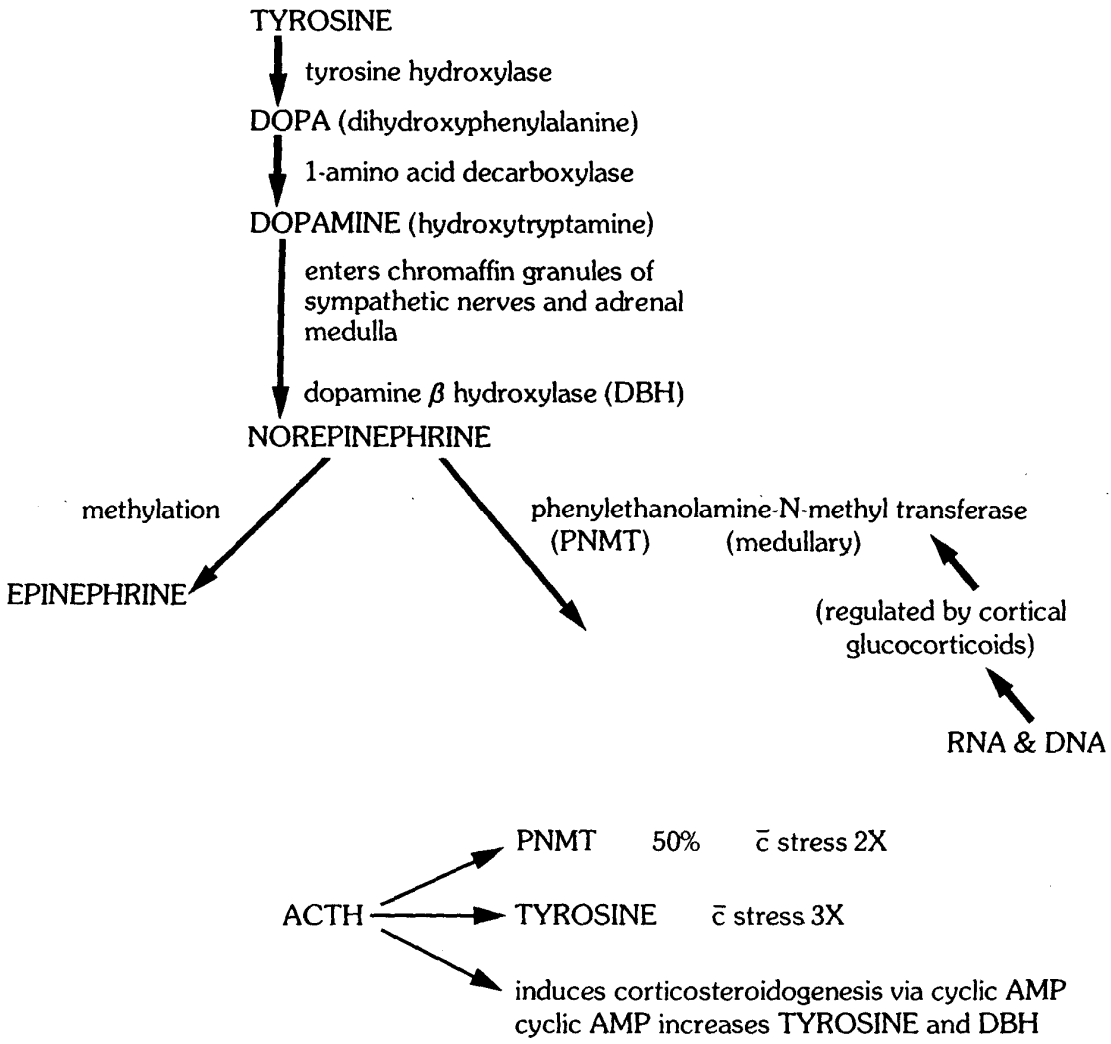
Norepinephrine is the neurotransmitter released from sympathetic nerve endings. In the extra chromaffin tissues norepinephrine is the only catecholamine. Under stress there is an increase in glucocorticoids by the adrenocorticotropic hormone of the pituitary gland from activation of the hypophysis and brain stem, i.e. hypothalamus.

Wurtman and Axelrod have given evidence that there is a functional relationship between the adrenal medulla and the adrenal cortex by phenylethanolamine-N-trans-ferase (PNMT) which is regulated by glucocorticoids produced in the cortex. Involved in this synthesis of PNMT by action at the level of RNA transition from DNA, PNMT is increased by 50 percent with stress and the tyrosine hydroxylase level increases threefold. Tyrosine is converted to dopa (1-3,4 dihydroxyphenylalanine) by tyrosine hydroxylase (TH), then 1-aminoacid decarboxylase rapidly decarboxylates dopa to
dopamine which enters the chromaffin granules of the sympathetic system and adrenal medulla where it is converted to norepinephrine by phenyl ethenolamine N methyltransferase (Fig. 8).

Friedhoff and Van Winkle have demonstrated that giving dopamine by infusion causes an increase in urinary 3,4-dimethoxy-phenylacetic acid in the urine. They also showed that a liver homogenate from a person with a positive DMPEA produced DMPEAA from dopamine and S-adenosyl-methionine. In porphyria, in the absence of inborn errors of metabolism, there are increased amounts of coproporphyrin I excreted in the urine indicating hepatic impairment. In hepatic porphyrin disease, whether hereditary or acquired with toxic agents, contains coproporphyrins I and III and their precursors are in the liver. The chemicals that provoke porphyria stimulate cytochrome synthesis in the liver thereby increasing the demand on heme: however, the capacity for heme synthesis appears to be limited by various enzyme defects as well as a home feedback mechanism on ALA synthetase. In the synthesis of hemoglobin RNA for protein synthesis, enzymes of the Krebs Cycle, and glycolysis are required. Functions of the liver include: conversion of protein to glucose (occurs only in the liver). deamination, glutamic acid transfer to pyruvic acid (glutamic acid inhibits glycolosis in the brain), transmethylation conversion of homocystine to methionine (the methyl group is furnished by choline and betaine), synthesizing of amino acids as glutamic and aspartic, the synthesis of protein requires energy derived from carbohydrates and fat of the oxidative catabolism first to ATP, and ATP free amino acids in the cytoplasm are enzymatically coupled to ATP and then become attached to RNA.

The porphyrin ring is synthesized from glycine, succinic acid, and one carbon fragment (formate) derived from glycine. Decarboxylation of the acetate side chains to methyl groups results in coproporphyrin. Philpott has described another mechanism for CNS dysfunction by the methylation process. Starting with methionine there may be a deficit in the methylation to cystine and homocysteine may be converted to homocystine which is a toxic substance. A

Figure 8.



Hypoglycemia releases catecholamines by a brain sensor

STRESS AND TYROSINE

deficiency of pyridoxal phosphate (B6), B3, B12, folic acid, zinc, manganese and/or magnesium can disrupt the methylation process. The pyridoxal phosphate is the prosthetic group or co-enzyme for mediating amino acid transfer. Homocysteine is found in fibroblasts, lymphocytes, brain and liver.

Clinicians working with allergies and sensitivities have noted that when patients are under stress their allergies and sensitivities to pollens, toxic substances and other antigens worsen. This may be understood in respect to stress on the adrenal glands with more demand placed on the cortical and medullary functions. I have noted that the adrenal soreness, that I have alluded to earlier, becomes worse when the patient is under stress and when the patient is better and not under stress the soreness wanes. In addition to seeing this in the allergic patient, I have seen this in the patients with glucose intolerance. Another factor to note that calls attention to the

importance of the adrenals in allergies is that in the use of corticosteroids there is a resolving of allergic symptoms and signs. We have seen both psychological and physical signs and symptoms in patients suffering from allergies.

More than a decade ago Dr. Carl Pfeiffer noted that vitamin B6 compensated for the apparent metabolic disorders that led to kryptopyrroles appearing in the urine of some patients. The amount varies with the individual biological state of the patient and the dosage range may be from 400 mg to 3,000 mg a day in divided doses. Here it is in order to review vitamin B6 which may be in the form of Pyridoxine, pyridoxal phosphate, or pyridoxamine phosphate. Pyridoxal phosphate and pyridoxamine phosphate are versatile co-enzymes participating in over fifty known enzymic reactions in which amino acids or amino groups are transformed or transferred. An example is pyridoxal phosphate being required as a coenzyme in the transamination reactions in which the alpha amino acid group of an amino acid is transferred to the alpha carbon of an alpha keto group acid. In this manner the amino acid group of L-alamine in the presence of alamine transaminase transfers the amino group to alpha ketoglutaric acid to form L-glutamine and pyruvate (Fig. 9). During the metabolic conversion of tryptophan by acetyl coenzyme A and the enzyme kynureninase to 3-hydroxyanthran-ilic acid pyridoxal is required and pyridoxal phosphate or large amounts of L-kynurenine (pyrrole ring) are excreted in the urine. This step is critical in the biosynthesis of nicotinic acid. Pyridoxal phosphate plays an important function in hemoglobin synthesis as a co-factor in forming a precursor to porphyrin. B6 plays an important role in the central nervous system. A deficit causes convulsions and uncontrolled excitement. Dr. Allan Cott has used B6 successfully in treating hyperactive and retarded children.

B6 is required for the synthesis of GABA, an inhibitory neurotransmitter. Pyridoxal phosphate is a prosthetic group of a number of enzymes which act upon amino acids, especially amino acid decarboxylases and the transaminases including that which is found in the erythrocyte. It is a co-factor with the enzyme kynureninase that metabolizes
kynurenine and 5-hydroxykynurenine to anthranilic and 5-hydroxyanthranilic acids with the latter going to form niacin or nicotinic acid.

Pyridoxine is required for the synthesis of porphyrins from delta aminolevulinic acid. Iron enters the porphyrin molecules to form hemoglobin, so a B6 deficiency leads to anemia with high serum iron levels. In alcoholics a deficiency is common because the liver is impaired for absorption of ethanol, crippling the breakdown of pyridoxal phosphate from food to Pyridoxine for absorption. Ethanol also causes a marked depletion of hepatic B6. Pyridoxal phosphate is required in the methylation processes of the catecholamines. B6 as pyridoxal phosphate decarboxylates amino acids transforming tryptophan to niacin or serotonin. Pyridoxine is required for the utilization of protein for energy. B6 is active in the synthesis of porphyrins for hemoglobin and in the synthesis of antibodies and tetra hydrofolic acid that is essential for the synthesis of RNA and DNA.

B6 is required for the synthesis of gamma aminobutyric acid (GABA)

B6 is a cofactor with the enzyme kynureninase.

B6 deficiency impairs the body to make glycine.

B6 is needed for porphyrin synthesis from delta aminolevulinic acid.

B6 is required for the prevention of neuropathies, skin disease and problems of the immune system, which are worsened by increasing protein intake.

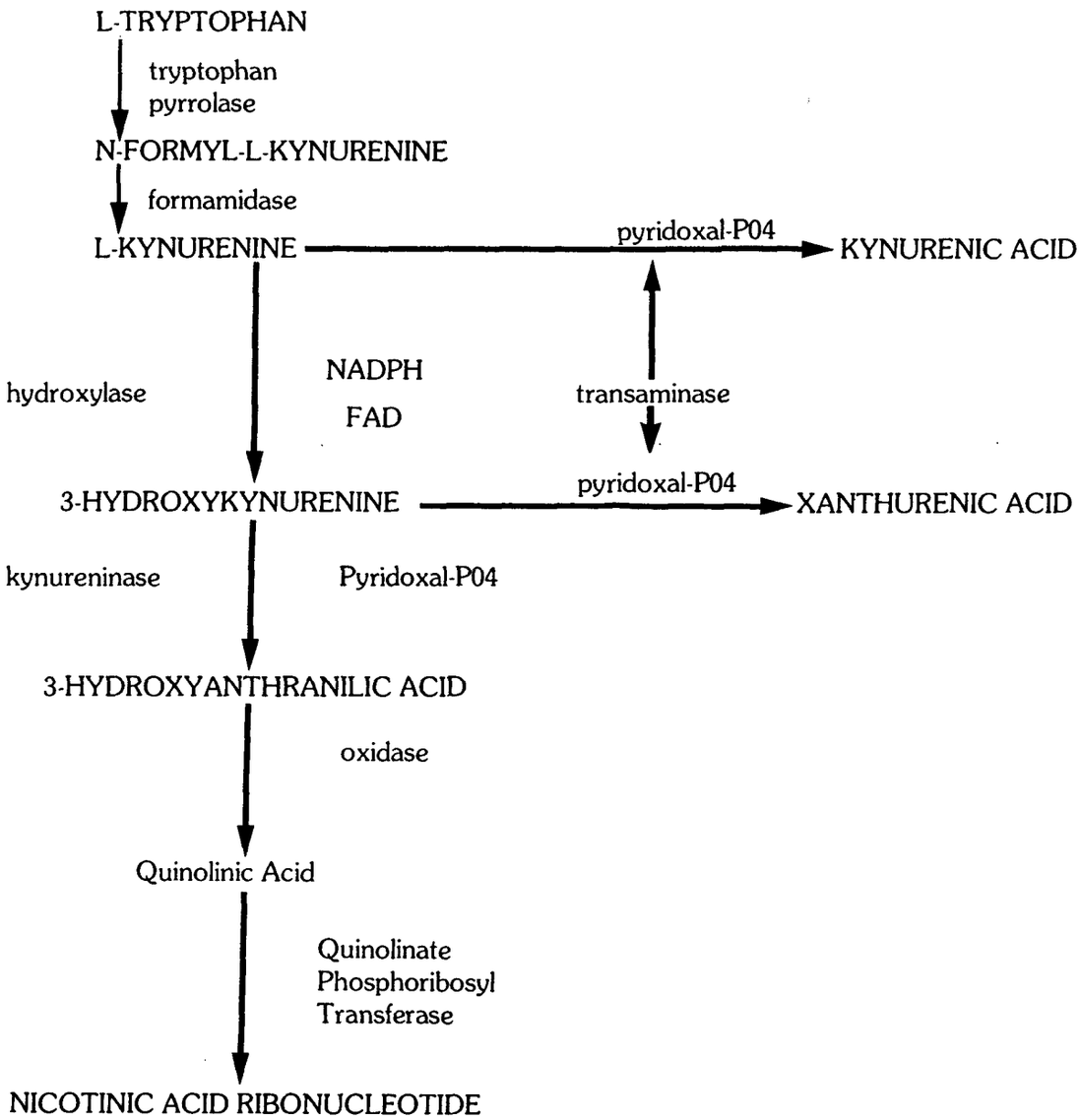
B6 levels are decreased by anemia, contraceptive pills, aging, G I disease, alcoholism, cirrhosis, uremia, Down's Syndrome and immunosuppressant diseases.

B6 is required for steroid hormones.

B6 requirements are increased in hyperthyroidism.

Contemporary medicine only recommends supportive treatment for patients suffering from porphyrin diseases, but bearing in mind what I have covered in this paper it is rational to use vitamin B6 as a specific treatment for those who show kryptopyrroles in the urine and perhaps for other forms of porphyrin diseases. I have successfully treated the patients that I have included

Figure 9.



Involvement of B-6, B-2, and B-3 in conversion of Tryptophan to Nicotinic Acid Micronutrient Interactions, Levander and Cheng, 1980, page 81

in this study with megavitamin doses of B6 so that the occurrence of kryptopyrroles in the urine was remarkably diminished or completely eliminated. This was along with symptomatic improvement with obvious reduction of signs and complaints. I've noted that when these patients are under stress, the need for increasing the dosage of B6 arises or there is a breakthrough of kryptopyrroles occurring in the urine with return of some of the symptoms complained of. Because I have found that allergy plays a

part in this picture, I have treated the allergy as part of the regime. Vitamin C has been useful for countering the histamine and facilitating detoxification. Other vitamins and minerals have been used for support of the adrenal function. Under extreme stress I have used adrenal extract and/or corticosteroids such as prednisolone 5 to 15 mg per day. Manipulation has been of value because with the correction of somatic correlates the patient is given a sense of relief and well being to a greater or lesser degree. Medications are used with respect to the specific complaints and diagnosis. For example, if a patient is suffering from depression, an antidepressive medication is used. If the major problem appears to be allergy, antihistamines are used. In the case of arthralgias, arthritic medication is used. There is a necessary customization of the medicinal regime.

Summary

There are a number of signs and symptoms that have gone unexplained that include somatic, visceral and neuropsychiatric areas. The patients with these maladaptations showing tenderness to pain over the adrenals, kryptopyrroles in the urine, glucose intolerance, allergies and psychiatric symptoms correlate under consideration of porphyrin disease.

Pathophysiology that may be involved was reviewed.

These patients may gain relief from the signs and symptoms when adrenal function is taken into account and supportive measures are instituted using measures that include adrenalcortical extract, steroids, vitamins (B6, B3, Pantothenic acid, Ascorbic acid,) and minerals (Zinc, Manganese), avoidance of refined foods and allergens as well as other toxic agents such as heavy metals.

In the clinical setting kryptopyrroles are readily tested for by a short method. With this method and the use of physical examination for adrenal soreness or pain, the progress of the patient may be monitored along with the evaluation of other signs and symptoms. Treatment for some porphyrin disease therefore may be more than just symptomatic but rather physiologic.

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APPENDIX A

METHODS OF DETERMINING KRYPTOPHYRROLES IN THE URINE

The first method is by a modification by C.C. Pfeiffer and it is a qualitative determination (long method).

This requires the urine collection container to be containing 1 to 2 grams of ascorbic acid and the patient voids directly into the container. This is required if the urine is not tested immediately.

The laboratory procedure is as follows:

1. Place 3 ml. of urine in a glass test tube. Add 3 ml. chloroform and stopper. Shake for two minutes.
2. Centrifuge for 5 minutes. Remove the top (aqueous) layer with a dropper and discard.
3. Add approximately 200 mg. anhydrous sodium sulfate. Shake briefly. If the liquid is not water-clear, add an additional 200 mg. and repeat the shaking. If the solution is not clear by this time, no more sodium sulfate will help. Ignore the cloudiness.
4. Place 2 ml. of the chloroform extract into a clean test tube and add 0.5 ml. 1% p-dimethyl-aminobenzaldehyde solution. Shake briefly.
5. Allow mixture to stand for 30 minutes.
6. Kryptopyrroles are determined by estimating the depth of the pink or mauve color as 0, trace, +1, +2, +3 or +4. A trace is barely detectable tinge.

Preparation of the 1% p-dimethylaminobenzal-dehyde solution is as follows:

1. In a graduate place 45 ml. of absolute methanol.
2. Slowly with mixing add 2.5 ml. concentrated sulfuric acid.
3. After the mixture has cooled, add additional methanol to make the volume up to 50 ml.
4. Add 0.5 grams of p-dimethylaminobenzal-dehyde. Stir until dissolved.
5. Store in a brown bottle away from light.

Note: The p-dimethylaminobenzaldehyde solution should be dated because the full strength is valid only for one week.

The short method or ultraviolet method that I used omitted the use of ascorbic acid in the urine collection container because I tested the urine immediately in the office promptly after the patient gave me a fresh specimen; otherwise, the collection procedure should be the same as in the long method.

The laboratory procedure is as follows:

1. Check the urine or urobilinogen. Over +4 will give false positives.
2. Fill two test tubes with 10 ml. of urine (approximate)
3. Add 10 drops of Ehrlich's Reagent to one tube. The second tube is for comparison.
4. Allow to stand for ten minutes.
5. Kryptopyrroles are now determined by viewing both test tubes at an oblique angle when they are placed in front of an ultraviolet light and estimating the pink or mauve color as 0, trace, +1, +2, +3, +4. A +1 is distinct reddish-violet when no urobilinogen is present.

Preparation of Ehrlich's Reagent is as follows:

1. To 50 ml. of distilled water add 50 ml. concentrated hydrochloric acid.
2. Add 2 grams of p-dimethylaminobenzalde-hyde. Mix to dissolve.
3. Store in a brown bottle in the refrigerator. Date this for full strength is only for about one month.

Note: Besides urobilinogen (cherry-red), other substances which may cause false positives are phenazopyridium (bright red), formaldehyde (yellow), bilirubin (greenish-yellow), and indole (red).

It is very important that the testing is done on fresh specimens and tested immediately.