

# The Revised Monoamine Theory of Depression: A Modulatory Role for Monoamines, Based on New Findings From Monoamine Depletion Experiments in Humans

G. R. Heninger<sup>1</sup>, P. L. Delgado<sup>2</sup>, D. S. Charney<sup>3</sup>

<sup>1</sup>Department of Psychiatry, Yale University and The Ribicoff Research Facilities of the Connecticut Mental Health Center, New Haven, CT USA

<sup>2</sup>Department of Psychiatry, University of Arizona, Tucson, AZ, USA

<sup>3</sup>Department of Psychiatry, Yale University and The West Haven Veterans Administration Medical Center, West Haven, CT USA

The original hypothesis that brain monoamine systems have a primary direct role in depression has been through several modifications during the past 30 years. In order to test this hypothesis and more fully characterize the role of serotonin and catecholamines in the pathophysiology of depression and the mechanism of action of antidepressant treatments, our research group has conducted a series of studies evaluating monoamine depletion induced brief clinical relapse following different types of antidepressant treatment of depressed patients. We have also studied the effects of monoamine depletion (SD) on depressive symptoms in depressed and recovered patients off medication and in healthy controls. Relapse to serotonin depletion or to catecholamine depletion (CD) was found to be specific to the type of antidepressant treatment, i.e., patients responding to selective serotonin reuptake inhibitors relapsed more frequently following SD than CD and patients responding to selective catecholamine reuptake inhibitors relapsed more frequently following CD than SD. Neither CD or SD increased depressive symptoms in clinically ill patients off treatment, or produced clinical depression in normal controls. However, recovered patients with a prior history of depression had a relapse with SD. Patients with obsessive compulsive disorder who improved on SSRI treatment, did not have an increase in OCD symptoms but those with prior depressive symptoms did have an increase in depressive symptoms with SD.

The findings that relapse during treatment is specific to the type of treatment and type of depletion, that neither SD or CD produced an increase in clinical depression in healthy controls or depressed patients off medication, and that recovered patients off medication have a return of symptoms following SD, forces a major revision of the current monoamine theories of depression. The new hypothesis most consistent with this new data is that the monoamine systems are only modulating "other" brain neurobiologic systems which have a more primary role in depression. The modulatory or "antidepressant" function of the monoamine systems appears to be only necessary during drug induced recovery and the maintenance of recovery after a prior episode. These clinical studies point to the need for more fundamental research on the interaction of monoamine systems with other brain neurobiologic mechanisms relevant to depression.

During this 30th anniversary year of the Anna-Monika Foundation, it is indeed fortunate that important new data is available which allows a revision and extension of the original monoamine hypothesis of depression. One of the first awards given by the Anna-Monika Foundation was for a paper entitled, "Norepinephrine Metabolism and Psychoactive Drugs in Endogenous Depression", which delineated some aspects of the monoamine hypothesis of depression (Schildkraut et al., 1968). That paper concluded: "the basic and clinical findings, moreover, are compatible with (but do not definitely establish) the catecholamine hypothesis of affective disorders, which proposes that some, if not all, depressions may be associated with a functional deficiency of norepinephrine at noradrenergic receptors in brain, while elations may be associated with excess of this amine". The functional deficiency of noradrenergic transmission in depression was inferred from the effects of imipramine-like drugs and monoamine oxidase inhibitors (MAOI) on catecholamine (CA) metabolism, since both of these types of drugs increase CA at adrenergic receptor sites. During these early years, evidence was also accumulating on the important role of serotonin (5HT) in affective disorders and a general hypothesis was put forward that depression was associated with a deficiency in the transmission within the monoamine systems (Bunney and Davis, 1965; Schildkraut, 1965; Coppen, 1967). Research in the late 1960's and early 1970's, provided partial support for the monoamine hypothesis of depression and this led to a more differentiated and complex hypothesis that there were two types of depression with differences in biochemical and pharmacologic properties (Mans, 1975). The lack of definitive evidence in cerebral spinal fluid of lower monoamine metabolites in depressed patients, the variable findings of monoamine metabolic excretion rates in body fluids, including plasma and urine, and the emerging basic pharmacologic studies in laboratory animals of antidepressant drug effects on receptor sensitivity, provided the evidence that supported a new hypothesis, that changes in monoamine receptor sensitivity were an important central aspect of the mechanism of action of antidepressant treatment (Sulser et al., 1978; Charney et al., 1981). In the following years there were a number of studies demonstrating that antidepressant treatment (ADT), indeed, was affecting monoamine receptor sensitivity in depressed patients; however, these studies did not provide evidence of a single or simple common mode of action across the various ADTs (Heninger and Charney, 1987).

NO  
Common  
MODE

One of the more important aspects of the monoamine receptor sensitivity hypothesis of antidepressant drug action involves the slow desensitization of the 5HT<sub>1</sub> receptor subtypes that inhibit 5HT release a progressive decrease in sensitivity of these receptors following selective serotonin reuptake inhibitor (SSRI) or MAOI treatment reduces their inhibitory effects and results in increased 5HT release at terminals. Tricyclic drugs such as desimipramine (DMI), produce an increase in 5HT receptor sensitivity at postsynaptic sites. Thus, all 3 types of drugs work to augment overall 5HT transmission (Blier and de Montigny, 1994). These studies have been extended with investigation of adrenergic alpha-2 heteroreceptors on 5HT nerve terminals where drugs such as mirtazapine, which blocks the inhibitory alpha-2 receptors on 5HT terminals, are thought to work by increasing 5HT release (de Montigny et al., 1995). The original monoamine hypothesis of affective disorders and its modification with the receptor sensitivity hypothesis of depression both presuppose a direct and predominant role for increased monoaminergic function in producing the antidepressant response. However, other neurobiologic factors must be involved in addition to monoamine transmitter levels, since MAOI plus tryptophan treatment very rapidly increases brain 5HT levels and although more efficacious than MAOI alone, this treatment does not produce an immediate rapid antidepressant response (Glassman and Platman, 1969).

In order to evaluate the importance of monoamine metabolism in depression and the mechanism of action of ADTs in depressed humans, we have utilized the method of depleting brain monoamine levels by reducing monoamine synthesis through manipulations of monoamine precursor pathways. Specifically, a tryptophan-free amino acid drink (AA drink) has been shown to dramatically reduce plasma tryptophan levels, which in laboratory animals studies has been demonstrated to markedly reduce brain 5HT and cerebral spinal fluid 5-hydroxyindolacetic acid (Moja et al., 1979; Young et al., 1976).

For catecholamine depletion, alpha-methyl-para-tyrosine (AMPT) is utilized to block the synthesis of 3,4-dihydroxyphenylalanine (DOPA) which is the common precursor in the synthesis of norepinephrine and dopamine.

The AA drink was previously used to lower plasma tryptophan in the study of mood effects in healthy male subjects. In these healthy male subjects a marked reduction in plasma tryptophan only resulted in very mild increases in dysphoric mood without producing clinical depression (Young et al., 1985; Smith et al., 1987). However, in contrast, when the 5HT synthesis inhibitor parachlorophenylalanine (PCPA) was given to depressed patients recently improved on antidepressant treatment, it can be seen in Table 1 that in all of the four patients treated with the MAOI, tranylcypromine, and the two patients treated with imipramine, there was a relapse with increased depressive symptoms following the PCPA. Three additional patients treated with imipramine did not have a relapse follow-

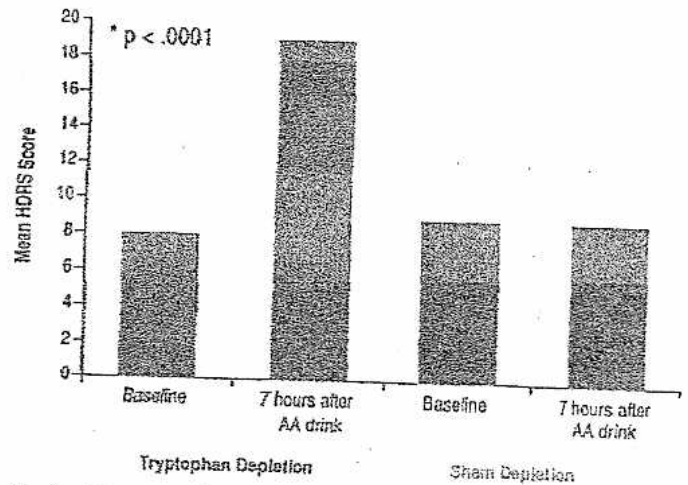


Fig. 1 Mean Hamilton Depression Rating Scale (HDRS) Scores (25 item scale) of 21 patients who had recovered while taking various antidepressant medications. HDRS baseline ratings obtained at 9 a.m. 24 hrs. before and 7 hrs. after the amino acid drink (AA drink) was administered.

\*P<.001 Paired t test, baseline vs. 7 hrs. after AA drink (Adapted from Delgado et al., 1990).

ing AMPT given up to 3.5 grams per day (Shopsin et al., 1975, 1976). These earlier studies by other investigators suggested that the use of the AA drink to produce SD might be a useful method to investigate the role of 5HT in depression and the mechanism of action of ADTs.

Effects of Serotonin Depletion in Recently Recovered Depressed Patients

In initial pilot studies we found that a 24 hour period of a low tryptophan diet augmented the plasma tryptophan lowering effects of the AA drink. Using this procedure an initial study was conducted in 21 recently remitted, depressed patients receiving different types of antidepressants. Total and free tryptophan levels decreased 87 and 91 percent respectively following the AA drink. It was found that 14 of the 21 patients had a relapse following the AA drink but not following a sham drink, which had tryptophan included in it. Relapse was defined as an increase in depressive symptoms so that the 25 item Modified Hamilton Depression Rating Scale (HDRS) increased by at least 50% and was greater than or equal to 17. The magnitude of these changes is illustrated in Figure 1. When evaluating the relationship between type of drug treatment and magnitude of relapse, it appeared that patients treated with the catecholamine reuptake inhibitor (CRI) desimipramine (DMI) were least sensitive to relapse, while patients treated with SSRI's (fluoxetine or fluvoxamine), had a moderate amount of relapse, and patients treated with MAOI

Ongoing treatment	Number relapsed/ number tested	Percent relapsed	Days until relapse	Days until recovery after pcpa stopped	Adapted from reference
Tranylcypromine	4/4	100%	1-4	2-7	Shopsin et al., 1976 Shopsin et al., 1975
Tranylcypromine	2/2	100%	1-3	2-3	

Table 1 Inhibition of serotonin synthesis by parachlorophenylalanine (pcpa) produces a return of depressive symptoms in patients who have responded to antidepressant treatment.

DA  
↓  
NE

HDRS  
↑ 50%  
? /  
SMA

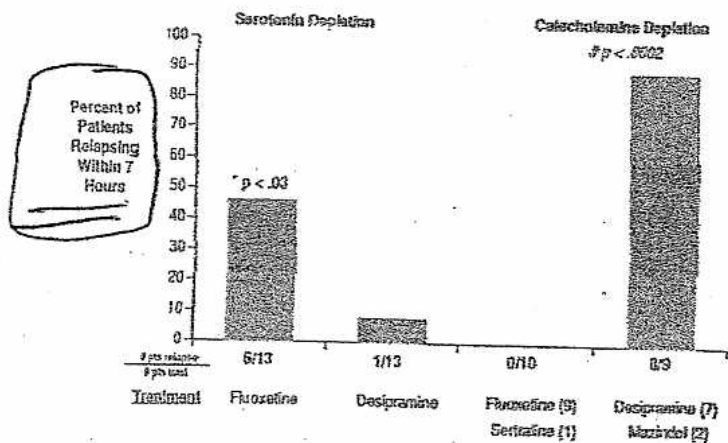


Fig. 2 The amino acid drink without tryptophan was used to produce serotonin depletion. Alpha methyl paratyrosine was used to produce catecholamine depletion. A greater than 50% increase in HDRS score and a score of 18 or greater was categorized as a relapse. \* = P < .03 Fishers Exact Test, Fluoxetine vs. Desipramine. # = P < .0002 Fishers Exact Test Fluoxetine and Sertraline vs. Desipramine and Mazindol. (Serotonin depletion adapted from Delgado et al., 1991 and Personal Communication, Delgado et al., 1995. Catecholamine depletion adapted from Miller et al., in press, a.).

were much more vulnerable to relapse. However, as listed in Table 2, it can be seen that the patients treated with SSRI also had a moderate degree of past history of treatment refractoriness, and the patients treated with MAOI had a much more severe past history of treatment refractoriness. Thus, it was not clear whether the past history of treatment refractoriness or type of drug treatment mainly contributed to the different relapse rates seen in Table 2.

Table 2 Type of antidepressant treatment and relapse during tryptophan depletion.

Type of antidepressant	Number relapse/ number tested	Percent relapse	Degree of prior treatment refractoriness
Desipramine	2/11	18%	None
SSRI	10/16	63%	Mild-Moderate
MAOI	6/6	100%	Severe

SSRI: Fluoxetine and Fluvoxamine, MAOI: Tranylcypromine and Phenelzine. (Adapted from Delgado et al., 1990 and Delgado et al., 1991a).

Number patients randomized to 2 treatments	Number patients responding	Prior number patients tested	Number of prior unsuccessful antidepressant trials	Mean Hamilton Ratings Baseline	Mean Hamilton Ratings highest rating 5 or 7 hrs. after depletion
DMI 22	15/20	13	None	8.7	9.4
FLU 21	15/18	13	None	7.8	12.4*

P < .02, Fisher's Exact Test, for number of patients with a greater than 5 point increase (i.e. DMI 0 of 13, FLU 5 of 13). Baseline rating obtained just prior to depletion. (Adapted from data in Delgado et al., 1991b and Personal Communication, Delgado et al., 1995).

Type of Antidepressant Drug Treatment and Vulnerability to Relapse Following Serotonin Depletion

In order to more thoroughly investigate the possibility that patients treated with SSRI's are more vulnerable than patients treated with CRI's as suggested in Table 2, a controlled study was conducted. Patients were randomized to either SSRI or CRI treatment and then when improved they ingested the AA drink. Table 3 summarizes the data from 43 drug free depressed patients who were randomly assigned to receive either fluoxetine (FLU) or DMI. All patients were either treatment naive (n=32) or had received previously successful antidepressant treatment (n=11). The therapeutic response of the two groups was essentially the same (DMI 15/20: FLU 15/18). Thirteen DMI responders and 13 FLU responders went on to AA drink testing. It can be seen in Table 3 that the baseline of the HDRS prior to depletion, was slightly higher for the DMI patients, but that they had a smaller mean increase in ratings than the FLU treated patients. The FLU treated patients had a mean increase of 4.6 as compared to the increase of 7 for the DMI treated patients. This data indicate that the differential response between SSRI's and DMI following SD (as seen in Table 1) is indeed related to the type of drug treatment.

Type of Antidepressant Drug Treatment and Vulnerability to Relapse Following Catecholamine Depletion

In order to evaluate the corresponding question of whether maintenance of the antidepressant response is dependent on adequate CA function, patients responding to either SSRI or CRI treatment were studied following AMPT. In Table 4, it can be seen that there was little difference in age or prior treatment refractoriness in the 9 patients who had recovered on CRI's vs. the 10 patients who had recovered on SSRI's. However, there was a much larger increase in the return of depressive symptoms following AMPT in the patients treated with CRI (an increase of 12.8) compared to the patients treated with SSRI's (an increase of 1.1). Thus, in contrast to SD which appears relatively more specific in producing relapse in patients treated with SSRI's than a CRI, the opposite relationship was found with CD where patients responding to CRI's are more vulnerable than patients responding to SSRI's.

Relationship of Relapse Rate to Type of Treatment and Type of Depletion

In Figure 2 the relapse rate is illustrated for the patients whose data is presented in tables 3 and 4. It can be seen that with serotonin depletion (SD) nearly half of the FLU treated patients relapsed but less than 10% of the DMI treated patients

Table 3 A controlled evaluation of tryptophan depletion in patients responding to desipramine compared to patients responding to fluoxetine.

RESPONDERS  
2 AA relapse



relapsed. With catecholamine depletion (CD) none of the 10 SSRI treated patients relapsed while nearly 90% of the SCRI treated patients relapsed. These data indicate that recently recovered patients on SSRI's are selectively vulnerable to SD while similar patients recently responding to CRI are selectively vulnerable to CD. Thus, during the antidepressant induced recovery process there appears to be a specific and selective dependence on adequate function of specific the monoamine system involved in the treatment.

Effects of SD and CD on Depressed Patients off Medication

In order to evaluate whether the magnitude of depressive symptoms is directly related to either 5HT or CA levels, a large number of patients have been studied who were clinically depressed and who have been off all ADTs for at least two weeks. In Table 5 the results of the studies are summarized. In the 43 depressed patients studied with SD there was no mean increase in HDRS compared to the day these same patients received a sham-control AA drink. Similarly in the 17 depressed patients off medications studied with AMPT treatment, there was no mean increase in the HDRS compared to the active placebo treatment with diphenhydramine. Thus, the data in Table 5 presents strong evidence that the magnitude of the depressive symptomatology during the depressive episode is not related to either 5HT or CA levels. There were many patients in these studies who had Hamilton Ratings between 20 and 25 indicating that the absence of an effect of the depletions was not due to the possibility that the HDRS could not increase.

Serotonin Depletion in Recovered Patients off Medication

In Figure 3 the results of the AA drink given to 10 patients who had a clinical remission following light therapy are presented. Patients all met criteria for recurrent major depressive episodes with a seasonal pattern equivalent to seasonal affective

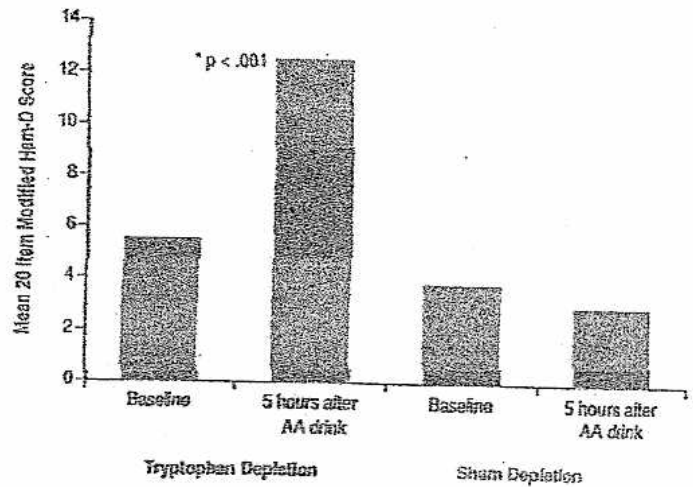


Fig. 3 Seven female and five male patients who had recovered from Seasonal Affective Disorder following light therapy, remission range, 3-7 weeks. \*P<.001. Paired t test 5 hrs. after tryptophan depletion compared to 5 hrs. after sham depletion. Six of 10 had a clinically meaningful relapse as indicated by a HDRS score over 12 with tryptophan depletion. None of the 12 had a HDRS over 12 with sham depletion. (Adapted from Lam et al., in press).

disorder. They were studied in winter. Following recovery with a score of less than 8 on the 21 item HDRS, they received either the tryptophan depleting AA drink or the sham-control drink while also continuing their morning light treatment. As can be seen in Figure 3, there was a clear, robust doubling of the HDRS scale following the AA drink with no change following the sham-control drink. This illustrates that relapse following serotonin depletion is not only dependent on prior drug treatments but also occurs following light treatment.

all  
3/2 weeks  
Depressed  
of HDRS  
No

10

Treatment	# Pts.	Mean age	Median number unsuccessful antidepressant trials	Median number prior depressive episodes	Mean Hamilton Ratings Pre AMPT Baseline	Mean Hamilton Ratings 24 hrs. after AMPT
Catecholamine uptake inhibitors	9	46	0	1	8.9	21.7*
Serotonin uptake inhibitors	10	40	1	0	4.8	5.9

\*P<.009, Students t Test, comparing the two types of treatment on change from PreAMPT baseline to 24 hrs. after AMPT. (Adapted from Miller et al., in press a).

Table 4 Catecholamine depletion produces a return of depressive symptoms in patients recently improved on catecholamine uptake inhibitors but not serotonin uptake inhibitors.

Depletion	Number patients	Mean Hamilton Depression Ratings just prior to depletion	Effects on depressive symptoms
Tryptophan	43	27	None*
Catecholamine	17	28	None

Table 5 Neither tryptophan depletion or catecholamine depletion produce changes in depressive symptoms in drug-free depressed patients.

\*The 16 patients (37%) whose mood improved the day following the test had a better longterm treatment response than the 10 tryptophan depletion patients (23%) whose mood worsened the day following the test (Tryptophan depletion adapted from Delgado et al., 1994 and Catecholamine Depletion adapted from Miller et al., in press b).

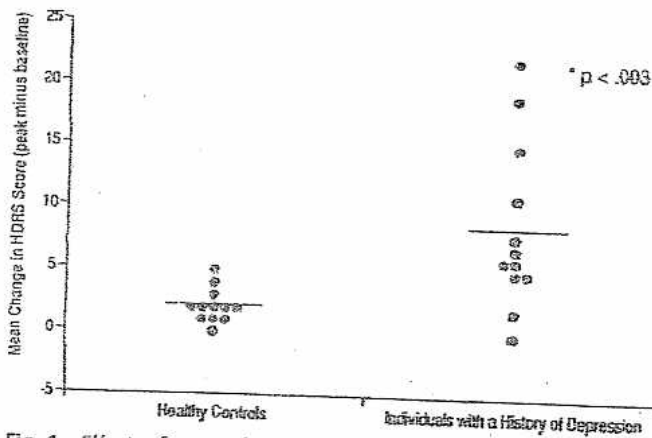


Fig. 4 Effects of tryptophan depletion in 12 individuals with history of depression: median 1-2 (range 1-5) prior episodes, median remitted 30 weeks (range 12-1040) and 9 of 12 had prior antidepressant treatment; compared to 12 healthy controls. Mean peak HDRS score at 5 or 7 hrs. after AA drink minus baseline. \* $P < .003$  students t test controls vs. individuals with past history of depression. 1 of 12 controls and 10/12 individuals with a history of depression had an increase of 5 or more HDRS points with tryptophan depletion (adapted from Moreno et al., 1995).

In order to evaluate the effects of serotonin depletion on patients who had recovered from a prior depressive episode but were off medication, 12 male and female patients with the median age of the onset of their depression in their mid-20's with the median of 1-2 prior episodes, who had been remitted from their prior episode median of 30 weeks, were studied with the AA drink procedure. All but 3 of the 12 patients had prior antidepressant trials. The mean HDRS prior to the AA drink was five. Patients were matched for sex and age to 12 controls whose mean HDRS prior to the AA drink was 1.3. It can be seen in Figure 4 that the individuals with a history of depression had an average increase of approximately 8 points on the HDRS compared to an increase of 2.4 for the healthy controls following the AA drink. It can be seen in Figure 4 that only one of the healthy controls but 10 of the 12 individuals with a history of depression had an increase of 5 or greater on the HDRS following the AA drink. The score for the three individuals who have never experienced ADP are 5, 6, and 7 points following the AA drink. These data indicate that individuals with a prior history of depression are vulnerable to relapse following serotonin depletion whether they have been treated with antidepressants previously or not (Moreno et al., 1995).

#### Effects of SD in Healthy Subjects

In Table 6, the results of six separate studies using the AA drink to produce SD are listed. It can be seen that in none of these 6 studies was there an increase in clinical depression reported. When more sensitive measures of dysphoric mood are used, such as an adjective check list, or the Profile of Mood States (POMS), or self ratings of happiness, the AA drink has been reported to produce mild increases in dysphoric mood or decreased ratings of happiness. The study of Benkelfat et al., (Benkelfat et al., 1995) of 19 men without a family history of depression and 20 men with a positive family history for depression is of interest. In this study, there was a mild increase in the POMS depression score in the family history positive

individuals following the AA drink. However, in neither subject group was there a significant increase in the HDRS and the change in the POMS depression score was not large or of clinical significance. Thus, the data in Table 6 on healthy subjects, indicates that SD following the AA drink does not produce clinical depression in healthy control males or females. It is of additional interest that AMPT does not produce depression in healthy subjects. However, following sleep deprivation (McCann et al., 1993) AMPT does increase POMS ratings of depression in healthy subjects (McCann et al., 1995). This suggests that when other brain abnormalities are produced in healthy subjects (e. g. through sleep deprivation) that monoamine depletion may have more direct effects on regulating mood.

#### Effects of SD on Drug Effects in Healthy Subjects

There is ample data from research on laboratory animals that the serotonin system interacts strongly with other neurotransmitter systems and can modify drug effects. In Table 6, the 3 studies listed, including the effects of morphine, yohimbine, and cocaine in volunteers, all indicate that the AA drink via SD is interacting significantly with these drug effects. It is of some interest that the AA drink did not effect pain tolerance in the cold pressor test but did significantly reverse the effects of morphine. In a similar way, there was a differentiation between the AA drink increasing subjective reports of nervousness following the anxiogenic drug yohimbine but it had no effect on yohimbine effects on cortisol or MHPG. The subjective report of high following intranasal cocaine was reduced by 20% following the AA drink but the cardiovascular response to cocaine was unaltered. Thus, these studies demonstrate selective effects of SD interacting with selected dimensions of drug effects in healthy subjects. Of major interest is the fact that following 48 hours of AMPT treatment, the AA drink which markedly depletes serotonin did not produce consistent increases in the HDRS or POMS depression scores in healthy subjects. Thus, the dual depletion of both CA and 5HT does not produce depression in healthy subjects, which demonstrates the resistance of these individuals to the effects of monoamine depletion. This contrasts to the relative sensitivity to monoamine depletion induced depression in individuals off medication with a past history of depression or who are on medication and recently recovered from depression.

#### Effects of SD in Other Non Depressed Psychiatric Diagnostic Groups

In the lower part of Table 6, four studies are listed where the AA drink has been administered to non depressed psychiatric patients. It is of considerable interest that patients with obsessive compulsive disorder (OCD) who have had a good clinical response to treatment with SSRIs do not have an increase in OCD symptoms with SD. Thus, the OCD symptomatology is apparently regulated by a neurobiologic system separate from those systems that regulate the depressive symptoms. This is even further validated by the fact in these exactly same patients, the patients with a prior history of depression who had depressive symptoms in conjunction with their OCD, did have an increase in depressive symptoms following the AA drink. It is also of interest that OCD patients who are off medications do not have a return of anxiety symptoms or panic attacks following the AA drink. In contrast, patients with bulimia nervosa who have been off medication, have an increase in ratings of

Table 6 Summary of studies of the effects of tryptophan depletion on depression and behavior in healthy subjects, drug effects in healthy subjects, and patients with different psychiatric diagnoses.

Type of Subject studied	% N male	Range or mean age	Experimental conditions	Clinically significant increase in HDRS	Major findings of tryptophan depletion	Reference
<b>Healthy Subjects</b>						
Volunteers	36	100	18 - 25	-	Increased depression ratings on adjective checklist Decreased accuracy on a dysphoric distractor task	(Young et al., 1985)
Volunteers	80	100	18 - 25	-	Increased depression ratings or adjective checklists, was not influenced by environment or instructions	(Smith et al., 1987)
Paid volunteers with negative family history	19	100	23	no <sup>a</sup>	No change in POMS depression score	(Benkelfat et al., 1994)
Paid volunteers with positive family history	20	100	24	no <sup>a</sup>	Increase in POMS depression score	(Benkelfat et al., 1994)
Paid volunteers	6	67	32	no <sup>a</sup>	Decreased self-ratings of "happy". No effect of fluoxetine on depletion induced changes in behavioral ratings	(Barr et al., 1995)
Controls	12	33	46	no <sup>b</sup>	Mean 2 point increase on HDRS, range (0 - 5)	(Moreno et al., 1995)
<b>Drug Effects in Healthy Subjects</b>						
AMPT treatment in paid volunteers	8	50	35	no <sup>c</sup>	Non significant 2 point increase in HDRS following AMPT. No effect of AA drink on HDRS or POMS depression score	(Salomon et al., 1995)
Morphine in paid volunteers	60	100	18 - 30	-	No effect on POMS depression score No effect on pain tolerance Significant reversal of morphine	(Abbott et al., 1992)
Yohimbine in paid volunteers	10	90	27	-	Increased nervousness following yohimbine. No effect on yohimbine induced cortisol or MHPG	(Goddard et al., 1995)
Cocaine in cocaine users	12	83	23 - 57	-	Reduced cocaine induced self ratings of "high" by 20 %	(Aronson et al., 1995)
<b>Non Depressed Psychiatric Patients</b>						
Patients with obsessive compulsive disorder who responded to SSRI treatment	15	53	36	yes	Did not increase OCD symptoms. Did increase depressive symptoms	(Barr et al., 1994)
Patients with panic disorder	8	50	42	-	No change in anxiety symptoms. Did decrease self reports of energy	(Goddard et al., 1994)
Patients with bulimina nervosa	20	0	24	-	Increased ratings of irritability, labile, mood, and retarded affect. Increased caloric intake	(Weitzin et al., 1995)
Adults with autistic disorder	20	80	30	-	No change in depression Increased global worsening of behavioral symptoms. No change in social relatedness or repetitive thoughts or behavior	(McDougle et al., in press)

a. Compared to changes during sham AA drink. b. Compared to baseline ratings 5 - 7 hrs earlier just prior to AA drink, no sham AA drink used. c. Compared to baseline of depletion day as well as to sham or quarter strength AA drink. - = Not evaluated.



irritability, labile mood and retarded affects and increased caloric intake following the AA drink, but no change in depression. An interesting study of adults with autistic disorder found that the AA drink induces increase in global worsening of behavioral symptoms but no change in social relatedness and no change in repetitive thoughts or behavior.

The findings of the effects of the AA drink in non depressed psychiatric patients are variable, since patients with OCD and panic disorder do not have a relapse of symptoms when off medication, but patients with bulimia nervosa and adults with autistic disorder who are off medication do seem to have some increase in symptoms related to their syndrome. The lack of relapse in OCD symptoms in SSRI treated and recovered OCD patients contrasts with the return of depressive symptoms in the same individuals. This would indicate that the 5HT dependent neurobiologic systems supporting antidepressant effects are separate from the 5HT systems involved in the anti OCD effects. The increase in some symptoms and not others in patients off medication with bulimia nervosa or autism suggest that the SD sensitive neurobiologic systems in these disorders are only part of the symptom complex of these illnesses.

#### Discussion

##### *Evidence that requires a revision of the monoamine hypothesis of depression*

The data obtained through the use of the monoamine depletion methods presented above can only be explained with a major revision of the monoamine hypothesis of depression. The new observations that necessitate this revision include:

1. Healthy subjects do not become depressed (at most there are only mild increases in dysphoric mood) with the same procedures that do increase depressive symptoms in patients recently recovered from depression either on or off medications.
2. When depressed, patients do not have an increase in symptoms following either SD or CD.
3. The monoamine depletion methods appear to be valid, as evidenced by the selective effects of the AA drink and AMPT in producing relapse in patients responding to either SSRI's or CRI's, respectively, and the effects of the AA drink in increasing yohimbine induced anxiety, and reducing morphine effects on pain tolerance and cocaine induced subjective reports of "high".
4. In addition, other studies have shown that there is a 7-21 day delay in the onset of the antidepressant response following combined MAOI and tryptophan treatment (Glassman and Platman, 1969) which in laboratory animals produces very rapid and large increases in serotonin in most brain areas.

These observations indicate that monoamine depletion induces clinical depression only in individuals with a prior history of depression and that rapid increases in monoamine levels do not produce a rapid antidepressant response.

##### *An important modulatory role of monoamines in depression*

Although the monoamines may not be a direct regulator of mood in depressed patients and healthy individuals, there is

considerable evidence that they play a critical role in generating and maintaining the antidepressant response, as indicated by:

1. Depletion of monoamines in recently recovered patients on antidepressant treatment produced a rapid relapse which is specific to the type of depletion and type of treatment.
2. Recovered patients who are off medication either following drug treatment, light treatment, or spontaneous remission have a rapid relapse when depleted of monoamines.
3. All of the effective antidepressants known to date, produce changes in monoamine receptor metabolism and receptor systems in laboratory animals consistent with the view that the antidepressant effects involve increased transmission in the monoamines systems.

Thus, the monoamine systems have a "necessary but not sufficient" role in the generation of the complete and rapid antidepressant response. This line of reasoning would then indicate that the interaction of the monoamine systems with other neurobiologic systems is necessary for the generation of antidepressant effects.

##### *Modulatory role of monoamines on other neurobiologic systems that could produce the antidepressant effect*

There is a large amount of data documenting the strong interaction of the monoamine systems with other brain neurotransmitter systems as well as interaction between the monoamine systems. This modulatory role of monoamine function could more clearly account for the observations mentioned above, such that monoamine modulation is necessary, but not sufficient for the antidepressant response.

Other systems that have been found to be altered in depression and by antidepressant treatments include:

##### *1. The glutamatergic neurotransmitter system*

Up to 40% of brain synapses involve glutamatergic neural transmission involving both ligand gated ion channels and G protein coupled receptors. It is of considerable interest that a wide variety of antidepressant treatments decrease the potency of glycine in blocking the binding of ligands (Paul et al., 1994). That the n-methyl-D-aspartate receptor system may be involved in the final common pathway of most antidepressants as indicated by the report that the antidepressant induced decrease potency of glycine follows a delayed time course and persists after the discontinuation of treatment. This index (decreased potency of glycine) was positive across 22 of 23 different drugs tested as compared to only 15 of 23 and 13 of 23 for beta adrenergic receptor down regulation or positive results on the forced swim test, respectively (Paul et al., 1994). Thus, glutamatergic neurotransmission (specifically the interaction of glycine with the n-methyl-D-aspartate receptor complex) may be one of the important "other" systems being affected by changes in monoamine transmission. There are many known relationships between the monoamine systems and glutamatergic neural transmission, but the specific pathways that may relate to the antidepressant induced decreased potency of glycine have not been clarified as yet.

②  
2-3  
0.5

⑦





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- George R. Heninger, M. D.  
Department Psychiatry  
Yale University and  
the Ribicoff Research Facilities  
Connecticut Mental Health Center  
New Haven, Ct  
U. S. A.