DEPRESSION AND THE TRICYCLIC ANTIDEPRESSANTS

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MEDICAL GRAND ROUNDS

November 17, 1977

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at Dallas

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INTRODUCTION

A recent study conducted for the Federal Drug Administration stated:

> *"While physicians might define good health as simply the absence of bad health, many laymen see good health as a state beyond the mere absence of any disorder, encompassing feelings of unlimited energy, freedom from anxiety and depression, and the presence of contentment and happiness."*
>
> --A study of Health Practices and Opinions conducted by National Analysts, Inc. for the Food and Drug Administration, Washington, D.C., 1972

Accepting the challenge to provide happiness, physicians write in excess of 214 million prescriptions each year for stimulants, sedatives, hypnotics, minor and major tranquilizers and antidepressants. Two-thirds of these medications, excluding major tranquilizers and antidepressants are prescribed by nonpsychiatrists (1). Twenty-four million prescriptions for tricyclic antidepressants are written each year, yet less than 20% of these originate with the nonpsychiatric physician. These statistics suggest that nonpsychiatrists seem hesitant to diagnose and manage depressive illness, yet commonly treat the associated anxiety states, insomnia or fatigue with other, possibly more dangerous, "nonspecific" psychotropic agents.

While every individual experiences sadness or grief, such episodes tend to be self-limited. Most individuals possess adaptive "prelearned coping behaviour" and are capable of "working through" depressive episodes such as grieving. There are, however, an estimated 12 to 20 million Americans that yearly experience depression as an illness, with intense and sometimes prolonged psychic and physical stress (2, 3). These individuals likely have a genetic or psychodynamic predisposition to depression. The incidence of suicide in such patients is significant. Each year between 22 thousand and 30 thousand suicides are reported in the United States. Conservative estimates suggest that suicides are under-reported by at least 50% (2,3). There are currently two million Americans with a past history of attempted suicide. These figures mandate a specific and scientific approach to the treatment of depression.

The rather remarkable advances in the neurobiology of affective disorders have been obscured for the nonpsychiatric

physician by problems within psychiatry concerning the nomenclature and definition of subtypes of affective disorders. A new nomenclature system (DSM-III) is now in field trials that should improve the clinical definition of depression.* The approach to the depressed patient currently depends on the conceptualization of depression along specialized frames of reference that depend on the indoctrination and prior training of the psychiatrist, researcher or primary care physician. Sadly, few medical schools offer formal training in psychopharmacology or psychodynamics for physicians wishing to enter fields of primary care. It is not surprising that such disorders are handled poorly, often with catastrophic results.

The internist, whether a "generalist" or a subspecialist is in a key position to diagnose, and in many cases manage, depression. In fact, depressed patients are likely to initially present to the internist because of associated somatic complaints (4). Masked depression, left unrecognized, too often results in repeated expensive and exhaustive diagnostic evaluations, "doctor hopping", drug abuse and may end in suicide (5). The internist must be alert to depression developing in: 1) Patients suffering a loss, real or symbolic, secondary to medical or surgical illness (myocardial infarction, amputation, etc); 2) Patients with a medical disease commonly associated with affective disorders (Cushing's hypothyroidism, etc.); and in 3) Patients on various drugs capable of inducing depression in susceptible individuals (reserpine, α-methyl DOPA, post amphetamine depression, etc.) Finally, the internist should be capable of providing an effective liason to psychiatric colleagues attempting to manage depression within the limitations imposed by associated medical illness, i.e. cardiovascular disease, hypertension, etc.

The grand rounds will briefly review advances in the understanding of depressive disorders, suggest diagnostic criteria and a simplified nosology, and explore the utility of the tricyclic antidepressants in the management of certain types of depression. The toxicity and adverse drug interactions of these agents will be reviewed and the local experience with acute overdose presented. In an attempt to place the hazards of tricyclic antidepressants in proper perspective, I have reviewed the experience at Parkland Hospital as well as the record of the Dallas County Forensic Pathology Department for all overdoses and overdose deaths

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* Diagnostic and Statistical Manual of Mental Disorders, III: The APA Taskforce on Nomenclature, March, 1977.

during a period beginning January, 1973 to May, 1977. The drugs most commonly responsible for overdose and successful suicide were "nonspecific" psychotropic agents (barbiturates, nonbarbiturates, sedatives and hypnotics) and analgesics (particularly propoxyphene) used for "symptom" relief in patients often with a psychiatric history for depression or prior suicide attempt. These drugs are of high abuse potential, have very little therapeutic utility, and can be particularly lethal in the acute overdose. Further, it is likely that these drugs will be misdirected by patients for nonmedical use. The Drug Abuse Warning Network (DAWN) estimates 5 % and 5 % of American adults use stimulants and sedatives respectively each year in a nonmedical fashion. Utilization of these drugs among adolescents both for experimentation and repetitive use is even higher (6).

The liabilities of "nonspecific" psychotropic therapy are too often tolerated for physician convenience and expediency. Perhaps no other clinical situation exists where patients are allowed access to hazardous drugs with minimal therapeutic benefit for the mere asking.

While specific psychotropic therapy for depression carries some risk of overdose, the chance to improve patient well-being and prevent suicide warrants drug intervention. Specific drug therapy for depression carries very little risk for prescription misdirection and drug abuse, but requires of the physician an understanding of the pathophysiology of depression and the pharmacology and toxicology of the antidepressant drugs.

Differential Diagnosis of Depression

Depression is a continuum from the most common emotional response to frustration, stress, or loss (symptom depression) to a pathological mood state (syndrome depression) defined by psychomotor retardation, dysphoria, hopelessness, loss of self esteem, guilt and suicidal preoccupation. This latter state is associated with a variety of vegetative and autonomic symptoms and may also manifest a delusional system in severely affected individuals. This syndrome either occurs *de novo* as a primary mood disorder ("endogenous" depression) or seconday to preexisting nonaffective psychiatric or medical illness ("reactive depression") (7).

TABLE I

*SIGNS AND SYMPTOMS IN DEPRESSED PATIENTS**

DYSPHORIC MOOD

Emotional: Sadness, apathy
Self-dislike
Crying Spells
Loss of Sense of Humor
Loss of Gratification
Remorse, Guilt, and Despair
Anxiety

Motivational: Avoidance
Indecisiveness
Increased Dependency
Suicidal Wishes

Cognitive: Negative self-concept
Hopelessness
Helplessness
Exaggeration of problems
Self-blame
General Pessimism

Delusional states possible

ASSOCIATED SOMATIC SYMPTOMS

Neurovegatative: Insomnia
Anorexia
Weight loss
Fatigue
Libido Loss
Concentration Difficulty

Autonomic: Psychomotor Retardation
Constipation
Palpitations
Sweats

Miscellaneous: Backache
Headache
(Multiple complaints without anatomic validation)

SIGNS FREQUENTLY PRESENT

Sad or distracted expression
Anxious, tense, or worried
Furrowed brow
Desire to avoid eye contact
Tendency to downward gaze
Unkempt physical appearance
Ill-fitting clothes (weight loss)
Spontaneous crying

* Compiled from general review articles (7-10)

To avoid confusion, once the above state is established, the term melancholia is preferred (11). At this point, the clinician can safely apply the dimensions of an illness to this syndrome (symptoms, signs, morbidity, mortality, course, prognosis, and therapeutic response).

The distinction between states of normal sadness, acute grief, and the various types of primary and secondary

depressions take on importance for the clinician because antidepressants are neither effective nor safe in the first instance (12) and in the latter, effective therapy seems to be specific within identifiable subgroups of patients (13).

A psychiatric diagnosis should impart information about the family and personal history, etiology, pathophysiology, prognosis, and anticipated therapeutic response of the individual patient.

TABLE II.

THE DSM-II CLASSIFICATION OF AFFECTIVE ILLNESSES

I. Major Affective Disorders (Psychoses)

Involutional Melancholia
Manic-Depressive Illness, Manic Type
Manic-Depressive Illness, Depressive Type
Manic-Depressive Illness, Circular Type

II. Other Psychoses

Psychotic Depressive Reaction

III. Schizophrenia

Schizophrenia, schizo-affective type
Excited
Depressed

IV. Neuroses

Depressive neuroses

V. Personality Disorders

Cyclothymic personality

The Diagnostic and Statistical Manual of Mental Disorders (DSM-II) is the official nosology of the American Psychiatric Association (14). This classification is of limited clinical value since patients with widely divergent historical, genetic, behavioral and biochemical characteristics are grouped together depending upon the severity of depression and the presence or absence of a "precipitating stress".

Therefore, the diagnosis of major affective psychoses is simply a "severe endogenous" depression, whereas psychotic depressive reaction implys a "severe reactive" depression.

A "precipitating stress" may not be reported by severely ill patients with depressed communicative skills (15). Several investigators (16,17,18) point to the finding that recovery interviews yield only slight differences between "endogenous" and "reactive" patients for antecedent psychosocial events. It is also possible that the psychosocial antecedents are coincidental, occur in an individual genetically or psychodynamically predisposed to depression, or result from abnormal behavior in the prodrome of a depressive episode (loss of a job, divorce, bankruptcy, etc.) (19, 20).

In the DSM-II, many patients with the genetic and behavioral history qualifying for the diagnosis of "major affective disorder" will be carried as "depressive neuroses" simply because their depressive episodes have been mild, or episodes of hypomania have been subclinical. This lack of diagnostic specificity probably accounts for the reports of Covi, et al. (21), that patients with depressive neuroses may respond to tricyclic antidepressants but not in as uniform a fashion as patients with major affective psychoses.

The term schizo-affective illness describes an endogenous depression with a psychotic, delusional overlay (flatness of affect, hallucinations, communicative incompetence and thought disorder) reminiscent of schizophrenia. Evidence is accumulating that the family history and anticipated therapeutic response in this group more closely resembles manic depressive illness than schizophrenia (22).

Finally, nonpsychiatric physicians seldom feel qualified to label patients as "personality disorders", further limiting the utility of this classification.

A SIMPLIFIED NOSOLOGY OF AFFECTIVE DISORDERS
(The Robins-Guze Classification)

The rate of primary affective disorders in the general population compared to the rate in relatives of depressed patients strongly suggested a genetic component (23, 24).

TABLE III

MEDIAN RISK FOR AFFECTIVE DISORDER IN GENERAL POPULATION AND FIRST DEGREE RELATIVES

	Number of Studies	Median Risk
General population	6	1.1
Parents	9	10.3
Sibs	7	10.7
Children	5	10.9

The risks of sibs developing depression is markedly increased if either or both parents are also affected (25).

TABLE IV

RISKS FOR AFFECTIVE DISORDERS IN SIBS, ACCORDING TO AFFECTIVE DISORDER IN PARENTS

	No. of probands (AD)	Total of sibs (corrected)	No. of sibs affected	Morbid Risk
Neither parent affected	329	522	64	12 ± 1.4%
One parent affected	91	128	33	26 ± 3%
Both parents affected	6	7	3	43 ± 19%

The results of seven twin studies, summarized below in pooled data foremat, reveals a concordance rate for affective disorders of 76% in monozygotic twins compared to 19% in dizygotic twins (22). Price, (26) in reviewing available literature, found a concordance rate of 67% (8/12) in monozygotic twins reared apart (1).

TABLE V

TWIN STUDIES OF AFFECTIVE DISORDERS

Author	Country	Concordant pairs/Total Pairs MZ (%)	DZ (%)
Rosanoff et. al. (1935)	USA	16/23 (70)	11/67 (16)
Kallmann (1954)	USA	25/27 (93)	13/55 (24)
Luxenburger (1942)*	Germany	47/56 (84)	12/83 (15)
Slater (1953)	England	4/8 (50)	7/30 (23)
de Fonseca (1959)	England	15/21 (71)	15/39 (38)
Harvald & Hague (1965)	Denmark	10/15 (67)	2/40 (5)
Kringlen (1967)	Norway	2/6 (33)	0/9 (0)
Total		119/156 (76)	60/323 (19)
Price (1968) MZ (%) Reared apart		8/12 (67)	

* from Gedda (1951)

Several large family studies (25,27) demonstrated a high genetic loading for affective illness in two consecutive generations for patients with a history of mania, whereas families without a history of mania display a low incidence of affective illness in two consecutive generations. These observations regarding the family history of patients with affective disorders lead to a new dichotomy utilizing primary (arising *de novo*) and secondary (arising in preexisting nonaffective psychiatric disorders) depression with two major subtypes of primary depression, unipolar and bipolar; which promises to be a more specific and clinically useful nosology of depression. (See following pages).

TABLE VI

PRIMARY DEPRESSION *

Definition
- An affective illness:
  - With no preexisting major psychiatric syndromes such as:
    - Process Schizophrenia
    - Hysteria: anxiety, phobic, and obsessive-compulsive neuroses
    - Psychopathology: chronic alcoholism, drug dependency
    - Homosexuality or other sexual deviation
    - Mental retardation and organic brain syndrome
  - Also excluded are affective reactions superimposed on life-threatening or incapacitating medical/surgical illnesses.
- Length of illness: at least one month
- Signs and symptoms:
  - Dysphoric mood (depressed, blue, despondent, hopeless, discouraged, fearful, worried, irritable)
  - Anorexia and/or unintentional weight loss; rarely hyperphagia
  - Insomnia or hypersomnia
  - Loss of energy with easy fatigability
  - Psychomotor retardation or agitation
  - Anhedonia (including diminished libido) and/or decreased interest in usual activities
  - Lowered self-esteem and self-reproach
  - Poor concentration, slow thinking, or mixed-up thoughts
  - Recurrent thoughts of death or suicide
- Subtypes
  - Unipolar single or recurrent episodes of depression with no history of mania or hypomania
  - Bipolar (true manic-depressive illness): single or recurrent episodes of depression with history of mania or hypomania

SECONDARY DEPRESSION

Signs and symptoms as under primary depression
Superimposed on:
- Either a preexisting nonaffective psychiatric illness
- Or paralleling the course of a life-threatening or incapacitating medical/surgical illness

See the next two pages for a suggested differential diagnosis of depression utilizing this classification.

*From Robins-Guze 28, 29)

TABLE VII

DIFFERENTIAL DIAGNOSIS OF DEPRESSION

	PRIMARY DEPRESSION		*SECONDARY DEPRESSION*		*REACTIVE DEPRESSION*
	Unipolar	*Bipolar*	*Pre-Existing Medical or Surgical Illness*	*Pre-Existing Psychiatric Illness*	*Acute Situational Loss or Grief*
Family History:					
Mania	-	+	No Relationship	Variable (Often "neurotic" depression in parents)	No Relationship
Depression	+	+			
Alcoholism	+	+			
Sociopathy	+	±			
Suicide	+	+			
Two generation affective illness	+	+			
Age at Onset	a. Positive history of: Alcoholism Sociopathy Depression < 30 years	Mid-30's	Determined by Underlying Illness	Determined by Underlying Illness	Most frequent in the elderly
	b. Family history - depression only > 40 years				
	Onset rapid	Onset rapid	Onset usually gradual	Onset gradual and fluctuating	Sudden
Clinical Features:					
Dysphoric mood	Arises *de novo*, recurrent or chronic.	Arises *de novo*, recurrent or chronic with hypomania or mania.	Depression arises during course of medical/surgical illness.	Depression occurs usually usually in association with preexisting neurosis.	Specific reaction to an identifiable loss
Vegetative Symptoms	Varies diurnally	Varies diurnally	Persistent	Influenced by day's effects and underlying disorder; tends to be worse in evening	Persistent
Autonomic Symptoms	Frequently present; May fluctuate with retardation.	Frequently present; Fluctuates with retardation.	Present	Present	Frequently Present
Delusions	Rare	Rare	Rare	Never	Rare, but possibly related to specific loss.
Concentration Difficulties	Impaired	Impaired	Variable	Fluctuates with underlying disorder.	Variable
Suicide Potential	Very Common	Very common	Common (should always presume possibility)	Common (attempts to manipulate others)	Can occur; incidence of natural death also increases, possibly due to a decrease in self-care.

DIFFERENTIAL DIAGNOSIS OF DEPRESSION (PAGE 2)

	PRIMARY DEPRESSION		*SECONDARY DEPRESSION*		*REACTIVE DEPRESSION*
	Unipolar	*Bipolar*	*Pre-Existing Medical or Surgical Illness*	*Pre-Existing Psychiatric Illness*	*Acute Situational Loss or Grief*
Duration of Illness	2 wks. to yrs. Avg. 3-6 months	2 wks. to yrs. Avg. 3-6 months	Persistent through illness	Days to Years Tends to be chronic but intermittent in nature. May disappear.	1-3 months
Follow-Up Course	Av. 1-3 Episodes/Lifetime	Average 3 Episodes/Lifetime	Persistent	Persistent	Resolved by majority of normal patients
Biochemical Markers	↑ Steroid Output Normal Platelet MAO Activity	↓ Steroid Output Normal Platelet MAO Activity	No Data	No Data	No Data
Neurophysiological Markers	"Reducer" of evoked potential	"Augmentor of evoked potential	No Data	No Data	No Data
Pharmacological Markers					
Tricyclic Antidepressants	Responders	May cause switch to mania or hypomania.	Not Indicated	May exacerbate underlying psychiatric disorder-occasionally helpful.	Not Indicated
Lithium Carbonate	May respond	Anti manic; has antidepressant qualities as well.	Not Indicated	Suggesting unipolar characteristics.	Not Indicated
MAO Inhibitors	1. Some pts resistant to tricyclics may respond well. 2. Familial tendencies for responsiveness	May be coupled with lithium therapy.	Not Indicated	Hysteria Dysphoria or Atypical Depression May respond.	Not Indicated
Phenothiazines	Several series show favorable response for thioridazine instead of tricyclic	Maybe useful in manic patients and for maintenance with lithium in schizo-affective types.	Not Indicated	Not indicated except for underlying disorder.	Useful for Agitation

The genetics of bipolar depression have been studied by Winokur (30), in 89 manic probands, comparing ill parent-ill child pairs. This study failed to demonstrate ill father-ill son pairs suggesting an x-linked genetic transmission. Such x-linked markers as Xg^a blood group and color blindness confirmed Winokur's observation in reviewing manic pedigrees (31). See family pedigree below.

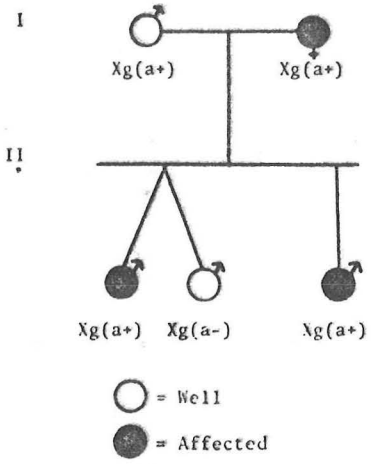
TABLE VIII Sex Relationships in Ill Parent—Ill Child Groupings in Families of 89 Manic Probands

	No. of pairs
Ill father - ill daughter	13
Ill father - ill son	0
Ill mother - ill daughter	17
Ill mother - ill son	17

$X^2 = 13.8855$, d.f. = 1, $P < 0.0005$

From Winokur, 1970.

FIGURE I



Mode of transmission: Xg(a+) linkage

Other forms of genetic transmissions have been theorized by Perris (32) in a review of 168 manic probands he discovered 32 ill father-ill son pairs. The composite of the pedigrees studied yielded a 15% incidence of first degree relative

involvement which suggested that transmission was through an autosomal dominant gene with reduced penatrance (approximately 30%) and variable expression (33). Polygenic inheritance for both bipolar and unipolar depression has also received support (34, 35).

Despite the utility of this simplified nosology and its subsequent validation by clinical (36), biochemical (37, 38) and pharmacological studies (39), it is becoming clear that each subtype is a heterogenous group. Bipolar disease seems to comprise two distinct species, one characterized by early onset with a typical manic-depressive history, and a second late onset group primarily manifesting mania (40). According to Fieve (41) a family history of mania in patients with bipolar disease, predicts a severe course, a higher incidence of suicide, and a good clinical response to lithium carbonate as compared to bipolar patients without a family history of mania.

Winokur et al. (42) favors the subdivision of unipolar depression into 1) "pure depressive illness" where the proband is a middle aged man with a positive family history of depression in first degree relatives of both sexes, and 2) "depressive spectrum disease" where the proband is a young woman with a history of depression in first degree female relatives and alcoholism and/or sociopathy in first degree male relatives.

Regardless of the predictive value of the family history in conjunction with a review of the antecedent psychosocial events, many patients will only be categorized properly after a therapeutic trial with specific antidepressants, for example 1) a "neurotic depressive" responding dramatically to a tricyclic antidepressant probably represents a patient with unipolar depression; or 2) a depressed patient treated with a tricyclic antidepressant developing hypomania suggests bipolar depression as the proper diagnosis.

Another of the instances where response to therapy may allow patient definition is in schizoaffective" depression. Genetic studies reveal a subgroup of patients similar to bipolar depressives who tend to be "lithium responsive" whereas patients with genetic features similar to schizophrenia

tend to be "lithium nonresponsive" (22). Prien (43) has found lithium carbonate effective in "mild" forms of schizoaffective illness, where as more severe cases usually require phenothiazines or butyrophenones. Shopsin and Gershon (44) reported that lithium carbonate often causes confusional states, delerium, and exacerbation of the underlying psychosis in schizophrenic patients. It seems that schizophrenic patients with secondary forms of depression may be differentiated from schizoaffective patients by treatment response.

THE PSYCHOBIOLOGY OF DEPRESSION

To simply categorize patients from a genetic or treatment response standpoint would deny the importance that personality traits, developmental, psychosocial, and physiological events play in the expression of depressive illness in the individual patient. Although biochemical markers are being developed for many subtypes of depressive illness, the possibility always remains that these alterations arise secondarily. It is prudent to review some of the recent advances in understanding the phenomenology of affective disorders.

Depression as a Response to Loss

The Abraham-Freud model (45) views depression as the "inward turning" of the agressive instinct in response to the loss of an ambivalently loved object. Depression is equated with "retroflexed anger" which is id directed. Bibring (46) conceptualized the depressive state as the end-result of lost self-esteem. Depression is said to supervene when the ego is simultaneously aware of a cherished goal, and helpless in its efforts to attain it, hence loss of self-esteem and self-love. Neither of these models allow scientific verification.

The Harlows (47) emphasized the role of attachment behavior as a primary environmental reinforcement. The disruption of attachment bonds represents a reinforcement withdrawal and may precipitate behavioral changes in man and infrahuman primates.

Spitz (40) described a syndrome, anaclitic depression developing in infants (six months to one year of age) separated from their mother. Apprehension, crying, gross

developmental retardation, slowness of movement, withdrawal, dejection and stupor developed, followed by anorexia, weight loss, insomnia, and finally death from superimposed infection or inanition. Surrogate mothers could prevent the catastrophic results of this syndrome. Only 15% of infants deprived of the maternal-infant attachment bond develop this syndrome.

In older children, a reaction occurring routinely upon maternal separation is characterized by a 1) "protest" phase (searching, restless, tearful behavior), 2) "despair" phase (apathetic withdrawal) and a 3) "detachment" phase (rejection of mother on return). (49).

Certain nonhuman primates have strong attachment bonding and characteristic behavior with bond disruption, allowing research models for the evaluating "early object loss", i.e. loss of attachment bonding. While anaclitic depression can be developed in monkeys, the impaired coping behavior and/or survival associated with maternal separation limits the utility of this model.

The disruption of peer bonds in infant rhesus monkeys results in behavioral reactions similar to infant-mother separation or a "protest-despair" reaction , while the disruption of peer bonds in juvenile rhesus monkeys (3-4 years of age) results in a "protest" reaction only (51). In monkeys experiencing object loss (peer-peer or mother-infant bond disruption) as infants, subsequent peer-peer bond disruption during the juvenile period results in a "despair" reaction, suggesting that early life experiences may program the individual for adult psychopathology (52). Whether a causal relationship exists in humans is unclear, despite the numerous retrospective studies in this area.

In each of the preceding models of depression, loss has been an important component of the conceptualization; loss of loved object, self-esteem or attachment bond. Man also cherishes symbolic possessions (power, status role, identity, and purpose for existence) that may become vulnerable when self-esteem is in jeopardy. Certain illnesses representing a sudden and real loss to a patient (myocardial infarction) may imply a much greater symbolic loss or threat of loss to the patient.

Depression as a Response to Helplessness

According to Beck (53), a negative intrepretation of one's own experiences coupled with a negative self-conception and general pessimism describe a "cognitive triad" characteristic of a depressive disorder. Whether this altered style of cognition develops as a result of depression or precedes the depressive illness is not clear but this model seems to have some research validity.

Seligman et al. (54) administered inescapable electric shock to dogs immobilized in a shuttlebox. In the first phase of the experiment, dogs received multiple exposure to repetitive shocks without the opportunity to escape. During a second phase, the animals were unharnessed and an escape from the shuttlebox was available. Multiple exposures to nonescapable adverse stimuli impaired the animals adaptive responses, so instead of jumping a small barrier to avoid shocking, these dogs "gave up", and accepted the noxious stimulus as though they had no other option; they had, as Seligman phrased it, "learned helplessness". This behavior could be terminated by repeatedly dragging the dog away from the noxious stimuli, thereby reassuring the animal that an appropriate response could result in "environmental reinforcement", i.e. the avoidance of punishment. These same workers pointed out that "learned helplessness" generalized beyond a stimulus-response specificity and became akin to a personality trait in these dogs. Seligman (55) suggests that a life-long experience of failure to control environmental reinforcers can lead to a state of "learned helplessness" which would support Beck's conceptual model of depression as a cognitive disorder.

Some behavioralists equate chronic frustration and anxiety with inescapable aversive stimulation. They suggest that depression may result from a maladaptive attempt to decrease the suffering associated with chronic anxiety (56). When coping fails and patients can no longer exert control over environmental reinforcements, they may seek reinforcement substitutes, i. e. sympathy, attention manipulation of family and physician ("the sick role") (57).

Depression as a Biological Event:

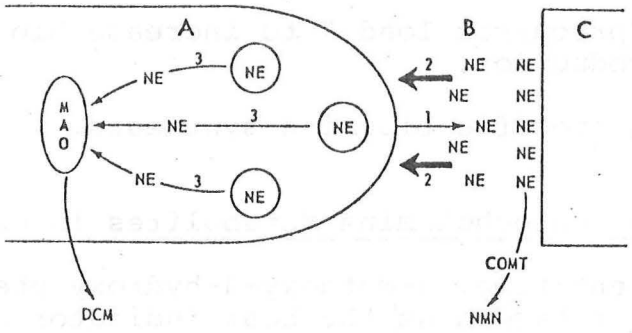
Two clinical observations in the mid-1950's allowed major conceptual advances in the neurobiology of affective disorders. First, it was noted that approximately 15% of hypertensive patients treated several months with high dose reserpine developed an "endogenous" type depression (58). Reserpine was known to deplete intraneuronal stores of norepinephrine, dopamine, and serotonin (59). The second observation was that the monoamine oxidase inhibitor, iproniazid, could produce euphoria or mood elevation in patients being treated with this agent for tuberculosis (60). The drug was known to be a potent intracellular and inter-synaptic inhibitor of catecholamine degradation (61). In clinical trials this agent was effective in a variety of depressed patients (62).

In 1957, the tricyclic antidepressants were introduced by Kuhn (63) who demonstrated the utility of imipramine in "endogenous depression". The peripheral pharmacology of this agent included its ability to block the reuptake of bioamines across the presynaptic membrane (64).

In the figure below the reuptake and storage of nor-epinenephrine is schematized. A similar mechanism is present for serotonin.

NORADRENERGIC NEURON AND RECEPTOR

FIGURE II



—Noradrenergic Neuron and Receptor. Schematic representation of a noradrenergic nerve ending (A), synaptic cleft (B) and receptor (C). NE=norepinephrine, NMN=normetanephrine, DCM=deaminated catechol metabolites; COMT=catechol-O-methyl transferase, MAO=monamine oxidase (within a mitochondrion); 1=discharge of norepinephrine into synaptic cleft and onto receptor, 2=reuptake of norepinephrine from synaptic cleft, 3=intracellular release of norepinephrine from storage granules into cytoplasm and onto mitochondrial monoamine oxidase. (Reproduced with permission from Schildkraut, J. J. and Kety, S. S., Science *156*: 21, 1967).

Thus, agents known to deplete CNS catecholamines and indoleamines act as depressants and drugs that increase catecholamines and indoleamines (either by decreased degradation or reuptake block) have antidepressant qualities.

Largely by pharmacological inference, a series of similar hypothesis implicating biologically active monoamines were developed. The "bioamines" include the catecholamines, dopamine and norepinephrine, the indoleamine, serotonin, and the quarternary amine, acetylcholine.

In the United States, Schildkraut (65-67) and Bunney (68) proposed the "catecholamine hypothesis of affective disorders" while Coppen (69) and Lapin (70) in England supported the "serotonergic hypothesis". Simply, each hypothesis presumes that depression is associated with an altered availability (depletion) of a specific-bioamine at important CNS receptor sites, regulating mood and behavior. Mania in this model represents the opposite (excess) alteration in the same amine. The desire to substantiate these theories fostered important neurobiological research.

The possibility that depression represents an abnormality in either catecholamines or indoleamine synthesis has been explored by:

1) Measuring the metabolites of bioamines in body fluids (particularly urine and CSF) after various treatment manuvers.

2) Giving "precursor loads" to increase biogenic amine production.

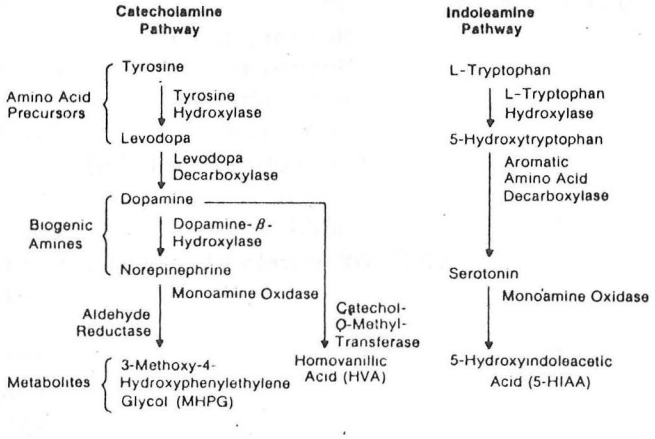
3) Blocking specific bioamine synthesis.

Quantification of Catecholamine Metabolites in Depression

At the present time, 3-methoxy-4-hydroxy phenylethylyene glycol (MHPG) is regarded as the best indicator of central noradrenergic activity since it is likely the major brain metabolite of norepinephrine (71, 72, 73). It is estimated that up to 50% of MHPG in urine is of cerebral origin (74). Several authors suggest that stress and motor activity elevate urinary MHPG (75, 76) and that low levels found in depressed patients reflect decreased motor and peripheral sympathetic activity (75). Schildkraut (77), however, showed no correlation between MHPG excretion and anxiety,

agitation or psychomotor retardation. The other metabolites of norepinephrine excreted into the urine are less than 5% cerebral in origin and are therefore of little clinical utility (78).

FIGURE III



—Catecholamine and indoleamine metabolic pathways.

The metabolite of serotonin, 5-HlAA (5 hydroxy-indole acetic acid) has been studied in the spinal fluid of depressed patients. Early studies were criticized because of possible differences between ventricular and lumbar 5-HlAA levels and the possibility of peripheral contribution, especially from the GI tract (79). Therefore, probenecid was administered in a number of studies because it blocked the possible peripheral contribution and prevented escape of the metabolite through the blood brain barrier (80). This would tend to minimize differences found between the ventricular and lumbar systems as the metabolite accumulates.

The results of studies measuring MHPG in urine and CSF as well as 5-HlAA (5 hydroxy-indole acetic acid) in CSF are summarized in the following tables.

TABLE IX

QUANTIFICATION OF METABOLITES OF BIOAMINES
IN DEPRESSED PATIENTS

Catecholamine Pathway:

Author	Body Fluid	Metabolite	Conclusion
Robins & Hart, a review of seven articles (78)	Urine (24 hr)	VMA Metanephrine Normetanephrine Epinephrine Dopamine (5% of cerebral origin)	Primarily reflects peripheral catecholamine metabolism. Was increased in mania, inconsistent findings for depression.
Schildkraut (71, 77)	"	MHPG (50% of cerebral origin)	Low in depression Corrects with successful tricyclic therapy.
Mass (81) and Beckman (76) and Goodman (76)	"	"	Patients with a low value respond favorably to imipramine; (blocks reuptake norepinephrine > serotonin); normal to high values respond to amitriptyline; (blocks reuptake of serotonin > norepinephrine.) Values predict response to tricyclics in unipolar patients only
Post (75)	"	"	Induced hyperactivity corrected low values to normal in depressed patients.
Gordon and Oliver (82)	Lumbar CSF	MHPG	Low values in depression
Shopsin (83)	"	"	No significant difference
Goodwin (84) and Post (75)	"	"	Low values in depression but remained low after successful recovery. May be high or normal in mania.
Sjoquist (85)	"	"	Low values predict good response to nortriptyline. (a specific blocker of norepinephrine reuptake)

TABLE X

QUANTIFICATION OF METABOLITES OF BIOAMINES
IN DEPRESSED PATIENTS

Indoleamine Pathway:

Author	Body Fluid	Metabolite	Conclusion
Ashcroft (86)	Lumbar CSF Level	5HIAA	Low in depression, mania, and often on recovery.
Ashcroft (86)	*Lumbar CSF Accumulation	"	Low levels returned to normal 8 hours after hydroxytryptophan loading
Coppen et al (87)	Lumbar CSF Level	"	Low in depression and mania
Dencker et al (88)	"	"	Low in depression and mania (no improvement with recovery)
Mendels (89)	"	"	Lower in "psychotic" than neurotic depression May reflect presence of psychosis.
Bowers (90)	"	"	Lower in schizophrenic patients
Goodwin and Post (91)	Lumbar CSF Accumulation	"	Low level predicts response to lithium
Van Praag (92)	"	"	Low level predicted response to 5 hydroxytryptophan loading
Asberg (93)	"	"	Low level predicts good response to 5 hydroxytryptophan loading; poor response to nortriptyline (blocks specifically norepinephrine reuptake)

* Accumulation refers to spinal fluid levels after probenecid block.

As sophistication grew in the measurement of catechol and indole metabolites, a new approach, "precursor loading" was applied to this technology with the expectation that similar results might be obtained in depression as had been seen with the administration of L-DOPA to Parkinsonian patients.

TABLE XI

Author	Precursor	Action	Conclusions
Catecholamine			
Bunney (94, 95)	L-DOPA	↑ dopamine; ↑ norepi ↓ serotonin	Ineffective as antidepressant; Occasionally caused a "switch" from depression to mania.
Indoleamine			
Coppen et al (96) Prange et al (97)	L-tryptophan	↑ serotonin	Antidepressant in a few patients; may potentiate MAOI antidepressants.
Murphy (98)	"	"	Negligible effect on unipolar patients; both antidepressant and antimanic in some bipolar patients.
Hullen (99)	"	"	Improvement in some lithium nonresponders.
Ashcroft (86)	"	"	Low serotonin CSF levels (reflected by 5HIAA) corrected to normal control values 8 hrs after precursor load.
Van Praag (92)	5 hydroxytryptophan 5HT	"	Only effective in a small number of patients with low pretreatment CSF 5HIAA accumulation after probenecid. Also low serotonin turnover in depression.

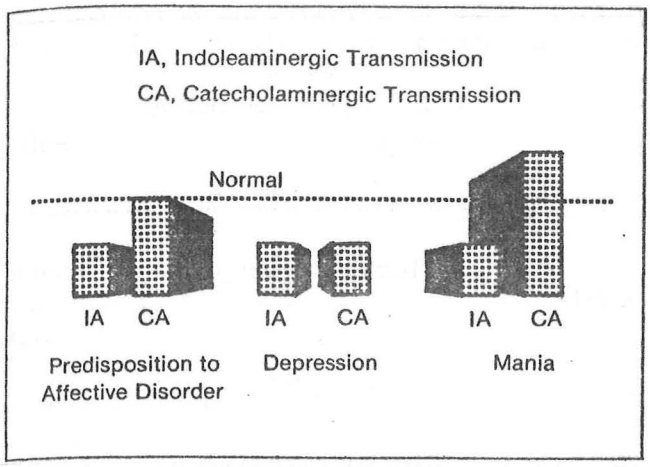
Another mechanism for delineating a specific bioamine's effect utilized various drugs capable of blocking bioamine synthesis.

TABLE XII

Author	Agent	Action	Behavioral Effects
Indolamine			
Jouvet (101)	PCPA (parachlorophenyl-alamine)	Blocks tryptophan	Agression, hyperarousal, hypersexuality, and insomnia.
Catecholamines			
Redmond et al. (102)	AMPT (α methyl para tyrosine)	Blocks tyrosine hydroxylase; lowers catecholamine levels.	(Antihypertensive) sedative in man, causes "depressive syndrome" in monkeys.
Brodie et al (103)	"	"	5 of 7 manic patients became less manic; 3 depressed patients became more depressed.
Clinical Observations	α methyl DOPA	Known to block dopamine decarboxylase, serves also as a fake neurotransmitter; lowers catecholamines	(Antihypertensive) sedation; occasionally depression in man.
Breese et al (104)	6-OHDA (6-hydroxy dopamine)	Permanent destruction of central catecholaminergic neurons. (Central sympathectomy)	Decreased locomotion, eating and drinking behavior, Passivity, social withdrawal; temporary in nature.

The sum and substance of these various reports suggest that serotonin turnover is decreased both in depression and mania. Less can be said of norepinephrine turnover in depression but high turnover rates are found in mania. Whether these biogenic amine alterations cause depression or result from it is not entirely clear. The most attractive of the various bioamine hypothesis, "the permissive theory" has been suggested by Kety (100) and Prange (97). Clearly the evidence exists that several bioamine abnormalities work in concert in the depressed or manic state. Newer evidence emphasizes the importance of central catecholaminergic-cholinergic imbalance in depression.

FIGURE IV

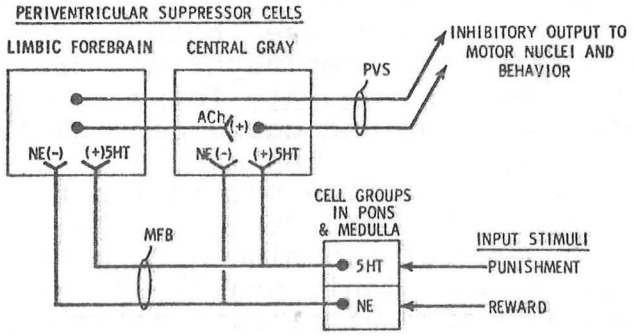


.—Proposed brain relations of biogenic amines, the permissive hypothesis of affective disorders.

THE REINFORCEMENT PATHWAYS (MFB-PVS)

As the neurophysiology of the diencephelon advances, more evidence points to the role that bioamines may have in this area. Wise, Berger and Stein (105) have demonstrated α noradrenergic "reward" receptors in the medial forebrain (MFB) bundle, as well as, serotonergic "punishment" receptors in the periventricular system (PVS) of the rat. Activation of norepinephrine cells in the lower brain stem, in response to reward or the avoidance of punishment, will inhibit acetylcholine mediated suppressor cells in the PVS. Reduction of the PVS inhibitory influence facilitates behavior. Signals associated with punishment or failure activate serotonergic cells and excite the PVS acetylcholine mediated suppressor cells which inhibit behavior.

FIGURE V



Previously Janowsky et al. (106) hypothesized that depression may represent an imbalance between central cholinergic and adrenergic neurotransmission, with mania representing the converse situation. Interesting clinical studies (107) report that physostigmine salicylate, a centrally active anticholinesterase, administered to depressed patients deepened the depression, but rapidly lysed manic episodes. The tricyclic antidepressants have significant anticholinergic effects which maybe beneficial in depression.

The Reticular-Activating System in Depression

Even in patients with severe psychomotor retardation a "central hyperarousal" is present associated with a disruption of REM (rapid eye movement) sleep patterns, and a disappearance of delta sleep (deepest non-REM sleep) (108). Serotonin depletion with the tryptophan hydroxylase inhibitor, paraclorophenylalamine, is known to cause arousal, aggressive behavior, hypersexuality and insomnia (109). Whether a serotonin deficiency is responsible for sleep disturbances in depression is not clear.

There is indirect evidence that residual sodium (intracellular and bound sodium) is increased in mania, and to a lesser extent in depression (110,111). Norepinephrine and serotonin reuptake and storage seems to be mediated through a carrier protein (112) dependent on the monovalent cations Na+ and K+ and the bivalent cations, Ca++ and Mg++. Studies of various transport systems suggest that the configuration of the substrate binding site on the carrier protein may be changed in such a way as to reduce the affinity of the substrate by changing the electrolyte concentration gradient. An increased intraneuronal sodium, present in mania and depression, could decrease the carrier's affinity for norepinephrine or serotonin (94). An acquired or genetic deficit in the Na+, K+ stimulated ATPase in depressed patients has not been demonstrated, but would be a plausible explanation for increased intracellular sodium. There is also very good evidence that cortisol hypersection occurs in depression which could mediate sodium retention (113). Increased intraneuronal sodium would lower the transmembrane potential of the neuron and hence the threshold for stimulation, hence hyperarousal occurs.

Lithium carbonate, the most specific antimanic agent is known to increase the reuptake and storage of norepineph rine, decrease norepinephrine release and probably stabilize

the cell membrane. In addition, it may inhibit cyclic AMP. The onset of action for lithium's effect on biogenic amine transport across cell membranes in animals (synoptosomes) (114) and in man (platelets) (115) of several days, parallel its accumulation within the cell. If a partial block of norepinephrine reuptake exists because of increased intra-neuronal sodium, (presumably by altered carrier protein affinity), the accumulation of intraneuronal lithium may reestablish the normal ionic gradient and receptor affinity (94). See Figure 6 . Lithium carbonate treatment has been shown to be accompanied by decreased residual sodium levels (110,111).

FIGURE VI

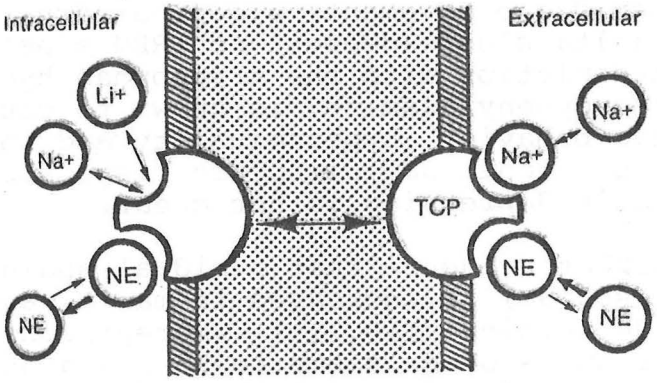


Fig 5.—Hypothesized transport system.

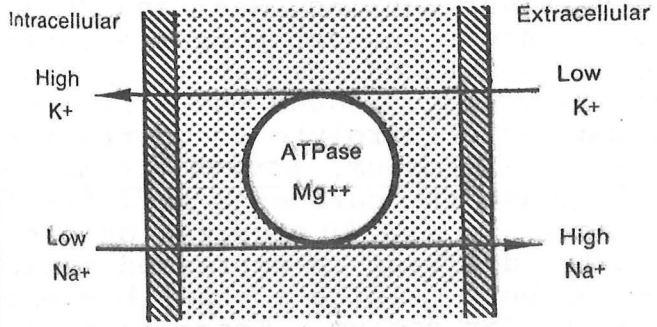


Fig 6.—Sodium pump mechanism.

from Bunney, W.E., et al. (94)

Neuroendocrine Aspects of Depression

Cortisol

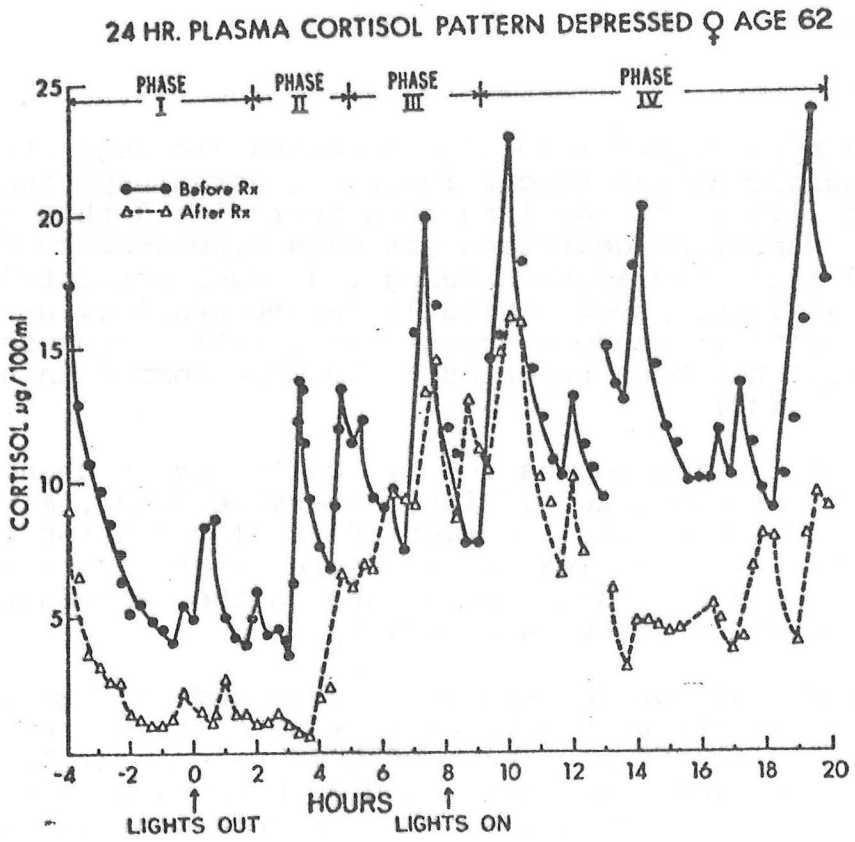
The hypothalmic releasing hormones are regulated by monoaminergic neural tracts involving norepinephrine and dopamine (116). It has long been appreciated that a substantial number of depressed patients hypersecrete cortisol with the usual explanation being that such patients are usually anxious, psychologically decompensating, or actively suicidal with tremendous stress (117, 118). Hypersecretion of cortisol has been reported to be more common in unipolar depression (38).

Patients with depression typically have a change in mood, loss of appetite, libido, agressive drive, sleep disturbances, etc. and a curious diurnal variation in symptoms. Several investigators suggested that a pituitary-adrenal disturbance could be unique to the depressive state and unrelated to stress and anxiety.

A link between depressive illness and the hypothalmic-pituitary-adrenal axis (HPA axis) was identified by independent groups studying the mechanism of ACTH release (119, 120). Normally, cortisol secretion occurs in seven to nine discrete episodes per 24 hours, the largest occurring between 5 and 9 A.M. with a peak of about 15 µg%. These discrete episodes occur as a result of "bursts" of ACTH secretion which is in turn mediated by corticotropin releasing factor (CRF) from the hypothalmus. The depletion of norepinephrine in animal brain markedly stimulates ACTH secretion (121).

The figure from Sachar (122) shows a serum cortisol pattern in a depressed patient before and after recovery. Notice that during depression the patient actively secretes cortisol when secretion is normally minimal, the plasma cortisol concentration is markedly elevated, and the number of major secretory episodes is increased to approximately 12 per 24 hours. The disturbance in neuroendocrine function extends through day and night, during sleep, and total cortisol secretion is nearly doubled during depression. The fact that hypersecretion occurs during sleep lessens the necessity to account for this phenomenon as stress mediated.

Figure VII



Carroll (123) studied 21 depressed patients compared to 10 schizophrenic patients with similar ratings for anxiety, stress, and psychological disintegration. Both groups demonstrated an elevated serum cortisol and high 24 hour urinary free cortisol. The depressed patients, however, did not suppress with dexamethasone as did the schizophrenics (Figures VIII, IX).

Figure VIII

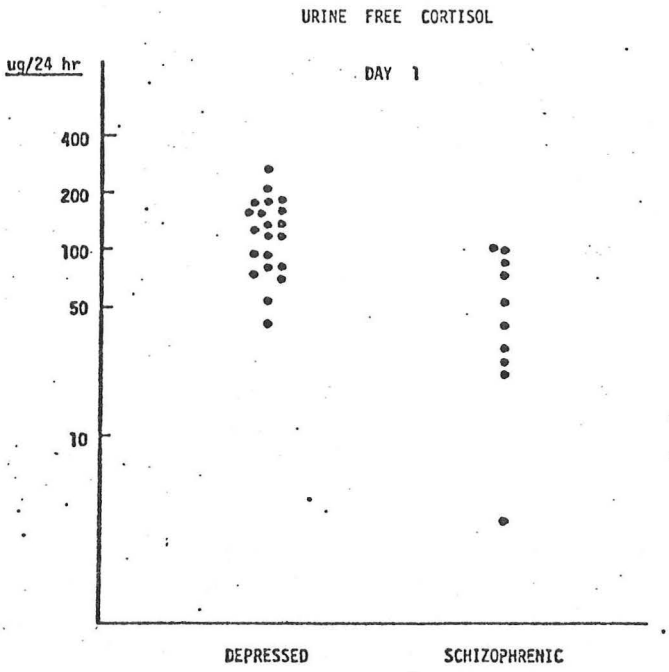
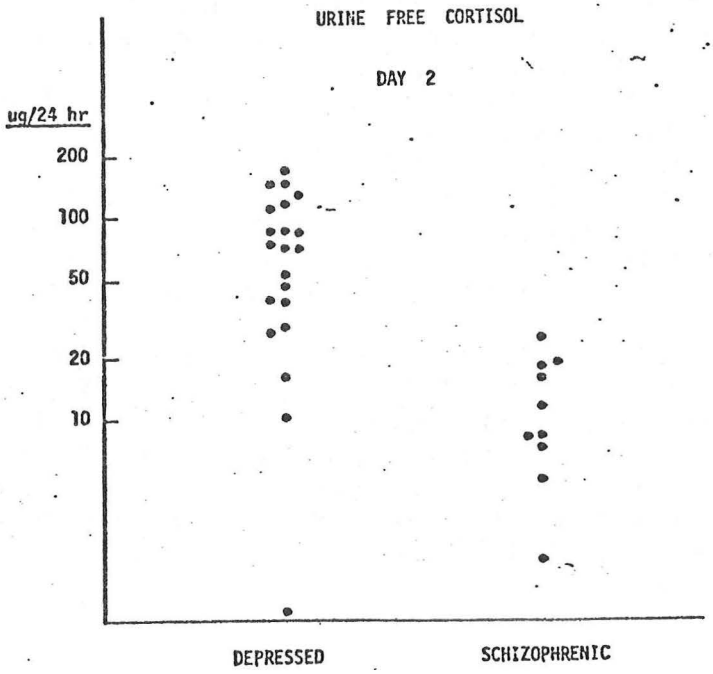


Figure IX



After recovery, the depressed patients again had a normally suppressible HPA axis with dexamethasone suppression:

Day 1	Depressed	Recovered
Plasma cortisol µg/100 ml		
0830	16.3 (8.0)	18.0 (5.1)
1630	12.2 (5.0)	8.5 (4.5)
Urinary Free Cortisol	134.0 (R 91-197)	79.0 (R 54-115)
Day 2		
0830	4.2 (R 2.2-9.9)	2.0 (R 0.7-5.8)
1630	6.5 (R 2.4-17.4)	2.0 (R 0.8-5.0)
Urinary Free Cortisol	60.0 (R 23-154)	13.0 (R 3.5-48)

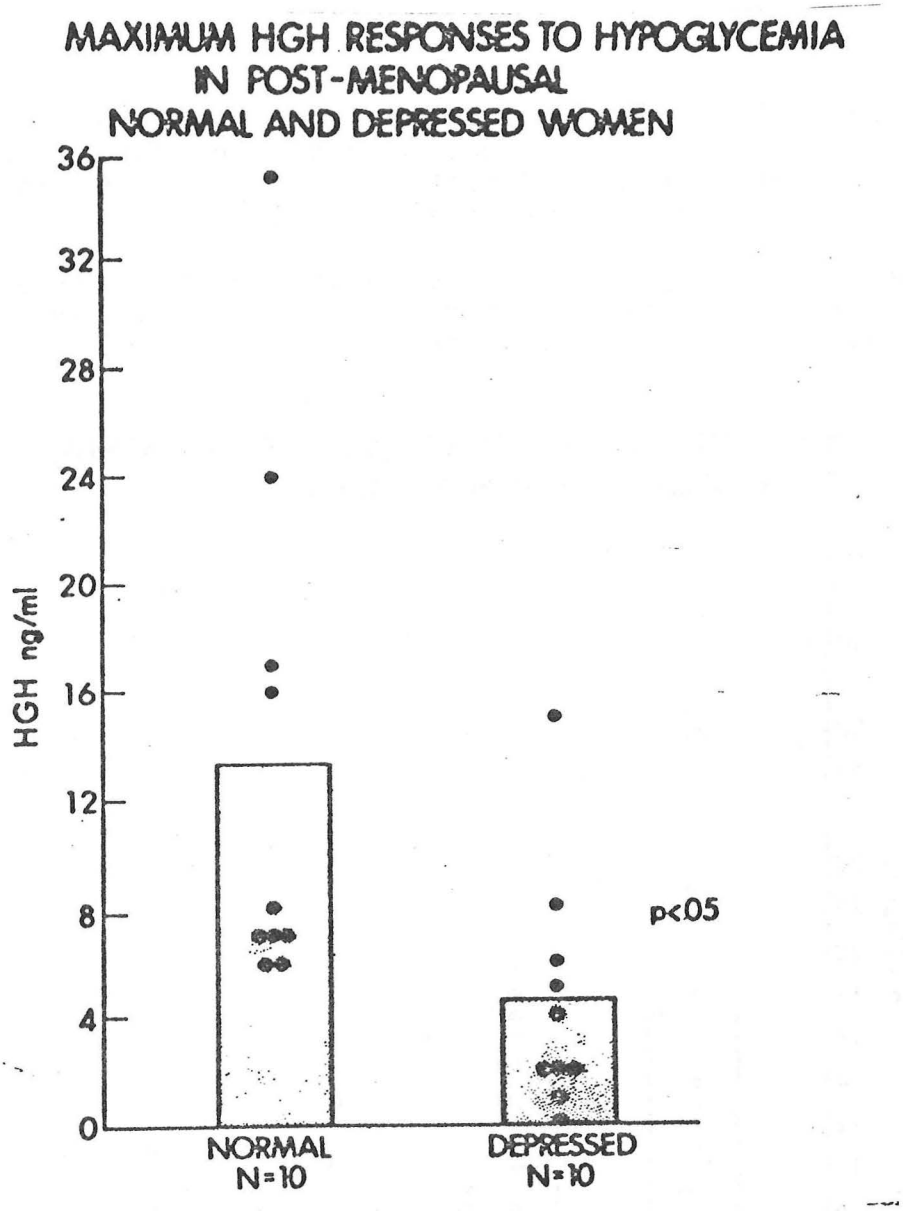
Caution should be exercised when intrepreting the dexamethasone suppression test in depressed patients, regardless of psychomotor retardation, since nonsuppressibility is more likely due to functional norepinephrine deficiency and loss of tight control over CRF and ACTH.

Growth Hormone

Another catecholamine regulated hormone is growth hormone, GH. The data indicate that all three bioamines, norepinephrine, dopamine, and serotonin stimulate GH release (116). The administration of norepinephrine alone has no effect on growth hormone release in normal subjects unless administered with a Beta blocking drug such as propranolol. The addition of an alpha blocker such as phentolamine to this regimen inhibits GH release. Of the three bioamines, norepinephrine is the likely mediator of GH release with alpha and beta adrenergic receptor mechanisms being involved.

Sachar (124, 125) focusing on postmenopausal women with unipolar depression (to eliminate possible estrogenic effects on GH release) studied the GH response to insulin-induced hypoglycemia. The age and absolute fall of the blood glucose were nearly identical in control and depressed women, yet the maximal GH response in the depressed women was only one-third that of normal controls.

FIGURE X



This group also reports that no difference exists between normals and unipolar depressed post-menopausal women when GH release in response to L-DOPA (a norepinephrine precursor) was evaluated. This would suggest that repletion of catecholamines with L-DOPA returns the GH release to normal.

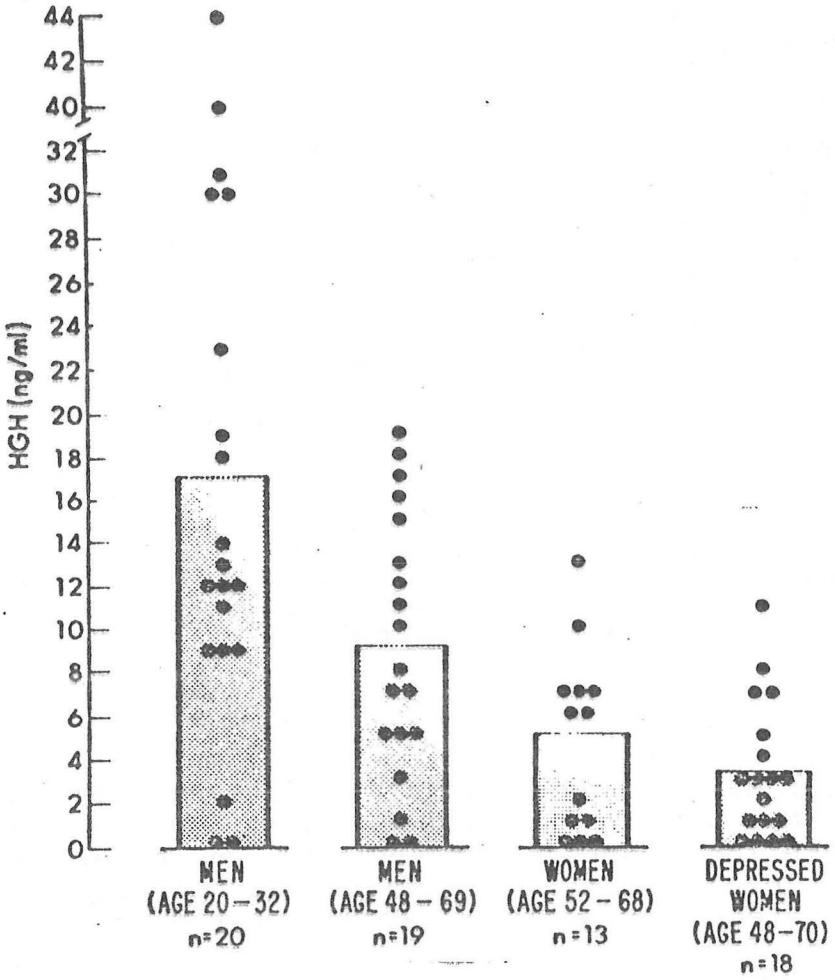
Gonadotropins

When gonadectomy or menopause occur, the secretion of luteinizing hormone (LH) rises markedly in response to the absence of estrogenic feed-back inhibition. Catecholamine depletion in animals blocks this rise in LH.

Sachar's group (124,125) suggest that this catecholamine regulated hormone is decreased in unipolar depressed postmenopausal women as compared to controls.

FIGURE XI

HGH RESPONSES TO L-DOPA IN YOUNG MEN, OLDER MEN, POST-MENOPAUSAL WOMEN, AND DEPRESSED POST-MENOPAUSAL WOMEN



Thyroid

In 1972, Prange reported that injection of thyrotrophin releasing hormone (TRH) had a mild antidepressant action of rapid onset and a blunted thyrotrophin (TSH) response in some depressed patients (132). Subsequent studies utilizing TRH with ECT and tricyclics as adjunctive therapy were largely unsuccessful (134). Trials with triiodothyronine have demonstrated an enhancement in the onset of action of the tricyclic, imipramine,in a group of depressed women (135). Prange, et al. (132) suggest that in addition to bioamine alterations in depression, a post-synaptic membrane receptor defect or insensitivity may be present that can be corrected by the administration of thyroid hormone. Noradrenergic receptor sites are known to be increased in number in response to spontaneous or induced hyperthyroidism supporting this theory. Wide acceptance of this modality of therapy is not likely since it seems to be effective only in a well defined depressive population.

Prolactin

Both bipolar and unipolar depressed patients showed an elevated basal prolactin level compared to normal subjects in response to insulin hypoglycemia, L-DOPA, and TRH (127).

Elevated levels of prolactin have been thought to reflect central dopaminergic depletion. Antipsychotic drugs like chlorpromazine, by virtue of its antidopaminergic properties raise prolactin levels sharply and may cause galactorrhea and gynecomastia (128-131).

ENDOGENOUS PEPTIDE NEUROTRANSMITTERS (The Endorphins and Enkephalins) Possible Role in Depression

Goldstein's (136) discovery of highly sterospecific "opiate receptors" for opiate alkaloids lead appropriately to a search for "endogenous opiates". Hughes (137) later discovered two pentapeptides (met-enkephalin and leu-enkephalin) in pig brain that had opiate receptor binding, with a potency greater than morphine. Analgesia offered by these agents was reversed by noloxone. Goldstein was finally successful in isolating a pituitary polypeptide with a higher molecular weight than the enkephalins but with more potency (50x > than morphine). The compound was later called β-endorphin.

Going back about ten years prior to this discovery, Li (138) described a lipoprotein isolated from the pituitary that had the ability to mobilize fat *in vivo*, and liberate free nonsterified fatty acids *in vitro*. He labeled the lipoprotein, lipotropin, as though it were a hormone. The amino acid sequence of this lipoprotein has been elucidated and within its structure, MSH and β-endorphin (residue 61-91) can be found. Within the β-endorphin molecule, the enkephalins are found (residue 61-65).

The bioassay for these compounds shows a pituitary distribution for β-endorphin, and a wide distribution of the enkephalins parallel to the areas previously described as having a high density for opiate receptors (139).

Periaqueductal grey - Area where direct electrical stimuli provide analgesia reversed by noloxone.

Medial thalmic nuclei - Area for sensory integration of visceral pain.

Solitary nuclei in brainstem - Area receiving visceral input from the vagus and glossopharyngeal nerves.

Area Postrema in brainstem - Contains the chemoreceptor trigger zone.

Spinal cord (found in a dense band which correlates with the substantia gelatinosa) in an area which is the first site within the CNS for integration of sensory input.

*The amygdala, an area with no association to analgesia but primarily involved with emotions has the largest number of opiate receptors.

These agents appear to be the sought after "endogenous opiates". Two other endorphins (α and γ) have also been derived from the parent lipotropin. These endorphins seem to have a regulatory role in temperature control, and may have important emotion and mood regulatory function. When β-endorphin is injected intracisternally in rats, they develop marked sedation, social withdrawal and catelepsy (140). These effects are reversed by noloxone.

Jacquet and Marks (141) remark at the similarity of this response to the usual response to neuroleptic agents in this

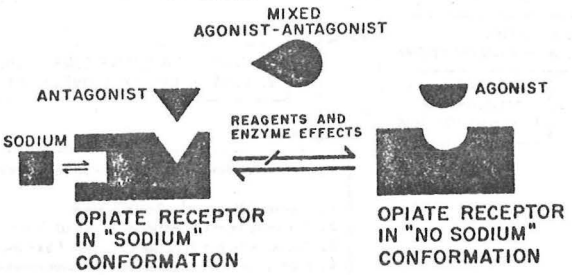
species. They suggest that an enzymatic defect in the cleavage of the parent lipotropin molecule could result in a psychopathologic state likely to be improved by neuroleptics.

The role these compounds may play in schizophrenia or depression is speculative but such a peptide neurotransmitter deficit might manifest as the anhedonia (inability to sense pleasure) commonly associated with the affective disorders. It is also possible that an abnormality in this system could produce an unrealistic indifference to aversive stimuli much the same way that morphine produces an analgesia (142).

It has further been noted that lithium decreases the "high" associated with heroin abuse. Since the agonist vs antagonist receptor configuration of the opiate receptors is also sodium dependent (see figure following) with sodium presence favoring an antagonist position, lithium may also affect this receptor site.

The endorphins promise an interesting research challenge for the next decade.

FIGURE XII



Model of Opiate Receptor Function (Adapted from Pasternak and Snyder

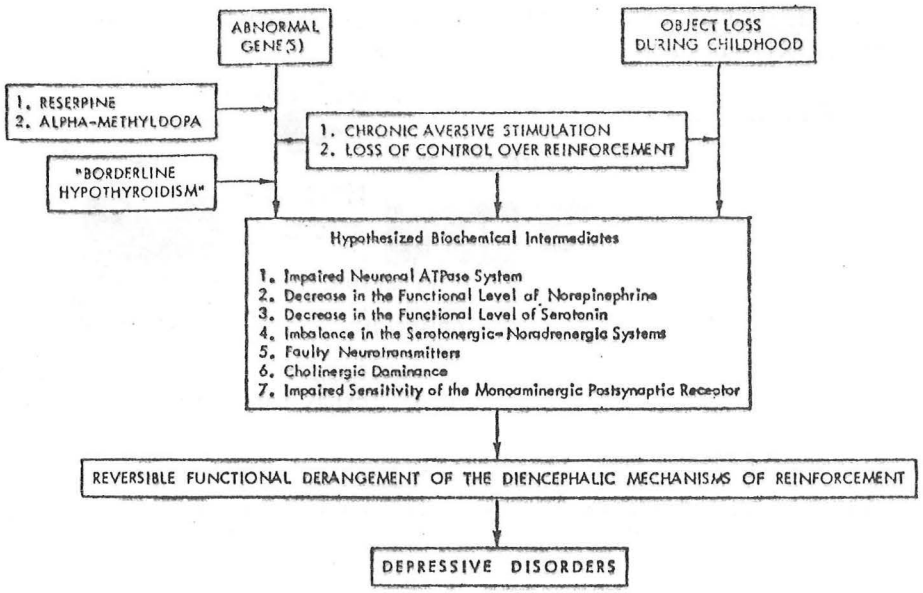
FIGURE XIII

Structure of the parent, lipoprotein. Residue 61-91 is β-endorphin.

Summary:

Regardless of the etiology of depression, be it a genetic predisposition, early object loss and/or bond disruption, or loss over environmental reinforcement, it is likely that the alteration in mood is mediated through biological intermediates. The evidence that these biological changes interfere with the processes of diencephalic reward or reinforcement allows an integration of psychoanalytical and behavioral formulation with the biochemical hypothesis of affective disorders. Akiskal and McKinney (7, 143) offer a "Unified Hypothesis" and a "final common pathway" of depression which seems most reasonable.

FIGURE XIV



A multidisciplinary model of the pathogenesis of depressive disorders.

SECTION II

THE TRICYCLIC ANTIDEPRESSANTS

Kuhn in 1957 (144), after screening two families of phenothiazine analogs, the dibenzazepines and dibenzacycloheptadiones, for antipsychotic effects, found that one of the new compounds, G-22355 (Imipramine Hcl) tended to exacerbate schizophrenic psychosis and cause agitation in patients with organic brain syndrome. Trying this drug in approximately 500 patients with various forms of depression, he reported marked clinical improvement in patients with "endogenous depression".

Clinical trials subsequently confirmed the efficacy of imipramine as compared to ECT and the MAO inhibitors (145-147). Because this drug offered an asthetic alternative to ECT and was likely safer than the MAO inhibitors, imipramine became widely accepted as a treatment modality for endogenous depression. Various cogeners of imipramine (from the dibenzazepines) and amitriptyline (from the dibenzacycloheptadiones) have subsequently been developed. The major cogeners of this group include the marketed N-desmethyl metabolites of imipramine (desmethylimipramine) and amitriptyline (nortriptyline), as well as doxepin (an amitriptyline derivative), triptyline and protriplyline. These drugs now account for greater than 24 million prescriptions per year. In many product formulations, perphenazine, a major tranquilizer is added. This review will not cover MAO inhibitors although they are still widely used in Europe and probably much safer than originally thought, nor will ECT be reviewed because of time limitations. Even today, ECT remains probably the most effective treatment modality for severe depression, especially in seriously suicidal patients. With modern anesthesia and muscle relaxants, the hesitancy to use this technique has declined.

FIGURE XV

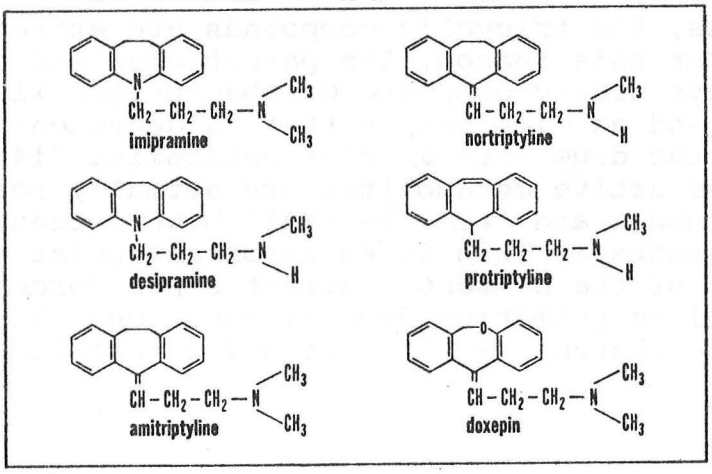


FIGURE XVI

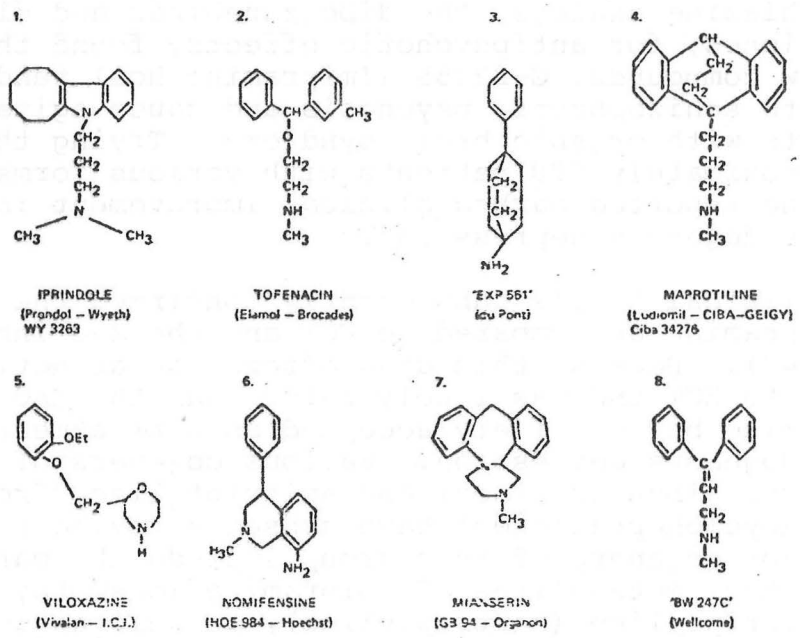


FIG. 1. Compounds, other than monoamine oxidase inhibitors and 'tricyclics', investigated for the treatment of depressive illness (list not exhaustive).

Pharmacodynamics:

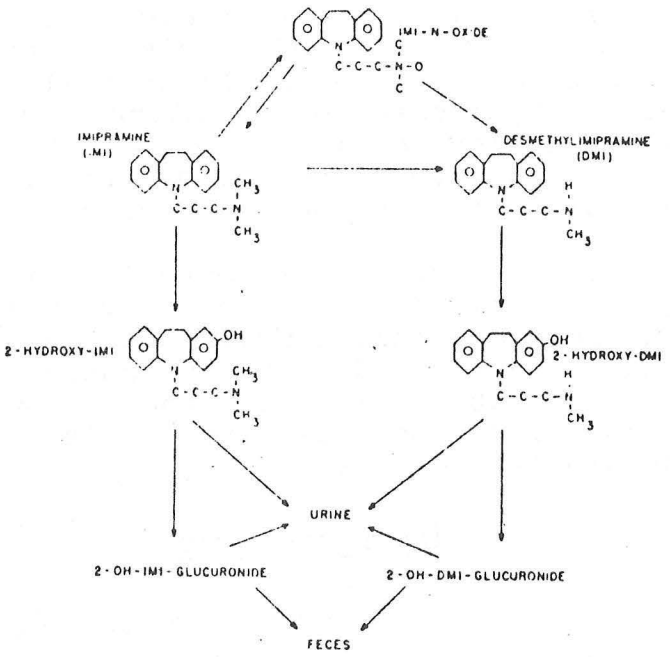
As a class, the tricyclic compounds are extremely lipophilic. For this reason, the parent drug and active metabolites have nearly complete GI absorption, wide tissue distribution, and an elimination that is dependent upon the conversion of the drug into a polar metabolite (148). The parent drug and active metabolites are actually reabsorbed in the renal tubule and from the small bowel because of their lipophilic character. This is an important point concerning the management of the overdose patient since forced diuresis is unsuccessful in promoting drug elimination. On the other hand, activated charcoal and castor oil catharsis may improve

the drug's elimination by interrupting a significant enterohepatic circulation. Since these drugs are highly tissue (tissue: serum ration of > 30:1) and protein bound, peritoneal and hemodialysis attempts during overdose have been of minimal benefit (149).

Radioactive tracer studies (150) have shown a 40% excretion of an orally ingested dose in the first 24 hours, and 70% excretion by 72 hours. These studies were in normal subjects and did not take into account genetic variations.

The tricyclics are biodegraded in three major enzymatic pathways:

FIGURE XVII



Metabolic pathway of imipramine.

Pharmacodynamics of Imipramine

Pathways

1. N-desmethylation - Occurs via the hepatic microsomal enzymes, producing an active nonpolar metabolite (example desmethyl-imipramine, nortriptyline desmethyldoxepin).

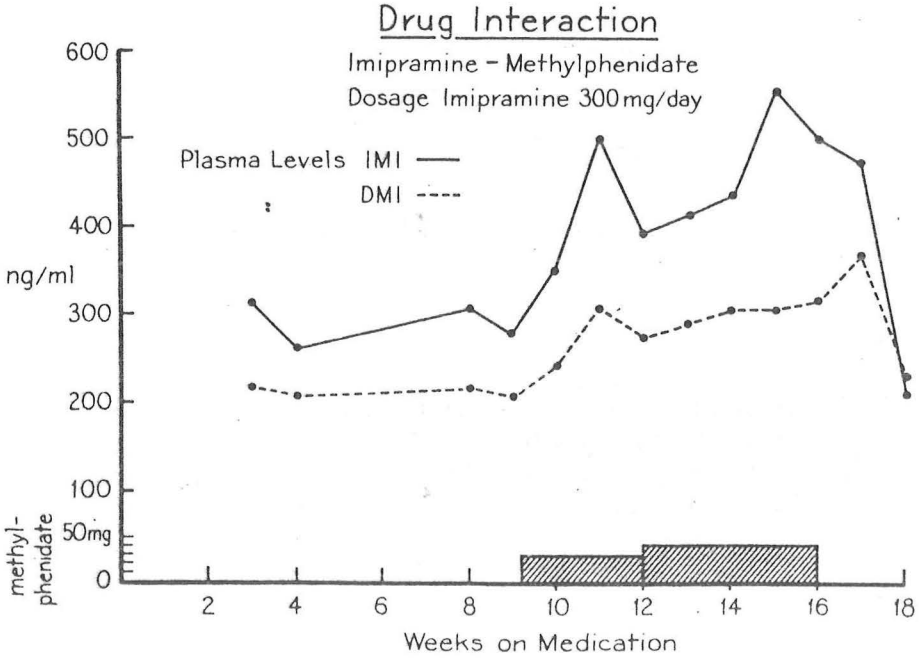
2. N-oxidation - Occurs via hepatic microsomal enzymes producing a reversible short-lived intermediate, only 1-2% of the drug is excreted as this intermediate, usually returns to parent compound or N-desmethyl metabolite.

3. Aromatic hydroxylation - The primary mechanism of biodegradation for the tricyclics is hydroxylation at the two position, This increases polarity and ends activity irreversibly. A glucuronide is formed that is easily excreted in bile or urine.

This latter enzymatic step is the rate limiting factor in tricyclic elimination. Various drugs enhance or block the drug's elimination via the cytochrome p450 system. Two to three fold differences in blood levels can be found with the addition of enzyme inducers (barbiturates) or with enzyme blockers (methylphenidate, chloramphenicol) (151). The tricyclics are themselves inhibitors of the cytochrome p-450 system and inhibit their own elimination, markedly prolonging drug half-lifes in the overdose situation.

Flemerbaum (152) reported that methylphenidate (Ritalin) when added to a tricyclic regimen previously unsuccessful would often yield a clinical remission. Wharton (153) later showed that methylphenidate had no antidepressant qualities of its own but did increase the steady state level of the tricyclics 2 1/2 times baseline levels. Chloramphenicol yields similar results.

FIGURE XVIII



The standard use of "night time hypnotics" (barbiturates, gluthethimide, etc.) may decrease the steady state tricyclic blood levels to a similar degree. When a hypnotic is necessary, the safer drug, flurazepan is suggested because it does not induce the cytochrome p450 system (154).

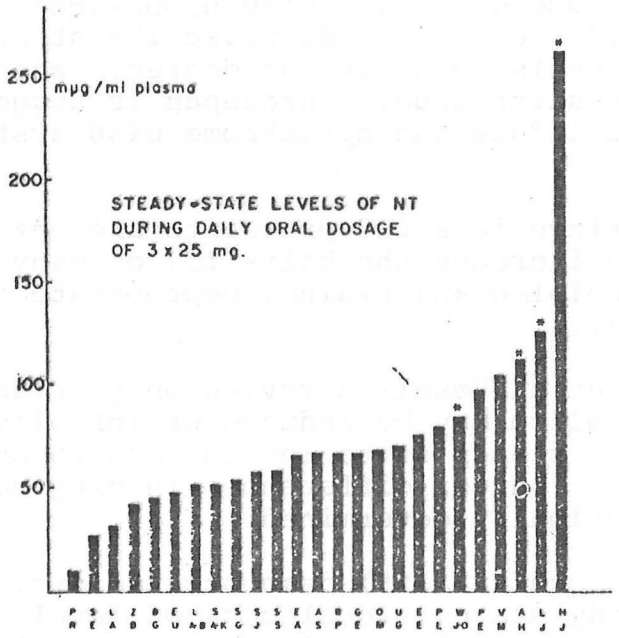
Since the tricyclic antidepressants are enzyme blockers, they increase the half-life of many drugs including propranolol, guanethidine, meprobamate and barbiturates (155, 156).

As pointed out in Vesell's review on pharmacogenetics (157), drug metabolism may be induced or inhibited by various agents but steady state levels tend to change only two to three fold. Larger differences in drug metabolism appear to be genetically determined.

Hammer and Sjoquist (158) demonstrated striking variations in the steady state tricyclic blood levels from one individual to another. Borga and associates (159) discounted the role of interindividual differences in plasma binding as concerns this effect.

Alexanderson (160) and Asberg (161, 162) have demonstrated differences as large as 40-fold in steady state levels for nortriptyline (these investigators used this drug to avoid active metabolites). This variance is four times greater than the variance seen with bishydroxycoumarin. The presence of "tricyclic resistent" families previously described may merely reflect inadequate blood and tissue levels in "fast metabolizers".

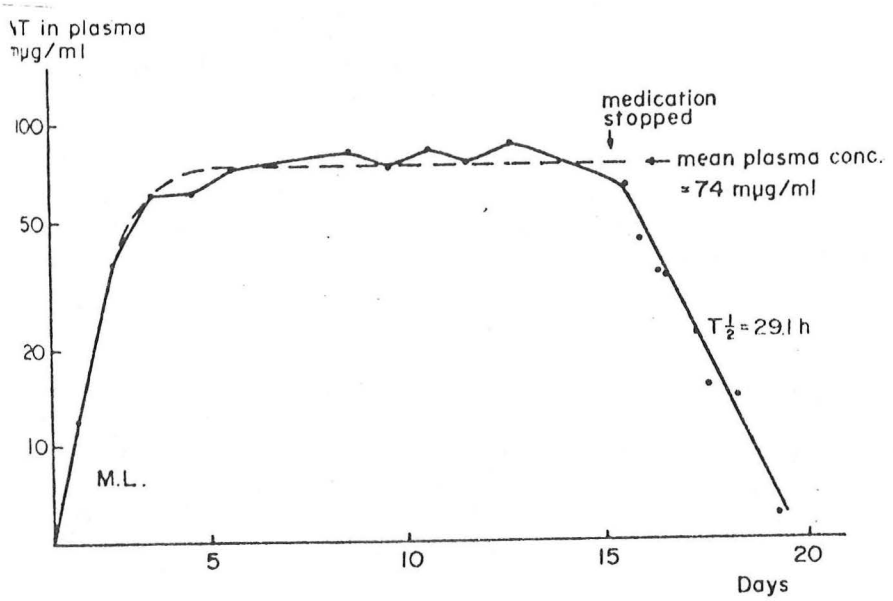
FIGURE XIX



.. Interindividual differences in steady-state plasma concentrations of nortriptyline. Each bar is based on 3-5 determinations. S.D. < 10% of the mean; • denotes subjective side effects.

Alexanderson et al. (160) has examined the rate of genetic vs environmental factors in tricyclic metabolism. In 12 pairs of dizygotic twins, not exposed to other drugs, he was able to show an eight-fold range of blood levels with intra and inter pair differences. In monozygotic twins, a significant interpair difference was noted but intrapair blood levels were nearly identical. In several sets of twin (two identical, three fraternal) one twin had been exposed to an enzyme inducing drug. This twin invariably had a lower steady state tricyclic level. At the end of one or two weeks, in patients not exposed to seconday drugs, a relatively stable steady state is achieved in the individual patient.

FIGURE XX



The plasma concentration of nortriptyline in a healthy human volunteer (M.L.) given 0.4 mg nortriptyline orally three times daily for 14 days.

Asberg (162) has reported a correlation between side effects and serum levels of nortriptyline in 29 patients. The patient's drug related complaints often overlapped with the complaints of a depressed patient making the study of doubtful benefit. This study did suggest that levels below 50 ng/ml were homeopathic, whereas increasing levels were associated with increasing side effects. This study is additionally hampered by the concomitant use of "night time hypnotics".

Kragh-Sorensen (163) studied 37 patients given 150 mg of nortriplyline daily. Patients reached a steady state within one week with levels ranging from 48 to 238 ng/ml. No concurrent medications were given in this study. A positive correlation between plasma levels and improvement in depressive systems existed for increasing levels, however levels more than 170 ng/ml showed a negative correlation for improvement. Five of seven "nonresponders" with plasma levels greater than 170 ng/ml were well and discharged from the hospital within one week of a dose reduction. These studies suggest a curvilinear response to increasing tricyclic blood levels, a "therapeutic window", similar to that previously described for diphenylhydantoin.

Biggs et al. (164) has attempted to use tricyclic plasma levels in an ambulatory population to identify "nonresponders" as either noncompliant or "fast metabolizers", however, it was virtually impossible to differentiate between the two types of patients using this criteria alone.

Very few clear cut or consistent clinical differences exist between antidepressant drugs, but the genetic or induced differences in drug metabolism require an individualization of dosage regimen.

Pharmacology

Adrenergic Effects

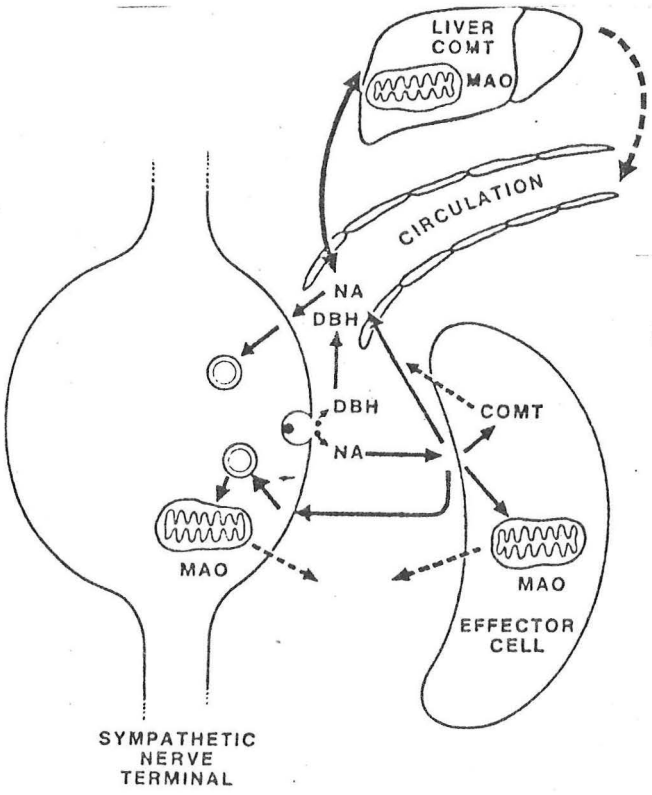
Axelrod (165) has demonstrated the ability of the tricyclic antidepressants to block serotonin and norepinephrine reuptake across the presynaptic membrane. This effect can be demonstrated in animal synaptasomes (114) and in human platelets (115), the most commonly used models of neuronal uptake. Several tricyclics have a specific reuptake block for either serotonin (clorimipramine) or norepinephrine (Maprotiline or nortriptyline). These agents have allowed a better definition of depressive subgroups that respond to one antidepressant and not to another. As suggested previously, it is likely that there are "serotonergic" depressions and "catecholaminergic" depressions.

While most of tricyclics share the reuptake blocking property, this acute effect may not be necessary for the antidepressant effect or it may lead to compensatory changes that actually are antidepressant in nature. One new agent, iprindole, blocks neither norepinephrine nor serotonin and yet is as clinically effective as imipramine.

Note: An analogy exists for the MAO inhibitors that also increases central norepinephrine activity acutely but requires a lag period for patient improvement. Octopamine is a naturally occurring amine formed from tyramine and stored in amine storage vessicles in nerve endings. This amine is released in response to nerve stimulation, however, it is a very weak agonist. Only very small quantities of this amine can be found in normals, whereas depressed patients on MAO inhibitors have up to 100-fold increases bringing up the possibility that these drugs exert their antidepressant effects via these "false neurotransmitters"; certainly the side effects of MAO inhibitors may be related to the accumulation of ordinarily minor amines.

Ordinarily norepinephrine is released by the nerve terminal, its action is ended by reuptake and storage in granules that prevent destruction by MAO(165). Enzymatic degradation by COMT occurs in the circulation, and MAO destroys the excess intracellular catecholamines. The reuptake block induced by tricyclics potentiate the postsynaptic response by increasing the substrate, norepinephrine, available to receptor sites. Tricyclics directly compete with norepinephrine for the reuptake pump sites on the presynaptic membrane.

FIGURE XXI

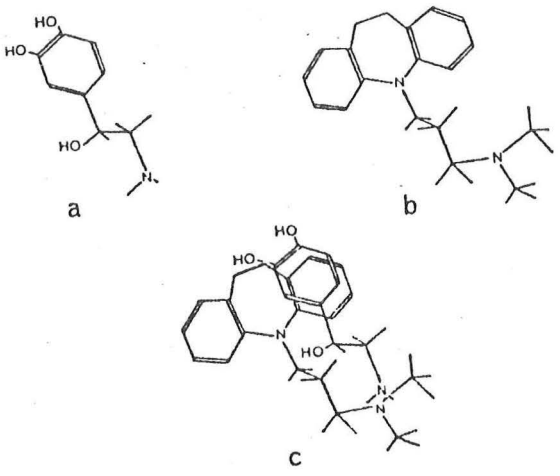


Fate of Noradrenaline at a Varicosity of the Sympathetic Nerve Terminal.

Noradrenaline (NA) is stored in dense core vesicles together with the noradrenaline-forming enzyme dopamine-β-hydroxylase (DBH). When the nerve is depolarized the vesicle discharges noradrenaline, and the soluble portion of dopamine-β-hydroxylase into the synaptic cleft by a process of exocytosis. Noradrenaline acts at the effector cell, and its actions are terminated by reuptake into the neuron, removal by circulation and subsequent metabolism in the liver or by metabolism in the effector cell by catechol-*O*-methyltransferase (COMT) and mitochondrial monoamine oxidase (MAO). Noradrenaline that leaks out of the vesicle is inactivated by intraneuronal monoamine oxidase.

From Axelrod

FIGURE XXII

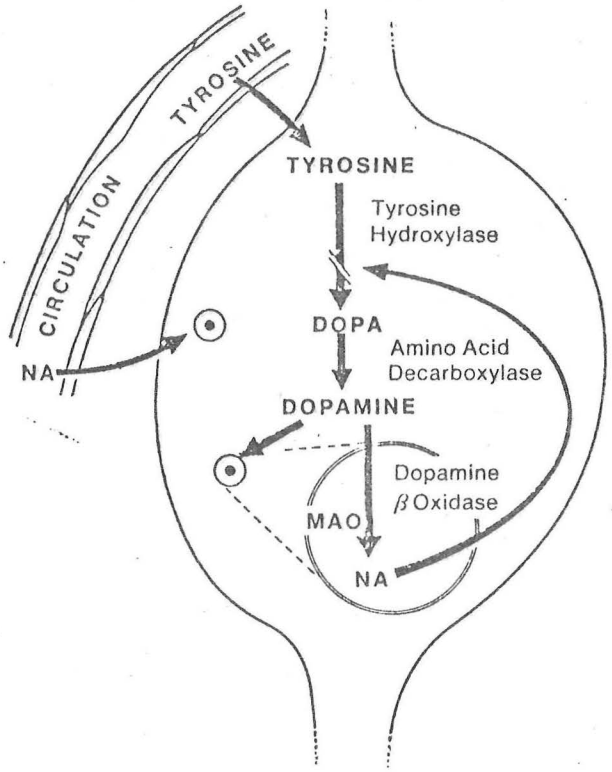


(a) The conformation of noradrenaline as determined by X-ray crystallography. (b) The proposed uptake site preferred conformation of imipramine. (c) The superimposition of the two molecules.

From Horn

Overtime, the excess norepinephrine in the presynaptic cleft causes feedback inhibition of the norepinephrine synthetic pathway at the tyrosine hydroxylase level (166), thereby decreasing norepinephrine turnover. It has also been suggested that the long term administration of tricyclics results in an improved postsynaptic receptor sensitivity (167).

FIGURE XXIII



Biosynthesis of Noradrenaline in the Sympathetic Neuron (Adapted from Axelrod J, Kopin IJ: The Uptake, Storage, Release and Metabolism of Noradrenaline in Sympathetic Nerves. Progr Brain Res 31:21-32, 1969). NA indicates noradrenaline, dopa dihydroxyphenylalanine, and MAO monoamine oxidase.

From Axelrod

These agents tend to deplete catecholamine stores especially in the heart (168), while raising serum catecholamine levels (169) and possibly enhancing postsynaptic responses, all teaming up to suggest an explanation for the increased sudden death in patients on tricyclic antidepressants with underlying heart disease.

These drugs by virtue of reuptake block, enhance the pressor response to norepinephrine, may dampen the pressor response to epinephrine and effectively block the pressor effect induced by sympathomimetic amines (tyramine) since they depend on the uptake pump to displace endogenous norepinephrine (64, 170 and 160).

FIGURE XXIV

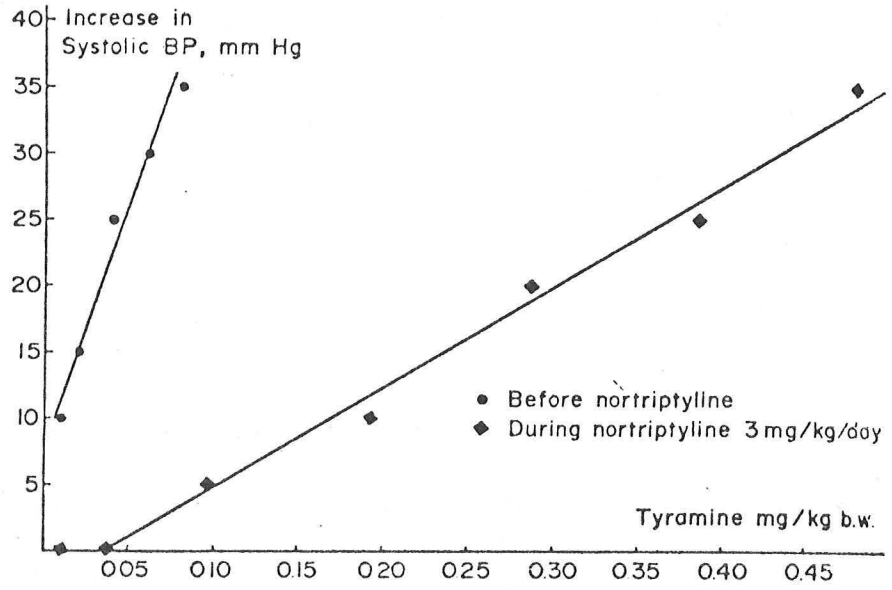


FIGURE 7. Relationship between systolic pressor effect and dose of tyramine in mg/kg before and during treatment with nortriptyline in one patient. Marked blockade of tyramine pressor effects by nortriptyline.

A very important interaction at the postsynaptic membrane occurs: at low doses adrenergic responses are enhanced, at higher doses, these same responses are blocked (164, 170). This may account for the commonly seen "mild hypertension" with mild overdoses and the profound hypotension, refractory to pressors, seen in massive overdose.

Anticholinergic effects:

The anticholinergic effects of the tricyclics can be demonstrated both by antagonism of direct vagal stimulation and peripheral blockade of ACH mediated responses (64, 170). The anticholinergic properties may be related to the drug's

side chain which resembles, to some degree, hexamethonium. Certainly, the major side effects of palpitations, sinus tachycardia, dry mouth, blurred vision, and facial flushing can be ascribed to this effect. Occasionally, an elderly patient will develop an "atropine-like psychosis" on the tricyclic antidepressants and the overdose patient may present with this syndrome.

It is prudent to avoid tricyclics in patients with glaucoma, prostatic hypertrophy, or bladder neck obstruction. Occasionally, an adynamic ileus will occur in an elderly patient on tricyclics and should be considered in that differential diagnosis.

The fine tremor seen with the elderly patient taking a tricyclic is likely a β-adrenergic mediated tremor. Tricyclics are not associated with the extrapyramidal disturbances common to phenothiazines because they have very little effect on dopamine reuptake and are anticholinergic. An occasional Parkinson patient may develop a psychotic or hypomanic response to tricyclics when given with L-DOPA.

Janowsky (106) theorized that anticholinergics may improve the dopaminergic-cholinergic balance in patients with Parkinson's. He has used this same logic to suggest that the anticholinergic effects of the tricyclic antidepressants may be able to lyze the "cholinergic dominance" of the depressive state. In support of his theory, he offers the response of depressed or manic patients to physostigmine salicylate, a centrally active anti-cholinesterase. Depressed patients had a deepening of their moods while manic episodes were quickly lyzed by the drug. Physostigmine promptly decreased the rapid speech, hyperactivity, punning, rhyming, etc. but had less of an effect on the gradiosity associated with mania. Had the drug been given for longer periods this might have also improved. Support for Janowsky and Davis comes from Rountree (171) who used an irreversible cholinesterase inhibitor (Diisopropyl fluorophosphate -DFP) which increases central ACTH levels for prolonged periods and found it capable of controlling recurrent manic episodes. A tendency toward deepening of depression with this agent was also noted. It may be that the anticholinergic properties of the tricyclics account for their antidepressant effects over time.

ADVERSE REACTIONS

Side Effects:
(expected, undesirable pharmacological effects)

The incidence of side effects with tricyclic antidepressants ranges between 15 to 30% (172, 173) with less than 5% considered major reactions. Keep in mind the side effects in depressed patients are often seen with placebo and the patients with secondary depression, most likely not to benefit from the drug, will be most likely to complain of side effects.

TABLE XIII

Frequency	
Common	Dry mouth, skin, facial flushing
Common	Blurred vision, impaired accomodation Mydriasis (contraindicated in glaucoma)
Overlap with Depression	Constipation
Occasional	Urinary retention (hazardous in patients with BPH or bladder neck obstruction).
Rare	Adynamic ileus (rarely in the elderly)
Common	Tachycardia, palpitations, dizziness
Occasional	Orthostatic hypotension
"	Difficulty with thinking and concentration
"	May precipitate hypomania
"	Fine non-Parkinsonian tremor in the elderly.
Overlap with Depression	Nightmares
"	Headaches
Common	Sedation with some agents (especially amitriptyline)
Rare	Photosensitivity
Rare	Skin Rash, pruritis
Rare	Edema
Common	Epigastric distress (nausea, vomiting, anorexia, diarrhea, peculiar taste sensations, etc.)

(Compiled from Goodman and Gilman (150) and Milke (174).

Toxic Reactions:
(unexpected, direct cellular or allergic reaction)

Non-Cardiac:

1. Allergic

   Rash, urticaria, generalized edema of the face and tongue.

2. Miscellaneous
   Hypersensitivity reaction

   a. Hepatic

      Cholestatic jaundice similar to that seen with phenothiazines has been reported by Short (175); several fatalities have occurred but this is a rare complication (176).

   b. Hematologic

      Agranulocytosis has been reported but is quite rare. Eosinophilia, granulocytopenia, and thrombocytopenia purpura have all been rarely reported (150). Rachmilewitz (177) isolated imipramine antibodies in two patients with thrombocytopenia purpura.

   c. Metabolic

      Paykel (178) describes excessive weight gain and carbohydrate craving that reversed with discontinuation of tricyclics. This will cause some patients to be noncompliant.

   d. Endocrine

      Menstrual irregularities, breast enlargement, and galactarrhea (180).

      Testicular swelling, impotence and gynecomastia in males (180). Libido ±

   e. Renal

      A rare, but well documented association, exist for vasopressin resistent diabetes insipidis. (181, 182).

f. Neurological

Cerebellar dysfunction (183) is reported but rare and reversible. May be characterized by ataxia, nystagmus, dysarthria, slurred speech, parasthesia. Atropine psychosis in the elderly may occur (184).

g. Withdrawal

An akathisia-like syndrome has been reported on withdrawal which promptly subsides with reinstitution of the drug (185).

Early reports describe muscle aches, coryza, nausea, vomiting, dizziness and anxiety on withdrawal which responed to reinstitution of drug (186).

Neonates of depressed mothers on tricyclics have been described who displayed tachycardia, tachypnea, sweating, cyanosis, irritability, and wakefulness during their first weeks of life (187).

Adverse Drug Interactions

Adverse drug interactions with the tricyclic antidepressants can in some circumstances, be life-threatening (see Table next page).

Of primary interest is the reaction between MAO inhibitors and the tricyclics that can result in a potentiation of the anticholinergic activity of the tricyclics resulting in tremors, fever, generalized clonic convulsions, delerium, hypertensive crisis and death (150). In Europe these drugs are used together, not infrequently, but recommendations in the United States call for a two week "washout" period when either drug is switched to the other.

For the clinician a series of more relevant drug interactions concerns the concomitant use of tricyclics with antihypertensive agents.

TABLE XIV

DRUG INTERACTIONS IN PATIENTS
ON TRICYCLIC ANTIDEPRESSANTS

Drug	Resultant Effects
Minor tranquilizers	Side effects additive for sedation. Librium may increase anticholinergic side effects; Valium does not.
Barbiturates, Gluthethimide Chloral Hydrate, etc.	↓ steady state tricyclic blood level; dangerous in suicide prone individuals.
Phenothiazines (188, 150)	Atropine-like side effects are additive; phenothiazine blood levels are increased; cardiotoxicity is additive.
Anticholinergics (for Parkinson's, peptic ulcer disease, etc.)	Effects additive, may precipitate adynamic ileus, psychosis, bladder distention, etc. in the elderly.
Amphetamines	Increases the response to amphetamines.
Methylphenidate (153)	1. Increased antidepressant blood levels 2. May cause paradoxical sedation.
MAO Inhibitors (150)	Hypertension, convulsion and hyperpyrexia. (suggested 2 week "washout" prior to switch from either drug)
Acidifier (NH_4Cl)	Antagonize Absorption
Alkalinizer	Increase absorption
Nitroglycerin	May potentiate orthostatic fall in blood pressure.
Antihypertensive Agents	
A. Guanethidine (168)	Typical Early Case Report: A 37 y/o NM with hypertensive cardiovascular disease, congestive heart failure (on digitalis) and renal insufficiency (creat. 10) required increasing doses of guanethidine without achieving blood pressure control (125 µg/day) while on imipramine 75 µg/day. He had seizure-like activity associated with a syncopal episode; became agitated, confused, combative and hallucinatory. Hypotension and bradycardia occurred on 8 different occasions over a 5 day period (to a supraventricular rate of 20).

Isoproterenol and metaraminol did not influence the rate. Finally, the patient failed to respond to supportive care. This care is often cited as an example of tricyclic guanethidine interaction, however an iotrogenic tricyclic overdose may have been responsible.

B. Guanethidine and related adrenergic blockers (156,150)

1) ↑guanethidine steady state levels.
2) If guanethidine is added to tricyclics, a block of guanethidine uptake across presynaptic membrane occurs, so despite higher blood levels, an attenuated effect on blood pressure occurs.

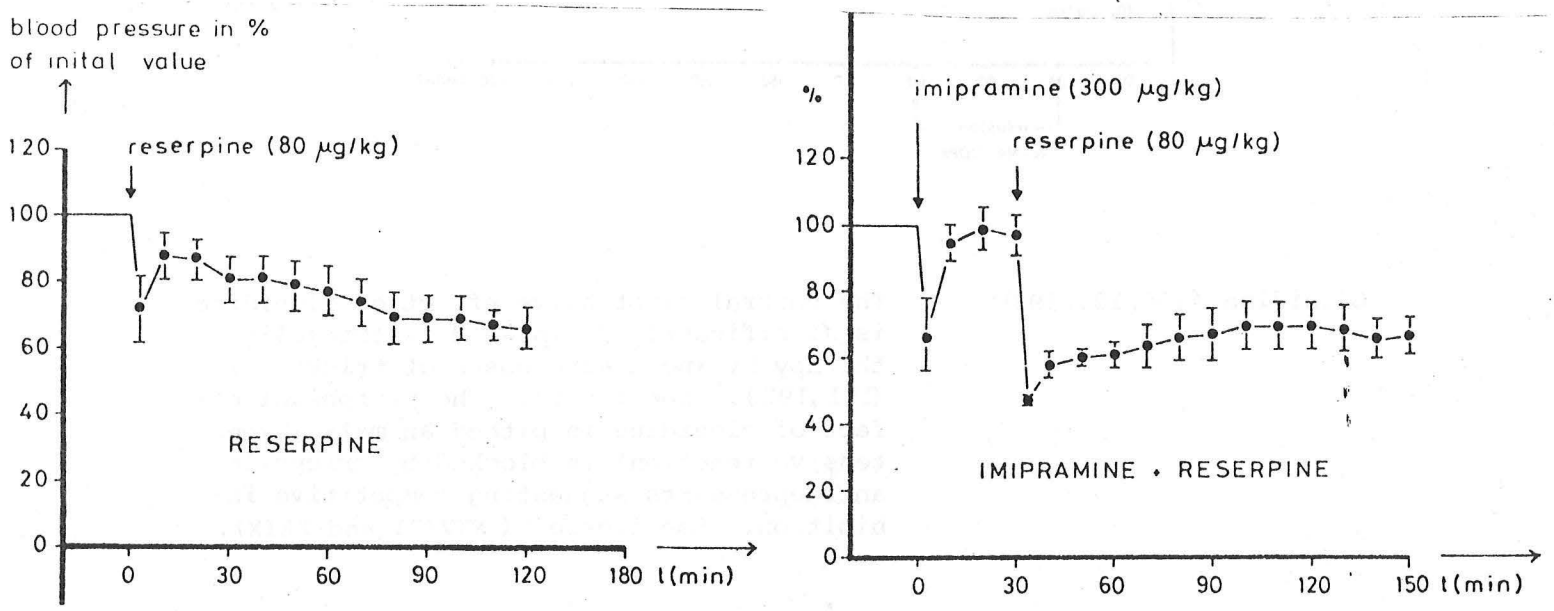
   If the tricyclic is then stopped suddenly, hypotension and shock may result.

3) If a tricyclic is added to guanethidine, the block in guanethidine uptake will slowly dissipate blood pressure control.

C. Reserpine (190)

Causes a transient hypotensive effect in animals pretreated with tricyclics (see figure). Antagonizes tricyclic's antidepressant effect. (Causes central norepinephrine, serotonin and dopamine depletion).

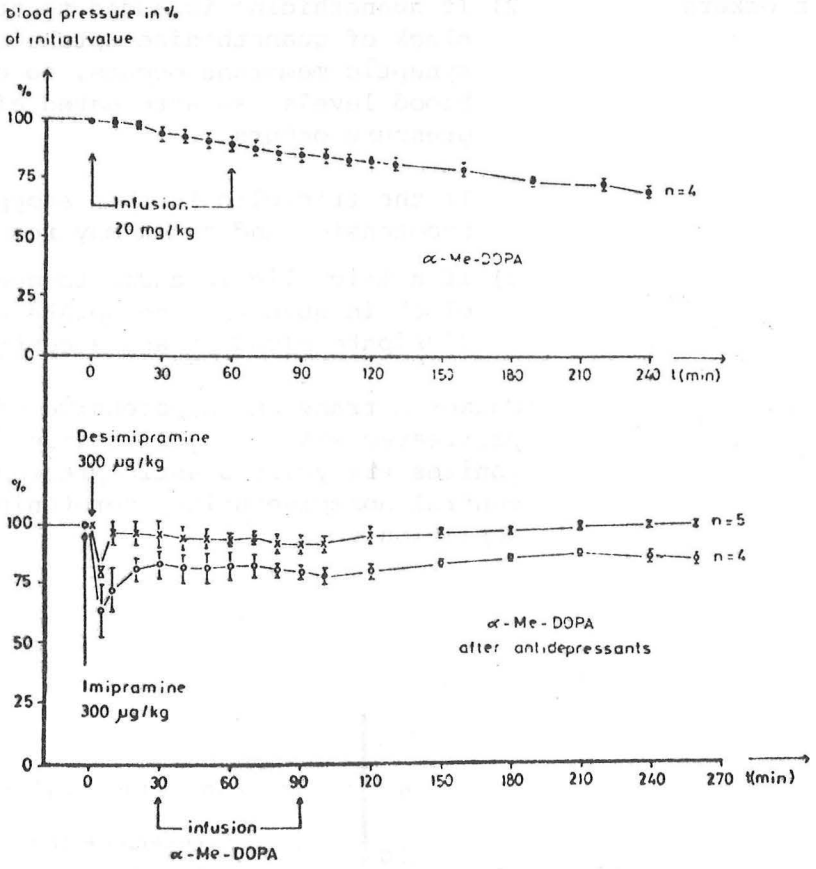
FIGURE XXV



α-methyl dopa (191, 192)

The central hypotensive effect was diminished by tricyclic therapy in the animal model. Pretreatment with tricyclic, prevented anti-hypertensive effect.

FIGURE XXVI



Clonidine (190, 191, 192)

The central hypotensive effect of clonidine is significantly diminished by tricyclic therapy by increasing doses of tricyclics (191, 192). See figure. The peripheral effect of clonidine in pithed animals (hypertensive reaction) is blocked by tricyclic antidepressants suggesting competitive inhibition. See figure (XXVIII and XXIX).

FIGURE XXVII

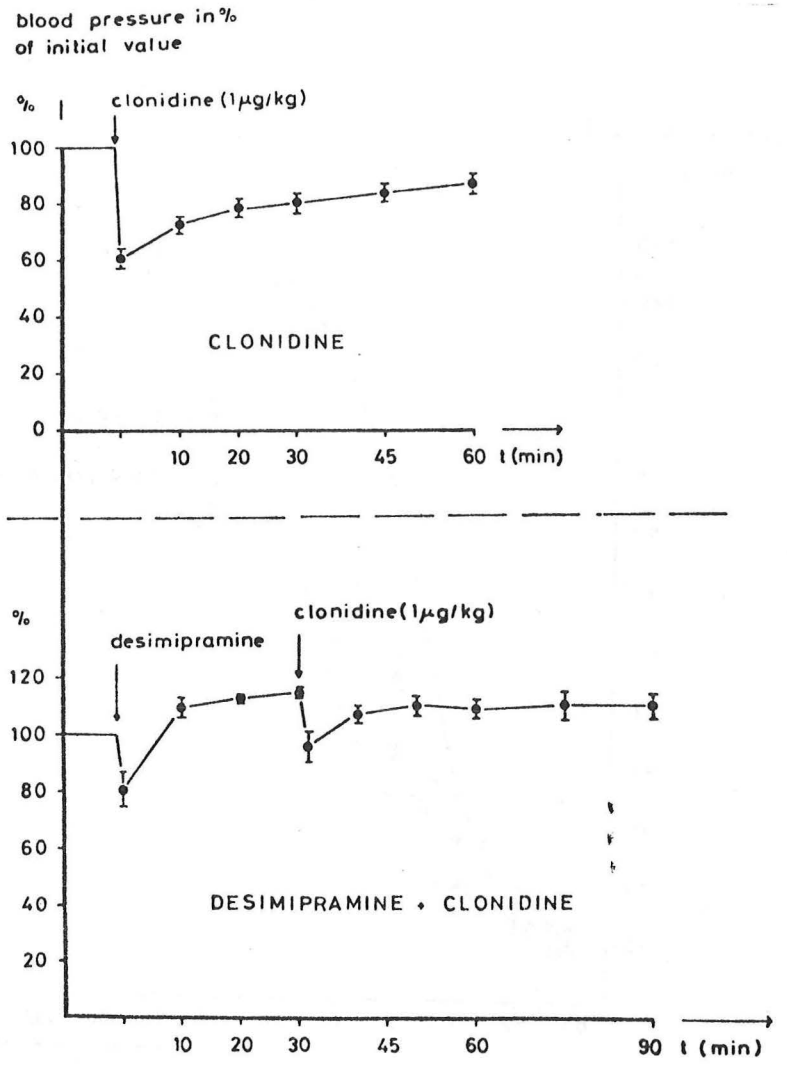


FIGURE XXVIII

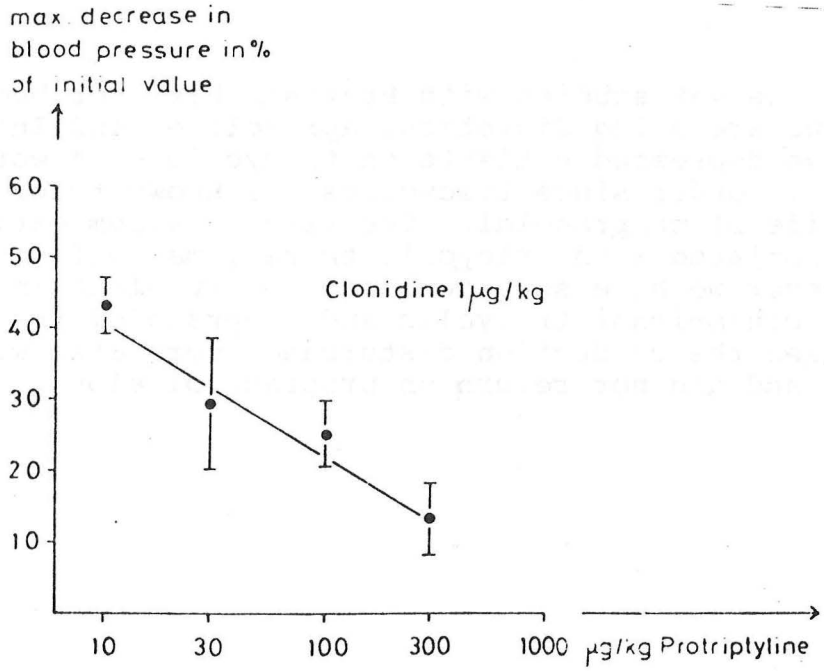
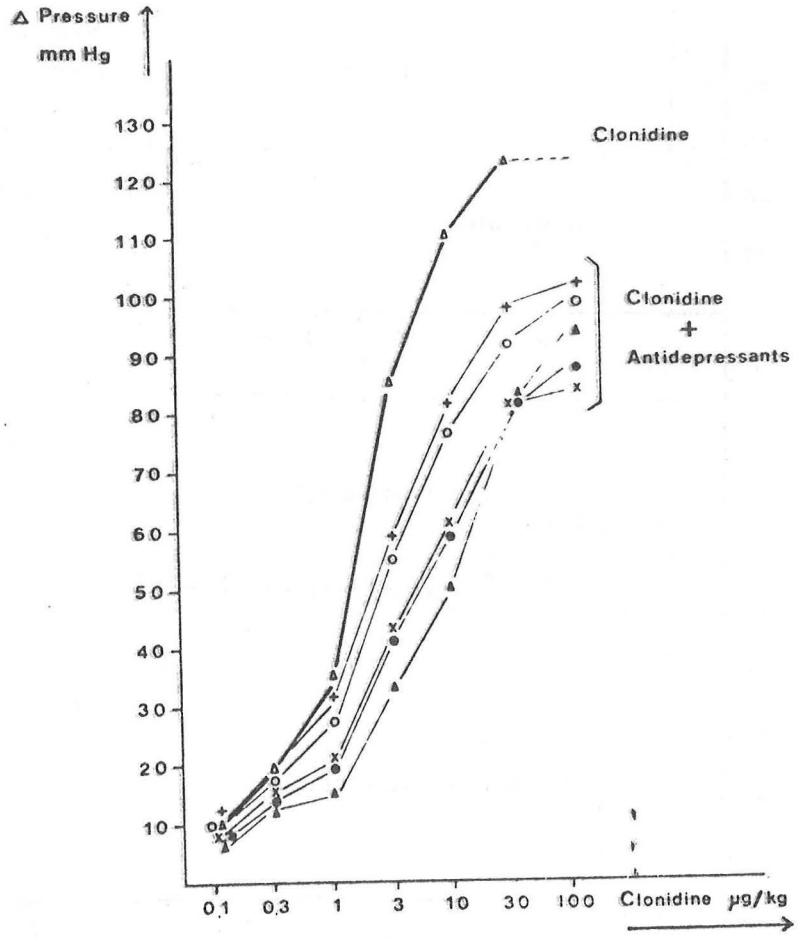


FIGURE XXIX



Note: As yet studies with Prazosin have not been done; currently we are using diuretics, apresoline, and Inderal for hypertensive depressed patients on tricyclics. A word of caution is in order since tricyclics are known to prolong the half-life of propranolol. The rise in serum catecholamine levels, associated with tricyclic therapy may offset this effect however we have seen two cases of AV block in the setting of concomitant tricyclic and propranolol therapy. In both cases the conduction disturbance corrected with drug withdrawal and did not return on propranolol alone.

CARDIOVASCULAR COMPLICATIONS OF THE TRICYCLIC ANTIDEPRESSANTS

The cardiovascular complications of tricyclic antidepressants represent several potentially hazardous adverse reactions. Very soon, after the widespread introduction of tricyclics, numerous isolated reports of untoward cardiovascular or vasomotor events began appearing. These original case reports only suggested a causal relationship until Muller (193) and Kristiansen (194) in 1961 described orthostatic hypotension, myocardial infarction and congestive heart failure in elderly patients (with either atherosclerotic heart disease or hypertension), temporally related to the initiation of imipramine therapy. These patients frequently exhibited a sinus tachycardia and on EKG revealed inverted or flattened T waves.

Sigg (195) investigated the cardiovascular effects of varying doses of imipramine in dogs. Myocardial contractility, heart rate and coronary blood flow were both increased by the low doses (.32 to 3 mg mg/kg) while the vasopressor response to a tilting manuver was reduced by approximately 50%. At 5 mg/kg, the vasopressor response to tilting was abolished. Increasing the dose (to 3-5 mg/kg) was associated with a negative inotropic effect and cardiac output was reduced and total peripheral resistance increased. Mean coronary flow remained increased. At higher doses (8 mg/kg) the blood pressure fell; the negative inotropic effect became more pronounced, and the heart rate slowed. This dose also was associated with a decreased coronary flow which could have been rate related. Imipramine was also noted to markedly prolong the inotropic effect of norepinephrine in isolated feline hearts and *in situ* dog hearts at low doses, while large doses diminish the contractile force.

Cairncross and Gerson (196) performed a similar set of experiments utilizing normal and hypertensive dogs, doses were increased from 0.5 to 8.0 mg/kg. Again low doses (0.5 to 2.5 mg/kg) in the normotensive animals produced no EKG changes but did cause tachycardia and a positive inotropic effect. At a dose of 5 mg/kg, extrasystoles were frequently noted. At a higher dose (8 mg/kg) a mean fall in systolic blood pressure of 33 mm Hg was observed. The EKG change included a broad biphasic QRS complex and depression of the ST segment. These changes were reversible with time. When imipramine was given to dogs with experimental neurogenic hypertension, the same EKG changes were seen with low doses (2.5 mg/kg) suggesting that increased heart work potentiates imipramine cardiotoxicity.

Alexander and Nino (188) described seven young men developing various cardiovascular complications while on psychotropic agents. This paper is frequently referenced to support the cardiotoxicity of tricyclic agents, however the major drugs employed were phenothiazines. Only four of seven patients received any tricyclic antidepressant and only one patient took a tricyclic only. A more appropriate conclusion would be that phenothiazines were additive to the cardiotoxicity of the tricyclics and vice versa. In this series several patients developed an acute myocardial infarction, congestive cardiomyopathy or conduction disturbance.

Richardson et al. (197) reviewed the experience with sudden death in a 2,000 bed neuropsychiatric hospital. Of 552 patients autopsied, 87 had received a phenothiazine. Twenty-one of the 87 patients had a sudden unexpected death of which nine could be explained. The remaining 12 patients had no demonstrable cause of sudden death. On review of these patient's records, eight had an abnormal EKG (1 LBBB, 1 RBBB, 1 AV Block, 5 Nonspecific ST-T wave changes). At a careful histological examination of the myocardium, a striking deposition of acid mucopolysaccharide material was demonstrated in the septum, left ventricle, and especially the papillary muscle. The material was distributed in the arterioles and arteriolar-capillary beds, especially in the subendocardium, suggesting a cardiomyopathy.

The depletion of cardiac catecholamines was suggested as the etiology of this abnormality by William and Sherter (168). Carlsson et al. (169) has shown that the circulating levels of norepinephrine during phenothiazine therapy approaches the levels found in patients with pheochromocytoma. The combination of catecholamine depletion and high circulating catecholamine levels may predispose to lethal arrhythmias.

Axelrod (166) has pointed out that both phenothiazines and tricyclic antidepressants block exogenously administered H_3-norepinephrine uptake by the myocardium and tricyclics are also known to deplete myocardial norepinephrine stores and likewise raise serum norepinephrine levels. It is therefore, likely, that a similar situation exists in the case of tricyclic antidepressants used chronically (198).

Moir et al. (199) utilizing a hospital drug surveillance system in Scotland described 13 sudden unexpected deaths in a group of 119 patients treated with amitriptyline who

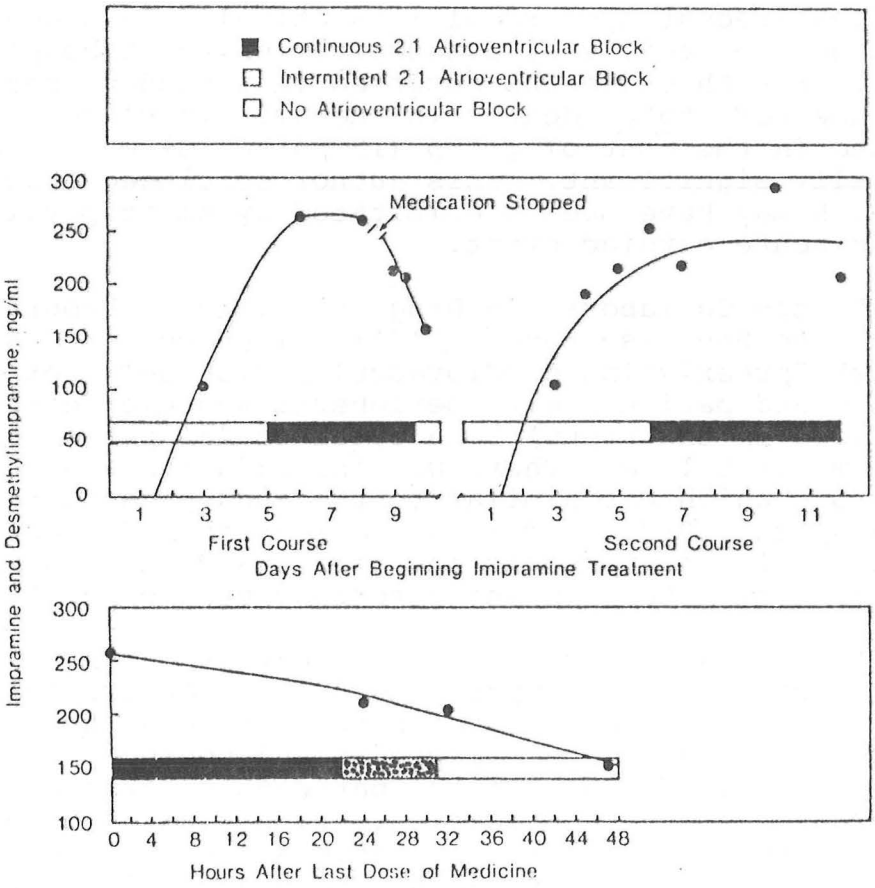
also carried the diagnosis of "cardiac disease" (25% had CHF, 25% were post-recent myocardial infarction). In a control group matched for age, sex, diagnosis, length of hospital stay, etc. only three deaths occurred in a sudden unexpected fashion, however, total deaths in the amitriptyline (23 patients) and in the control group (15 patients) were not statistically significant. This author concluded that the sudden death may have been precipitated by amitriptyline in the face of an acute cardiac event.

The Boston Collaborative Drug Surveillance Program challenges the Scottish report (173). They compared 80 patients with "preexisting cardiovascular disease" (not acute necessarily and patients with peripheral vascular disease were included in the group) to a total of 260 patients who received amitriptyline. There was one sudden death (0.4%) in this group which was similar to the sudden death rate for the hospital (0.3%). The one patient that died suddenly was a patient in the "preexisting cardiovascular disease" category with hypertension and arteriosclerotic heart disease.

The frequency of drug attributed cardiac arrhythmias or heart block was 2.5% compared to 5.8% in amitriptyline nonrecipients. The incidence of shock, syncope, hypotension and CHF was the same among recipients and nonrecipients (3.8%). The overall mortality rate of the patients on tricyclics was 5% compared to the nonrecipients with 8.2%. These last two studies clearly are not comparable since the presence of cardiac disease was not assured by the diagnostic criteria employed by the Boston group and their patients were probably less ill.

The results from the previous studies are less than crisp and offer very little information to the prescribing physician. A well evaluated conduction disturbance in a 74 year old man on imipramine was reported by Kantor (200). The patient had a three year history of a RBBB; six days after imipramine therapy was started (200 mg/day), he developed an asymptomatic 2:1 AV conduction block. When drug therapy was discontinued the patient's AV conduction returned to normal. Because he was severely depressed, a transvenous pacemaker was placed and he was rechallenged with imipramine on two occasions, and as the serum level of imipramine approached 200 ng/ml the patient developed AV block again suggesting a dose related conduction abnormality. The conduction disturbance resolved each time the medication was discontinued as the blood level fell below 200 ng/ml. (see figure) His bundle recordings during pacemaker implantation revealed normal AV nodal conduction.

FIGURE XXX



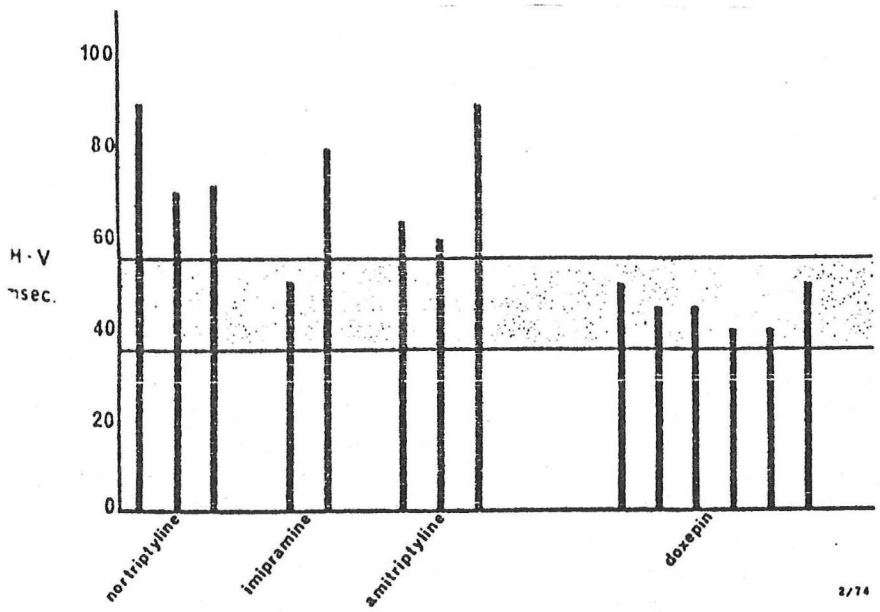
—Top, Concentration of imipramine and its psychoactive metabolite desmethylimipramine plotted against days after beginning drug administration during two separate treatment courses. Solid bars indicate the occurrence of 2:1 atrioventricular block. Bottom, Concentration of imipramine and desmethylimipramine plotted against hours after discontinuation of drug treatment. Solid bars indicate period of continuous 2:1 atrioventricular block. Stippled bars indicate intermittent periods of 2:1 atrioventricular block.

Conduction abnormalities in the course of tricyclic therapy has been evaluated prospectively by Davies (201). Thirty-two depressed, but otherwise normal, patients were assessed before and after two weeks of treatment with imipramine, nortriptyline and doxepin, each 50 mg T.I.D. The cardiac changes included an increase in the sinus rate of 9 beats/min (±14) in 26 patients and an increase pR interval of 0.015 sec. (± 0.024 sec) in all 32 patients. A RBBB pattern developed in three patients. QT intervals remained normal.

A second study in 12 depressed but ambulatory patients was then undertaken utilizing His bundle electrocardiography to evaluate cardiac conduction after patients had reached a steady state tricyclic level. Five of 12 patients demonstrated a prolonged HV interval at a dose level of 200 ng/ml.

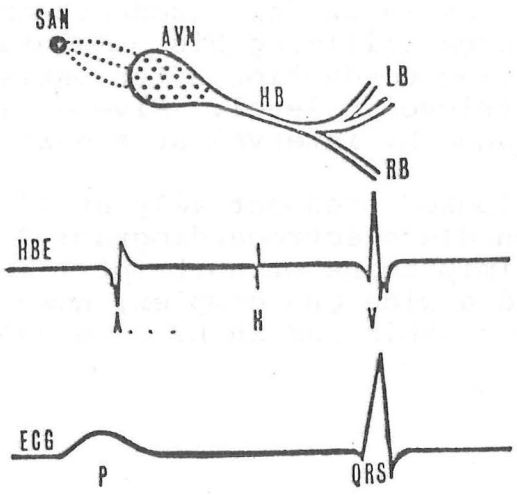
This group looked prospectively at 14 overdose patients using the His bundle electrocardiogram; 7 of 8 patients taking amitriptyline, imipramine or nortriptyline had prolonged HV intervals and a wide QRS complex, however six patients overdosing with doxepin had an HV interval still in the normal range.

FIGURE XXXI



Effect of overdosage (> 500 mg) of T.A.D. on distal conduction. The shaded area represents normal H–V conduction ne (35 to 55 msec).

FIGURE XXXII



Normal AH = 50 – 120 msec.

HV = 35 – 45 msec.

His Bundle ECG compared with normal ECG.

Tricyclic antidepressants besides their anticholinergic and adrenolytic actions on the heart also exhibit a quinidine-like action which may account for some of the direct myocardial depression and conduction disturbances seen in the overdose situation. As with quinidine, excessive blood levels of the tricyclics prolong the pR, QRS, and QT intervals. Recently, Bigger et al. (202) treated two elderly depressed patients with marked ventricular ectopy and reported a change in the character of the extrasystoles (multifocal to unifocal) and a marked reduction in the number of extrasystoles. The coupling intervals were noted to increase in a similar fashion to quinidine. Since imipramine has such a long half-life, the authors suggested its trial as an antiarrhythmic. At the present time the hazards of therapy seem to outweigh the advantages of this utilization of imipramine.

FIGURE XXXIII

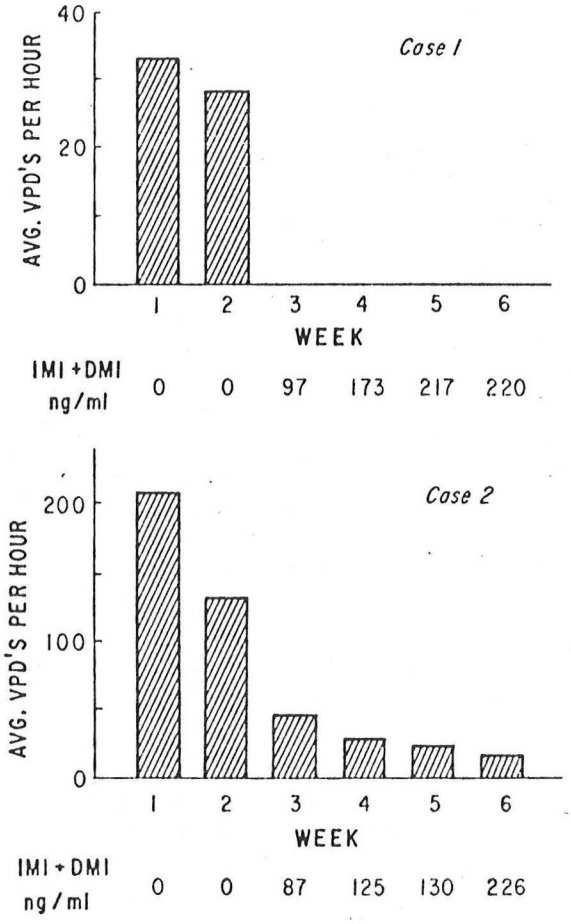


Figure 1. Effects of Imipramine Hydrochloride on Ventricular Premature Depolarizations in Cases 1 and 2.

IMI denotes imipramine, DMI desmethylimipramine, and VPD's ventricular premature depolarizations.

TRICYCLIC OVERDOSE AND MANAGEMENT

Numerous brief clinical reports highlighting the cardiotoxicity of imipramine overdose began to appear shortly after the release of the drug for clinical trials (149, 203-206). Conduction abnormalities (prolonged pR, QRS, and QT intervals), supraventricular arrhythmias, refractory congestive heart failure and pulmonary edema, and myocardial necrosis were mentioned in isolated reports of severe overdose (207-209).

Ten years of clinical use passed before a large series of tricyclic overdose was reported by Noble and Matthew (210) from a regional poison control center in Edinburg, Scotland. This study is of value in its description of the clinical presentation of 100 consecutive patients, however, these cases were collected during a period when recommended dosage for tricyclic antidepressants could be achieved with 10 mg and 25 mg tablets and prior to the tendency for mixed drug overdose. Eighty of their patients took a pure tricyclic overdose (compared to our recent study of 274 tricyclic overdoses, approximately 50% had taken a second, third or fourth drug). No deaths occurred in their series and no patient had a respiratory or cardiac arrest; it is likely that a large number of their patients would not require hospitalization if managed now in our emergency room at Parkland. The Parkland experience with overdose (225, 226) reveals that tricyclic overdoses more likely result in admission compared to the general experience with overdoses, and our problem with this overdose is steadily increasing.

FIGURE XXXIV

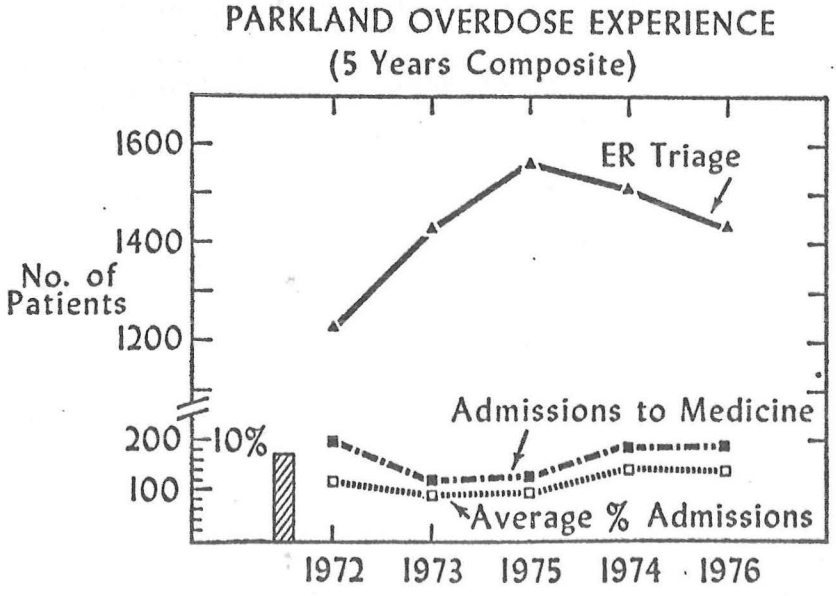
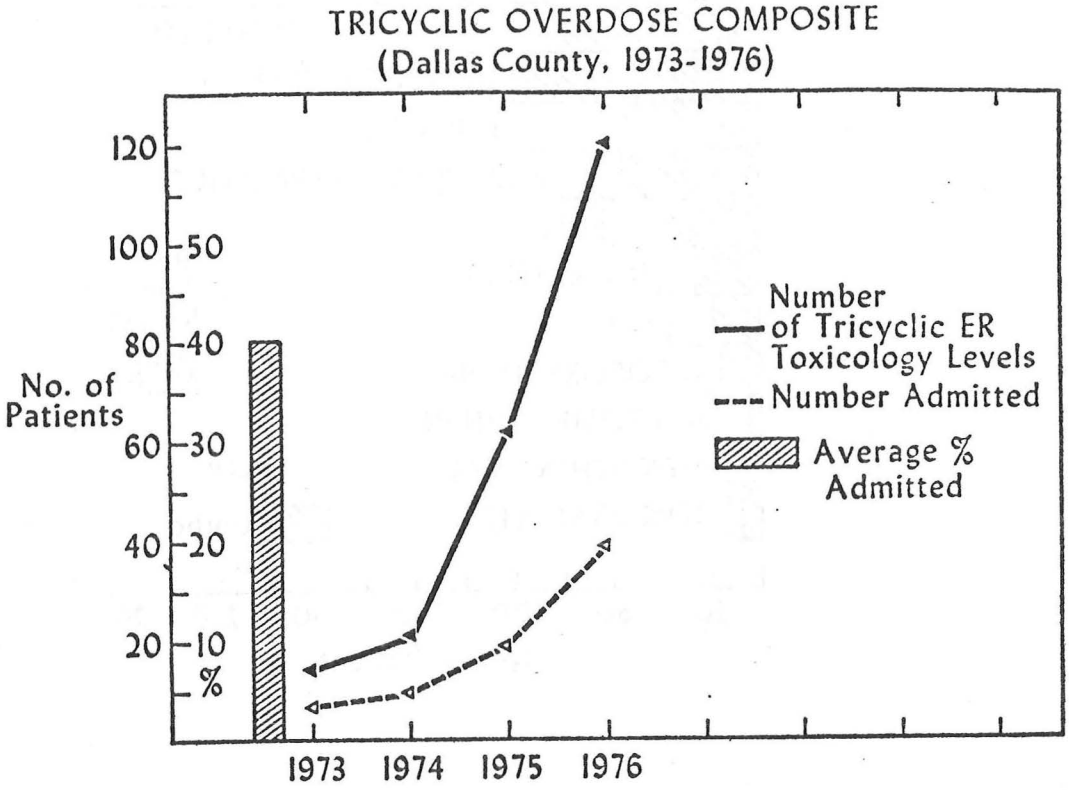


FIGURE XXXV



Note: The currently recommended dose of tricyclic varies from product to product, however, with amitriptyline, imipramine and doxepin, 150 mg to 300 mg/day are now used for severe depression, often in a single "night time" dose to improve compliance and decrease side effects. This dose does maintain an adequate steady state tricyclic blood level. Newer tablet sizes have been formulated in 50, 75 and 150 mg sizes. These larger dose forms should be utilized in the hospital setting initally, or prescribed in small numbers to ambulatory patients. Manipulative overdose gestures are seldom carried out with any forethought as to the strength of the individual tablet, however, the quantity of tablets taken suggests a tendency among patients not really intent on suicide, to gesture with less than a full prescription. In the case of 150 mg tricyclic tablets, this may change manipulative behavior into a successful (undesired) suicide.

FIGURE XXXVI

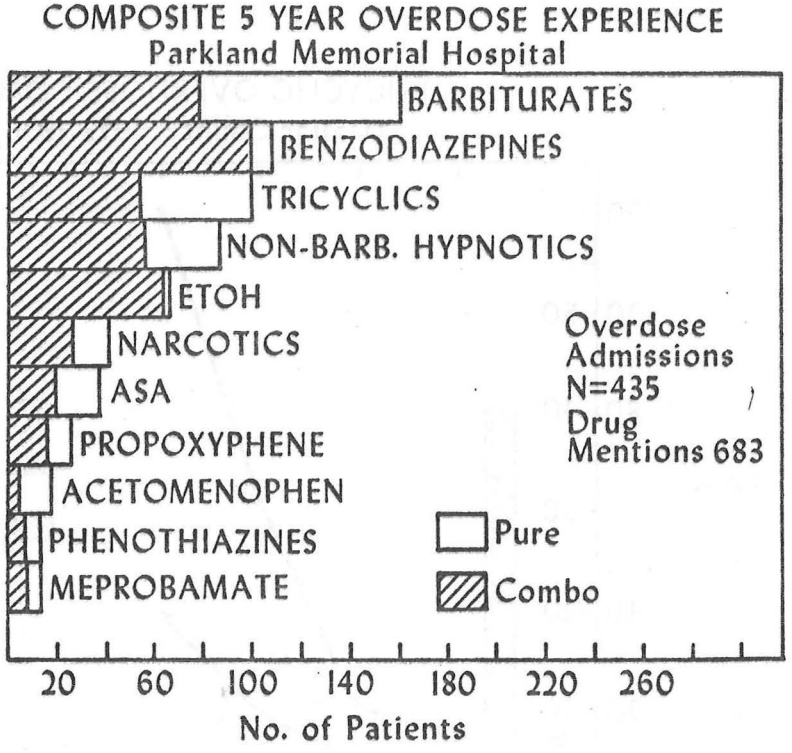
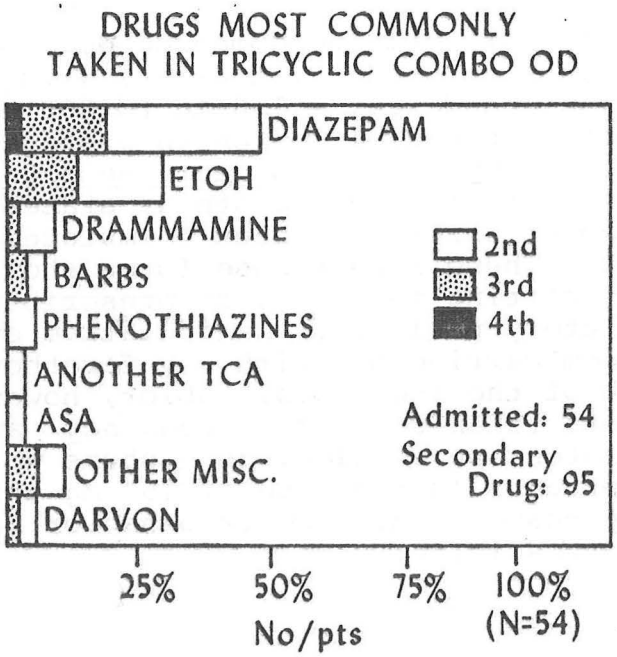


FIGURE XXXVII



In Noble and Matthew's series, fifty-one patients became comatose (mean duration of coma was 6.4 hours - longest being 18 hours). Neurologic abnormalities however frequently persisted up to 72 hours manifested by an organic brain syndrome. During the overdose 43% manifested an irritable, hyperkinetic state with many quasipurposeful movements. Jerking and pyramidal signs were seen in early coma but disappeared with deepening of coma. Six percent developed visual hallucinations, and 4% had generalized seizures. Greater than two-thirds of their patients manifested at least one sign of atropine poisoning. Hyperpyrexia developed in a smaller number of patients.

They noted that 76% of the patients had some decrease in blood pressure during the first four hours of the overdose; an initial 26 patients had a rise in blood pressure and later, 16 of these experienced a fall in pressure below their normal recovery value.

In 53%, the EKG revealed a sinus tachycardia; in 3% a conduction defect (type not described) but the severe complications of QRS widening, ventricular arrhythmias, bradycardia, AV block and asystole were not encountered. Only 6% of these overdose patient required intubation and supportive care alone was successful. The average number of pills taken was 26 (25 mg tablets) with a maximum dose equivalent of 91 25 mg tablets. This also differs from our local experience. Prescriptions are often written for more than 100 tablets. Chronic care facilities may prescribe several months supply and the tendency in American pharmacies is to provide competitive prices for prepackaged quantities of 100, 200, 300, etc., therefore the quantity of drug taken in our admission and forensic experience is greater than for the Scottish group.

The severity of symptoms on clinical presentation are dose related and a progression of symptoms may be rapid, almost apoplectic at times, because of the rapid absorption of these drugs.

The anticholinergic properties account for a blend of autonomic and central nervous system signs related to the tricyclic blockade of muscarinic receptors and manifest primarily as an atropine-like poisoning ("mad as a hatter", "red as a beet", etc.)

TABLE XV

ATROPINIC SIGNS

Peripheral

Sinus tachycardia
Normal or mildly elevated blood pressure
Mydriasis
Facial flushing
Decreased sweating
Hyperpyrexia (uncommon)
Decreased bowel motility
Bladder distention
Decreased salivation and bronchial secretion

Central

Delerium, agitation, combative behavior
Visual Hallucinations
Irritability to tactile or vocal stimuli
Pressure of speech; slurred speech
Memory disruption
Disorientation

The above symptoms are common in the mild to moderate overdose, but as the size of the overdose increases (in reference to the patients tolerance to the drug) ataxia, and inability to maintain posture supersede the agitation. Patients may go from a semicomatose state to an agitated combative state when exposed to noxious stimuli. Hyper-reflexia is common at this point and Babinski responses can often be elicited. Neurological status, blood pressure, respiration, and cardiac function need to be monitored for progression to a more serious stage, but few patients require intubation at this point and blood pressure tends to be normal. The above symptoms may respond remarkably to the IV administration of physostigmine salicylate (218-222).

FIGURE XXXVIII

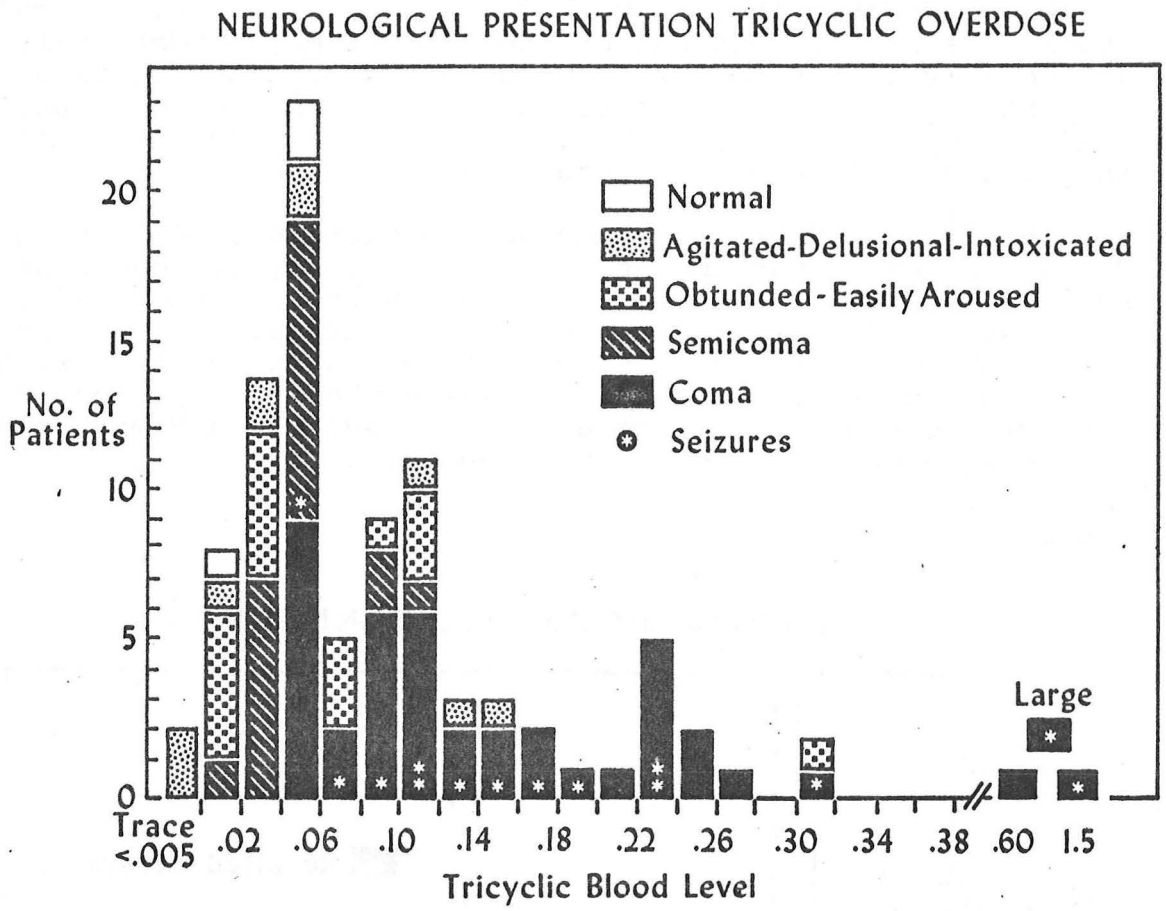


FIGURE XXXIX

NEUROLOGIC PRESENTATION N=95	%
Normal	1
Agitated-Intoxicated	10
Obtunded	22
Semi-coma	22
Coma	45
Seizures	15
(6 of 15 pts. with siezures died) 43%	

In the case of a massive overdose, or when the clinical picture described above deteriorates into a deepening coma, hyperreflexia may continue or the patient may become areflexic (especially if a secondary drug sedative overdose is also present), generalized seizure activity is likely to ensue, followed by a deep coma. During this phase choreoathetosis and myoclonic jerking may occur (217).

Unlike the Scottish study we experienced 12 CPR episodes during the early management phase of 94 tricyclic overdose admissions (225). Figures following in the protocol reflect the results of this study. Respiratory arrest occurred only in association with seizure activity or in association with a combined overdose except in one case where the patient was a respiratory cripple, from a previous suicide attempt complicated by ARDS, empyema, and pneumonia.

FIGURE XXXV

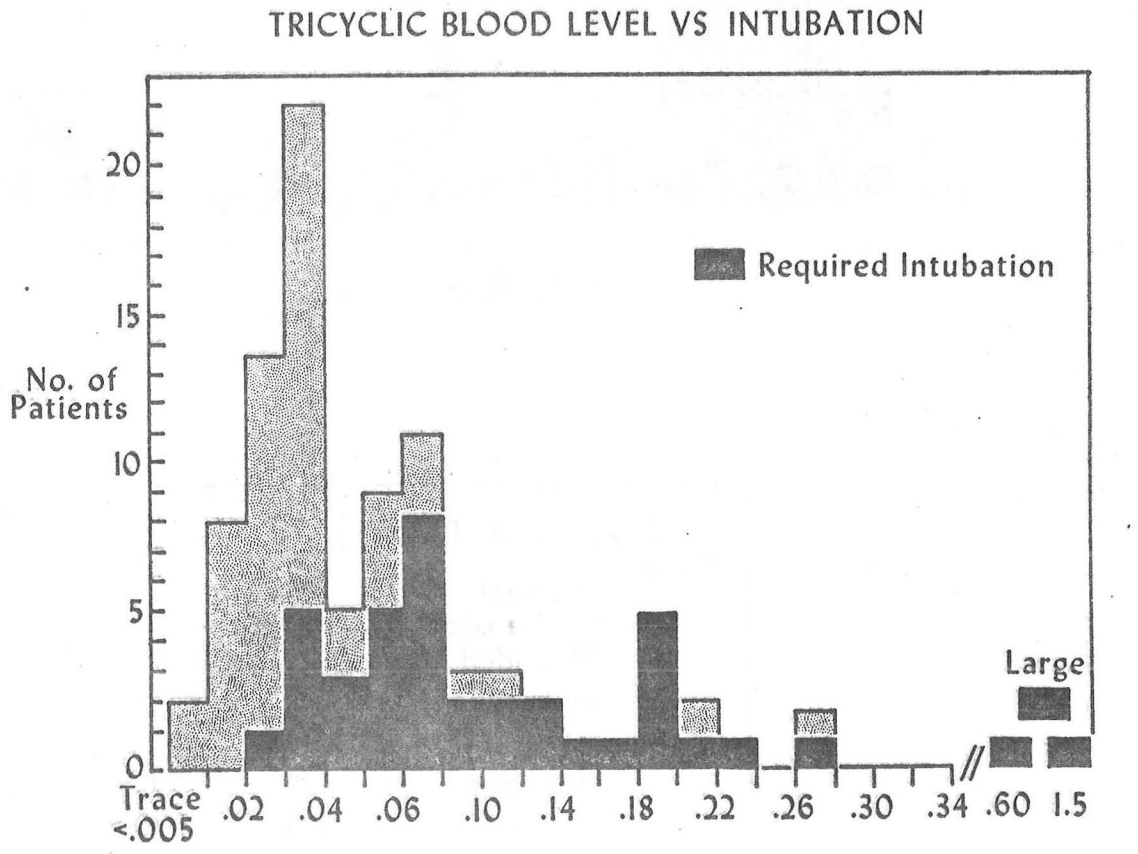


TABLE XVI

PULMONARY COMPLICATIONS	%:
Intubation Required	43
Pulmonary Infiltrates	19
ARDS	5
Pneumonia (Documented)	9
Pneumothorax	1
Empyema	1
Traumatic Intubation Requiring Tracheostomy	1
"Plugged ET" Tube	1

In a similar fashion we found very little correlation with outcome for patients presenting with hyperpyrexia (5 patients R = 102° - 104°) or hypothermia (6 patients R = 91° to 95°). Presenting blood pressure was only predictive for the hypotensive range, 6/8 patients required CPR with systolic BP < 80, 2/6, systolic blood pressure < 90, 1/5, systolic blood pressure < 100, and one patient arrested with a blood pressure of 150 systolic during a tracheostomy procedure. After the arrest, profound and refractory hypotension developed. The blood pressure values were not predictive of the tricyclic blood levels in the individual patient.

Sudden, unexpected seizures with the attendant increase in muscular activity and respiratory compromise often herald a catastrophic outcome. Seizures occurred in 15 of our patients and six of these died (43%). The respiratory and metabolic acidosis occurring during seizure activity seemed to precipitate further cardiovascular toxicity, in that widening of the QRS complex progressed rapidly and AV blocks occurred just preceding, parallel to, or just after seizure activity in our fatal cases. A low pH is known to favor the release of tricyclic compounds from tissue and protein binding and may account for this rapid downhill course leading on to bradycardia, refractory hypotension and asystole. Sodium bicarbonate has been used successfully in pediatric overdoses to shorten the QRS interval and suggest that

acidosis must be corrected as promptly as possible. The excess lactate production during seizure activity may also impair myocardial performance and contribute to heart failure.

FIGURE XXXVI

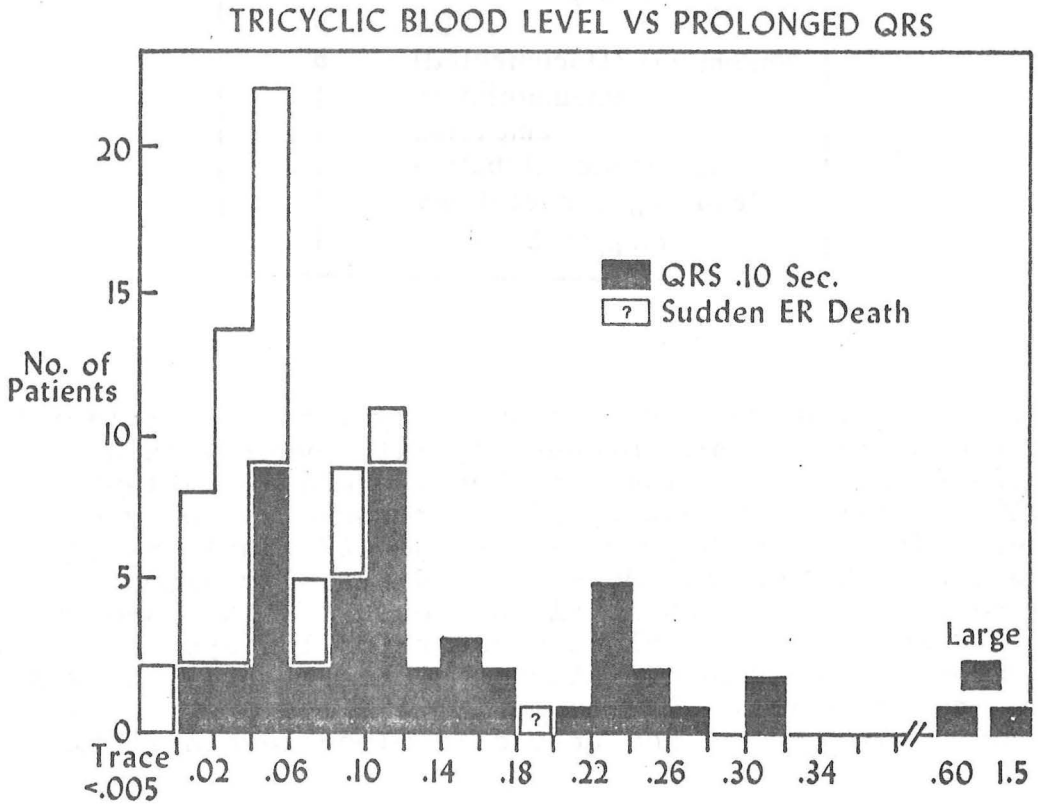


TABLE XVII

EEG MANIFESTATIONS ON PRESENTATION
(95 PATIENTS)

ARRHYTHMIAS	PERCENT
Sinus tachycardia	72
Atrial flutter	1
PAT	1
Bradycardia	3
Idioventricular	2
Ventricular or junctional tachycardia	4
Asystole	3

TABLE XVIII

EKG MANIFESTATIONS ON PRESENTATION
(95 PATIENTS)

BLOCK	PERCENT
Wenkebach	1
AV Dissociation	2
RBBB Like	42
LBBB Like	3
LPH	1
LAH	1

Thorstrand (213) and Biggs (214) each reviewing a series of tricyclic overdoses points to the clinical utility of the EKG in assessing the severity of the overdose. Our study in a much larger population confirms their reports. Sinus tachycardia is frequently present as a nonspecific anticholinergic effect. PR and QT prolongation are suggestive of a more serious overdose. Thus far the most useful criteria for assessing clinical severity in this otherwise unpredictable situation is the width of the QRS complex or the presence of AV block. A QRS complex of .10 sec. is suggestive of severe overdose and as the QRS widens beyond this point a large number of patients develop coma, seizures, respiratory insufficiency, serious arrhythmias and myocardial depression. This conduction disturbance occurs beneath the AV node as indicated by a prolongation of the HV interval of the His Bundle electrocardiogram (215).

The presence of bizarre QRS widening often heralds the onset of AV block or bradycardia. This effect is not only on the conduction systems but involves the quinidine-like direct myocardial depression seen with massive overdose. Decreased cardiac output results in a worsening of the metabolic acidosis and refractory hypotension and failure ensue, thus a viscious cycle is in motion. At this point CPR has limited success. Pacemakers were inserted in several patients during the resuscitative effort, and despite a good position, confirmed at post mortem, the capture did not occur.

Recently, temporary pacemaker insertion and overdrive pacing in a patient with a widened QRS and AV block but still adequate cardiac output yielded a successful ventricular capture and a patient salvage (EKG No. 3- see appendix included in protocol) with an uneventful recovery and discharge to a psychiatric facility after 72 hours.

Pacemaker placement in anticipation of conduction abnormalities is not warranted routinely since supportive management and drug elimination over the first 24 hours of an overdose usually allows the disturbance to resolve. The presence of a widened QRS with second degree AV block (QRS > 11), or a widening QRS complex (QRS .14 - .24) with or without associated hypotension are justification for pacemaker insertion in anticipation of more serious conduction disturbances which impair the heart's ability to maintain blood pressure and cardiac output.

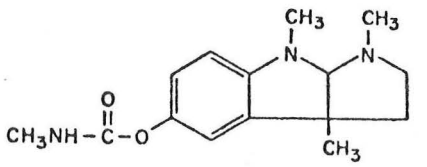
Because of associated hypotension the patients are often given excessive volume loads of saline which may exacerbate the cardiac failure. The use of pressors is of little benefit since high catecholamines and reuptake block are already present. In massive overdose sympathetic postsynaptic receptors are blocked by tricyclics. Metaraminol and norepinephrine have no place in the management of hypotension in this overdose and are likely only to potentiate arrhythmias and increase heart work. Dopamine has been used in a number of our patients but with less than spectacular results. It is imperative that acidosis and seizure activity be controlled since this may do more to improve cardiovascular hemodynamics than pressors.

The rhythm disturbances seen in tricyclic overdose are a particular problem since they often coexist with conduction abnormalities. Cardiac monitoring is suggested for 72 hours, however, in patients with a normal EKG (sinus tachycardia resolved; no arrhythmias or conduction delay) monitoring most likely is only necessary 24 hours after return of the EKG to normal, (if toxicology levels also show a declining drug level). Lidocaine is the antiarrhythmic of choice for ventricular arrhythmias since it will not as likely compound the conduction disturbance which might be expected with procainamide or quinidine (very similar wide bizarre QRS complex are seen in toxic doses with these antiarrhythmics). Propranolol may also slow AV conduction and further compromise myocardial performance and seems best avoided in this clinical circumstance.

Physostigmine salicylate and neostigmine have been successfully employed in the control of supraventricular tachycardias (223). It has also been reported to decrease QRS width and AV block (224), and in a few isolated reports, control recurrent ventricular tachycardia. This agent is very effective in its control of central and peripheral

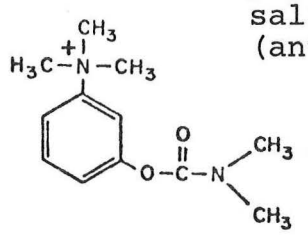
anticholinergic symptoms and has particular value in awakening a patient for whom concern exists about the need for endotracheal intubation. This drug should be used for refractory arrhythmias and for the neurological complications. The drug is short-lived and repeated doses are necessary every 30 minutes to 2 hours. Slow IV infusion of 1 to 2 mg is suggested (fast IV infusion may induce seizures) and a repeat dose can be given in 15 minutes if no response occurs. This agent should be pursued until a clinical response or cholinergic parasympathetic side effect occurs.

FIGURE XXXVII



PHYSOSTIGMINE
(Eserine)

physostigmine
salicylate
(antilirium)



NEOSTIGMINE
(Prostigmine)

TABLE XIX

Cholinergic Side Effects

Hypersalivation
Rhinorrhea
Increased broncial secretion
Dyspnea
Epiphora
Miosis
Hyperhidrosis
Emesis, diarrhea
Abdominal and biliary colic
Urinary frequency
Bradycardia

Note: If cholinergic excess occurs it can promptly be controlled by the administration of peripheral anticholinergics such as glycopyrrolate (Robinul) in a dosage of 1/5 to 1/10 the equivalent of physostigmine, or methscopolamine bromide (Pamine) in a dose of .75 to 1 mg for 3.0 mg of physostigmine. Atropine should be avoided since it has a central effect.

The contraindications to physostigmine include pregnancy, myotonia congenita or atrophica, glaucoma, mechanical bowel obstruction or bladder neck obstruction, ulcerative colitis, peptic ulcer disease, diabetes, gangrene, coronary artery disease and second degree heart block.

This agent is also useful in the management of overdose involving many over-the-counter preparations containing belladonna alkaloids, or anticholinergicsfor Parkinsonism or peptic ulcer disease.

TABLE XX

Drugs and Chemicals That May Produce Central Anticholinergic Syndrome*

- Antidepressants
  - Amitriptyline (Elavil)
  - Amitriptyline & perphenazine (Triavil Etrafon)
  - Desipramine (Norpramin, Pertofrane)
  - Doxepin (Sinequan, Adapin)
  - Imipramine (Tofranil)
  - Nortriptyline (Aventyl)
  - Protriptyline (Vivactil)
- Antipsychotic drugs
  - Phenothiazines (especially thioridazine)
- Antihistamines
  - Chlorpheniramine (Ornade, Teldrin)
  - Diphenhydramine (Benadryl)
  - Orphenadrine (Disipal)
  - Promethazine (Phenergan)
- Ophthalmic preparations
  - Atropine, 1% ophthalmic solution
  - Cyclopentolate (Cyclogel)
  - Tropicamide (Mydriacyl)
- Antispasmodics
  - Clidinium (Quarzan, & in Librax)
  - Methantheline (Banthine)
  - Propantheline (Probanthine)
- Antiparkinson agents
  - Benztropine (Cogentin)
  - Biperiden (Akineton)
  - Ethopropazine (Parsidol)
  - Procyclidine (Kemadrin)
  - Trihexyphenidyl (Artane, Pipanol, Tremin)
- Proprietary drugs (hypnotics, analgesics, antiasthmatics)
  - Asthmador (belladonna or stramonium alkaloids)
  - Compoz (scopolamine, methapyriline, pyrilamine)
  - Excedrin-PM (methapyraline)
  - Sleep-Eze (scopolamine, methapyraline)
  - Sominex (scopolamine, methapyraline)
- Belladonna alkaloids
- Toxic plants
  - Bittersweet (*Solanum dulcamara*)
  - Potato leaves & sprouts (*S tuberosum*)
  - Deadly nightshade (*Atropa belladonna*)
  - Jimson weed or "loco" weed (*Datura stramonium*)
  - Mushrooms (especially, *Amanita muscaria*, which contains an atropine-like principle)

Despite its place in this protocol, lavage or ipecac emesis, charcoal administration and catharsis are primary management procedures. Charcoal does bind tricyclics, and combined with catharsis interrupts a significant enteroheaptic circulation. The anticholinergic properties of these drugs may cause adynamic ileus and delayed drug absorption may continue as reflected by increasing blood levels (this may account for some of the "late sudden" deaths reported with tricyclics). Castor oil, an irritant cathartic is necessary since osmotic agents such as Citrate of Magnesia cannot overcome ileus.

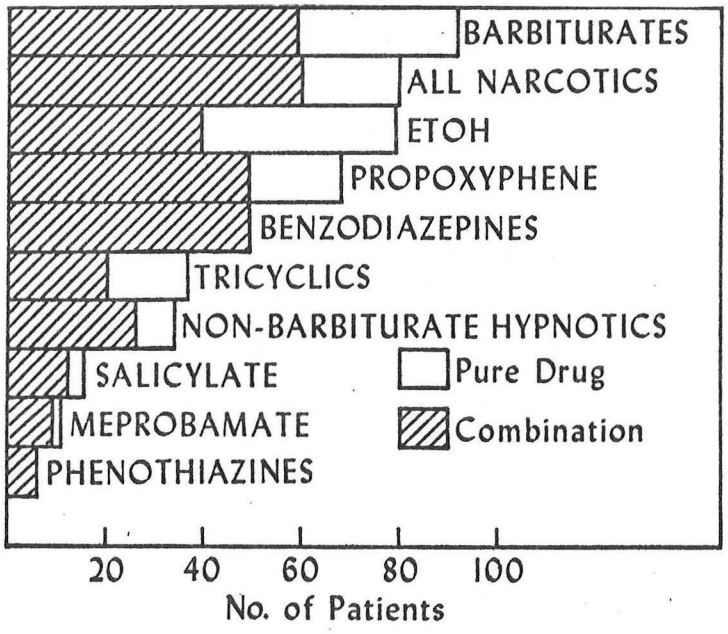
Other avenues for enhanced drug elimination are ineffective emphasizing the necessity of removing the drug from the GI tract as quickly as possible. It is reasonable to repeat charcoal and catharsis in the second 24 hours of hospitalization if initial blood levels were high.

The Parkland Experience

The experience with tricyclic overdose at Parkland Hospital includes 274 ingestions, 94 requiring hospitalization in an intensive care situation, with 7 deaths (7.5%). Women outnumbered men 3:1 but age, amount consumed, and tricyclic blood levels were similar as was mortality and morbidity. Two additional deaths were seen by physicians and reviewed by the Dallas County Forensic Pathology Department, they are included in our "Hospital or ER Deaths". An additional 30 cases of fatal tricyclic overdose came to the attention of the Dallas County Forensic Pathology Dept. during this same period. Figure XXXVIII compares the total number of fatal drug ingestions for Dallas County during that same period.

FIGURE XXXVIII

OVERDOSE-DEATHS BY DRUG CATEGORY
Dallas County, 1973-June 1977



There was a marked tendency for combination overdose (48/94 admissions, 6/9 hospital or ER deaths, 20/30 forensic cases).

High drug levels were associated with a poor outcome. A trend for serious complications and/or death in mixed drug overdose was seen at lower tricyclic blood levels.

	Hospital or ER Deaths	Secondary Drugs Mentioned	Forensic Deaths
No. of	3	Ethanol	11
drug	3	Diazepam	10
mentions	2**	Phenothiazine	5*
	1	Barbiturates	5*
		nonbarbiturate hypnotics	4*
		Flurazepam	3
		Meprobamate	2*
		Propoxyphene	2**
		ASA	1

Mean tricyclic Blood level (mg%):

Mixed OD (R = .06 to .31)

Pure OD (R = .107 to 1.12)

Mixed (R = (.05-.94)
Pure (R = 0.1 - 6.9)

MLL level (Dallas County Forensic Path. 0.5)

*Each asterisk represents one potentially lethal secondary drug.

The inclusion of cases taking a potentially lethal dose of a secondary drug prohibits conclusion concerning the role of the tricyclic blood level in mixed overdose where fatalities occurred with levels ordinarily not associated with severe complications. The following tables review tricyclic blood levels in patients presenting to the Parkland Emergency Room with amitriptyline, imipramine, and doxepin overdoses and compares their disposition and outcome to the toxicology. A summary table of all tricyclic overdose deaths and their blood levels is also appended.

FIGURE XXXIX

AMITRIPTYLINE OD BLOOD LEVELS

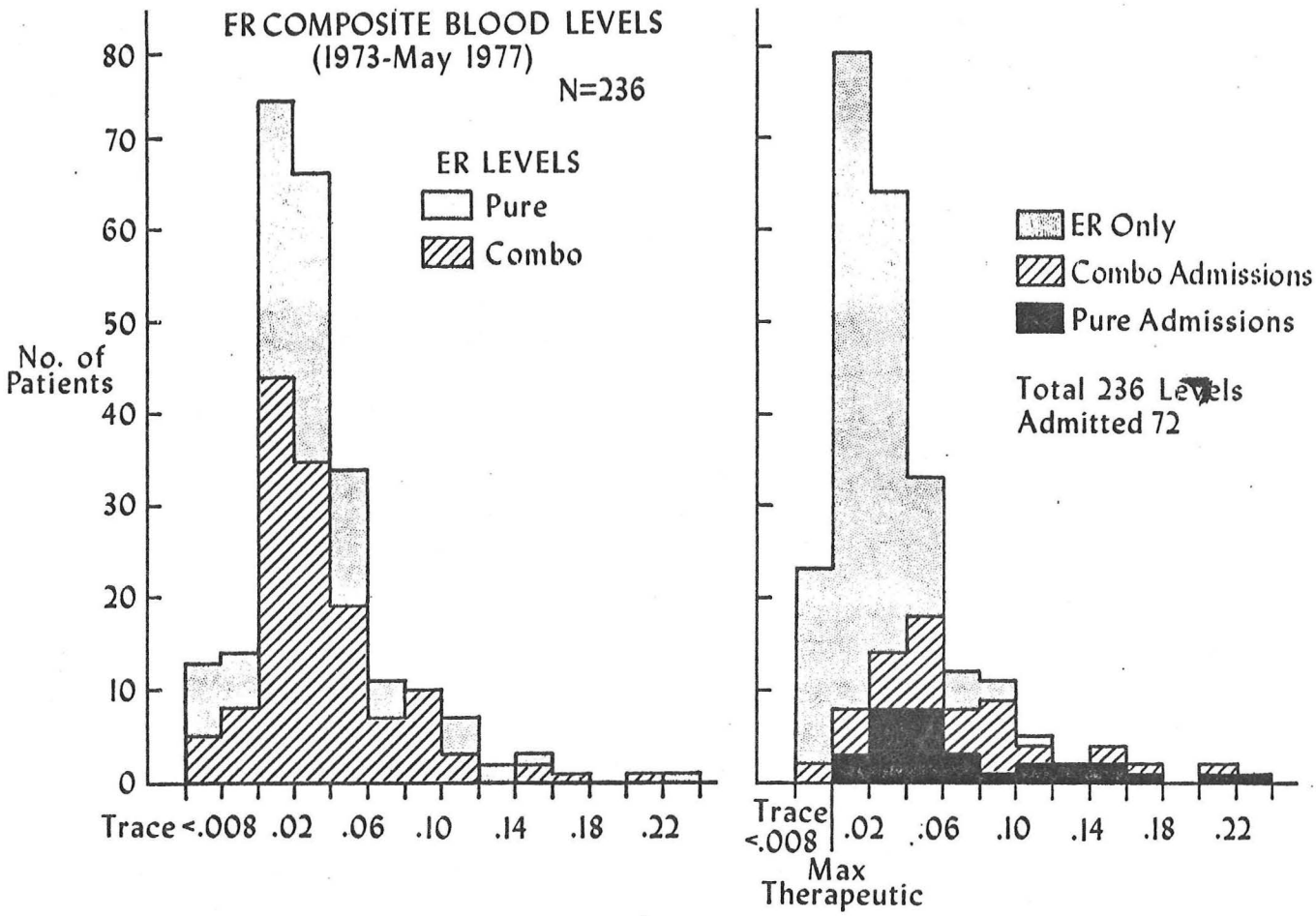


FIGURE XL

AMITRIPTYLINE OD

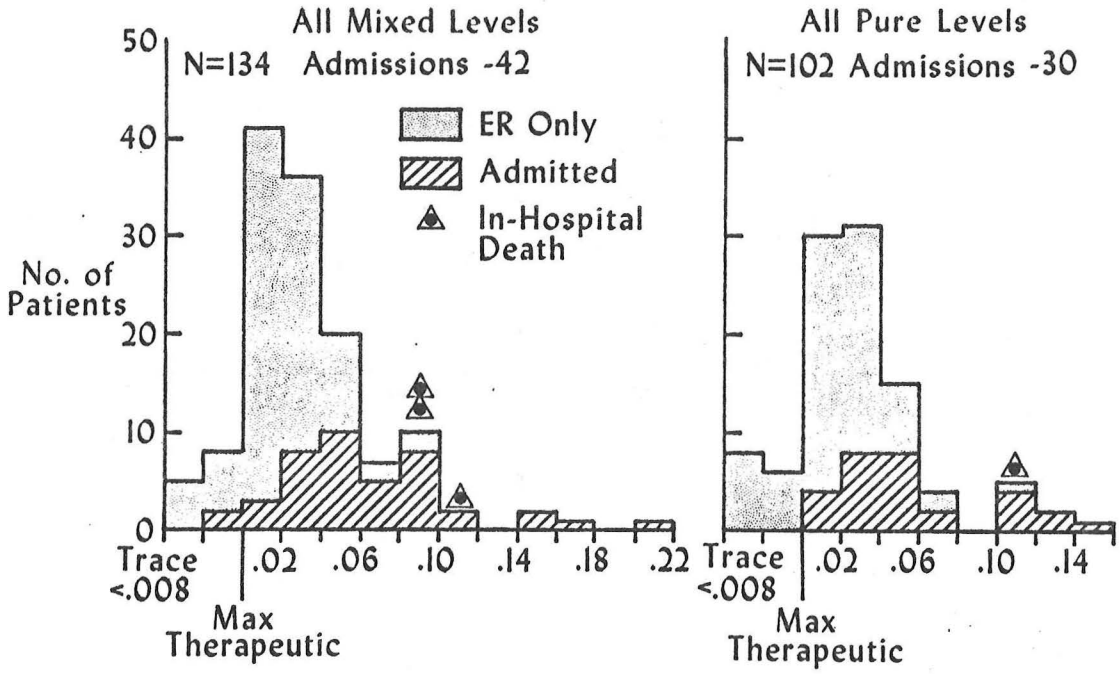


FIGURE XLI

DOXEPIN AND IMIPRAMINE LEVELS VS OUTCOME

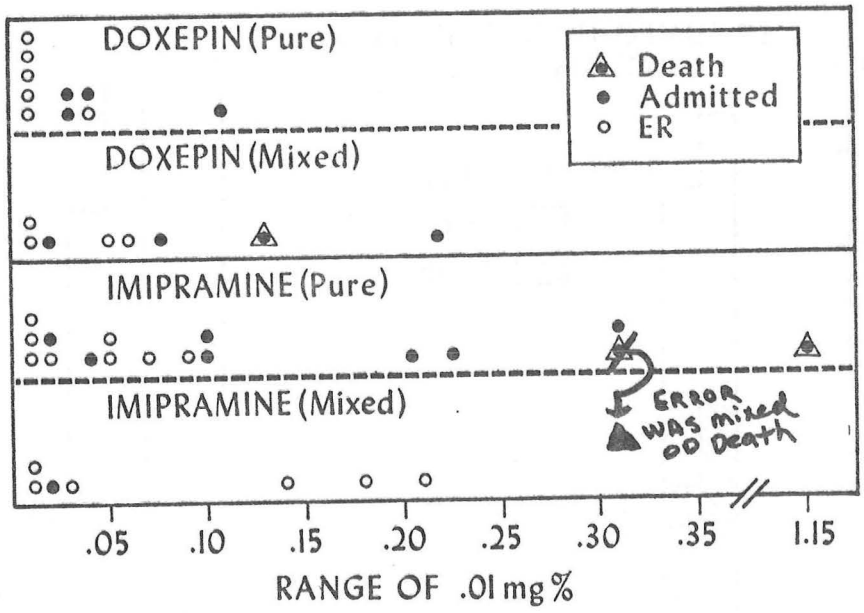
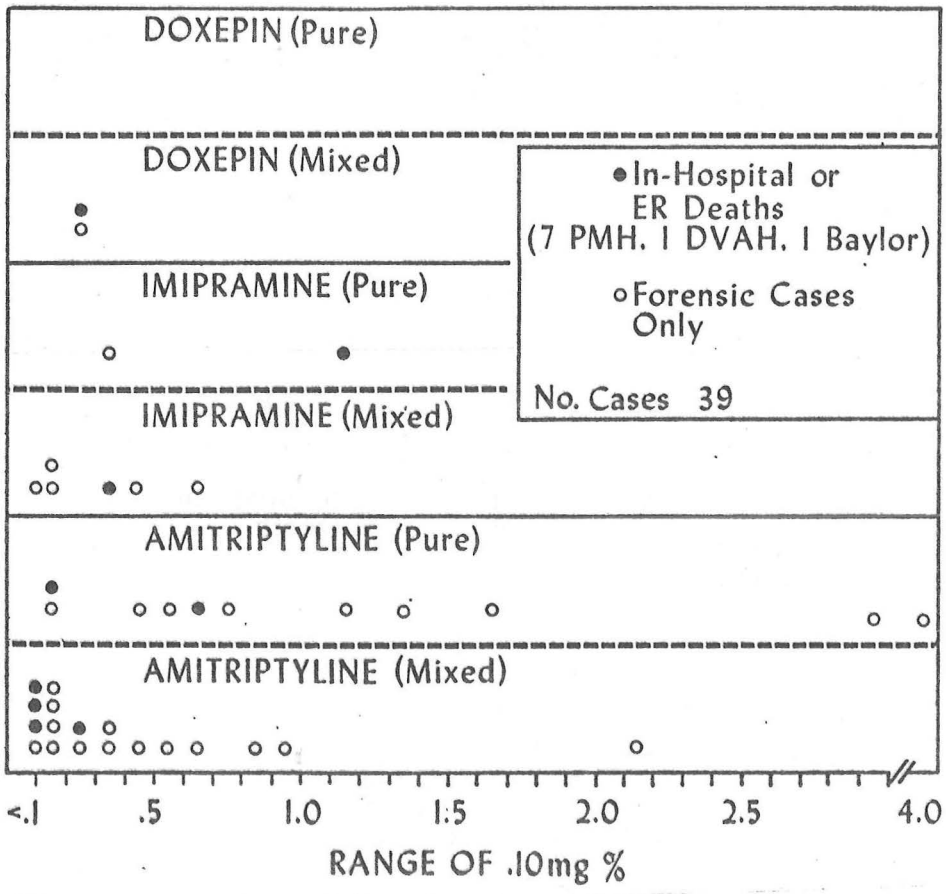


FIGURE XLII

TRICYCLIC BLOOD LEVEL IN FATAL CASES
(Five Years — Composite Experience for Dallas County)



Treatment Summary:

The treatment of tricyclic poisoning requires prompt transfer to an intensive care situation with continuous cardiac monitoring. The onset of life-threatening symptoms may be extremely rapid. Resuscitative measures should be close at hand. Supportive care is usually all that is required (respiratory support, volume control, correction of acidosis, treatment of seizures), and the "basics", lavage and catharsis should not be overlooked. The EKG provides an accurate guide to the severity of the overdose and the abnormalities described in the protocol warrant admission, regardless of the patients neurological or respiratory presentation.

Physostigmine salicylate should be used with appropriate precautions in this overdose situation and the addition of any drug to the management regime should be balanced against the risk of potentiating the tricyclic toxicity. Sodium bicarbonate may be an effective agent when QRS widening and cardiovascular deterioration occurs in association with acidosis. Finally, pacemaker insertion should be considered with advancing conduction delays complicated by hypotension or decreased cardiac output.

Finally, the patient must not be forgotten after the crisis resolves. Psychiatric intervention is mandatory, for the patient remains at increased risk for successful suicide until effective antidepressant therapy is established or the acute situational reaction has passed. Beck's suicide scale may be of benefit in deciding whether or not a patient is likely to resort to suicide. Even if the overdose is considered manipulative in nature, it distinguishes a very ill patient likely to repeat the overdose, sometimes with success despending primarily on the "tools at hand". See Beck's suicide ideation scale in appendix).

The utilization of the tricyclic antidepressants for the ameloriation of depression carries attendant but acceptable risks. These risks can be minimized by careful attention to possible adverse drug interactions and the avoidance of secondary drugs that may decrease the tricyclic's efficacy and provide a weapon for self-destruction.

ACKNOWLEDGEMENT

I wish to thank Mrs. Flora Toney for her assistance with the Parkland Audit on "Suicide Attempt with Tricyclic Overdose" conducted for the Parkland Audit and Ethics Committee by Drs. Anderson and Lee.

CASE REPORTS: HOSPITAL OR ER TRICYCLIC DEATHS

HOSPITAL DAYS	AGE/SEX RACE	BLOOD LEVELS MG %	RESPIRATORY COMPLICATIONS	CVS COMPLICATIONS	NEUROLOGICAL COMPLICATIONS
ER Death	21/F/LA	Amitriptyline .19 Phenobarb. FA .200	Intubated post seizure; "plugged" ET tube discovered during CPR	B/P 110/80; sinus tachycardia; asysole. RBBB during CPR.	Came in alert; progressed rapidly to seizures, coma; T 104F
ER Death	21/F/W	Imipramine .31 Ethanol 0.042 Diazepam 0.03	Intubated post seizure.	B/P 122/92, fell suddenly to 70/50; CPR initiated, asystole on EKG; the preceding rhythm had been sinus tachycardia with prolonged PR (pt. was not on monitor at time of arrest); Pacemaker placed after arrest; failed to capture.	Came in alert; progressed rapidly to seizures, coma; Sudden arrest.
4 Hours	25/M/W	Imipramine 1.12	Intubated in ER; Airway protected by paramedics prior to ER arrival.	B/P 80/60, "VT" at home (by telemetry). On arrival at PMH, a junctional rhythm with RBBB was present. Admitted, arrested 4 hrs later after developing "wide, bizarre QRS, hyoptension, cyanosis. Pacemaker placed during arrest, failed to capture (good position at post mortem exam).	Coma, seizures at home; areflexic on arrival.
3 Hours Dallas VA Hosp. Case	38/M/W	Amitriptyline .63	Intubated with deepening coma and areflexia	BP 80/50, ST 110; alert on admission, RBBB pattern with progressive widening of the QRS. Tachycardia interrupted by brief episode of AV dissoc.; BP fell to 50/30, CVP ↑ 24, S3 developed, QRS >.24 secs, and a pacemaker was placed, did not capture; pt went on to develop idioventricular rhythm, V-fib and asystole.	Alert on arrival; became obtunded, progressing to coma and areflexia; recurrent seizures postintubation.

(SEE EKG STRIP IN PROTOCOL FOR THIS PATIENT'S CPR COURSE)

CASE REPORTS: HOSPITAL OR ER TRICYCLIC DEATHS
(PAGE 2)

HOSPITAL DAYS	AGE/SEX RACE	BLOOD LEVELS MG %	RESPIRATORY COMPLICATIONS	AV COMPLICATIONS	NEUROLOGICAL COMPLICATIONS
4 Hours	35/F/W	Amitriptyline .16 Nortriptyline .07 Chlorpromazine 3.70* Diazepam .04 Ethanol .249	Intubated post seizure	Arrested on arrival to Baylor ER, admitted to the MICU. QRS showed RBBB. 3 hrs later, AV block, hypotension, & cardiac arrest occurred. EKG showed a junctional rhythm progressing to an idioventricular rhythm, and finally asystole. Could not be resuscitated.	Ingestion 1 hr PTA. Seizures on ER presentation. Initially improved with physostigmine and sodium bicarbonate. Diazepam and DPH controlled seizures until second arrest when continuous seizure activity occurred.
BAYLOR CASE - ADMISSION EKG IN PROTOCOL					
13 Days	57/F/W	Amitriptyline 0.097 ASA 19.0	Intubated; Developed ARDS, Pseudomonas Pneumonia.	B/P 0/0 on arrival; ST 120, QRS .10-.11 RBBB like, → CPR started, patient progressed to asystole; resuscitation successful but prolonged. B/P 80/0 after CPR, EKG ICRBBB.	Seizure, coma, anoxic encephalopathy.
20 Days	29/M/W	Amitriptyline .107	Intubated; developed ARDS, Pneumonia, DIC, etc.	ST 110, Normal QRS widened to a bizarre pattern; .14 sec, AV dissoc. followed. A bradycardia (R 20) occurred. Was unresponsive to Isuprel but improved with correction of respiratory & metabolic acidosis. RBBB persisted for approx. 36 hrs. Normal EKG at death.	Seizures in ER; coma followed; became arousable 2 days later; never alert post CPR.
8 Days	35/F/W	Doxepin 0.13	Intubated for respiratory arrest; developed ARDS; died of respiratory insuffiency.	ST 100, QRS .12, B/P 80/50; Cardiac arrest x 2 over first 72 hours.	Seizures, apnea, anoxic encephalopathy.

CASE REPORTS: HOSPITAL OR ER TRICYCLIC DEATHS
(PAGE 3)

HOSPITAL DAYS	AGE/SEX RACE	BLOOD LEVELS MG %		RESPIRATORY COMPLICATIONS	AV COMPLICATIONS	NEUROLOGICAL COMPLICATIONS
8 Days	58/F/W	Amitriptyline Thioridiazine	.06 .44*	Obese patient, "intubated prophylactically" to allow lavage. Pt. was comatose, reflexic. An airway laceration complicated the nasotracheal intubation necessitating an emergency tracheostomy to maintain an airway compromised by subcutaneous and mediastinal emphysema. ARDS developed, died of respiratory complications.	B/P 150/90; ST 100; EKG 1st AV block, QRS .10 During the tracheostomy resp. acidosis developed the QRS widened; bradycardia, and hypotension followed. Arrest occurred during the trach procedure. CPR of 40 min.	Comatose, reflexic. After CPR, recurrent seizures and anoxic encephalopathy ensued.

* Potentially lethal secondary drug.

MEDICAL RECORD | PROBLEM ORIENTED PROGRESS NOTES

PROBLEM DATE | NO.

Format - Problem title (Do not abbreviate) S - Subjective O - Objective A - Assessment P - Plans. (All notes must have signature and title of person making entry.) Continue on reverse.

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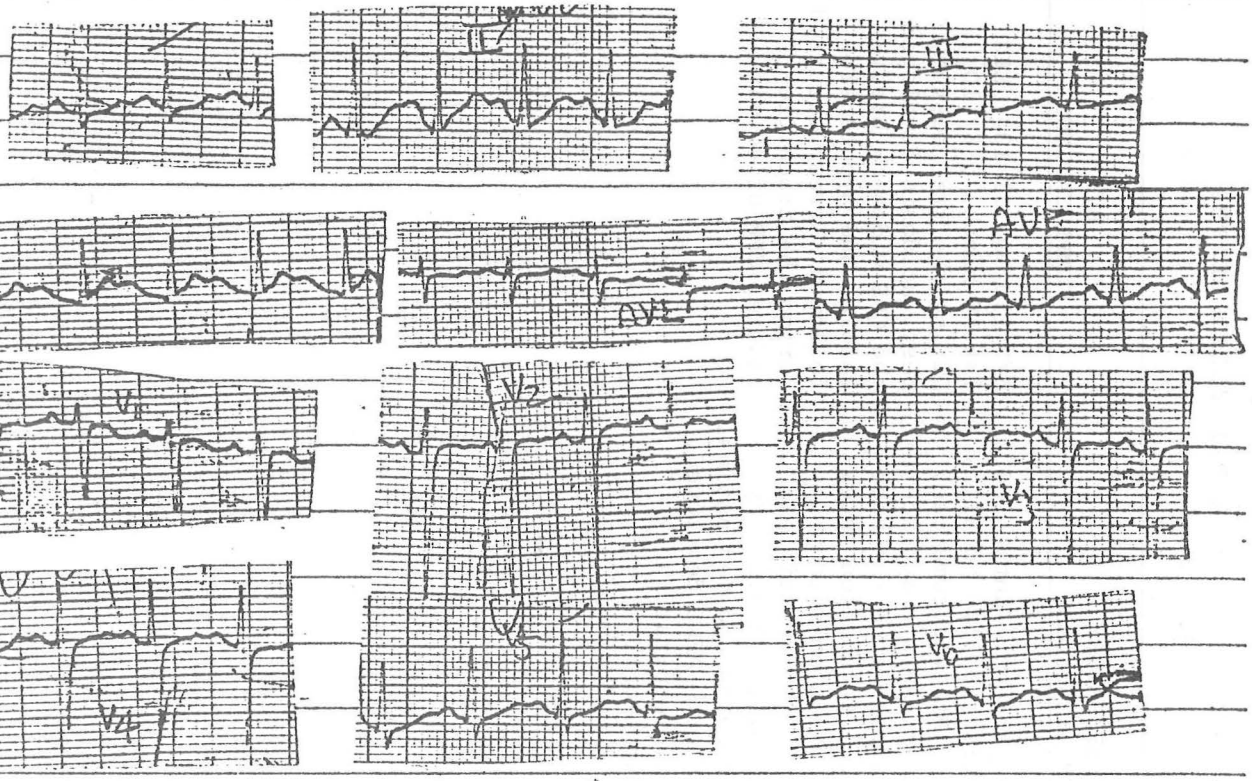

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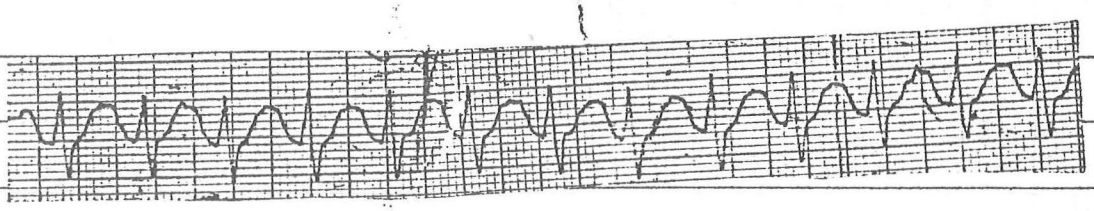

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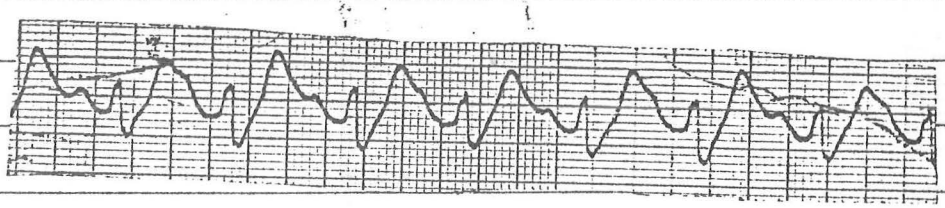

DALLAS VA CASE REPORT: EKG series #1

DATE | NO. | CONTINUE FORMAT SAME AS ON FACE OF FORM

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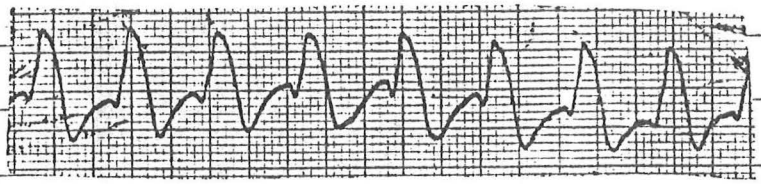

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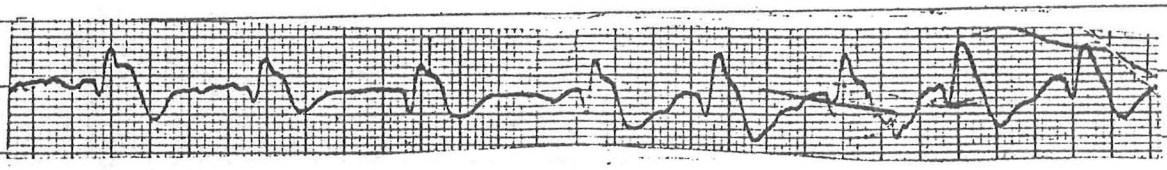

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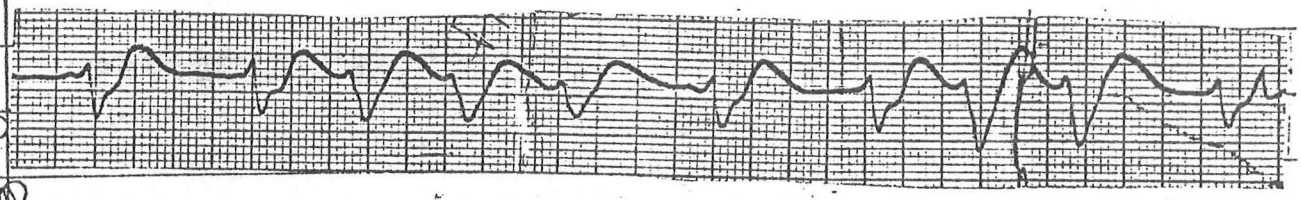
BP 50/30
CVP 3
S3 Gallop



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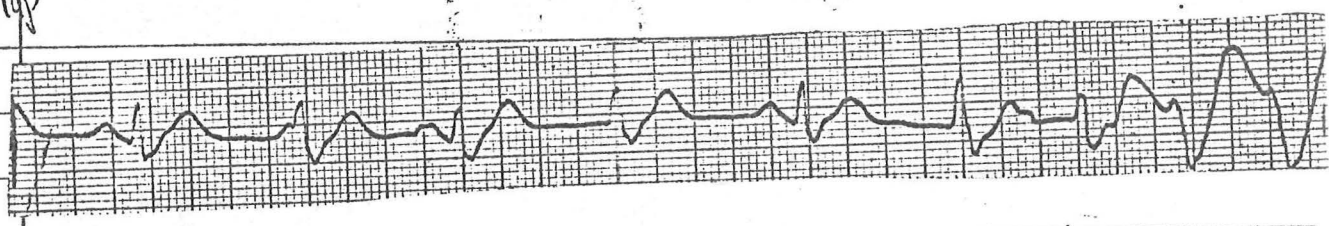

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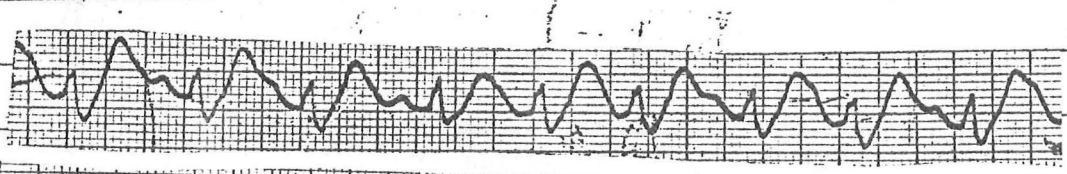
Lead I



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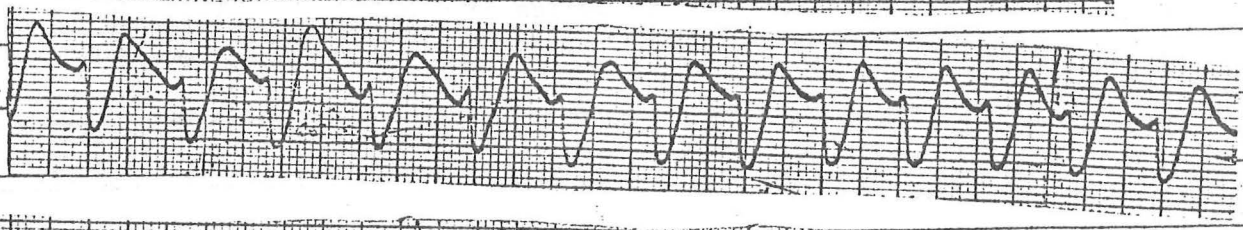
Lead II



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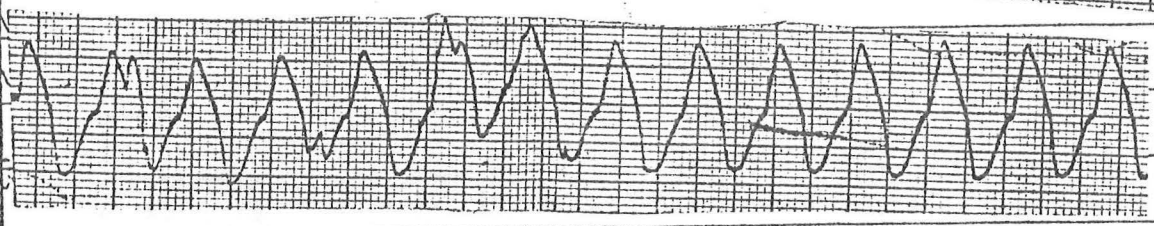
Lead V
BP 30/20
CVP 24
on Dopamine



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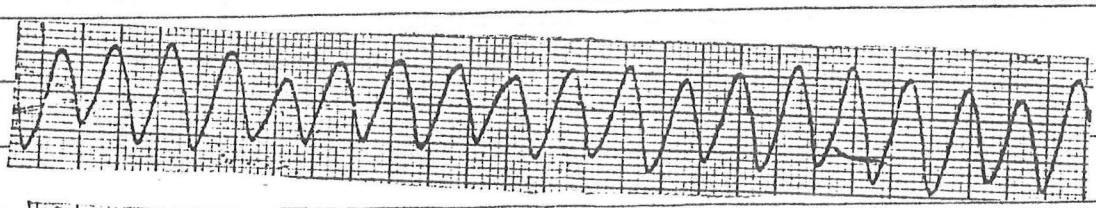

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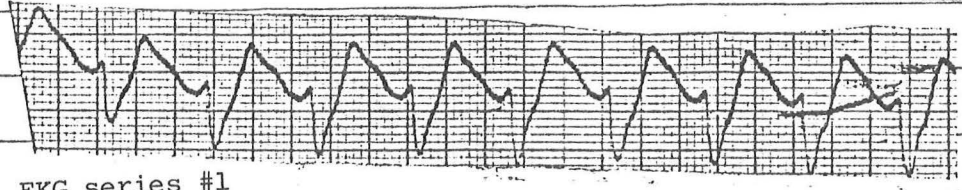

EKG series #1

MEDICAL RECORD | PROBLEM ORIENTED PROGRESS NOTES

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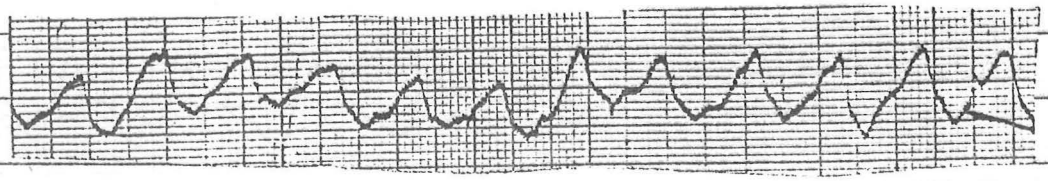

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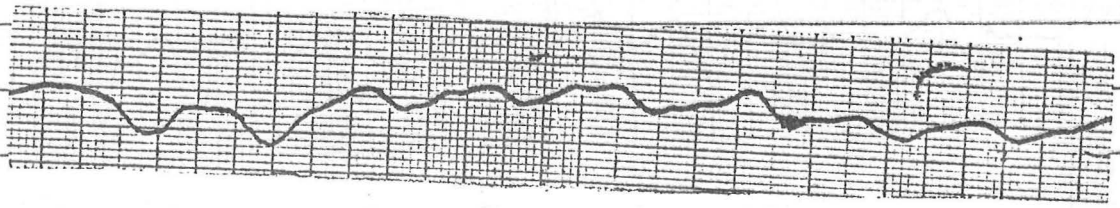
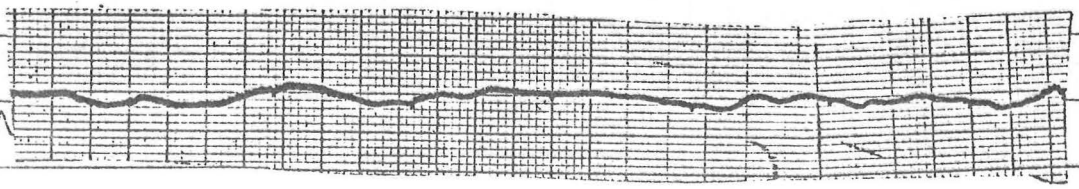
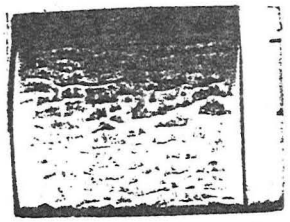
Lead II



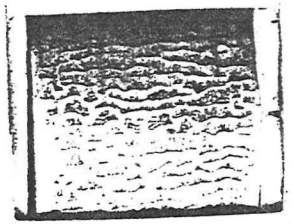
8:35 AM
Lead II
Premature
P



Dallas VA Case Report
EKG series #1



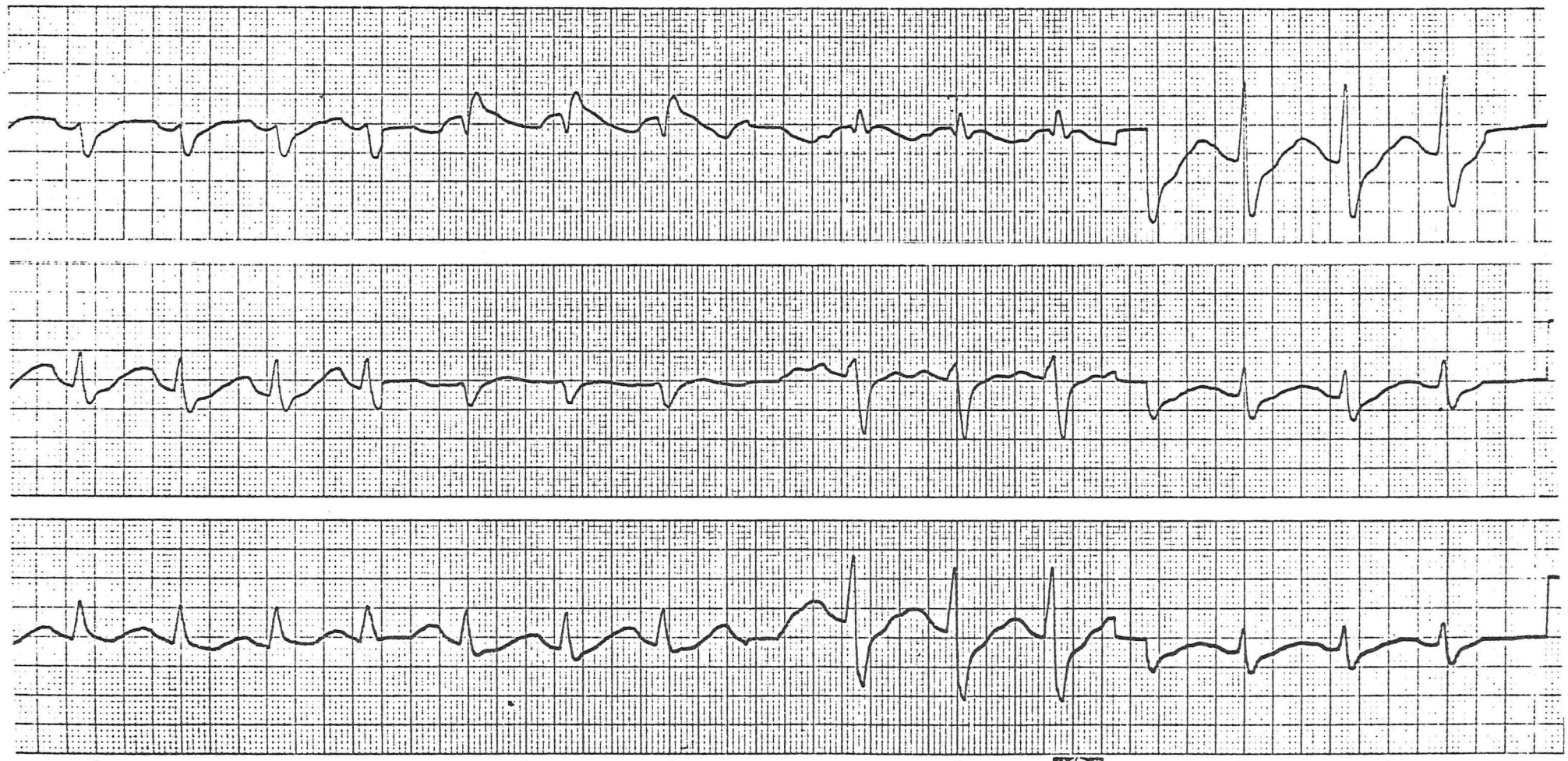
BAYLOR CASE REPORT
Admission EKG, #2



CARDIOLO

AXIS

V1 – V2 – V3 | V4 – V5 – V6 | CAL. 1



HEWLETT • PACKARD | MEDICAL EL

LEADS 1-2-3 | AVR – AVL – AVF | V1 – V2 – V3 | V4 – V5 – V6 | CAL. 1 M

EKG series #3- An 18 year old girl with amitriptyline overdose, transferred to PMH from East Texas, Arrival EKG

LEAD FORMAT

I	AVR	V1	V4	X
II	AVL	V2	V5	Y
III	AVF	V3	V6	Z

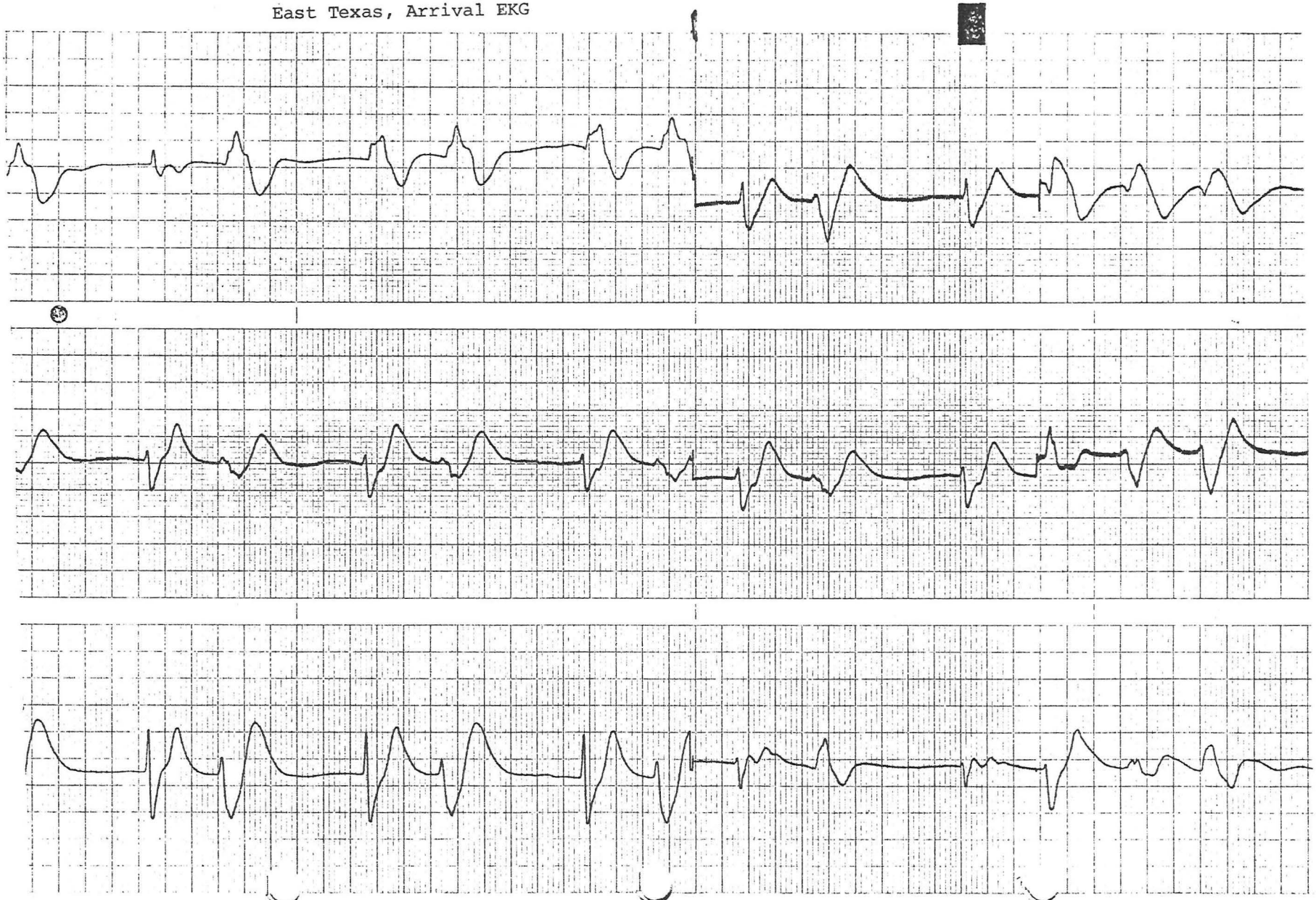
RATE_____ PR_____ QRS_____

QT_____ AXIS_____

DRUGS_____

OPTIONAL

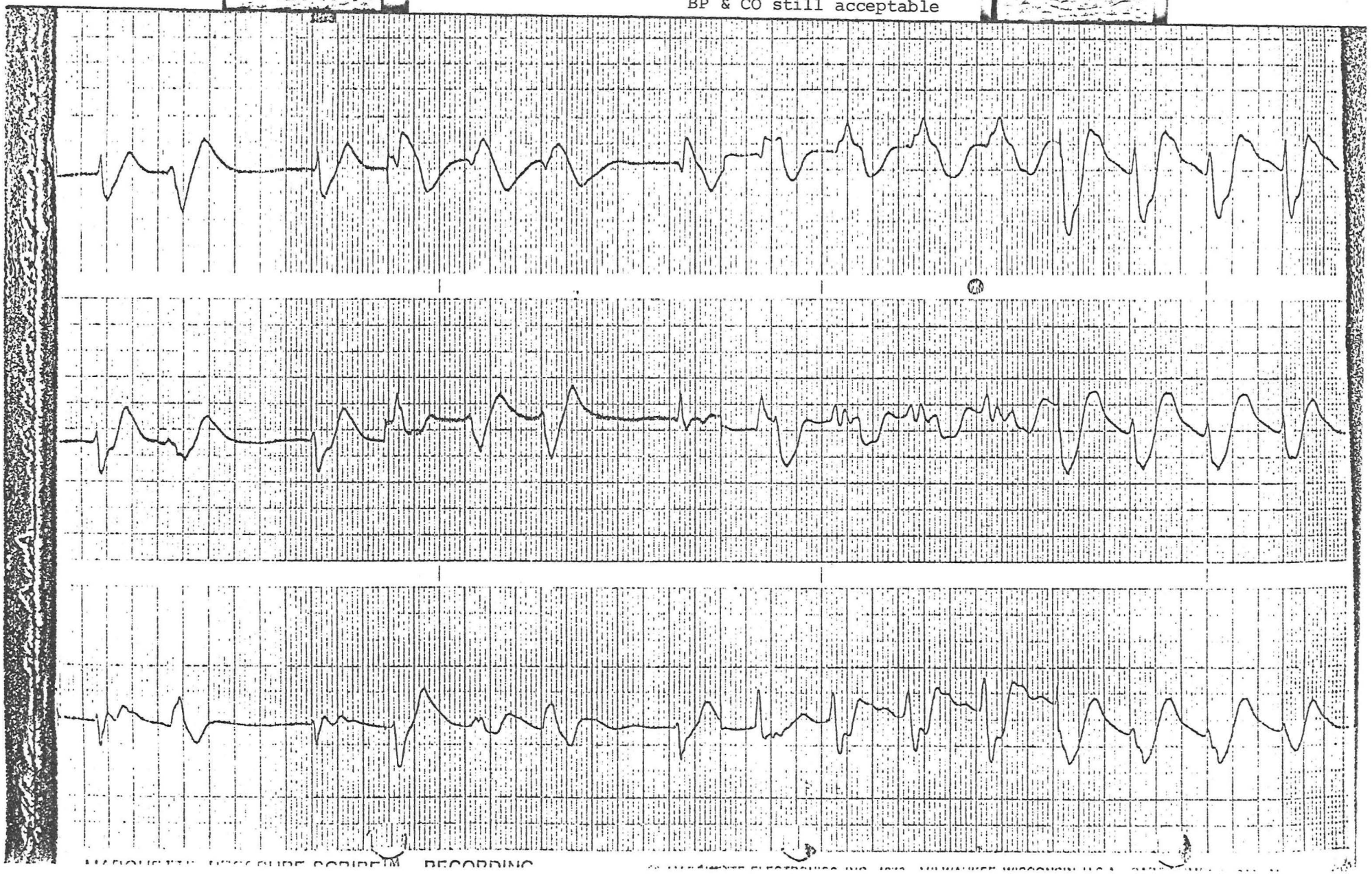
SPLIT CAL PULSE AT LEFT INDICATES 1/2 STD. ON PRECORDIAL LEADS ONLY

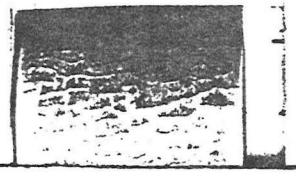


WAUKEE, WISCONSIN, U.S.A. - PART NUMBER 9040-201

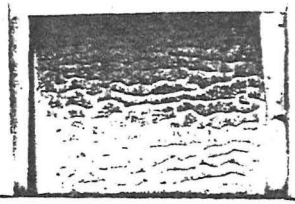
MARQUETTE PRESSURE-SCRIBE™ RECORDING

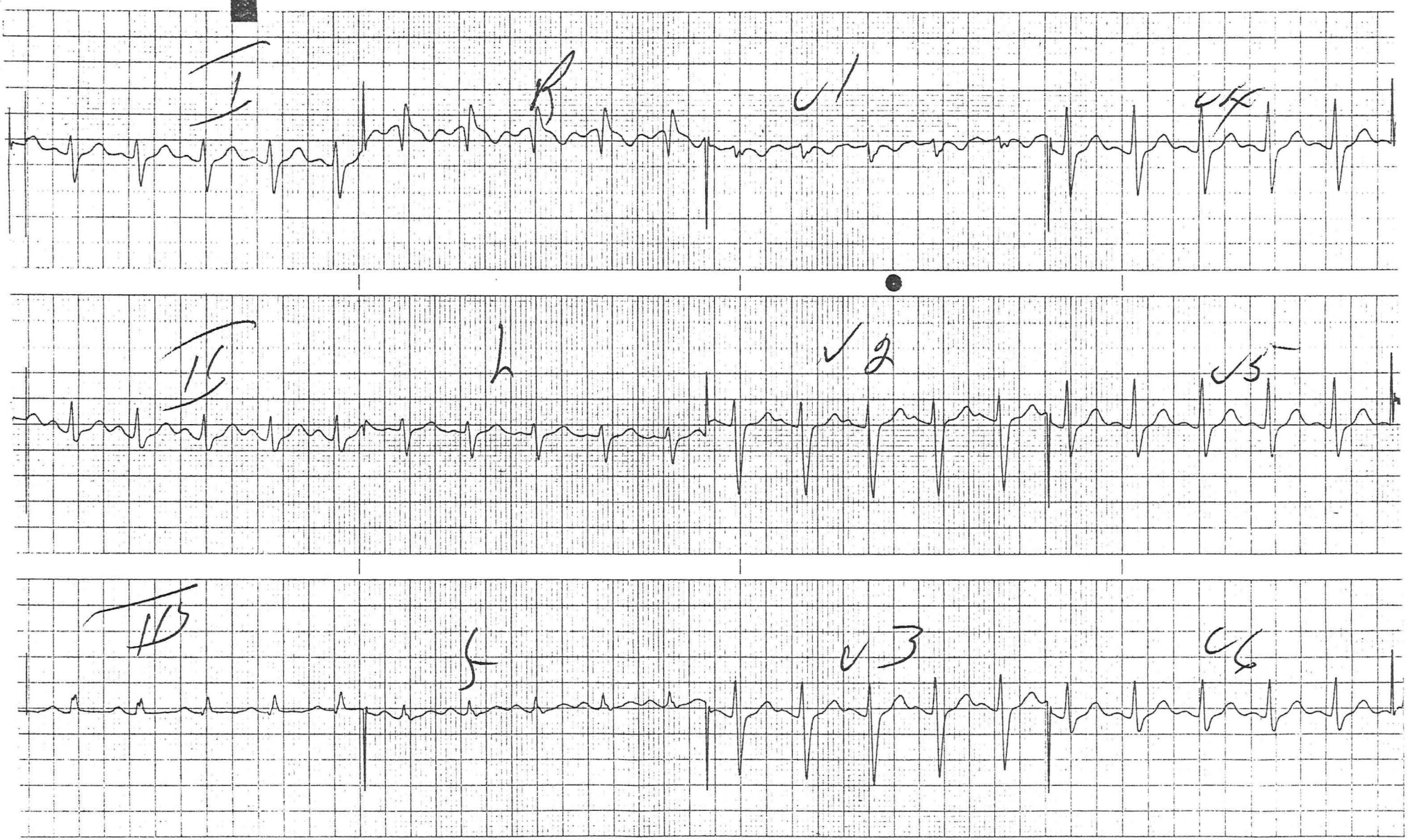
EKG series #3 Rhythm just prior to
to pacemaker insertion,
BP & CO still acceptable





EKG series #3 EKG after discontinuation of of temporary pacemaker 24 hours later.





MARQUETTE PRESSURE-SCRIBE™ RECORDING

BECK'S SUICIDAL IDEATION SCALE

"The situations and responses it lists are meant to be guidelines for a very unstructured interview. The interviewer should cover them all in his questioning, but he shouldn't hew to them at the expense of inter-reaction with his patient."

1. Another's* report of patient's intent to attempt suicide
   0. No intent, or very slim chance
   1. Possibility, or will try under certain conditions
   2. Definite intent

2. Patient's report of own intent to attempt suicide
   0. Wants to live
   1. Isn't sure, doesn't care, or is "waiting to see"
   2. Definitely wants to die

3. Patient's attitude toward living
   0. Gives good reasons for living
   1. Says reasons for dying equal or outweigh reasons for living
   2. Sees no reason for living

4. Patient's feelings about his suicidal thoughts
   0. Feels negative, frightened, or disturbed about them
   1. Is in acute distress or is ambivalent about them
   2. Accepts or welcomes them

5. Specificity of ideation
   0. Has abstract and general thoughts (i.e., I'm thinking of suicide") without visualizing specific events or circumstances related to suicide as: method, place, funeral, or results of death
   1. Has thought of some specific events or circumstances related to the act of suicide
   2. Has considered many specific events or circumstances related to the act of suicide

6. Urgency of ideation
   0. No urgency--keeps his thoughts under control
   1. Is afraid he will be driven to do something he doesn't want to do, and/or wants someone to control him
   2. No longer makes any attempt to keep suicidal thoughts under control, and may in fact be carrying the thoughts into action

7. Time course of ideation
   0. Isolated and fleeting thoughts at well-spaced intervals
   1. Frequent isolated thoughts, periods of persistent thoughts (hours or more) at well-spaced intervals, or habitual thoughts
   2. Current and persistent thoughts, occupying the patient's mind in a manner he finds unusual

*Family member or close friend

8. Patient's perception of sources of help
   0. Has numerous and reliable sources
   1. Sources exist, but are few or unreliable
   2. Has nowhere to turn

9. Seeking help
   0. Has not sought help because he hasn't felt a need for it
   1. Has sought help or is seeking help
   2. Has not sought help because he doesn't want interference with his suicidal thoughts or plans

10. Preparations for death
    0. None
    1. None, but has thought about them
    2. Have been made or are under way

11. Suicide note
    0. Not thought about
    1. Considered, but not planned out or written
    2. Planned out or written

12. Method
    0. Not thought about
    1. Possibilities have been considered but no method picked out
    2. Has been definitely chosen

13. Means by which method will be put to use
    0. Have not been obtained or worked out (as, pills not purchased, type of pill not decided, means of hanging not decided)
    1. Have been obtained or worked out to some extent, but are not instantly accessible or ready to be put to use
    2. Are ready at a moment's notice

14. Plan
    0. Not thought about
    1. Possibilities being considered, but none is definite
    2. Definite plan worked out

15. Stage of plan
    0. Not ready to put into effect
    1. About to be put into effect
    2. Is nearing completion

SCORING:

Responses are presented in increasing order of seriousness--a "0" response is cause for negligible concern, while a "2" is cause for greatest concern. A cumulative score of 15 represents a severe risk of suicide.

SUICIDE BEHAVIOR - DIAGNOSIS & MANAGEMENT

Resnik

FACTOR	HIGH RISK	LOW RISK
Age	45 - over	45 - under
Sex	Male	Female
Race	White	Non-white
Marital status	Separated, divorced, widowed	Single, married
Employment	Unemployed	Employed
Health	Poor	Good
Living arrangements	Alone	With others
Mental condition	Nervous/Mental Disorder (including alcoholism)	Normal
Method	Hanging, firearms jumping, drowning	Cutting, gas, co-poison
Potential consequence of method	Likely fatal	Harmless
Police description of condition of patient	Unconscious/ semi-conscious	Normal, disturbed, drinking, ill
Suicide note	Yes	No
Previous attempt	Yes	No
Disposition	Admitted to Psychiatric Center	Discharged to self or relative

Scale = 1 for each category of high risk (score 0-14)

Score of 4 was cut off point.

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