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# CURRENT PROBLEMS IN CLINICAL TOXICOLOGY

## 1. Organic Phosphorus Ester Intoxication

As a suicide attempt, a 25 year old W/F ingested approximately 300 cc of Ortho Fruit Tree Spray Insecticide. Some 45 minutes later she arrived at ER. She was confused, salivating profusely, weak, had nonreactive miotic pupils. She had vomited several times. After arrival, muscle fasciculations were noted. This was a combined intoxication including both Malathion and DTT. If the insecticide was undiluted and the amount taken correct then this represented a profound intoxication, at least of Malathion. The patient received PAM and atropine and within a period of about 4 hours had little or no effects of intoxication. However, some 12 hours later she again was weak, with muscle fasciculations, increased secretions and confused and lethargic. Serum cholinesterase was in the 0.05 units/hour range without PAM and would rise to 0.20 units/hour while PAM was administered. All signs and symptoms would improve with the administration of PAM and atropine. PAM and atropine administration were continued for about 9 days. The patient eventually recovered.

## 2. Dextro Propoxyphene Overdose 1

Immediately after informing her family that she had just taken an unknown number of Darvon capsules, this 18 year old B/F fell to her knees and began to have a generalized convulsion. On arrival at ER she was not breathing and there was some question just how long she had not been breathing. Nevertheless, she was resuscitated without great difficulty and brought to MICU. Naloxone was used with apparent benefit. Her course was 4 days during which time she had only a marginal circulatory system which eventually failed. There were no other convulsions. She never regained consciousness. Toxicologic examination disclosed large amounts of propoxyphene in the liver.

## 3. Darvon Overdose 2

A 39 year old W/F took an unknown number of 65 mg Darvon capsules approximately 8 hours prior to arrival at ER. On arrival she was unresponsive except to deep pain. Pupils pin point. Respirations varied between 8-12 per minute and appeared shallow. She was admitted to MICU. Shortly after arriving in MICU she had a generalized tonic clonic convulsion. She had received 0.8 mg of Naloxone in ER which had brought her respiratory rate to 19-22 and perhaps decreased the depth of coma. For the next 8 hours she had repeated convulsions, more prominent on right side of body. Naloxone was used in ever increasing doses in an effort to control these; however, after 12.4 mg was used without apparent benefit, diazepam was substituted. Although convulsions continued, each could be controlled by IV diazepam. The following day the patient awoke and eventually recovered.

4. Methaqualone Intoxication

A 26 year old W/M was brought to ER in coma some 6 to 8 hours following the oral ingestion of 30-35 Quaalude tablets (approximately 10 gm). On arrival he was intubated and underwent gastric lavage. His vital signs were normal. His pupils were dilated but did react to light. All reflexes present and equal. There was some response to deep pain. He was transfered to MICU. On being transfered to bed, he stopped breathing. He was immediately connected to a positive pressure breathing machine. BP 70/0, P 120, Temp 98. Over the next several hours he required respiratory control. The depth of coma decreased and he again tripped the machine. BP came up with saline infusion. Tachycardia slowed. No muscle rigidity was noted. An admission ECG was not remarkable. Later the patient stated that he had abused both uppers and downers for the past 12 to 18 months. He also stated he had taken less than 20 Quaalude (obtained from his sister's prescription) and no other drugs.

5. Heavy Metals - Arsenic Poisoning

An 18 year old female was seen in consultation about four months after she had ingested about 0.92 gms of $A_s$ as arsenic trioxide in a suicide attempt. At that time she had acute gastrointestinal symptoms characterized by severe abdominal pain and watery diarrhea of about 1 hour duration. On admission to a hospital she received 3.0 mg/kg B.W. BAL, repeated q4h for three doses. This was followed by q8h injections of 1.5 mg/kg for 48 hours. The dose was then reduced to 1.0 mg/kg q12h for about 48 hours. At that time the patient had no gastrointestinal signs or symptoms. She complained of "shotting pains" in her legs and feet which was thought to be the result of BAL therapy. Therapy was, therefore, discontinued with relief of symptoms. No urinary arsenic values were obtained. No azotemia developed. However, decreased sensation in feet developed. At the time of consultation, patient had complete bilateral "dropfoot", no proprioception in feet and no response to light touch or pin prick from toes to mid-calf bilaterally. The dosage schedule for BAL was not unlike that recommended in Goodman and Gilman.

6. Organic Solvents - Carbon Tetrachloride

A 22 year old female sought medical aid for nausea and vomiting of 48 hours duration. She had had a severe sore throat some 2-3 days prior to the onset of her gastrointestinal symptoms. There were no significant physical findings, however, a routine urinalysis disclosed RBC and RBC casts. Following admission, she was seen in consultation. She had evidence of mild liver dysfunction and a hospital course typical of acute tubular necrosis. History eventually developed that: 1) Three days prior to admission she cleaned a sofa pillow (with $CCl_4$ containing solvent). 2) The day after cleaning she had 2 vodka martinis and fell asleep on the recently cleaned pillow. She recovered.

7. Amphetamine

An 18 year old male received an intravenous injection of an unknown amount of dissolved Dexidrine tablets. He was hyperactive following injection and insisted upon running. Eventually he broke from his friends and was later found some six miles away by police in a confused, "drunken" state. On admission to the emergency room a small amount of dark reddish bronw urine was obtained. He was essentially anuric for 2 days oliguric for 10 days. He diuresed and recovered. This is thought to be an example of myoglobinuria secondary to amphetamine OD.

8. Narcotics - Oral Methadone Intoxication

A 44 year old woman was an on and off hard narcotic user. She applied to a Methadone treatment center for help and received sixty 10 mg tablets for her first week's therapy. She immediately took 49 tablets and arrived at the ER comatose. She responded to Naline to some extent and was admitted to the ward. She had a low $pO_2$ for about 72 hours without $CO_2$ retention or metabolic acidosis. Chest x-rays which were at first compatable with pulmonary edema slowly resolved. $pO_2$ returned to normal. Heart appeared to decrease in size over the 36 hours after admission. Venous pressure was not measured.

9. Sedative Drug Intoxication - Anoxic Injury

Following discovery, this 44 year old woman was admitted in a comatose state. Blood Placydil level was discovered to be 9 mg%. On admission, vital signs were normal, but pupils were dilated and fixed. Blood gases, obtained after intubation, were normal. However, BP slowly fell to the point that pressors were needed to maintain minimal urine output, and eventually all response to Norepinephrine was lost. At about 98 hours post admission asystole unresponsive to all measures occurred. At post, evidence of cerebral anoxia was found.

10. Barbiturate Intoxication - Gastric Contents

A 24 year old woman, a known barbiturate addict, was placed in jail. There a cellmate observed the patient take many 100 mg Seconal capsules. Some 12 hours after ingestion and coma, the cellmate reported her observation. On admission the patient was in anesthetic coma. Gastric lavage revealed a red fluid. This fluid and subsequent washings were assayed for Seconal content and found to contain 6.8 gms.

11. Doriden Intoxication - High Blood Level

The patient, a 54 year old male, in a modestly intoxicated state threatened suicide. When scorned by his wife he ingested 11 to 13 gms of Doriden. This action, having no immediate effect, the patient drank about one pint of vodka in a matter of minutes. Coma quickly developed. On arrival in the ER a short time later, his blood Doriden level was found to be 12.4 mg%. He recovered from his intoxication only to die of a mediastinitis secondary to tracheostomy.

12. Analeptics - A Possible Role

The patient was a 45 year old woman with a long history of alcoholism. She had ingested about a pint of isopropyl alcohol which had induced a profound coma. Although intubated, secretions were a problem. However, when an infusion of Emivan was given prior to endotracheal tube suctioning, she could be induced to cough. She made an uneventful recovery. What part the analeptic played is of course unknown.

## COMMON POISONINGS

The problem:

In the United States per year -

21,000 suicides
2,700 deaths from drugs
2,100 deaths from barbiturates

9,000 deaths from chemicals
4,500 of these suicides
1,100 due to pesticides

For each suicide there are 15-20 attempts

In one year, over 60 x $10^6$ prescriptions for tranquilizers; 46 x $10^6$ for barbiturates.

ADMISSIONS TO PARKLAND FOR DRUG OVERDOSE AND POISONING

| Year | 1962 | 1963 | 1970-71 Sept. - Aug. | 1971-72 Sept. - Aug. | 1972-73 Sept. - Aug. |
|---|---|---|---|---|---|
| Total | 23 | 53 | 102 | 76 | 62 |

I. Concepts in Clinical Toxicology:

A. Alter metabolism - Although of potential, thus far only useful alteration that can be made is the block of methyl alcohol, and perhaps ethylene glycol, metabolism by ethyl alcohol.

B. Alter absorption - Two practical approaches at this time:

1. Forced emesis and gastric lavage.

Forced or induced emesis

1) Distention of stomach with fluid followed by mechanical stimulation of gag reflex.

2) Syrup of ipecac - oral use only
a) 5-20 ml
b) Time to emesis may be prolonged (> 20 min).

3) Apomorphine - parenteral use only

   a) 5 mg subcutaneously or perhaps IV, 20 to 50 µgms/Kilo
   b) Rapid response (5-10 min).

4) Irritant emetics should not be used.

5) Emetics may not be useful in many tranquilizer intoxications.

Gastric lavage

Only method in comatose patients. Should not be undertaken in caustic or petroleum poisonings. Patient should have endotracheal tube in place before lavage (very important with Doriden).

1) Use only isotonic saline
2) Three to six liters
3) In most intoxications, gastric tube should be removed after lavage.

2. Use of adsorption and/or chelation agents.

At the present time, chelation agents are used mostly in chronic industrial intoxications, and the results are often dubious.

Adsorption agents appear to have a role in acute drug intoxication.

In Aqueous Solution: Adsorption by 1.0 gm Activated Charcoal*

| Substance | mg Adsorbed |
|---|---|
| Mercuric Chloride | 1800 |
| Morphine | 800 |
| Atropine | 700 |
| Sodium Barbital | 150 |
| Barbiturates; short acting | 300-350 |
| Salicylic Acid | 550 |
| Alcohol | 300 |

*Modified from: Andersen, A.H. Experimental studies on the pharmacology of activated charcoal. Acta Pharm. and Tox. 2:69, 1946.

Adsorption of Drugs and Poisons by Activated Charcoal from Simulated Gastric Fluid*

| Good | Moderate | Poor | Not At All |
|---|---|---|---|
| Amphetamines | Meprobamate | $FeSO_4$ | Tolbutamide |
| Primaquine | Chlorpromazine | Malathion | Substance not soluble in acid aqueous solute. |
| Chlorpheniramine | Quinine | DDT | |
| Colchicine | Chloroquine | Boric Acid | |
| Dilantin | Quinidine | Methyl Carbamate | |
| Aspirin | Methyl Salicylate | | |
| Iodine | Doriden | | |
| Phenol | | | |
| Darvon | | | |

*From: Decker, W.J. et al. Tox. and Appl. Pharm. 13:454, 1968.

3. Decrease intestinal transit time. No good method in deeply comatose patient. We use castor oil to attempt this.

C. Alter excretion -

1. Using existing pathways:

Forced diuresis: If substance is excreted into urine, diuresis will invariably increase excretion, but unfortunately, only to a limited degree in most instances.

Bromide Intoxication

| Treatment | Serum $[\bar{Br}]$ Half Life, Hrs.* |
|---|---|
| None | 432 |
| NaCl | 30-65 |
| Osmotic Diuresis | 37 |
| Mercurial and NaCl | 9-16 |
| Ethacrynic Acid | 1.7-5 |
| Hemodialysis | 0.8-2.1 |

*Modified from: Adamson, J.S. et al. Ann. Int. Med. 65:749, 1966.

Forced diuresis plus urine alkalinization of urine: This is very effective therapy and usually the therapy of choice in Aspirin and Phenobarbital intoxication. Unfortunately, no other common substances meet the criteria for alkaline diuresis.

2. Using artificial pathways:

Peritoneal dialysis: Perhaps adequate for methyl alcohol intoxication. Most likely of little use in other intoxications.

Hemodialysis: Of use in methyl alcohol intoxication. Of debatable use in other intoxications except when renal or hepatic function is significantly reduced.

See references regarding oil dialysis, activated charcoal dialysis, and exchange resin perfusion.

Percentage Of Drug Remaining In Plasma After Dialyzing*

| Drug | Dialysis solution alone | | | Dialysis solution with activated charcoal | | |
|---|---|---|---|---|---|---|
| | 1 Hr | 3 Hr | 5 Hr | 1 Hr | 3 Hr | 5 Hr |
| d-Amphetamine | 50 | 41 | 43 | 48 | 20 | 6 |
| Meprobamate | 81 | 53 | 51 | 74 | 30 | 8 |
| Phenobarbital | 65 | 47 | 50 | 56 | 18 | 10 |
| Glutethimide | 87 | 87 | 81 | 86 | 51 | 18 |
| Methyl Salicylate | 67 | 63 | 54 | 63 | 30 | 15 |
| Aspirin | 73 | 64 | 62 | 57 | 27 | 19 |
| Pentazocine | 75 | 56 | 50 | 75 | 48 | 18 |
| Secobarbital | 73 | 51 | 31 | 53 | 35 | 13 |
| Methaqualone | 83 | 73 | 65 | 78 | 53 | 37 |
| Chlordiazepoxide | 100 | 100 | 90 | 98 | 98 | 50 |
| Diazepam | 90 | 87 | 66 | 82 | 65 | 43 |
| Diphenylhydantoin | 100 | 93 | 87 | 93 | 80 | 60 |
| Chloroquine | 72 | 61 | 58 | 59 | 48 | 43 |
| d-Propoxyphene | 94 | 71 | 56 | 82 | 62 | 48 |
| Amitriptyline | 91 | 71 | 66 | 85 | 66 | 57 |

*From: Decker et al. Tox. and Appl. Pharm. 18:573, 1971.

Gastric suction might be helpful in some drug intoxications, but insufficient data to evaluate.

D. Antidotes - Few clinically useful substances in existance.

Anti Narcotic - Closest to true antidotes.

Naloxone (Narcon) - Currently the most appropriate anti-narcotic drug available. Is probably devoid of depressant effects (especially respiratory).

Levallorphan (Lorfan); Nalorphine (Nalline) - Older anti-narcotic drugs now superseded by Nalorone.

Cyclozocine - Not yet clinically available, but probably will be as useful as Naloxone.

Heavy Metals - Not true antidotes, but rather chelating agents.

For Arsenic and Mercury:

BAL (British anti-lewisite; dimercaptopropynol; Dimercaprol).

In suspected or known arsenic or mercury intoxications:

1. Initial dose of BAL 5 mg/Kilo, repeated every 4 hrs if diagnosis confirmed.
2. Amount of BAL per injection can be decreased if amount of arsenic ingestion small; e.g., less than 0.5 gm, but frequency of BAL dosage should remain at q4h until 24 hour urine $A_s$ is less than 0.1 mg.

Side Effects of BAL

1. Rise of both systolic and diastolic BP
2. Nausea
3. Burning sensation in the lips, mouth, throat - constriction and pain in throat and of chest, down arms and into hands
4. Conjunctivitis, lacrimation, rhinorrhea and salivation
5. Tingling in hands
6. Burning in penis
7. Excessive sweating
8. Abdominal pain

Pain at injection site. Rarely accompanied by significant reaction. Overdose in children may cause convulsions. Fever common in children.

None of these effects of BAL are consistently altered by the administration of ephedrine, as previously reported.

For Lead Intoxication:

Calcium disodium edetate (EDTA) - Chief side effect - renal damage, probably of little consequence. DEDTA has also been used; not accepted as a drug at this time.

Penicillamine (cuprimine) - Used mainly in children for chronic treatment of lead intoxication. With prolonged use may be nephrotoxic.

See reference for combination EDTA and BAL therapy.

For Iron Intoxication:

Deferoxamine (Desferal) - Probably the most toxic of the chelating agents in clinical use at this time.

Organic Phosphate Pesticides:

Pralidoxime chloride (Protopam, 2 PAM-Cl)

Chelates with certain organic phosphate pesticides, apparently capable of removing toxin from cholinesterase, thus reactivating the enzyme.

Dosage not altogether settled. Apparently one of the safest antidotes.

Apparent Side Effects

| | |
|---|---|
| Excitement | Blurred Vision |
| Confusion | Tachycardia |
| Dizziness | Muscle Weakness |
| Headache | Muscle Rigidity |

Side effects are generally mild, and of course in some cases apparent side effects may be the result of atropine and/or the pesticide.

From animal experimental results, 2 PAM may have other pharmacological effects. In high concentrations it produces neuromuscular block not related to cholinesterase activity. The drug depolarizes skeletal muscles and nerves. Other effects: direct effect on respiratory center (demonstrated in cats) and inhibition of cholinesterase (demonstrated in rabbits). (See reference #53).

II. Heavy Metals:

Because of strict controls on metals such as mercury and thallium, arsenic is the major metal to consider in adult intoxication.

A very high percentage of patients with arsenic intoxications should live with early, adequate therapy. Shock and renal failure prevent adequate therapy and prognosis is poor.

In adults, lead intoxication is generally a chronic illness of industrial origin. Several references regarding chelation therapy are given.

III. Organic Solvents:

Aside from Ethyl alcohol, carbon tetrachloride and isopropyl alcohol are the most common organic solvent intoxications of consequence.

Important to remember that industrial accidents with organic solvents most commonly give rise to coma (as with an anesthetic) which is frequently accompanied by anoxia. Direct toxic action to organ systems by these solvents is not common. However, see references.

IV. Pesticides: Three major classes - 1. Organophosphorus ester
2. Carbamate Insecticides
3. Chlorinated Hydrocarbon

Although the chlorinated hydrocarbon pesticides are relatively non-toxic to man (with ingestion, the solvent is frequently more toxic than the pesticide), for ecological reasons an increase in the use of organophosphate pesticides, and thus intoxications is to be expected.

(The main source of arsenic for intoxication purposes is in pesticides.)

Symptoms and Signs in Organophosphorus Intoxication

| Symptoms | Signs |
|---|---|
| 1. Blurred Vision | 1. Miosis |
| 2. Nausea | 2. Tearing |
| 3. Tightness or Fullness in chest | 3. Salivation |
| 4. Headache | 4. Excessive respiratory tract secretions |
| 5. Abdominal Cramps | 5. Vomiting-Diarrhea |
| 6. Weakness | 6. Ataxia |
| | 7. Muscle Fasciculations |
| | 8. Coma |
| | 9. Papilledema |
| | 10. Convulsions |

Drug treatment in organophosphorus intoxication:

1. Atropine - First dose 1 mg - if no effect, increase to 2 mg and repeat at 30 minute intervals until effect apparent. Repeat 2-4 mg doses to maintain effects. In severe intoxications as much as 50 mg/24 hr may be needed.

2. 2 PAM - Given IV only. Give 1.0 gm slowly. If no improvement in 30 minutes repeat dose (some suggest increasing dose to 2.0 or 2.5 gms; see references). To maintain improvement give from 0.1 to 0.5 gm/hr as an infusion. Always use in conjunction with atropine.

Further Points:

a) 2 PAM does appear to have a beneficial response in Malathion intoxication
b) 2 PAM is clinically useful in treating CNS manifestations of organophorphorus intoxication

In pesticide poisoning, remember that the solvent may be more life-threatening than the pesticide; watch for: 1) marked CNS depression, 2) Kerosene-like pneumonia.

Carbamate insecticides:

Most common compound Sevin. These compounds are reversible inhibitors of cholinesterase. Treat intoxication with atropine if needed. 2-PAM is probably contraindicated.

| Chlorinated Hydrocarbon Pesticides | Organophosphorus Pesticides |
|---|---|
| Aldrin | Parathion |
| Chloradane | Methyl Parathion |
| DDT | Diazinon |
| Dieldrin | EPN |
| Endrin | TEPP |
| Lindane | Bidrin |
| Heptachlor | Carbophenothion |
| Kelthane | Dichlorvos |
| Methorychlor | Dimethoate |
| Perthane | Merinphos |
| DDD | Malathion* |
| Thiodan | Methyl Demeton* |
| Toxaphene | Phosphamidone* |
| | Azinphosmethyl* |
| | Paraoxon* |

*2 PAM-Cl may not be effective in these intoxications.

Organophosphorus compounds may have effects on nerve and muscle tissue other than the anticholinesterase effects. Recently one has been shown to inhibit ionic conduction at the motor end plate (see reference #53A).

V. Amphetamines:

Important toxic effects in acute intoxication are cardiac arrythmias, hyperpyrexia and rarely myoglobinuria.

VI. Sedative Drugs:

All drugs in this class can produce coma when taken in excessive amounts. However, the barbiturates and narcotics as sub-classes produce the deepest coma and for that reason are apparently the most dangerous. The tranquilizers (and perhaps the tricyclic anti-depressant drugs) produce a less threatening coma. For convenience, many sedative drugs are lumped into the tranquilizer group for toxicologic purposes.

A. Narcotics - with "hard" narcotics, the principle problem in acute intoxication is pulmonary edema. Myoglobinuria and renal failure are also seen in patients that abuse or overdose with narcotics.

Dextro Propoxyphene Intoxication

Darvon, a very mild analgesic drug, has, over the past few years, become a major problem because of: 1) its abuse and 2) increasing frequency of use in suicide attempts. In both instances death appears unusually common. During 1970-71 41 cases were studied by Dallas County Medical Examiner's Office (see references).

Darvon intoxication is similar to codeine intoxication in that both cause coma with convulsions. Sudden, rather unexplained death can follow a convulsion.

Three other aspects of Darvon intoxication are noted:

1. Pulmonary edema
2. Direct cardiac toxicity
3. Nephrogenic diabetes insipidus

Whether any of these are specific for Darvon is questionable (see references).

B. Tranquilizers and Tricyclic antidepressants - In intoxications, mortality appears primarily controlled by the patient's general health. However, cardiac arrythmias produced by, especially, the phenothiazines and the tricyclic drugs can be serious and difficult to control. In our recent experience, every patient with tricyclic antidepressant drug overdose has shown at least some degree of heart block. There were no deaths.

C. Barbiturates and Barbiturate-like drugs - These drugs account for the highest mortality in drug intoxication.

## Some Non-Narcotic Coma Producing Drugs

### Type A

Chlormezanone (Trancopal)
Emylcamate (Striatran)
Meprobamate (Equanil, etc.)
Oxanamide (Quiactin)
Phenaglycodol (Vetran)
Mebutamate (Capla)
Carisoprodol (Soma)
Hydroxyzine (Atarax, Vistaril)
Ectylurea (Levanil, Nostyn)
Chlordiazepoxide (Librium)
Hydroxyphenamate (Listica)
Mephenoxalone (Trepidone)
Carbromal (Adalin)
Bromisovalum (Bromural)
Chloral Betaine (Beta-Chlor)
Methylparafynol (Dormison)
Petrichloral (Periclor)
Buclizine (Softran)
*Chloral hydrate (Somnos, Noctec, Loryl)
+Chlorpromazine (Thorazine)
+Promazine (Sparine)
++Trifluorperazine (Stelazine)
Amitriptyline (Elavil)
Dexmethylimipramine
Nortriptyline (Aventyl)
Imipramine (Tofranil)
Desipramine (Pertofram)

*Perhaps should be classed as a type B drug, however, dose is usually not high enough to produce deep coma.

+Coma unusual

++Coma rare

## Barbiturate and Barbiturate-like Drugs

### Type B

Barbital (Veronal)
Mephobarbital (Mebaral)
Metharbital (Gemovil)
Phenobarbital (Luminal)
Amobarbital (Amytal)
Aprobarbital (Alurate)
Butabarbital (Butisol)
Diallylbarbituric acid (Dial)
Probarbital (Ipral)
Talbutal (Lotusate)
Vinbarbital (Delvinal)
Cyclobarbital (Phanodorn)
Heptabarbital (Medomin)
Hexethal (Ortal)
Pentobarbital (Nembutal)
Secobarbital (Seconal)
Hexobarbital (Cyclonal, Evipal, Sombulex)
Methitural (Neraval)
Methohexital (Brevital)
Thiamylal (Surital)
Thiopental (Pentothal)
Allylbarbituric acid (Sandoptal)
Butethal (Neonal)
Cyclopentenyl allybarbituric acid (Cyclopal, Cyclopen)
Butallylonal (Pernocton)

Methyprylon (Noludar)
Ethinamate (Valmid)
Diazepam (Valium)
Glutethimide (Doriden)
Ethchlorvynol (Placidyl)
Methaqualone (Quaalude, Parest, Somnafac, Sopor, Biphetamine T, Optimil)

Although barbiturates are involved in more overdose deaths than any other drug (Seconal and Phenobarbital are the leaders), some other drugs in this class are of critical interest.

### Glutethimide - (Doriden)

1. Coma with dilated pupils
2. Multiphasic coma
3. Sudden apnea
4. Gastric bleeding - rare
5. Hemoglobinuria - rare

Methyprylon - (Noludar)

1. Mentioned because it is chemically similar to Doriden. Both piperidinediones
2. Properties otherwise similar to Seconal

Methaqualone - (Quaalude, etc.)

1. Pupils may dilate with coma
2. Sudden apnea
3. Multiphasic coma possible
4. Possible convulsions during coma
5. Muscle rigidity
6. Gastric bleeding
7. Abnormal ECG
8. Prolonged prothrombin time
9. Hypothermia
10. Spontaneous vomiting
11. Increased oral and bronchial secretions
12. Positive Babinski

The Benzodiazepines - A group of chemically related drugs in which it is difficult to class some of the individual drugs as A type or B type.

Chlordiazeporide (Librium)
Oxazepam (Serax)
Nitrazepam (Mogadon)
Flurazepam (Dalmane)
Diazepam (Valium)

Sedative Drug Intoxication:

Non-comatose patient:

1. Slurring of activated charcoal P.O.
2. Induce emesis
3. Retain vomitus for lab
   Blood) for lab
   Urine)
4. Give 10-50 gm activated charcoal P.O.
5. Give cathartic

Comatose patient:

1. Intubate
2. Start IV and obtain blood sample
3. Gastric lavage
   a. Instill activated charcoal during and after
4. Instill cathartic

5. For hypotension:
   a. Check oxygenation
   b. Give salt to expand volume
   c. Use pressors as a last resort
6. Reduce fever
7. Maintain modest diuresis

VII. Analeptics:

The exact role of these drugs in treatment of drug overdose is not clear. At this time, the two safest analeptics appear to be doxapram and ethamivan. It seems doubtful that either will alter overall mortality from drug intoxication.

General References:

1. Goodman, L.S. and Gilman, A. Editors, The Pharmacological Basis of Therapeutics. Fourth Edition. The Macmillan Co. New York, 1970.

   Gives the most information for the least time investment of any volume available.

2. Graham, J.D.P. Diagnosis and Treatment of Acute Poisoning. Oxford University Press. New York, 1962.

   The best text-book-type book dealing with clinical toxicology available at this time. Unfortunately, somewhat out of date and biased by British overdose customs.

3. Gleason, M.N., Gosselin, R.E. and Hodge, H.C. Clinical Toxicology of Commercial Products: Acute Poisoning. 2nd Edition. Williams and Wilkins, Baltimore, 1963.

   Has the composition of many products and non-prescription drugs. It would be more convenient if the non-prescription drug formulas were available in a volume by themselves.

4. Drug Dependence. A Guide for Physicians. American Medical Association. Chicago, 1969.

   A general review with suggested therapy of drug withdrawal and comments on acute intoxication with "abused" drugs.

5. Loomis, T.A. Essentials of Toxicology. Lea and Febigern, Philadelphia, 1968.

   An outline of the concepts of clinical toxicology.

6. Falconer, M.W., Patterson, H.R. and Gustafson, E.A. Current Drug Handbook 1970-72. W.B. Saunders Co., Philadelphia, 1970.

   A listing, with side effects and toxic effects of all prescription drugs. Plans are to publish every two years. Drugs easily found by either chemical, generic or trade names.

7. Dreisback, R.H. Handbook of Poisoning. 6th Edition, Lange Medical Publications, Los Altos, Calif., 1969.

   Contents of some non-prescription drugs can be found in this publication. New edition every 2 years.

8. Toxicity Bibliography, Nat. Lib. of Med.

   Published quarterly. This publication has titles of papers (with authors and journal) pertaining to all phases of toxicology.

Concepts of Toxicology:

9. Gosselin, R.E. and Smith, R.P. Trends in the therapy of acute poisoning. Clin. Pharm. Therap. 7:279, 1966.

A good review of the problem. Best information on use of emetics and lavage. A rather prolonged discussion of dialysis of drugs; little helpful information but does contain most important references on drug dialysis.

10. Dimijian, G.G. and Radelat, F.A. Evaluation and treatment of the suspected drug user in the emergency room. Arch. Int. Med. 125:162, 1970.

10A. Dimijian, G.G. Office evaluation and treatment of the drug user. Drug Therapy 1:7, 1971.

Practical approaches to problems related not only to drug overdose but to drug abuse in general.

11. Picchioni, A.L. et al. Activated charcoal vs "Universal Antidote" as an antidote for poisons. Tox. & Appl. Pharm. 8:447, 1966.

Universal Antidote = Activated Charcoal, MgO, and Tannic acid.
2 parts 1 part 1 part

In this study, it appears that the effectiveness of activated charcoal was blunted by the presence of MgO and/or Tannic acid. Therefore, activated charcoal should be used alone.

12. Decker, W.J., Combs, J.H., and Corby, D.G. Adsorption of drugs and poisons by activated charcoal. Tox. & Appl. Pharm. 13:454, 1968.

In vitro study - simulated gastric fluid - pH 1.5. (See table)

12A. Levy, G. and Gwilt, P.R. Activated charcoal for acute acetaminophen intoxication. (Letter) J.A.M.A. 219:621, 1972.

Authors state that their preliminary investigations show that activated charcoal is effective in preventing absorption of this very toxic material.
Note: Tylenol is acetaminophen (325 mg Tablet).

13. Corby, D.G., Decker, W.J., Moran, M.J. and Payne, C.E. Clinical comparisons of pharmacologic emetics in children. Pediatrics 42:361, 1968.

Neither gastric lavage nor emetics (apomorphine and syrup of ipecac) always effective in emptying the stomach of ingested materials.

14. Reinhard, J.F. and Spector, E. Effects of phenobarbital, phenylbutazone, 3,4-benzprene or 3-methyl-cholanthrene on ethanol metabolism in the rat. Tox. & Appl. Pharm. 17:12, 1970.

    Although phenobarbital "activates" ethyl alcohol dehydrogenase in liver, the reason that there is toxic protection from ethanol must lie in brain metabolism since same blood levels ethynol produce sleep in no phenobarbital group and no sleep in the phenobarbital group.

14A. Rappolt, R.T. Use of oral DDT in three human barbiturate intoxications: Hepatic enzyme induction by reciprocal detoxicants. Clin. Tox. 6:147, 1973.

    Very unconvincing clinical report of use of DDT in three patients with phenobarbital intoxication. Nevertheless, this sort of therapy may represent a trend for clinical toxicology.

15. Muller, D.J. Bromide intoxication continues to occur. Texas Med. 64:72, 1968.

    In a one year period in John Peter Smith Hospital (Ft. Worth) 5 cases seen on psychiatric service.

    Beside prescription drugs (NaBr, KBr, $NH_4B_4$ & LiBr, separately or in combination), Bromides sold over the counter include Miles Nervine, Sleep tablets, Bromo-Seltzer, Nytol, Bromural Carbromal.

16. Seliskar, J.E., Shipman, K.H. and Kennison, H.B. Bromide intoxication treated with ethacrynic acid. Ann. Int. Med. 65:1341, 1966.

    In a single patient, show fair results which almost certainly could have been improved if larger amounts of the diuretic had been used.

    Probably, and certainly in the comatose patient, furosemide is the diuretic of choice given parenterally in doses not to exceed 600 mg/day.

17. Schmitt, G.W. et al. Ethacrynic acid enhanced bromuresis. A comparison with peritoneal and hemodialysis. J. Lab. Clin. Med. 68:913, 1966.

    Using fairly high doses of diuretic, the plasma bromide half-life was 3 times that of hemodialysis. But since diuretic therapy can be continuous, it is beneficial in the treatment of Br. intoxication. However, see below.

18. Adamson, J.S. et al. Treatment of bromide intoxication with ethacrynic acid and mannitol diuresis. Ann. Int. Med. 65:749, 1966.

    In this study, the serum Br half life was very close to that obtained with hemodialysis.

20. Macpherson, C.R., Milne, M.D. and Evans, B.M. The excretion of salicylate. Brit. J. Pharm. 10:484, 1955.

In this experimental study in humans, the underlying principles for the treatment of aspirin intoxication by means of diuresis and alkalinization of the urine were given. However, it is evident that this method of treatment still hasn't become universally known.

21. Ferguson, R.K. and Boutros, A.R. Death following self-poisoning with aspirin. J.A.M.A. 213:1186, 1970.

Main interest in this case is that blood aspirin level was only 46.5 mg% on admission, but had risen to 115.2 mg% 8 hrs. later. Although lavage with 6 liter N/A was used on admission, no tablets were returned. Patient should have had induced vomiting on admission since she was alert at that time.

22. Segar, W.E. and Holliday, M.A. Physiologic abnormalities of salicylate intoxication. New Eng. J. Med. 259:1191, 1958.

23. Robin, E.D., Davis, R.P. and Rees, S.B. Salicylate intoxication with special reference to the development of hypokalemia. Am. J. Med. 26: 869, 1959.

For clinical descriptions of cases and abnormalities found, these are informative papers. For the most part, their suggestions for therapy are of little worth, however.

23A. Reimold, B.W., Worthen, H.C. and Reilly, T.P. Salicylate poisoning. Comparison of acetazolamide administration and alkaline diuresis in the treatment of experimental salicylate intoxication in puppies. Am. J. Dis. Child. 125:668, 1973.

Quantitative data of great interest in given for experimental aspirin intoxication. Diamox did not appear to be that much more effective than $HCO_3$ alone.

24. Jorgensen, H.E. and Wieth, J.O. Dialysable poisons. Lancet 1:81, 1963.

A rather widely quoted paper of the praises of dialysis, but the things that they found easiest to treat by dialysis were phenobarbital-like drugs, bromide, methanol. These poisonings perhaps can be handled equally well by other measures.

25. Avram, M.M. and McGinn, J.T. Extracorporeal hemodialysis in phenothiazine overdosage. J.A.M.A. 197:182, 1966.

A satisfactory study showing, by isotope technique, that phenothiazines are not dialyzable.

26. Markham, T.N., Dodson, V.N. and Eckberg, D.L. Peritoneal dialysis in quinine sulfate intoxication. J.A.M.A. 202:1102, 1967.

Although the patient did well after ingesting 3.84 gms of quinine, it would seem unlikely this was the result of the removal of 415 mg by peritoneal dialysis.

27. Mandebaum, J.M. and Simon, N.M. Severe methyprylon intoxication treated by hemodialysis. J.A.M.A. 216:139, 1971

Hemodialysis may have removed less than 0.5 gm per hour of dialysis of Noludar from a patient who took 22.5 gms. Questionable if the dialysis was useful. Although not entirely clear from the paper, apparently 4.3 gms of drug was recovered from the stomach on admission (2-12 hrs after ingestion). Other reports on dialysis of this drug are even less convincing.

28. Ginn, H.E., Matter, B.J., Shinaberger, J.H., et al. Clinical experience with lipid dialysis. J. Clin. Invest. 47:40a, 1968.

Lipid dialysis has been used in Doriden, Seconal, Nembutal, trifluoperazine and camphor intoxication. Although good clinical response was said to have resulted, only in the case of camphor was the amount of drug recovered by dialysis measured. See below.

29. Ginn, H.W., Anderson, K.E., et al. Camphor intoxication treated by lipid dialysis. J.A.M.A. 203:230, 1968.

In a single example, this form of dialysis was found to remove 6.56 gms of the ingested 12 gms of camphor in 4 1/2 hrs. This is the kind of drug removal that is needed in intoxications, but alas, camphor can hardly be called a common poisoning.

30. King, L.H., Jr., Deckerd, J.F., et al. A clinically efficient and economical lipid dialyzer. Use in treatment of glutethimide intoxication. J.A.M.A. 211:652, 1970.

Describes the use of lipid dialysis in a single patient. Although the blood levels fell during dialysis, there was never a high level (< 3 mg%) and the total ingested dose was low (5.25 gms).

30A. Welch, L.T., Bower, J.D., Ott, C.E. and Hume, A.S. Oil dialysis for ethchlorvynol intoxication. Clin. Pharm. Therap. 13:(Part 1)745, 1972.

Again it is difficult to evaluate results, but with in vitro studies with dog blood; in about 45 min. dialysis, blood contained 50% of the drug that it contained at 0 time with water dialysis, and 25% with oil dialysis. The critical questions still is - is the total amount of drug removed from a patient clinically significantly increased by 1) dialysis of the standard type and 2) further increased by oil dialysis?

31. Decker, W.J., Combs, H.F., Treuting, J.J. and Banez, R.J. Dialysis of drugs against activated charcoal. Tox. and Appl. Pharm. 18:573, 1971.

An in vitro study showing enhanced removal of a number of drugs into an activated charcoal containing dialysis bath.

32. Rosenbaum, J.L., Kramer, M.S., Raja, R. and Boreyko, C. Resin hemoperfusion: A new treatment for acute drug intoxication. New Eng. J. Med. 284:874, 1971.

A new attempt to use exchange resins in removal of drugs. This resin (Amberlite X AD-2) appears to be more effective and less dangerous than previous ones, although platelet adsorption is still a problem. Appears to be very effective in seconal removal; less effect for other barbiturates (except phenobarbital), Doriden, Placydyl.

Heavy Metals:

33. Goodman, L.S. and Gilman, A. The Pharmacological Basis of Therapeutics. Second Edition, pp 949-945, The Macmillan Co., New York, 1955.

This affords the best description of the pharmacology, toxicology and clinical use of BAL (Dimercaprol) available, although even here, the recommended use of BAL should be thought of as conservative.

34. Doolan, P.D., Hess, W.C., and Kyle, L.H. Acute renal insufficiency due to bichloride of mercury. New Eng. J. Med. 249:273, 1953.

An interesting case report of a fatal intoxication with comments on BAL intoxication. Of importance is the observation that hemodialysis can remove complexed BAL, the blood level being lowered by 60% in one 4 hr. dialysis. BAL plus dialysis is the only therapy in an intoxicated renal failure patient. The question of effectiveness remains to be proved.

35. Sanchez-Sicilla, L., Seto, D.S., Natoru, S. and Kolff, W.J. Acute mercurial intoxication treated by hemodialysis. Ann. Int. Med. 59:692, 1963.

Despite the rather misleading title, this paper presents interesting case histories. Note that all but one patient received less than adequate BAL therapy.

36. Hammond, P.B. The effects of chelating agents on the tissue distribution of lead. Tox. & Appl. Pharm. 18:296, 1971.

Both EDTA and DTPA primarily remove lead from bone, not soft tissue where the real damage is. Whether penicillamine removes lead from soft tissue or not remains to be proved.

37. Selander, S. Treatment of lead poisoning. A comparison between the effects of sodium calcurmeditate and penicillamine administered orally and intravenously. Brit. J. Ind. Med. 24:272, 1967.

Intravenous CaEDTA gave the highest lead removal, but both oral and IV penicillamine were effects. The author concludes that mild lead intoxication can probably be treated best by oral penicillamine.

38. Chisholm, J.J., Jr. The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood. J. Pedrat. 73:1, 1968.

Although dealing with childhood intoxication, this paper gives good information regarding chelation therapy. The author is very much in favor of using the combination of BAL plus CaEDTA in lead poisoning.

Organic Solvents:

39. Butler, T.C. Reduction of carbon tetrachloride *in vivo* and reduction of carbon tetrachloride and chloroform *in vitro* by tissues and tissue constituents. J. Pharm. Exp. Therap. 134:311, 1961.

From these studies, author suggested that clevage of the C-Cl bond resulted in the production of free radicals and that these were the toxic entities in $CCl_4$ intoxication.

40. Recknagel, R.O. Carbon tetrachloride hepatotoxicity. Pharm. Rev. 19: 145, 1967.

A complete review of the subject with the author's hypothesis presented which, in brief, is that free radical formation from reduction of $CCl_4$ results in lipoperoxidation with destruction first of the endoplasmic reticulum.

41. Dambraushas, T. and Cornish, H.H. Effect of pre-treatment of rats with carbon tetrachloride on tolerance development. Tox. and Appl. Pharm. 17:83, 1970.

$CCl_4$ pre-treatment produced tolerance and slowed the conversion of $CCl_4$ to $CHCl_3$.

42. Wel, E., Wong, L.C.K. and Hine, C.H. Potentiation of carbon tetrachloride hepatotoxicity by ethanol and cold. Tox. and Appl. Pharm. 18:329, 1971.

From experiments in rats, these authors conclude that the ethonal and cold potentiation of the $CCl_4$ hepatotoxicity is the result of increased release of norepinephrine incident to either alcohol or cold.

43. Stewart, R.D., et al. Acute carbon tetrachloride intoxication. J.A.M.A. 183:994, 1963.

Of importance here is that it is suggested that the renal damage might be obviated by the early institution of an osmotic diuresis after ingestion. This is supported by a case report, but of course needs experimental verification. Likewise, it has been reported, but with little evidence that $CCl_4$ can be removed by peritoneal dialysis.

44. Stewart, R.D. and Andrews, J.T. Acute intoxication with methylchloroform (Trichloroethane). J.A.M.A. 195:904, 1965.

A good account of the toxicology of trichloroethane, the major industrial substitute for carbon tetrachloride. Chiefly, CNS depression, but liver and kidney abnormalities can be present. In oral intoxication, causes nausea and severe diarrhea.

44A. Stewart, R.D. Methyl chloroform intoxication. J.A.M.A. 215:1789, 1971.

45. Meckler, L.C. and Phelphs, D.K. Liver disease secondary to tetrachloroethylene. J.A.M.A. 197:662, 1966.

This compound is commonly encountered in the dry cleaning industry. This is a case report of acute, severe, non-fatal liver damage in a woman exposed to the vapor for 2 1/2 months. Many believe these are idiosyncrasies or hypersensitivities rather than true intoxications.

46. Stewart, R.D. Acute tetrachloroethylene intoxication. J.A.M.A. 208:1490, 1969.

Another substitute for carbon tetrachloride in industry which is probably relatively non-toxic. But in large amounts produces CNS depression and in this case mild liver dysfunction without renal involvement. Renal damage has been reported.

47. Baerg, R.D. and Kimberg, D.V. Centrilobular hepatic necrosis and acute renal failure in solvent sniffers. Ann. Int. Med. 73:713, 1970.

Case reports of Carbona® sniffers. Carbona is approximately 50% Trichloroethylene and 50% petroleum distillates. Authors conclude hepatic and renal damage due to trichloroethylene. Good bibliography of trichloroethylene toxicology. Do not consider the possibility of $CCl_4$ being present as an impurity in organic solvents.

48. Peterson, D.I., Peterson, J.E., and Harding, M.G. Experimental treatment of ethylene glycol poisoning. J.A.M.A. 186:955, 1963.

In rats and monkeys, ethanol appears to inhibit oxidation of ethylene glycol and results in increased urinary excretion. Perhaps then, ethanol and dialysis is the treatment of choice as in methyl alcohol intoxication.

49. Røe, O. The roles of alkaline salts and ethyl alcohol in the treatment of methanol poisoning. Quart. J. Stud. Alcohol. 11:107, 1950.

Since ethyl alcohol can block the metabolism of methanol, and since methanol metabolism is slow to begin with, ethyl alcohol can be given in hopes of reducing the toxicity of methanol by preventing formation of poisonous metabolites.

50. Marc-Aurele, J. and Schreiner, G.E. The dialysance of ethanol and methanol: A proposed method for the treatment of massive intoxication by ethyl or methyl alcohol. J. Clin. Invest. 39:802, 1960.

There may well be instances where dialysis is indicated in methyl alcohol intoxication in particular. Peritoneal dialysis appears equally effective. Use of dialysis for other alcohols (see below) might also occasionally be indicated. Certainly, even with dialysis, ethanol therapy for methyl alcohol intoxication should be instituted.

51. King, L.H., Bradley, K.P., and Shires, D.L. Hemodialysis for isopropyl alcohol poisoning. J.A.M.A. 211:1855, 1970.

Although capable of producing prolonged coma, this intoxication is generally not fatal. However, in this case about 1 liter was ingested, and perhaps dialysis was helpful, maybe lifesaving. Amounts removed not quantitated. Blood levels: Initial 400 mg%; after 5 hrs. dialysis 100 mg%.

52. Wills, J.H., Jameson, E.M. and Coulston, F. Effects on man of daily ingestion of small doses of isopropyl alcohol. Tox. and Appl. Pharm. 15:560, 1969.

In 8 men doses of either 2.6 mg/Kilo or 6.4 mg/Kilo daily for six weeks had no ill effects. Acetone in urine present only twice in a subject on the higher dose.

Pesticides:

53. Namba, T., Nolte, C.T., Jackrel, J. and Grob, D. Poisoning due to organophosphate insecticides. Acute and chronic manifestations. Am. J. Med. 50:475, 1971.

This is a review article with case presentations with all the important references on the subject. This is the best review of the use of PAM and its physiological and pharmacological effects.

53A. Kuba, K., Albuquerque, E.X. and Barnard, E.A. Diisopropylfluorophosphate: Suppression of ionic conductance of the cholinergic receptor. Science 181:853, 1973.

An example of work demonstrating actions of organophosphorous compounds other than just cholinesterase inhibition.

54. Milby, T.H. Prevention and management of organophosphate poisoning. J.A.M.A. 216:2131, 1971.

A short review giving treatment, but most important, listing the numerous compounds by chemical and trade name that have anticholinesterase activity.

55. Medical News, Quoting Taylor, W.J. Russell. J.A.M.A. 217:1315, 1971.

This News account tells how to treat organophosphate pesticide poisoning in a most simple, straight-forward way. (Interestingly, although pesticide intoxications are declining, they still account for 12% of chemical deaths per year). Advocates the atropine, Aramine, PAM (1 gm ql2h*) therapy. If the patient lives 2 days, death is unlikely.

*Dosage not settled as yet. May be as much as 2.5 gms should be given, followed by similar or smaller dose in 30 min. See; Sim, V.M. J.A.M.A. 192:403, 1965.

56. Warren, M.C. et al. Clothing-borne epidemic. Organic phosphate poisoning in children. J.A.M.A. 184:266, 1963.

A good example of skin absorption from contaminated clothing, even though the contamination had occurred 8 months previously.

57. Reich, G.A., Gallaher, G.L. and Wiseman, J.S. Characteristics of pesticide poisoning in south Texas. Tex. Med. 64:56, 1968.

An interesting, well-developed epidemiological study.

58. Arterberry, J.D. et al. Potentiation of phosphorus insecticides by phenothiazine derivatives. J.A.M.A. 182:848, 1962.

59. Gaines, T.B. Poisoning by organic phosphorus pesticides potentiated by phenothiazine derivatives. Science 138:1260, 1962.

Clinical and experimental evidence presented.

60. Gitelson, S. et al. Poisoning by a malathion-xylene mixture. J.A.M.A. 197:819, 1966.

In this case, the solvent may have been as toxic as the "poison".

61. Coble, V., et al. Acute endrin poisoning (chlorinated hydrocarbon insecticide). J.A.M.A. 202:489, 1967.

A report of 4 accidental severe intoxications where the main problem was CNS stimulation (to the point of convulsions). This is the prototype story for this class of insecticide. Prognosis is good if hypoxia is prevented.

Amphetamines:

62. Espelin, D.W. and Done, A.K. Amphetamine poisoning. New Eng. J. Med. 278:1361, 1968.

A description of the clinical picture:
Moderate O.D. - sweating, tachycardia, mydraisis, confusion and hyperactivity
Severe O.D.---- In addition to above; cardiac arrhythmias, delirium, convulsions and hyperpyreria

63. Espelin, D.E. and Done, A.K. Amphetamine poisoning: Effectiveness of chlorpromazine. New Eng. J. Med. 278:1361, 1968.

It is suggested that since many persons are taking both barbiturates and amphetamines that barbiturate to sedate an amphetamine intoxication may not be useful. Showed in children with pure amphetamine O.D. that chlorpromazine could probably perform the role of barbiturate.

64. Espelin, D.E. and Done, A.K. Amphetamine poisoning. New Eng. J. Med. 278:1361, 1968.

In poisoning, dextroamphetamine (Dexedrine), methamphetamine (Desoxyn, Methedrine), phenmetrazine and carboryphen all give similar clinical pictures. In most cases only minor supportive care is needed. In severe intoxications, convulsions and/or cardiac arrhythmias may develop. In severe intoxication, the authors suggest that chlorpromazine be used to abate both CNS and sympathetic NS abnormalities. Suggest 1.0 mg/Kilo IM. (Cut dose in half if Dexedrine and barbiturate combinations have been taken.)

65. Ginsberg, M.D., Hertzman, M. and Schmidt-Norvara, W.W. Amphetamine intoxication with coagulopathy, hyperthermia, and reversible renal failure. A syndrome resembling heat stroke. Ann. Int. Med. 73: 81, 1970.

After ingestion of about 2.2 gms, rectal temperature quickly rose above 108°F. The renal failure appears to be the result of muscle necrosis and myoglobinuria, although the authors prefer the hypothesis that the high body temperature damaged the kidney.

Sedative Drugs - Narcotics, Tranquilizers, Tricyclic anti-depressants, Barbiturate and Barbiturate-like drugs.

Narcotics:

66. Fink, M. Narcotic antagonists in opiate dependence. Science 169: 1005, 1970 (4 Sept.).

A brief report discussing the therapeutic use of cyclazocine and naloxone.

67. Hammond, A.L. News and Comment: Narcotic antagonists: New methods to treat addiction. Science 173:503, 1971.

More, particularly about problems with cyclazocine and naloxone theory for narcotic dependence.

67A. Evans, L.E.J., Roscoe, P., Swainson, C.P. and Prescott, L.F. Treatment of drug overdosage with Naloxone, a specific narcotic antagonist.

A clinical report of the use of Narcan in narcotic O.D. Dose usually is from 0.4 to 12. mg. This antagonist appears to really work on pentazocine (Talwin) overdose. Unfortunately, no observations with Darvon overdoses were made.

67B. Waldron, V.D., Klimt, C.R. and Seibel, J.E. Methadone overdose treated with maloxone infusion. J.A.M.A. 225:53, 1973.

This appears to be a rational approach to Narcan therapy. Perhaps this is the way it should be used to control Darvon overdose convulsions.

68. Lynch, K., Greenbaum, E. and O'Loughlin, B.J. Pulmonary edema in heroin overdose. Radiology 94:377, 1970.

Points out that, on x-ray, the pulmonary edema may appear in only one lung or one lobe of a lung, although the latter is rare.

69. Morrison, W.J., Wetherill, S. and Zyroff, J. The acute pulmonary edema of heroin intoxication. Radiology 97:347, 1970.

A short article with good discussion and references together with a description of the pulmonary x-rays in the syndrome.

70. Bogartz, L.J. and Miller, W.C. Pulmonary edema associated with Propoxyphene (Darvon) intoxication. J.A.M.A. 215:259, 1971.

In 2 patients, pulmonary edema followed large ingestion of Darvon, however, both patients had severe acidosis and hypoxia and manifested increased venous pressure (one had dilated left heart). Perhaps Darvon can produce pulmonary edema of the narcotic type, but in these two cases, fluid administration to acidotic patients seems a more likely cause.

71. Fraser, D.W. Methadone overdose. Illicit use of pharmaceutically prepared parenteral narcotics. J.A.M.A. 217:1387, 1971.

If the histories of the two patients presented here can be accepted, then it appears that overdosing with pure narcotic can not only produce pulmonary edema, but can give rise to myoglobinuria. The problem is that a history from an addict is not reliable.

71A. Kjeldgaard, J.M., Hahn, G.W., Heckenlively, J.R. and Genton, E. Methadone-induced pulmonary edema. J.A.M.A. 218:882, 1971.

A convincing report that appears to show that: 1) pure drug can produce pulmonary edema; and 2) pulmonary edema can result from oral ingestion. See our case No. 8, this protocol.

71B. Frand, U.I., Shim, C.S. and Williams, M.H. Methadone-induced pulmonary edema. Ann. Int. Med. 76:975, 1972.

Report of two interesting cases of methadone overdose producing pulmonary edema. As pointed out here, there is still nothing new regarding the mechanism of narcotic induced pulmonary edema.

71C. Garriott, J.C., Sturner, W.Q. and Mason, M.J. Toxicologic findings in six fatalities involving methadone. Clin. Tox. 6:163, 1973.

These cases from Dallas County Medical Examiner's Offices. From autopsy results 5 of the 6 had pulmonary edema.

72. Chapman, J.E. and Walaszek, E.J. Antagonism of some toxic effects of Dextropropoxyphene by nalorphine. Tox. and Appl. Pharm. 4752, 1962.

In rats it was shown that nalorphine could prevent the convulsions produced by toxic amounts of Darvon.

72A. Fiut, R.E., Picchioni, A.L., and Chin, L. Antagonism of convulsive and lethal effects induced by propoxyphene. J. Phar. Sci. 55:1085, 1966.

Narcan apparently can control Darvon induced convulsions, at least in rodents.

73. Qureshi, E.H. Proporyphene (Darvon) poisoning. J.A.M.A. 188:470, 1964.

In addition to convulsions, ECG changes are frequently induced by Darvon OD. These include bigeminy, prolongation of QRS, right bundle branch block, and ST-T wave changes.

74. Gary, N.E. et al. Acute Darvon intoxication. Arch. Int. Med. 121: 453, 1968.

A case report showing that convulsions may herald the onset of a downhill course. Also, from the results in this patient, dialysis probably not useful.

74A. Tennant, F.S., Jr. Complications of Propoxyphene abuse. Arch. Int. Med. 132:191, 1973.

Description of an epidemic of Darvon abuse in the U.S. Army in Germany. Note that: 1) sudden respiratory arrest was noted; 2) Pulmonary edema was noted in autopsy cases.

74B. Young, D.J. Proporyphene suicides: Report of nine cases. Arch. Int. Med. 129:62, 1972.

Emphasize the very toxic nature of overdose with Darvon. Tissue and blood levels given, but for better data see next reference.

74C. Sturner, W.Q. and Garriott, J.C. Deaths involving propoxyphene. A study of 41 cases over a two year period. J.A.M.A. 223:1125, 1973.

This report from the Dallas County Medical Examiner's Office. Gives excellent data on quantitative aspects of Darvon levels in biologic fluids and tissues.

74D. McCarthy, W.H. and Keenan, R.L. Propoxyphene hydrochloride poisoning. Report of the first fatality. J.A.M.A. 187:460, 1964.

From the data given, it appears that the patient did develop nephrogenic diabetes insipidus. That it was the result of Darvon intoxication is certainly not clear. No mention made of serum [Ca] or [$K^+$].

74E. Bower, B.F., Wegienka, L.C. and Forsham, P.H. In vitro studies of the mechanism of polyuria induced by propoxyphene (Darvon). Proc. Soc. Exp. Biol. Med. 120:155, 1965.

Appeared to show that both Levo and Dextro forms of the drug blocked the action of antidiuretic hormone on the in vitro toad bladder. Suggested that Darvon might be useful in treating inappropriate ADH syndromes.

74F. Kean, E.W. Propoxyphene Pellets (Letter) J.A.M.A. 225:524, 1973.

It seems in Darvon caps, Propoxyphene was in the form of red pellets which could be removed. Lilly has been making Darvon-N since 1970. However, at the end of 1972 their patent on Darvon expired. Now a number of mgf. are making capsules with Propoxyphene pellets again.

74G. Chernish, S.M., Wolen, R.L. and Rodda, B.E. Adsorption of propoxyphene hydrochloride by activated charcoal. Clin. Tox. 5:317, 1972.

In a study using humans, it appears that activated charcoal is effective in preventing absorption of orally taken Darvon.

74H. Kersh, E.S. Treatment of propoxyphene overdosage with maloxone. Chest 63:112, 1973.

Two rather moderate OD's responded well to Narcan. Neither patient, however, had convulsions.

74I. Fisch, H.P., Wards, J., Yeung, J. and Davis, P.J. Pulmonary edema and disseminated intravascular coagulation after intravenous abuse of d-propoxyphene (Darvon). South. Med. J. 65:493, 1972.

A case report of a known heroin addict who presented with pulmonary edema several hours after the IV injection of seven 65 mg Darvon caps. One other case has been reported of pulmonary edema after IV injection of Darvon (see Butz, W.C., J. Foren. Sci. 14:317, 1969) but foreign material unrelated to Darvon injection was found in the pulmonary circulation in that case.

Tranquilizers and Tricyclic Anti-depressants:

75. McKown, C.H., Verhulat, H.L. and Crotty, J.J. Overdosage effects and danger from tranquilizing drugs. J.A.M.A. 185:425, 1963.

A good review of the effects and results in tranquilizer overdosage.

76. Cruz, I.A., Cramer, N.C. and Parrish, A.E. Hemodialysis in chlordiazepoxide (Librium) toxicity. J.A.M.A. 202:438, 1967.

Little evidence that dialysis was useful in this patient, particularly since no Librium could be recovered in the dialysis fluid.

77. Zbinden, G., et al. Experimental and clinical toxicology of chlordiazepoxide (Librium). Tox. and Appl. Pharm. 3:619, 1961.

In 22 patients attempting suicide, the common findings were sedation, ataxia, dysarthria, while sleep and coma rare. Authors, representing the manufacturer, regarded the drug as safe.

78. Maddock, R.K. and Bloomer, H.A. Meprobamate overdosage: Evaluation of its severity and methods of treatment. J.A.M.A. 201:999, 1967.

As a result of the fast metabolism of the drug, coma in overdose cases is usually less than 40 hrs. However, very large intakes may produce blood levels of 20 mg% or over and more prolonged coma. These severe cases should be treated by forced diuresis, which significantly increases excretion. Also hemodialysis is effective, but probably seldom needed.

79. Jenis, E.H., Payne, R.J. and Goldbaum, L.R. Acute meprobamate poisoning. A fatal case following a lucid interval. J.A.M.A. 207:361, 1969.

An interesting case report with two important points:
1) Biphasic course seen occasionally with this drug is probably the result of delayed absorption of a relatively water insoluble compound (thus, similar to Doriden).
2) Large amounts of this drug may stay in the stomach for many hrs. 25 gms was found in the stomach at autopsy. Death occurred > 28 hrs after ingestion. (Amount taken by patient not known). A three liter gastric lavage was undertaken at time of admission.

80. Schnell, R.C. and Miya, T.S. Influence of carbonic anhydrase inhibition on hypothermic response and brain distribution of chlorpromazine. Tox. and Appl. Pharm. 17:239, 1970.

Inhibition of carbonic anhydrase raises brain chlorpromazine. Although not investigated by these authors, this may well represent an instance of altered drug distribution by change in extracellular and/or intracellular pH.

81. Gebhart, G.J., Plaa, G.L. and Mitchell, C.L. The effects of ethanol alone and in combination with phenobarbital, chlorpromazine, or chlordiazepoxide. Tox. and Appl. Pharm. 15:405, 1969.

A complicated study in mice showing, among other things, that chlorpromazine might retard the disappearance rate of ethanol from the blood.

82. Zileli, M.S., Telctar, F., Deniz, S. et al. Oxazepam intoxication simulating non-keto acidotic diabetic coma. J.A.M.A. 215:1986, 1971.

83. Frings, C.S. Absence of interference of oxazepam with glucose determination. J.A.M.A. 217:1244, 1971.

Serax overdosage can cause an apparent hyperglycemia. In the case reported by Zileli it appeared as a hyperosmotic coma. Fortunately, the false positive reaction for glucose does not appear in the urine. Frings claims the "glucose reaction" is due not to Serax, but the filler in the capsule with the drug.

84. Harthorne, J.W., Marcus, A.M. and Kaye, M. Management of massive imipramine overdosage with mannitol and artificial dialysis. New Eng. J. Med. 268:33, 1963.

Patient took 5.375 gms of Tofranil (215 tablets) and survived. Hypotension, coma and hyperpyrexia were the main problems. Hemodialysis was shown not to remove the drug.

85. Stinnett, L., Valentine, J. and Abrutyn, E. Nortriptyline hycrochloride (Aventyl) overdosage. J.A.M.A. 204:69, 1968.

In a patient of 105 lbs, 600 mg produced about 15 hours of coma. Also: bradycardia (QRS ↑) hypotension, and fixed dilated pupils.

Perhaps Desipramine (Pertofran) and Imipramine (Tofranil) have even more cardio-toxic effects.

86. Royds, R.B. and Knight, A.H. Tricyclic anti-depressant poisoning. Practitioner 204:282, 1970.

Report of three cases. Most important: Tricyclic overdoses can produce coma, cardiac arrhythmias, and hyperglycemia. Evidence that these patients benefited from peritoneal dialysis is poor.

87. Fletcher, G.F., Kazamia, T.M. and Wenger, N.K. Cardiotoxic effects of Mellaril: Conduction disturbances and supraventricular arrhythmias. Am. Heart J. 78:135, 1969.

88. Freeman, J.W., Mundy, G.R., Beattie, R.R. and Ryan, C. Cardiac abnormalities in poisoning with tricyclic antidepressants. Brit. Med. J. 2:610, 1969 (June).

A good account of the arrythmias that can be seen with OD's with this group of drugs. Note that the phenothiazines can produce similar effects when overdosed but perhaps to a lesser extent. See below.

89. Sjöqvist, F. et al. The pH-dependent excretion of monomethylated tricyclic antidepressants in dog and man. Clin. Pharm. and Therap. 10:826, 1969.

Both desmethylimipramine and nortriptyline excretion can be increased by acidifying the urine, but unfortunately only to a small extent. Gastric lavage might remove more drug than renal excretion, but again amounts are low.

89A. Duvoisin, R.C. and Katz, R. Reversal of central anticholinergic syndrome in man by physostigmine. J.A.M.A. 206:1963, 1968.

Used with good results in 26 patients with adverse results from scopolamine and atropine and suggests its use in other intoxications. See reference below.

89B. Slovis, T.L., Ott, J.E., Teitelbaum, D.T. and Lipscomb, W. Physostigmine therapy in acute tricyclic antidepressant poisoning. Clin. Tox. 4:451, 1971.

Perhaps as an extension of the above reported observations, these authors report good response in reversing both cardiac and CNS signs in this type of intoxication. Needs conformation before use in any but desperate circumstances. Authors also suggest a period of at least 72 hrs observation in these intoxications because of recurrence of signs of CNS and cardiac toxicity.

Barbiturate and Barbiturate-like Drugs:

90. Dobos, J.K., Phillips, J. and Covo, G.A. Acute barbiturate intoxication. J.A.M.A. 176:268, 1961.

This is a very early report suggestive that in the last analysis, recovery is related to "intensive and meticulous supportive care". Comments on analeptics important only for the high incidence of arrhythmias with amphetamine.

91. Myschetzky, A. and Lassen, N.A. Urea-induced, osmotic diuresis and alkalization of urine in acute barbiturate intoxication. J.A.M.A. 185: 936, 1963.

These authors, from the Intoxication Center in Copenhagen have one of the best survival records of any clinic in the world. However, they are against and do not practice: 1) gastric lavage, 2) giving fluids for shock, 3) use of analeptics or 4) dialysis. They do advocate diuresis (with urea) and alkalization of the urine and claim this decreases the length of coma. I expect their good results are the result of excellent pulmonary care and general nursing.

92. Henderson, L.W. and Merrill, J.P. Treatment of barbiturate intoxication, with report of recent experience at Peter Bent Brigham hospital. Ann. Int. Med. 64:876, 1966.

A review of 62 cases covering years 1957-1963. Conclude that conservative therapy is probably adequate in most cases. Show that blood levels correlate poorly with the length of coma. Authors are incorrect about use of gastric lavage, and make essentially unsupported statements regarding the use of analeptics.

93. Setter, J.G., Maker, J.F. and Schreiner, G.E. Barbiturate intoxication: Evaluation of therapy including dialysis in large series selectively referred because of severity. Arch. Int. Med. 117:224, 1966.

Advocates dialysis; reports that both peritoneal and hemodialysis are effective, but figures for drug removal not given. Reports also that forced diuresis shortens coma (both in long and short-acting drugs).

94. Hadden, J., Johnson, K., Smith, S., Price, L. and Giardina, E. Acute barbiturate intoxication: Concepts of management. J.A.M.A. 209:893, 1969.

A study of 50 patients divided into three groups: 1) conservative, 2) forced diuresis (mannitol), and 3) peritoneal dialysis. It is concluded that methods 2) and 3) are not helpful, except that a patient with severe renal or hepatic disease might be helped by dialysis. Took a fixed untested position against analeptics.

95. Johanson, W.G., Jr. Massive phenobarbital ingestion with survival. J.A.M.A. 202:1106, 1967.

Some 21 hours after a patient had ingested 16 gms of phenobarbital, at least 3.2 gms was removed from the patient's stomach.

96. Victor, L.B., Gordon, E.L. and Greendyke, R.M. Barbiturate intoxication. New York J. Med. 68:2090, 1968.

Points out, by way of two cases, that significant amounts of drug may be in the stomach long after ingestion (1 1/2 to 2 1/2 days). In one, 5 gms of phenobarbital was found 1 1/2 days after ingestion.

97. Bunn, H.F. and Lubash, G.D. A controlled study of induced diuresis in barbiturate intoxication. Ann. Int. Med. 62:246, 1965.

Able to show increased barbiturate clearance with diuresis, but probably overrate its clinical significance.

98. Bloomer, H.A. A critical evaluation of diuresis in the treatment of barbiturate intoxication. J. Lab. Clin. Med. 67:898, 1966.

99. Bloomer, H.A. Limited usefulness of alkaline diuresis and peritoneal dialysis in pentobarbital intoxication. New Eng. J. Med. 272:1309, 1965.

Shows that with short acting barbiturates, diuresis gave a small increase in excretion of the drug; alkalinization had no effect; peritoneal dialysis was not able to significantly remove drug. Marked increased excretion of phenobarbital could be affected by both alkalinization and forced diuresis.

100. Hadden, J., Johnson, K., Smith, S. et al. Acute barbiturate intoxication. Concepts of management. J.A.M.A. 209:893, 1969.

In a study of 50 intoxications (only 3 phenobarbital) there appeared to be no difference noted when conservative therapy was compared with forced diuresis or peritoneal lavage. No fatal cases.

101. Kelley, W.N., Richardson, A.P., Mason, M.F., and Rector, F.C. Acetazolamide in phenobarbital intoxication. Arch. Int. Med. 117:64, 1966.

By means of a forced, alkaline diuresis and the administration of Diamox excretion rates of as much as 0.1 gm per hour could be obtained. This is approximately 10 times the no therapy excretion rate.

102. Burnstein, N. and Stauss, H.K. Attempted suicide with methyprylon. J.A.M.A. 194:1139, 1965.

A severe case of Noludar intoxication (30 gms) with recovery with conservative therapy. There was circumstantial evidence that a significant amount of the drug was removed by gastric lavage.

103. Westervelt, F.B. Ethchlorvynol (Placidyl) intoxication. Experience with five patients, including treatment with hemodialysis. Ann. Int. Med. 64:1229, 1966.

Although the author reports a removal rate of drug of about 0.2 gms/hr by means of hemodialysis, it is not clear that this rather low rate altered the clinical course in any of the patients.

104. Melville, K.I., Joron, G.E., and Douglas, D. Toxic and depressant effects of alcohol given orally in combination with Glutethimide or secobarbital. Tox. and Appl. Pharm. 9:363, 1966.

In dogs, the enhancement of toxicity of glutethimide or secobarbital, at least in this study, appeared to be the result of a prologation of drug concentration in the blood. This was thought to be the result of increased absorption of the drug when alcohol was given. The drugs are soluble in alcohol.

105. Szot, R.J. and Murphy, S.D. Phenobarbital and dexamethasone inhibition of adrenacortical response of rats to toxic chemicals and other stress. Tox. and Appl. Pharm. 17:761, 1970.

In rats, subanesthetic doses of phenobarbital block adrenal stress reaction.

106. Maher, J.F., Schreiner, G.E. and Westervelt, F.B., Jr. Acute glutethimide intoxication (63 patients). Am. J. Med. 33:70, 1962.

Good clinical description of these intoxications. Strong proponents of dialysis therapy.

107. Maher, J.F. Determinants of serum half-life of glutethimide in intoxicated patients. J. Pharm. and Exp. Therap. 174:450, 1970.

The serum half-life averaged 40.1 hrs. and was reduced in hemodialyzed patients to 14.6 hrs. Forced diuresis had no effect on the serum half-life. But, serum half-life may not be an important clinical parameter.

108. Chazan, J.A. and Cohen, J.J. Clinical spectrum of glutethimide intoxication: Hemodialysis re-evaluated. J.A.M.A. 208:837, 1969.

Concludes that hemodialysis is not of value.

109. Chazan, J.A. and Farella, S. Glutethimide intoxication; a prospective study of 70 patients treated conservatively without hemodialysis. Arch. Int. Med. 128:215, 1971.

Concludes that dialysis is rarely needed. Found poor correlation between either plasma or spinal fluid drug levels and duration of coma and morbidity. Presumably then, serum half-life is not a meaningful clinical parameter.

110. Wright, N. and Roscoe, P. Acute glutethimide poisoning, conservative management of 31 patients. J.A.M.A. 214:1704, 1970.

There seemed to be a fair correlation between blood levels and depth of coma or length of coma. 5 patients developed papilledema (perhaps because of anoxia). One of 31 patients died and this patient was actually killed in another hospital with fluid overload. Authors believe that dialysis not necessary.

111. Comstock, E.G. Glutethimide intoxication. (Letter) J.A.M.A. 215:1668, 1971.

In support of the above paper, the author here states that he has treated 28 patients with severe intoxication by conservative means; e.g., no dialysis, and had no deaths. He also states that Chazan's series has been exteded to 70 patients with 98.5% survival.

111A. Henderson, L.W., Metz, M. and Wilkinson, J.H. Serum enzyme elevation in glutethimide intoxication. Brit. Med. J. 3:751, 1970.

An interesting report of severe intoxication in 2 females who both showed marked elevation of serum CPK (isoenzyme for skeletal muscle) several days following ingestion of drug.

111B. Asbell, N. Clinical evaluation of a new nonbarbiturate sedative - hypnotic, 2-methyl-3-olyl-4-quinazolone: Double blind study. J. Am. Geriatrics Soc. 10:1032, 1962.

Typical of the drug studies we don't need. Would have the reader believe that Quaalude is a non-toxic, non-addicting drug.

111C. Inaba, D.S., Gay, G.R., Newmeyer, J.A. and Whitehead, C. Methaqualone Abuse. "luding out". J.A.M.A. 224:1505, 1973.

111D. Pascarelli, E.F. Methaqualone abuse, the quiet epidemic. J.A.M.A. 224:1512, 1973.

Two papers that present the problems that have been observed in both abuse and overdose with methaqualone.

111E. Johnstone, R.E. et al. Apnea following methaqualone ingestion. Ohio State Med. J. 67:1018, 1971.

Case report - one patient with large Quaalude OD. Had dilated pupils and sudden apnea. Claim is made that hemodialysis was helpful in treatment, but again no measure of the amount of drug removed.

112. Mandy, S. and Ackerman, A.B. Characteristic traumatic skin lesions in drug-induced coma. J.A.M.A. 213:253, 1970.

Pathologically, these lesions show necrosis of the eccrine sweat gland epithelium in both the erythematous and bullous lesions. These authors believe these lesions induced by trauma, but admit that in some cases, sweat gland excretion of drug may play a role.

113. Shubin, H. and Weil, M.H. Mechanism of shock following suicidal doses of barbiturates, narcotics and tranquilizer drugs with observations on effects of treatment. Am. J. Med. 38:856, 1965.

Showed that even with hypotension, vascular resistance may be normal or increased. The cause of the hypotension is hypovolemia, presumably the result of pooling in the comatose patients. Fluid therapy is superior to pressor therapy in these comatose patients.

114. Shubin, H. and Weil, M.H. Shock associated with barbiturate intoxication. J.A.M.A. 215:26, 1971.

After establishing proper ventilatory control in the comatose patient, hypotension can usually best be treated by the administration of fluids.

115. Mackintosh, T.F. and Matthew, H. Do unconscious poisoned patients need prophylactic penicillin? Lancet 1:1252, 1965 (June 12)

From a controlled study, the answer is no.

116. Hiader, I. and Oswald, I. Electroencephalographic investigation in acute drug poisoning. Electroenceph. Clin. Neuroph. 29:105, 1970.

Continuous recordings were observed in 125 patients most with barbiturate OD. Complete electrical silence was observed in 15 patients, 11 of whom made a complete recovery.

117. Hiader, I. and Oswald, I. Late brain recovery processes after drug overdose. Brit. Med. J. 1:318, 1970 (May).

Authors claim, and present some case material to support the idea, that in many instances of acute drug intoxication tolerance and withdrawal symptoms may occur. Withdrawal type symptoms and signs may occur from one to three weeks after the overdose episode.

118. Essig, C.F. Addiction to nonbarbiturate sedative and tranquilizing drugs. Clin. Pharm. Thera. 5:334, 1964.

119. Essig, C.F. New sedative drugs that can cause states of intoxication and dependence of barbiturate type. J.A.M.A. 196:126, 1966.

At least these drugs here listed can give rise to the withdrawal syndrome:

Glutethimide - Doriden
Meprobabmate - Miltown, Equanil, Meprospan, Meprotabs
Methyprylon - Noludar
Ethchlorvynol - Placidyl
Chlordiazeporide - Librium
Diazepam - Valium
Ethinamate - Valmid

It is pointed out that only barbiturates are effective in the treatment of convulsions of withdrawal. Dilantin and phenothiazines are ineffective.

Analeptics:

120. Silipo, S., Hagedorn, C., Rosenstein, I.N., et al. Experiences with Ethamivan (Emivan): New respiratory stimulant and analeptic agent. J.A.M.A. 177:378, 1961.

Gave infusions of 8 mg/min to intoxicated patients. May have been beneficial in mild intoxication. An uncontrolled study.

121. Wheeldon, P.J. and Perry, A.W. The use of ethamivan in the treatment of barbiturate poisoning. Canad. Med. Ass. J. 89:20, 1962.

Gave priming doses of 400 to 500 mg IV followed by continuous infusions of up to as much as 4-5 mg/min. Although the authors conclude this was helpful in treatment of these patients, it is, as are most such "studies", entirely uncontrolled.

122. Chernick, R.M. and Young, G. Evaluation of ethamivan (Emivan) as a respiratory stimulant in barbiturate intoxication and alveolar hypoventilation in emphysema and obesity. Ann. Int. Med. 60:631, 1964.

Concluded that, at least in mild intoxication, Emivan may be useful. Not a controlled study.

123. Hoagland, R.J. and McCarty, R.J. Treatment of drug induced coma: Effectiveness of methylphenidate. Am. J. Med. Sci. 247:189, 1963.

Again, an uncontrolled study. Nothing but good results; no serious bad effects. However, few of the patients appeared to have large drug intakes, and some of the "responses" seemed to have occurred too long after Ritalin administration.

124. Ticktin, H., Epstein, J., Shea, J.G. and Fazekas, J.F. Effect of methylphenidate hydrochloride in antagonizing barbiturate-induced depression. Neurology 8:267, 1958.

Important point here is that Ritalin does not increase cerebral $O_2$ consumption in barbiturate depression. It is assumed other analeptics may, and this could result in brain damage in an anoxic patient.

125. Funderburk, W.H., Oliver, K.L. and Ward, J.W. Modification of cerebral blood flow in dogs with doxapram hydrochloride. Tox. and Appl. Pharm. 13:67, 1968.

At 5 mg/Kilo, BP and CBF increased followed by a short period of ↓ CBF. At 40 mg/Kilo there was a prolonged period of ↓ CBF. Authors conclude that this is the result of ↓ $pCO_2$

126. Ward, J.W., et al. Toxicologic studies of Doxapram hydrochloride. Tox. and Appl. Pharm. 13:242, 1968.

In dogs, death occurred at 50 mg/Kilo/day or above. Convulsions might result from cerebral anoxia incident to ↓ CBF caused by ↓ $pCO_2$

127. Adriani, J., Drake, P. and Arens, J. Use of antagonists in drug-induced coma. J.A.M.A. 179:752, 1962.

A paper, which apparently has been essentially ignored, presenting view that modern analeptics (Mezimide, Ritalin, and Emivan) are of value by their ability to raise reflex activity, not, however, necessarily shortening the length of coma. (Doxapram should probably now be considered in this group).

128. Wolfson, B., Siker, E.S., and Ciccarelli, H.E. A double blind comparison of doxapram, ethamivan, and methylphenidate. Am. J. Med. Sci. 249:391, 1965.

Probably the best study of analeptics. Perhaps Doxapram more effective than Emivan in stimulation of respiration. However, Doxapram may produce hypertension, tachycardia, arrhythmias, muscle rigidity and vomiting; affects intensified in patients receiving sympathomimetic drugs or monoamine oxidase inhibitors.