Diagnosis and Management of Toxicoses (9-Aug-1999)

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1. Antemortem Diagnosis

The diagnosis of toxicological diseases on the basis of signs alone is not only very often difficult or impossible but may be dangerous as well. Each body system can react in a limited number of ways, producing clinical signs, and there are thousands of toxic agents that may affect these systems. In addition, when a clinician observes an animal with signs of illness or poisoning he may see only one phase of the syndrome. Toxicological diseases may be acute or chronic, and the clinical presentation will vary depending upon the route, extent, and frequency of exposure; the species involved; the time elapsed since the most recent exposure; and many other factors.

A confirmed toxicological diagnosis often rests upon appropriate findings, including: a) exposure history, b) clinical signs, c) time of onset, d) duration of effects that are compatible to the toxic potential of the agent involved, as well as e) detection of the toxicant in the animal to confirm exposure (e.g., blood Pb), and in some cases, f) specific evidence of pathophysiologic derangement (e.g., acetylcholinesterase inhibition).

Even when an individual animal may no longer benefit from laboratory confirmation, positive or negative laboratory results may ultimately protect other animals or humans from toxic substances or missed diagnoses. Many specific antidotes have inherent toxicity, and their use in unconfirmed cases of poisoning can sometimes be hazardous. Also, clinical signs alone are not considered determinative evidence when presented in court. Therefore, efforts to obtain a specific diagnosis constitute time well spent.

The 5 basic routes of exposure to poisoning are: ingestion, cutaneous (topical), inhalation, injection (or envenomation), and ocular. Most toxicoses result from the oral ingestion of a toxicant, but some chemicals including many insecticides, phenols, and other lipophilic substances may also be efficiently absorbed through intact skin. Abraded skin may absorb some substances that otherwise might not reach toxic concentrations following dermal exposure. Of course, many volatile, aerosolized, or even solid particulate agents may be absorbed from the respiratory tract. For most agents, the rate of absorption is injection > respiratory > oral > topical. The route of exposure often influences the choice of specimens for confirmation. In addition to toxicosis due to systemic absorption of a compound, many compounds (e.g., corrosives) may result in direct tissue damage.

Identifying the Source

When poisoning is suspected, efforts should be made to determine the possibility and likelihood of exposure. Encourage the client to look in all places to which the animals have access. Be persistent and have them contact you after the search. If on a house or farm call, look with the client. If suspected toxicants are found, they should be saved for laboratory submission. When containers are found, read the ingredients list and any antidotal procedures (bearing in mind that some labels are out of date with regard to treatment recommendations). When toxic plants are suspected and there is evidence of significant
consumption, be sure to get specimens for identification. Plants may be wrapped in wet newspapers and placed in a plastic bag prior to shipment (preferably with cold packs) to the laboratory or to a local botanist for identification.

Specimens from Animals
Care to avoid cross contamination of any sample by a potential toxicant is absolutely essential. It is therefore advisable to obtain specimens from animals before handling suspected source materials. If at all possible, before treatment is begun, refrigerate specimens of whole blood (10 - 20 ml with calcium EDTA as the anticoagulant) and freeze samples of serum (10 - 20 ml). Smaller specimens may be sufficient for certain tests. Volumes obtained may be reduced in particularly small species/individuals. In addition, save liberal portions of vomitus, urine, and feces for laboratory analysis. If vomitus cannot be collected and if gastric lavage is indicated, the initial lavage washings (using water only), should be submitted. The vomitus or lavage washings should be frozen in a tightly sealed jar. If topical exposure is suspected, hair may be frozen in a sealed container and submitted for analysis.

Feed and Water
When feed contamination is suspected, representative specimens of the material being consumed immediately prior to the onset of apparent toxicosis must be obtained. Delays in securing such samples may result in continued exposure to the toxicant and the subsequent absence of remaining feed for toxicologic analysis. For dry concentrate feedstuffs, obtain 2-kg samples of a composite from several areas of the incriminated feed. If moisture concentration is 13% or less, such feed can generally be shipped with no special method of preservation. Higher moisture feeds and forages should be kept frozen prior to and during shipment to the laboratory. When volatile substances are suspected as feed contaminants, however, the feed should be placed in clean glass jars and tightly capped and frozen. Water specimens may be similarly preserved and, if not filled more than 2/3 full, usually tolerate being frozen (in a tilted position) prior to shipment. In attempting to determine an antemortem diagnosis, one must remember that only a few toxicological tests can be done on a "stat" basis by most laboratories, e.g., blood lead, acetylcholinesterase. Due to the difficulties in chemical analysis for many toxicants, delays in receiving results of days to weeks must be anticipated. Serum chemistry, serum electrolytes, and other clinical diagnostic tests may rapidly contribute to a specific diagnosis (e.g., hypercalcemia in cholecalciferol toxicosis).

2. Postmortem Diagnosis
At necropsy it is essential to obtain a complete set(s) of specimens for chemical analysis and a complete set(s) of tissues for histopathology and other (e.g., bacterial and/or viral) studies. Many toxicologic diagnoses rely not only on residues of the toxicant but also on compatible lesions and/or the absence of evidence of other diseases capable of causing similar clinical effects. Specimens for analysis should be individually frozen and double bagged (with a paper label marked in pencil between 2 tightly sealed Whirl-Pack bags). The following specimens should be routinely collected: stomach or rumen contents, intestinal contents, feces, 1/2 of the brain, liver (without the gall bladder or bile contamination), kidney, body fat, and urine. Specimens should be large (i.e., up to 250 grams of stomach or intestinal contents, parenchymal organs, or body fat). In case of dermal exposure contaminated skin should be bagged, frozen, and submitted. In such cases, specimens of internal organs must not be contaminated from contact with the skin. Repeated cleaning or changing of instruments and gloves may be desirable after the skin has been reflected from the animal. Similar concerns exist when higher concentrations of toxicants may be present in the gastrointestinal tract than in organs for analysis.

3. Management Introduction
Goals for the management of acutely poisoned animals are ordinarily addressed in the following sequence: first stabilize vital signs; second-clinical evaluation; third-prevent continued exposure to the toxicant; fourth-administer an antidote if available; fifth-facilitate removal of the absorbed toxicant; and sixth-supportive therapy and observation. Different antidotes counteract the effect of toxicants in various ways. Many "antidotes" are directed toward achieving stabilization of vital signs, decreasing exposure, or facilitating removal whereas other "antidotes" specifically antagonize the toxicant at a primary or secondary site of action. The excessive reliance on an antidote's action can be dangerous.

Often treatment of a patient must begin before a diagnosis is clearly established. The vast majority of toxic substances do not have specific antidotes, and even when an antidote can be used, the patient will often benefit equally from supportive therapy, which offsets the toxic effects on the animal. In either case logical steps toward preventing further absorption and detoxification of the animal are usually of substantial value.
It is wise to caution animal owners regarding hazards from human exposure to toxic substances (on the skin, in vomitus, in the environment, etc.) as well as animal kicks or bites. Keep in mind that a poisoned animal may no longer perceive or react to its owner in the usual way. Acutely ill animals that can be seen immediately should not be treated at home. Removal to the veterinary facility or a separate holding pen should be used to separate the animal(s) from potential environmental sources. A change of food and water is often recommended until the source of the toxicant is known.
4. Stabilizing Vital Signs
The objective is to preserve the life of the animal regardless of the etiology, buying time for detoxification to occur and for specific antidotes to have their pharmacological action. When multiple animals, e.g., herds, flocks, kennels or catteries, are involved, a system of triage may be necessary. Careful medical managements including restoration of fluid and electrolyte balance and maintenance of adequate respiratory function is associated with a higher survival rate than reserving treatment until "heroic" measures are necessary.

a) Maintenance of Respiration
It is important to emphasize the needs for: 1) a patent airway, 2) adequate ventilation, and 3) prevention of aspiration of vomitus. Generally, a patent airway can be provided using a cuffed, inflated endotracheal tube provided that the animal is comatose or anesthetized. If the animal is extremely weak, convulsing, or has absent postural and/or swallowing reflexes and begins to vomit prior to intubation, inversion of the animal so that the head is lower than the rest of the body may clear the pharynx. Aspiration of the respiratory tract may be necessary. In larger animals the head may be lowered and the anterior thorax elevated to accomplish the same objective, e.g., placing the animal on an incline. After clearing the pharynx, endotracheal intubation can then follow.

When forced ventilation is needed for a prolonged period of time, ventilation with moistened room air is usually preferred over oxygen. Mechanical or manual forced ventilation may be necessary for poisoned animals suffering from paralysis, severe CNS depression or, rarely, when deep anesthesia is necessary to control convulsions. Assistance of ventilation is also the preferred method of correcting respiratory acidosis. In cases of profound anemia and/or hemorrhage, such as may occur in anticoagulant rodenticide poisoning or hypoxia resulting from various causes, minimal handling and oxygen cages may be of temporary benefit.

b) Maintenance of Cardiovascular Function
Provision of adequate respiratory ventilation, hydration, acid-base, and electrolyte balance are all necessary for normal cardiopulmonary function and oxygen exchange. Certain toxicants cause severe vomiting or diarrhea with resulting electrolyte and fluid imbalances. Ingestion of excessive quantities of drugs, especially diuretics can lead to extreme electrolyte alteration. Furthermore certain toxicants or toxic metabolites, such as oxalic acid, may bind calcium sufficiently to result in a hypocalcemic state. Thus, when cardiovascular dysfunction is associated with a toxic insult, correction of imbalances of calcium, sodium, potassium and acid-base status may result in restoration of normal function. Blood samples for electrolyte, blood glucose, and serum chemistry determinations should be collected before initiating fluid therapy. ECGs may be monitored and appropriate measures taken to reestablish homeostasis.

Fluid Therapy
Clinical guides to the assessment of fluid balance include features of serious flow volume overload (e.g., pulmonary edema) and volume contraction (e.g., skin turgor). If shock or hypotension occurs, balanced electrolyte solutions (e.g., lactated Ringer's solution) or normal saline are often indicated. Central venous pressure (normal for canine = 0 - 5 cm H2O), urinary output, and body weight measurements may be monitored to avoid fluid overload and help adjust flow rate.

<table>
<thead>
<tr>
<th>Percent Dehydration</th>
<th>Clinical Signs</th>
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<tr>
<td>5 - 6</td>
<td>Loss skin turgor, dry mouth, depression, oliguria, hypotension, shock</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
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Remember that dehydration alone can influence various clinical pathology findings, e.g., increased PCV, increased BUN (prerenal azotemia), and elevated total protein. An adequate quantity of fluids must be supplied to replace deficits from previous losses. In addition, daily maintenance fluid requirements and on-going fluid loss (e.g., vomiting, diarrhea, polyuria) must be taken into account. In diarrhea, loss of sodium, potassium, magnesium, calcium, and bicarbonate can be expected. Ions lost through vomiting include chloride, sodium, and potassium.
Complications of Fluid Therapy

1. Never give hypotonic or hypertonic fluids by any route other than intravenous.
2. Complications associated with intravenous fluid therapy include:
   a. Overload (pulmonary edema, medullary washout),
   b. Thrombophlebitis and endocarditis,
   c. Pyrogenic reactions,
   d. Air embolism,
   e. Exsanguination (must be considered in coagulopathies, e.g., anticoagulants), and
   f. Extravasation of fluids.

There is no single fluid that will fulfill the fluid requirements of all patients. A general guideline for maintenance fluid requirements is 50 - 80 ml/kg/day. Specific fluid guidelines are beyond the scope of this review; however, in the following conditions, appropriate fluid therapy includes:

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Fluid</th>
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<tbody>
<tr>
<td>Hypercalcemia secondary to cholecalciferol ingestion</td>
<td>0.9% saline</td>
</tr>
<tr>
<td>Lactic acidosis, e.g., secondary to salicylate ingestion, or shock from</td>
<td>Saline and dextrose with bicarbonate; later</td>
</tr>
<tr>
<td>any toxicosis</td>
<td>acidosis controlled, lactated Ringer's solution.</td>
</tr>
<tr>
<td>Ethylene glycol toxicosis</td>
<td>Saline initially, then lactated Ringer's</td>
</tr>
<tr>
<td></td>
<td>solution alternated with 5% dextrose;</td>
</tr>
<tr>
<td></td>
<td>bicarbonate may be added according to need</td>
</tr>
<tr>
<td>Conditions causing hemoglobinuria and myoglobinuria</td>
<td>Fluid therapy (saline) with added bicarbonate to lessen the likelihood of precipitation of hemoglobin or myoglobin in renal tubules</td>
</tr>
</tbody>
</table>

Blood Transfusion Therapy:
1. Calculation of blood replacement volume:

\[
\text{ml of Donor Blood in Anticoagulant needed} = \frac{\text{body weight (kg)} \times C \times (\text{PCV desired} - \text{PCV recipient})}{\text{PCV donor}}
\]

where C is a constant depending upon the species involved. C = 90 (dog), 70 (cat). In larger animals, a general guide of 10 - 20 ml/kg could be used for clinically anemic animals.

2. Indications:
   a. PCV < 12 - 20%, depends upon history and clinical signs.
   b. Restoration of oxygen-carrying capacity.
   c. Hypovolemia, anemia, dyspnea.
   d. Fresh whole blood or plasma therapy used for volume restoration and coagulation factor replacement. Remember transfused platelets have short half-lives in the body.

3. Contraindications:
   a. Immune-mediated hemolysis.
   b. Blood group incompatibility.
<table>
<thead>
<tr>
<th>Species</th>
<th>Major Blood Group</th>
<th>Minor (involved with most transfusion reactions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat</td>
<td>A (73%)</td>
<td>B (23%), AB (1%)</td>
</tr>
<tr>
<td>Dog</td>
<td>F, C (98%)</td>
<td>A (40%), Tr (45%), other (see note below)</td>
</tr>
<tr>
<td>Horse</td>
<td>Multiple</td>
<td>Aa</td>
</tr>
<tr>
<td>Cow</td>
<td>Multiple</td>
<td>-</td>
</tr>
</tbody>
</table>

**Note** - Dog blood group current nomenclature "dog erythrocyte antigen" group (DEA), for example, A = DEA 8, Tr = DEA 7.

In many species (e.g., horse, cow, dog, cat), it is generally safe to administer transfusions to a recipient which has not received blood or blood components previously.

4. **Transfusion reactions:**

   a. Clinical signs of transfusion reactions include urticaria (most frequent), fever, hemolysis with hematuria, and anaphylaxis (arrhythmias, hypotension, cardiopulmonary arrest).
   b. Resultant renal failure secondary to hemolysis can occur.
   c. Hemolysis-May be acute or delayed.
   d. Acute hemolytic crisis within minutes-tremors, vomiting, urinary and fecal incontinence, transient fever, and prostration. More severe signs-dyspnea, paraparesis, and convulsions. DIC and shock, death possible.
   e. If see signs of reactions-stop transfusion and administer IV fluids. Check urine for hemoglobin/blood hemolysis.
   f. Most dogs recover in 12 - 24 hours.
   g. Circulatory overload; vomiting, cough, pulmonary edema may occur.
   h. Hypocalcemia due to blood containing sodium citrate. Other signs of citrate toxicosis include muscle fasciculations, arrhythmias, and collapse.
   i. Metabolic alkalosis from citrate that has been metabolized in stored blood to bicarbonate??
   j. Hyperkalemia-Stored (aged) blood has a high percentage of hemolyzed erythrocytes which results in the release of potassium.
   k. Small amounts (1 - 5% of total volume to be administered) should be given, then the animal should be observed closely for 10 - 15 minutes for anaphylactic reactions.
   l. Whole blood is given if red blood cell mass or platelets (use fresh plasma or fresh whole blood) are required.

**Acid Base Disturbances**

In the poisoned patient, acid base homeostasis may be disrupted by a variety of mechanisms. Acid base balance may be disrupted because: 1) the toxicant or its metabolites have acidic or basic character; 2) the agent causes seizures or other forms of profound exertion; 3) the agent causes circulatory impairment of peripheral tissues (usually secondary to shock); 4) the agent causes respiratory dysfunction; 5) the agent causes vomiting or diarrhea; and/or 6) the treatment (e.g., diuretics) causes electrolyte imbalance. Acidosis is the most commonly encountered acid base disturbance. Metabolic acidosis develops from a loss of extracellular bicarbonate (e.g., diarrhea), gain of hydrogen ion and decrease in bicarbonate concentration (e.g., aspirin ingestion), or from dilution of extracellular bicarbonate. Further classification of a metabolic acidosis into 2 general categories, based on the presence or absence of an elevated anion gap, may contribute to a diagnosis. For example, a partial list of toxicants resulting in an elevated anion gap includes ethylene glycol, methanol, and salicylates. Clinical signs of metabolic acidosis include tachypnea, vomiting, depression, and arrhythmias.

To correct metabolic acidosis (decrease in serum bicarbonate generally less than 18 - 22 mEq/L), fluids with added sodium bicarbonate (1 - 3 mEq/kg administered in fluids over 1 - 3 hours: an 8.4% solution sodium bicarbonate = 1 mEq/ml) are used. This is important with toxicosis due to ethylene glycol, metaldehyde, and aspirin among other agents. Blood gases and blood and urine pH are monitored to assess the need for and the success of bicarbonate therapy. Rapid alterations in pH with bolus dosages of alkalinizing agents must be avoided. Too rapid an administration of bicarbonate has been associated with cardiac arrest, hypotension, CSF acidosis, hyperosmolality, and vomiting. Other alkalinizing agents that have been investigated include sodium lactate, sodium acetate, and trihydrromethyl aminomethane (THAM). Metabolic alkalis (sodium bicarbonate greater than 27 mEq/L) may be due to retention of excessive bicarbonate or loss of
hydrogen (e.g., vomiting). Due to the resulting hydrogen ion gradient, intracellular hydrogen ions are exchanged for extracellular sodium and potassium resulting in hypokalemia. The resulting alkalemia depresses the central respiratory center and chemoreceptors resulting in hypoventilation and hypercapnia (respiratory compensation). Causes of metabolic alkalosis include diuretics, hypercalcemia, blood transfusions (remember stored whole blood is high in citrate which is converted to bicarbonate). Clinical signs of metabolic alkalosis include arrhythmia, increased neuromuscular irritability (e.g., tetany). To correct alkalosis, which is rarely a problem, fluid therapy (0.9% NaCl) with potassium chloride supplementation is generally effective. Ammonium chloride (200 mg/kg/day, divided dose) may be given orally.

**Cardiac Arrhythmias** - Treatment for cardiac arrhythmias may be required in some toxicoses. An arrhythmia is an abnormality in the rate, origin, or regularity of myocardial depolarization or other disturbance in impulse conduction. The clinical effects of an arrhythmia may result from:

1. Changes in the heart rate,
2. Loss of synchrony in atrial and ventricular contractions,
3. Heartbeat irregularity,
4. Changes in ventricular contractility. Clinical signs in an animal with an arrhythmia may include depression, weakness, ataxia, dyspnea, exercise intolerance, syncope, seizures, and/or death. Arrhythmias may also be suspected on the basis of physical exam findings including jugular pulse (may be normal in some cases), pulse deficits, and auscultable changes in heart sounds.

Methods available for the termination of arrhythmias include:

1. Physiological maneuvers (e.g., ocular pressure with some atrial tachycardias, temporary AV block);
2. Correction of acid base, electrolyte, or fluid disorder;
3. Oxygen therapy;
4. Antiarrhythmic drug therapy; and
5. Other supportive therapy. Remember, in many cases, correcting an underlying disorder may "cure" an arrhythmia without the use of antiarrhythmic drugs. When used, antiarrhythmic therapy should be specific for the type of arrhythmia present and the species involved.

Antiarrhythmic drugs are classified into 4 major categories based upon the drug's mechanism of action. Class I drugs interfere with fast current sodium channels and include quinidine, procainamide, and lidocaine. Class II drugs are β-adrenergoreceptor blockers and include propranolol and metoprolol. Class III drugs (e.g., bretylium) prolong the duration of the action potential. Class IV drugs are calcium-channel blockers; the prototype drug of this class being verapamil. Class I drugs have been subdivided into 3 subclasses. Class IA drugs (e.g., quinidine, procainamide) have a moderate effect on conduction velocity and prolong repolarization. Class IB drugs (e.g., lidocaine, phenytoin) have mild effects on conduction velocity and shorten repolarization. Class IC drugs (e.g., encainide, lorcaignide) markedly depress conduction velocity but have little or no effect on repolarization.

**Horses** - Anticholinergic agents including atropine or glycopyrrolate are used to treat bradyarrhythmias in horses. Ventricular rates less than 20 - 25 bpm should be treated. Remember that intestinal motility can be depressed (up to 9 hours after a single injection of atropine) following use of these agents. Doses (IV) of atropine (0.02 mg/kg) and glycopyrrolate (0.005 mg/kg) have been recommended for treatment of serious bradycardia due to increased parasympathetic tone (e.g., organophosphorus insecticide toxicosis). The best course of action is to administer atropine (only when needed) in fluids IV while frequently auscultating the abdomen in order to avoid induction of stasis. Side effects of atropine administration include diminished respiratory, salivary, and GI secretions, increased respiratory dead space, colic, and death.

In the horse, cardiac arrhythmias are treated with quinidine, procainamide, and propranolol. Quinidine is the most frequently used drug for the following types of arrhythmias: ventricular tachycardia, ventricular premature depolarization, atrial flutter, and atrial premature depolarization. Quinidine prolongs the QRS and QT intervals at therapeutic concentrations. The recommended dose of quinidine in the horse is 0.5 mg/kg IV every 10 minutes until 4.0 - 6.0 mg/kg total or 20 mg/kg oral every 2 hours until 60 - 80 g total. Large or toxic doses of quinidine can prolong the PR interval as well. Side effects of quinidine therapy in the horse include pharyngeal swelling, hypotension, depression, diarrhea, nervousness, and anorexia. Horses receiving large dosages may experience laminitis, tachypnea, and tachycardia. Sodium bicarbonate at 0.5 - 1.0 mEq/kg IV may be used to reverse some signs of quinidine toxicity.

**Contraindications** for quinidine therapy include shock, congestive heart failure, digoxin toxicity, cardiomyopathy, and bundle branch blocks. Treatment of sinus tachycardia is with propranolol.

A **partial list** of possible agents which could cause life-threatening arrhythmias in the horse include organophosphorous/carbamate insecticides, Japanese Yew, Oleander sp., Foxglove (Digitalis), digitalis, digoxin, and Rhododendron, among others. Note: calcium administration is contraindicated for digitalis compounds and the toxins present in Rhododendron.

Remember in the case of the horse, autonomic-induced arrhythmias may be due to excessive vagal stimulation and may be normal in the healthy horse. Using exercise as a means of diagnosis of arrhythmias (physiologic arrhythmias disappear when the heart rate is elevated) would be dangerous in the potentially poisoned equine.

**Canine/Feline** - Before attempting treatment of a cardiac arrhythmia, it is important to establish the possible agent involved and determine whether the animal is on any medication, especially digitalis. Remember that digitalis can cause almost all known arrhythmias. Treatment of an underlying cause of an arrhythmia (e.g., metabolic acidosis) may eliminate the
arrhythmia or facilitate its therapy.

On a practical basis, antiarrhythmic agents can be divided into drugs for tachyarrhythmias or drugs for bradyarrhythmias. Some of the more common cardiac arrhythmias which may be expected in toxicoses include:

1. Sinus bradycardia - Regular sinus rhythm with a heart rate less than 60 - 70 bpm in dog and less than 160 bpm in cat. If clinical signs, e.g., syncope or weakness, are associated with the arrhythmia, treatment should be considered. Parenteral atropine (0.01 - 0.2 mg/kg IV, IM) or glycopyrrolate (0.005 - 0.01 mg/kg IV, IM) would be initial antiarrhythmics of choice. Potential agents which may result in sinus bradycardia include organophosphorus/carbamate insecticides, β-blockers, calcium channel blockers, digitalis, and phenothiazines.

2. Sinus arrest (SA node does not produce conduction impulse) or sinoatrial block (conduction disturbance from SA node) when asymptomatic does not require therapy. These conduction blocks can result from propranolol or digoxin toxicity.

3. AV blocks - Second-degree AV block (intermittent AV blockade) and third-degree AV block (no AV conduction) can also be caused by digitalis toxicity. Third-degree AV blocks generally require artificial pacing. Second-degree AV blocks can be treated with atropine, dopamine (3 - 5 mg/kg/minute), or isoproterenol (1 mg in 250 ml D5W drip slowly at .01 mg/kg/minute to effect).

4. Atrial standstill is a potentially life-threatening arrhythmia and can be associated with hyperkalemia. Hyperkalemic states can be the result of increased exogenous K+ load (e.g., excess KCl, blood transfusions), decreased renal excretion of potassium (e.g., toxicosis associated with potassium sparing diuretics, lithium, captopril, nonsteroidal anti-inflammatory drugs), and cellular shifts (e.g., due to digoxin, amphetamines, and 2nd rhabdomyolysis). If hyperkalemia is suspected (e.g., spiked T waves), the following therapies designed to shift potassium intracellularly may be of value: saline therapy, sodium bicarbonate (1 - 2 mEq/kg), or regular insulin (0.5 - 1.0 unit/kg) with dextrose (2 gm dextrose/unit insulin).

5. Atrial tachycardia: originates from an atrial focus other than the SA node, arrhythmia may be secondary to digitalis toxicosis. Causes weakness, hypotension, and syncope. Vagal maneuver (e.g., ocular pressure) can terminate atrial tachycardia.

6. Atrial flutter (rates > 300 bpm) and supraventricular tachycardia or atrial fibrillation may also occur but are rarely observed in toxicosis.

7. Ventricular premature complexes (VPCs) arise from ventricular ectopic foci and are commonly associated with a pulse deficit. Indications for treatment include: a) high rates 20 - 30 bpm, b) runs of VPCs, c) multiformal QRS complexes, d) R on T phenomenon, and e) clinical signs, e.g., syncope, dyspnea, weakness. VPCs rarely require therapy in the cat, and in this species, propranolol (0.04 - 0.06 mg/kg slowly IV) or the more β1 selective blocker, metoprolol would be indicated. In the dog, VPCs are commonly treated with lidocaine hydrochloride (without epinephrine, 2 - 4 mg/kg IV slowly to maximum 8 mg/kg, constant IV rate infusion 25 - 75 mg/kg/minute) or procainamide (6 - 8 mg/kg IV over 5 minutes, constant rate infusion 25 - 40 mg/kg/minute). Phenytoin has been recommended for digitalis-induced VPCs (30 - 35 mg/kg oral TID). A beta blocker may also be of value in conjunction with phenytoin and atropine for digitalis poisoning.

8. Ventricular Tachycardia - May result in syncope, seizures, hypotension, etc. Antiarrhythmic therapy is generally warranted in most animals with ventricular tachycardia unless an underlying cause (e.g., electrolyte imbalance) can be identified and corrected. Lidocaine hydrochloride without epinephrine (2 - 3 mg/kg IV slowly) is the primary antiarrhythmic of choice in dogs. Constant infusion therapy may be required. Nonresponsive tachyarrhythmias, may require additional antiarrhythmic therapy, e.g., procainamide. When these fail, a β-blocker such as metoprolol may be of value.

Side Effects
As in all classes of therapeutic agents, antiarrhythmics have associated potential adverse side effects. Phenytoin should not be administered to cats since small oral or IM doses have resulted in clinical toxicity, primarily manifested by hepatotoxicity. Lidocaine is potentially neurotoxic in the cat and may cause tremors and convulsions, in addition to cardiac conduction disturbances, bradyarrhythmias, hypotension, and sinus arrest. Convulsions have been reported in the horse following administration of an IV bolus of lidocaine. Note: in the treatment of cardiac arrhythmias, lidocaine without epinephrine should be administered.

Digitalis glycosides can be used for the treatment of congestive heart failure and certain cardiac arrhythmias (e.g., supraventricular premature complexes, atrial flutter/fibrillation, supraventricular tachycardia). Signs of digitalis intoxication include increased P-R interval, AV block, prolonged QRS, and arrhythmias. Clinical signs of digitalis intoxication in the horse include anorexia, depression, and diarrhea. In addition to these signs, small animals may commonly vomit.
Untoward side effects of propranolol therapy include decreased contractility, bronchoconstriction, and bradycardia. Potential contraindications to β-blocking drug use include: obstructive airway disease, congestive heart failure, bradycardia, hypoglycemia, and impaired AV conduction.

Note - These notes are not intended to be all inclusive and the reader is directed towards more comprehensive therapy reviews.

c. Control CNS Stimulation

Convulsions - Whenever possible, seizure treatment should be directed at the primary disease if it can be recognized. Seizures may be classified as partial or generalized. Generalized (grand mal) seizures are the most common form of convulsions in animals. Clinical signs include combinations of visceral (e.g., salivation, urination, defecation) and somatic (e.g., paddling, clonic limb activity) motor activity in addition to behavioral derangements. Many cases, in which seizures occur as a result of a toxicosis, will require treatment for status epilepticus or repeated seizure episodes. The treatment of status epilepticus must be considered a medical emergency due to potential adverse sequelae (e.g., hypoxia, acidosis, etc.) if untreated.

Small Animals - Diazepam (Valium ®) (0.5 mg/kg IV or IM doses may be repeated every 10 minutes for 3 doses) may be used to control seizures from a wide variety of etiologies and therefore serves as a desirable choice for management of an animal (especially a dog) in convulsions, in which the causation is unclear. When diazepam fails, generally phenobarbital (6 mg/kg IV to effect) is tried next. If seizures persist, pentobarbital (slowly to effect) is usually used. Methocarbamol (Robaxin ®) (44 - 200 mg/kg IV start with low dose and give to effect) may be given when indicated for skeletal muscle relaxation IV. Injectable methocarbamol (Robaxin ®) contains a polyethylene glycol vehicle which may be contraindicated in animals with impaired renal function. Adverse reactions in dogs and cats include vomiting, hypersalivation, weakness, and ataxia. Glycerol guaiacolate (Guailaxin ®) has been used to allow animals to relax enough to induce vomiting, but this application is controversial. Guaiifenesin will also relax pharyngeal and laryngeal muscles and an animal may suffer loss of control of its airway. A dark quiet room with very frequent or constant monitoring is very important.

Hyperactivity

CNS stimulation from excessive exposure to amphetamines, or to some hallucinogens, such as LSD and phencyclidine have been treated with phenothiazine tranquilizers, but this therapy was not reliable enough to be widely accepted. As a rule, the phenothiazine tranquilizers are best avoided as they may aggravate CNS depression and in other cases be epileptogenic. If tranquilization is required (e.g., self-trauma), diazepam (2.5 - 10 mg IV PO to effect) should be considered.

d. Control CNS Depression

Remember that the presence of a toxicant does not necessarily account for an animal's neurological status. For example, some agents (e.g., barbiturates) may cause profound hypotension with resultant cerebral hypoxia in addition to their direct depressant effects. In addition, head trauma may result secondarily from the effects of a toxicant (e.g., falls, etc.). Repeated complete neurological examination of severely depressed or comatose animals is warranted to monitor status as well as response to therapy. The use of analeptics is at best debatable since it is difficult to stabilize the animal receiving these drugs. Convulsions and rebound depression following withdrawal are undesirable side effects associated with older preparations. Clearly the best and only worthwhile respiratory stimulant is doxapram (Dopram-V®). This compound exerts its effect via stimulation of peripheral carotid chemoreceptors. The dosage of Dopram-V® is 1 - 10 mg/kg IV. Doxapram may be repeated in 15 - 20 minutes if needed. Some human protocols additionally employ a slow drip of doxapram HCL. Doxapram is compatible with 5% dextrose or normal saline but not with alkaline solutions. In doses greater than those used to stimulate respiration, CNS stimulation by doxapram may result in seizures. The drug is considered to have a narrow margin of safety. Other adverse effects (reported in humans) include hypertension, arrhythmias, and dyspnea. After the period of stimulation, deepening of the comatose state usually reoccurs, but sometimes not to the original extent. Sometimes judicious stimulation may increase the activity of the CNS to the point that the restoration of vital function may secondarily produce a further awakening effect. The use of naloxone is recommended for the treatment of exogenous opiates (e.g., morphine, codeine). Naloxone has replaced levallorphan and nalorphine in clinical treatment because it lacks agonist activity. Naloxone's duration of action is short (45 - 90 minutes), and in the treatment of opiate-induced coma, higher doses may be required. Naloxone is administered in dogs at .04 mg/kg IV, IM, or SC and is repeated as needed. Experimental and clinical data in rabbits and humans indicate that naloxone is efficacious when administered by the endotracheal route. A nonspecific arousal effect has been attributed to naloxone with reports in human clinical cases of the reversal of nonopiate central nervous system depression from barbiturates and benzodiazepines.
Flumazenil has been shown to be an effective treatment for CNS depression associated with benzodiazepine overdose in dogs. The drug is a specific benzodiazepine antagonist with a very wide therapeutic index. The dose is based on an estimate of diazepam intake (1 mg flumazenil /25 mg diazepam) and is given intravenously. Duration of activity is approximately 2 hours. Re-dozing may be required in cases of severe toxicosis.

Physostigmine
Is an alkaloid extract of the Calabar bean. Its active constituent is an uncharged carbamate cholinesterase inhibitor. The use of physostigmine for its nonspecific arousal effect has been advocated in humans poisoned with tricyclic antidepressants, ivermectin, benzodiazepines, phenothiazines, barbiturates, and ketamine. It also is used for life threatening toxicosis from atropine and related compounds. The use of physostigmine has become associated with considerable controversy, however. Adverse effects associated with physostigmine include convulsions, cholinergic crisis (e.g., hypersalivation, bradycardia, dyspnea), variable levels of consciousness and possible death. Physostigmine is rapidly metabolized and requires repeated administration (every 30 - 60 minutes) to maintain its effects. Due to its clinical limitations and possible adverse side effects, its general use as an analeptic cannot be recommended.

e. Control Body Temperature
Hypothermia may occur during anesthesia, heavy sedation or coma. Body temperature may decrease below the calibration of a rectal thermometer during prolonged anesthesia. Such a condition may occur during the course of therapy for strychnine poisoning. Vital physiologic processes and the rate of metabolic degradation of poisons are depressed when body temperature is subnormal. Blankets and circulating warm water pads may be helpful in maintaining body temperature. If heat lamps are employed, be careful to avoid burning the animal. It is best to use these only at a distance to heat the environment rather than the animal directly. Animals with poor perfusion are more likely to be burned. Turn the animal often and check the temperature to avoid hyperthermia. Conventional heating pads can also cause burns and should be avoided. Hyperthermia often occurs with persistent seizures. Hyperthermia is controlled with ice or cold baths. Concomitant dehydration may occur and should be controlled. Hyperthermia may also be a problem with toxicosis due to uncouplers of oxidative phosphorylation, e.g., disophenol (DNP), pentachlorophenol and dinitrophenol. With poisoning from these agents it is important to keep the animals calm and as cool as possible even before the onset of signs. Elevated body temperature from either exercise or ambient temperature tends to precipitate acute toxicosis. Antipyretic drugs are generally not indicated in toxicant induced hyperthermia.

5. Preventing Continued Absorption of the Toxicant
a. Dilution
The oral administration of water or milk is frequently recommended in the initial management of poisoning. This recommendation is based upon the potential for dilution of a toxicant with delayed or decreased gastrointestinal absorption. In several studies, large volumes of water apparently increased gastrointestinal absorption and decreased oral LD50 when a chemical was given concurrently with water. The administration of water or milk to facilitate dilution of a toxicant has therefore become controversial. It is still generally recommended that dilution with water or milk may be useful, along with demulcents and gastrointestinal protectorants in the management of corrosive ingestions.

Corrosive Ingestions
Various sources of alkaline corrosives include lye (concentrated sodium hydroxide), drain cleaners, some electric dishwashing detergents, phosphate detergents, bleaches, and batteries. Alkaline batteries may cause intestinal necrosis if they become opened in the GI tract. Most liquid chlorine bleaches, dilute ammonia, and other weaker alkaline corrosives may result in burns but are less caustic to the esophagus. In general, alkaline corrosives are considered more damaging since their ingestion results in a liquefactive necrosis. Acids more commonly produce a coagulative necrosis which minimizes tissue penetration. Granular or solid lye more commonly adheres to mucous membranes, and their ingestion is associated with a higher incidence of pharyngeal and esophageal burns. Esophageal injury in the absence of mouth or pharyngeal burns can occur and may require careful esophagoscopy, barium swallows, or other radiologic evaluation for diagnosis. The use of chemical neutralizing agents (e.g., vinegar, sodium bicarbonate) has been demonstrated to be associated with increased tissue damage and is contraindicated. Emetics are also contraindicated, and due to possible esophageal damage, gastric lavage is also unadvisable. Dilution of orally ingested strong acids or alkalis or other irritating substances with milk or as a second choice water does not "prevent exposure" per se, but it may serve to prevent exposure to sufficient concentrations which may otherwise exert much more serious mucosal and/or submucosal corrosion. Administration of demulcents such as milk, egg white or kaolin-pectin preparations may be of further value in protecting the damaged mucosae. To be effective, the demulcent must be used very
soon after exposure to the toxicant.

For further protection of the damaged mucosa of the digestive tract, the use of the anti-ulcer medication sucralfate may be tried. Sucralfate is available through human pharmacies and is an anti-ulcer agent comprised of an anionic, sulfated disaccharide. The drug inhibits pepsin and binds bile acids. It also forms a polymer when in contact with water molecules and hydrochloric acid, as in the stomach. The paste-like polymer formed by sucralfate is believed to adhere to the gastroduodenal mucosa, especially in ulcerated areas where it locally buffers acidity. Sucralfate has been shown to bind to acute gastric erosions caused by other agents such as aspirin. The barrier formed by the sucralfate therefore tends to protect the ulcer from acid, bile and pepsin so that healing can occur.

Only 5% of administered sucralfate is absorbed from the gastrointestinal tract so that the remainder is available to act at the digestive system mucosae. Sucralfate is very low in toxicity. Animals have tolerated doses of 12 g/kg. Sucralfate is dosed in the dog based upon extrapolated human dosage schedules.

The role of steroids in the prevention of esophageal strictures in animals that have experienced deep circumferential burns of the esophageal mucosa is unclear. Evidence from animal studies indicate the use of steroids may reduce stricture formation, and their use for 1 - 2 weeks post-ingestion may be warranted.

b. Removal of the Toxicant from the Gastrointestinal Tract

- A review of the physiology of emesis is helpful in understanding the pharmacology of emetics. There are five stimuli that induce emesis in animals. These are:

1. direct stimulation of the central nervous system by foreign chemicals (xenobiotics) in the blood
2. pharyngeal stimulation (transmitted via the glossopharyngeal nerve: cranial nerve IX)
3. visceral irritation (transmitted via visceral afferent fibers in the sympathetic or vagal (X) nerves or the spinal cord)*
4. vestibular (labyrinth) stimulation (accounts for motion sickness: transmitted via the acoustic nerve (VIII)
5. stimulation from connections to the cerebral cortex (fear, pain, head injury, increased intracranial pressure, etc.).

*Visceral efferents of the stomach and upper intestinal tract are incorporated into the vagus (X) nerve. However, stimulation from irritation of the lower intestinal tract or urinary tract is carried to the brain via visceral efferents in the spinal cord.

All of these stimuli cause input into the emetic center. The emetic (vomiting) center is an accumulation of nuclei in the reticular formation of the posterior medulla. The emetic center requires prolonged and continual stimulation by afferent input before the summation of these stimuli is sufficient to induce emesis. Temporal and spatial summation of input from the chemoreceptor trigger zone (CTZ), and the vagal, glossopharyngeal and other nerves occurs within the emetic center. This also appears to occur with information coming from the reticulospinal tract.
The Afferent Connections of the Vomiting Center

Chemoreceptive neurons (the CTZ) are located in the area postrema of the medulla. The unique structural arrangement of the capillary endothelium of this region in conjunction with these specialized neurons allows the area postrema to monitor the concentrations of xenobiotics and other chemicals in the blood. This function of the area postrema is made possible by the absence of the blood-brain barrier since the capillaries of this region have large gap junctions. Immediately adjacent to these "porous" capillaries are the chemoreceptive neurons which are stimulated when a threshold concentration of a xenobiotic is reached. The chemoreceptive neurons have direct internuncial connections with the emetic center.

Repeated stimulation of the vestibular organ may also cause emesis. Generally this requires a prolonged and rhythmic motion to which the animal is not accustomed, such as occurs during travelling. Vestibular input to the emetic center may rarely occur with inner ear dysfunction. These impulses are mediated indirectly through interconnecting internuncial neurons.
Diagrammatic presentation of the transmitter mechanisms associated with chemoreceptor trigger zone.

The act of vomiting is a complex and highly coordinated process. This coordination occurs in the vomiting center. In the pre-emesis phase ptyalism is usually observed. This is rapidly followed by relaxation of the stomach musculature and dilation of the pyloric region of the stomach. At this point reverse peristalsis of the duodenum commences. Swallowing of air, then inspiration against a closed glottis creating a reduced pressure in the thorax is accompanied by an increase in abdominal pressure from respiratory movement (contraction) of the abdominal musculature. Contraction of the pylorus, relaxation of the body of the stomach, gastric reflux and esophageal collapse occur in cyclic repetitions. The gastric contents are forcefully expelled by contraction of the abdominal wall against a caudally moving diaphragm. The flattening of the diaphragm that results is reportedly responsible for opening the cardiac sphincter. During this process, the esophagus relaxes and the stomach expels its contents into the esophagus. Some workers indicate that the stomach actually invaginates into the esophagus. They report that, in dogs, the stomach may reach the level of the fifth rib. With sufficient stimulation, the vomiting process may be repeated every two to three minutes for several hours unless there is medical intervention.

**Contraindications To the Use of Emetics**

Emetics are never given to rodents, rabbits, horses or ruminants. Rodents are incapable of vomiting; rabbits and horses reportedly do not have a stomach wall strong enough to safely tolerate emesis; and safe and effective doses of emetics have not been defined in ruminants.

Neither emesis nor gastric lavage are recommended in cases where strong alkali, acid, or other highly corrosive materials have been ingested. The extreme contracture of the musculature during vomiting may be sufficient to rupture an already damaged esophagus or stomach leading to spillage of ingesta into the surrounding tissues with secondary mediastinitis or peritonitis.

The esophagus, unlike the rest of the digestive tract does not have a significant protective coating of mucus secreted by goblet cells and is quite susceptible to caustic and corrosive materials. The initial exposure of the esophagus to a corrosive agent may destroy the protective epithelium leaving the muscular layer exposed and thereby next in line to be damaged if the corrosive substance is brought back up. Constriction of fibrous tissue laid down during healing, may lead to stricture...
Hydrocarbon products include gasoline, kerosene, paint thinner, solvents, turpentine, mineral spirits, lighter fluids, furniture polish, and insecticides. Aspiration of hydrocarbons has been attributed to inhalation of the hydrocarbons during emesis. Although, the irritating properties of gastrointestinally absorbed hydrocarbons that volatilize in the lungs appears to be essentially the same as those observed with aspiration pneumonia, only extremely large quantities of ingested hydrocarbons are likely to be associated with substantial pulmonary complications from absorption alone. Hydrocarbons with low viscosity have a greater aspiration risk than hydrocarbons with high viscosity. The volume of the liquid ingested is less important than the viscosity in determining aspiration potential. Gasoline, xylene, toluene, lighter fluid, and mineral seal oil all have low viscosity and are associated with a high risk of aspiration. Clinical signs associated with hydrocarbon ingestion include cough, dyspnea, tachypnea, depression, bronchospasm, tremors, cardiac arrhythmias, seizures, and vomiting. Ingestion of chlorinated hydrocarbons, e.g., trichloroethanes, carbon tetrachloride, and methylene chloride is also associated with hepatotoxicity, and one of the metabolites of methylene chloride is carbon monoxide. Aromatic nitro and amino compounds (e.g., nitrobenzene, nitrophenol, nitroaniline) may cause methemoglobinemia in some species. The presence of coughing following ingestion should alert the clinician to potential aspiration. The presence or absence of coughing is not conclusive for aspiration having occurred.

Treatment of hydrocarbon ingestion is directed towards symptomatic and supportive therapy. It is important to keep in mind that pulmonary complications are the most common life-threatening clinical problem. In general, petroleum distillates are poorly absorbed from the gastrointestinal tract. Thus, kerosene (given intragastrically at 22 ml/kg to dogs with transected esophagi) or charcoal lighter fluid (given intragastrically at 10 ml naphtha/kg to rats) did not cause significant illness or lesions. However, the potential pulmonary effects of other hydrocarbons after ingestion may be greater. For example, rats given turpentine (hydrocarbon comprised primarily of secondary and tertiary cyclic terpene alcohols = 80% terpenes) orally (at a dose of 5 ml total dose: animal weight not specified) developed pulmonary edema and hemorrhage. The oral toxicity and aspiration hazard of most high-viscosity hydrocarbons (e.g., paraffin wax, tar, etc.) is so low that removal is seldom a concern. Some human clinical toxicologists have recommended the use of emetics if large (> 1 ml/kg) amounts of medium-range-viscosity (e.g., gasoline, kerosene, turpentine) hydrocarbons have been ingested. However, due to the apparently low risk of pulmonary problems from ingested hydrocarbons, emesis is no longer recommended by most toxicologists. Emesis is never recommended for the ingestion of low-viscosity (e.g., mineral seal oil, furniture polishes) hydrocarbons because of the increased risk of aspiration into the lungs.

Emetics should not be given to animals that are hypoxic, dyspneic, seizuring, extremely weak, comatose, lacking normal pharyngeal reflexes, or suffering other marked neurologic impairments that could lead to aspiration pneumonia. Emetics should **not** be given to animals that already have vomited profusely or when they have vomited blood. Emetics are **never** given to sedated animals. Also, emetics **never** should be given to animals that have endotracheal or intragastric tubes in place. During seizures the gag reflex may be lost and vomiting may result in aspiration. Also, if the animal has ingested a CNS stimulant, further stimulation associated with vomiting may precipitate seizures. Thus, inducing emesis **often is contraindicated** following exposure to CNS stimulants.

Previous administration of drugs with anti-emetic activity will sometimes block the effects of emetics (see Table I). Individuals poisoned by noncorrosive substances, but not candidates for emesis, may often benefit from gastric or enterogastric lavage.

**Hydrocarbon Controversy**

The use of either emetics or lavage in cases of volatile hydrocarbon ingestion is controversial. Commonly ingested hydrocarbon products include gasoline, kerosene, paint thinner, solvents, turpentine, mineral spirits, lighter fluids, furniture polish, and insecticides. Aspiration of hydrocarbons has been attributed to inhalation of the hydrocarbons during emesis. Although, the irritating properties of gastrointestinally absorbed hydrocarbons that volatilize in the lungs appears to be essentially the same as those observed with aspiration pneumonia, only extremely large quantities of ingested hydrocarbons are likely to be associated with substantial pulmonary complications from absorption alone. Hydrocarbons with low viscosity have a greater aspiration risk than hydrocarbons with high viscosity. The volume of the liquid ingested is less important than the viscosity in determining aspiration potential. Gasoline, xylene, toluene, lighter fluid, and mineral seal oil all have low viscosity and are associated with a high risk of aspiration. Clinical signs associated with hydrocarbon ingestion include cough, dyspnea, tachypnea, depression, bronchospasm, tremors, cardiac arrhythmias, seizures, and vomiting. Ingestion of chlorinated hydrocarbons, e.g., trichloroethanes, carbon tetrachloride, and methylene chloride is also associated with hepatotoxicity, and one of the metabolites of methylene chloride is carbon monoxide. Aromatic nitro and amino compounds (e.g., nitrobenzene, nitrophenol, nitroaniline) may cause methemoglobinemia in some species. The presence of coughing following ingestion should alert the clinician to potential aspiration. The presence or absence of coughing is not conclusive for aspiration having occurred.

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aspiration pneumonia may be delayed for 6 - 8 hours following aspiration, necessitating serial radiographs.

**Indications for Emetics**

The use of emetics in emergency treatment of poisoning is a matter requiring good clinical judgment. Various toxicants are absorbed at different rates and in different parts of the gastrointestinal tract. Small uncharged molecules (e.g., ethylene glycol) or charged acidic drugs (e.g., aspirin) which receive a proton in the highly acid environment of the stomach are often absorbed comparatively rapidly, directly through the gastric mucosa. Basic drugs (e.g., amphetamine) are charged in the stomach, and are therefore poorly absorbed in this location. It follows that to be maximally effective when dealing with compounds absorbed directly from the stomach, emesis must be used as rapidly after exposure as possible.

At times radiographs of the abdomen may reveal the location of sufficiently radiodense or radiolucent ingesta which may be of use when deciding whether to employ an emetic. Some drugs and toxicants delay gastric emptying. Therefore, no strict rule of thumb applies to how long after ingestion an emetic may be of benefit.

Emesis is generally more efficient than lavage in removing the offending material from the stomach. The response to emetic drugs varies but gastric emptying is generally effective in removal of 40 - 60% of the chyme from the stomach when vomiting successfully occurs. Pharyngeal stimulation is only rarely effective and when vomiting occurs only roughly 25% of the stomach content is removed. Note: Do not forget to freeze the initial vomitus for analytical confirmation.

The veterinarian must be concerned with the need for sufficient mass in the stomach to be propelled by the physical events that comprise retching and vomiting. This is especially important when an animal has not recently eaten food but has consumed a low volume, highly toxic poison. In such instances, when an emetic is to be given, feeding just before administration of the emetic is likely to be of some benefit. Fatty foods, which tend to enhance the absorption of lipid soluble agents, such as many organic pesticides and other toxicants should generally be avoided.

<table>
<thead>
<tr>
<th>Table 1. Antiemetic Drugs that are Common Accidental Poisonings</th>
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<tr>
<td>Phenothiazine tranquilizers</td>
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<tr>
<td>Marijuana</td>
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<tr>
<td>Diazepam and other benzodiazepine compounds</td>
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<td>Barbiturates</td>
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<td>Antihistamines, especially those which act on the H1 receptors</td>
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<tr>
<td>Dimenhydrinate (Dramamine ®)</td>
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<td>Codeine</td>
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<td>Antidepressants</td>
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<td>Meprobamate</td>
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**Specific Emetics:**

**Apomorphine** - Apomorphine is the drug of choice in dogs, but despite attempts, a safe, effective dose has not been established for cats. Its mechanism of action is stimulation of dopaminergic receptors in the chemoreceptor trigger zone and perhaps stimulation of the emetic center itself. Apomorphine is sold in 6 mg tablets which are used to make a solution for administration via the conjunctival sac or IV.

**Advantages of the use of apomorphine in dogs include:**

1. The vomiting response is fast and dependable. Following intramuscular administration, emesis occurs in an average of 4.5 minutes but, vomiting is occasionally prolonged. After intravenous administration, however, emesis is produced immediately and is of short duration (1 - 2 minutes) (therefore the intravenous route is preferred). Intracconjunctival use (crush part of a tablet in a syringe with a few drops of water-administer by drop into conjunctival sac) is convenient and usually effective but is somewhat less likely to be successful than intravenous use. However, the dosage can be partially regulated by washing the conjunctival sac free of unabsorbed apomorphine. In experimentally dosed dogs, the percent recovered of an orally administered dose of barium sulfate has been reported as 78% when apomorphine was given simultaneously with barium, 64% when given 30 minutes later, and 25% when given 60 minutes later.

2. The emetic effect is usually temporary, particularly when the drug is given intravenously. Apomorphine and other morphine-like drugs also inhibit the firing of the emetic center. The aim of apomorphine therapy, therefore, is to excite the chemoreceptor trigger zone before the emetic center is inhibited. In both areas the effect is concentration dependent. Since the area postrema is devoid of histologic features of the blood-brain barrier, substances in blood will transport into the chemoreceptor trigger zone more rapidly than into the emetic center. However, if the apomorphine is absorbed slowly, as from oral administration, the concentration gradient between the chemoreceptor trigger zone...
and the emetic center may not be sufficient to result in the desired sequence of events.

Disadvantages of apomorphine include:

1. It is not recommended for cats because safe and effective dosages have not been demonstrated and it would appear that the cat is much less sensitive to apomorphine-induced emesis than the dog. Also, reportedly apomorphine is not particularly effective in swine.
2. Overdosage in dogs may result in CNS depression, respiratory depression or rarely in restlessness, excitement or even convulsions. Other side effects include protracted vomiting. CNS and respiratory depression may be reversible with the pure narcotic antagonist naloxone.
3. It is unreliable when given by mouth.
4. Apomorphine solutions must be made up fresh as they are unstable in light or air. If the solution is green the tablet has already partially decomposed and reliable emesis is no longer assured.
5. Previously absorbed antiemetic drugs may prevent vomiting subsequent to apomorphine administration.

The dosage of apomorphine in dogs is 1M-0.04 mg/kg and IV-0.03 mg/kg.

**Note** - different texts recommend 0.02 - 0.04 mg/kg; apomorphine has been experimentally evaluated at higher doses of 0.066 or 0.05 mg/kg. Apomorphine comes as a hypodermic tablet (6 mg) to be dissolved in sterile water prior to use. **Note**: One source (Booth and McDonald, 1982) indicated that pretreatment with naloxone IV, at a dose of 0.04 mg/kg, did not prevent apomorphine induced emesis in dogs. This reference goes on to suggest that potent antagonists of apomorphine include haloperidol, spiroperidol and pimozide; and states that these drugs possess "pure dopamine receptor blocking activity".

**Morphine** - As with apomorphine, morphine usually stimulates the chemoreceptive neurons before it depresses the emetic center. Therefore it has both emetic and antiemetic activity. Morphine, however, stimulates the chemoreceptor trigger zone at a site different from that stimulated by apomorphine. Morphine is used as an emetic in dogs but it is much less reliable than apomorphine. Also, one of the most readily available preparations contains atropine which is contraindicated due to delayed intestinal transit time which can result in increased toxicant absorption. Unlike the case of apomorphine, naloxone will block the emetic effect of morphine in the dog. Since Nalline® (nalorphine) and Lorphan® (levallophan) have narcotic agonist action as well as antagonist action and thus may depress the central nervous system, the more "pure" narcotic antagonist naloxone, also called Narcan®, is preferred to counteract apomorphine-associated depression. The recommended dose of naloxone for dogs is 0.04 mg/kg IV, IM, or SQ.

**Syrup of Ipecac** - **Avoid** using the fluid extract of ipecac as it is highly toxic. Toxic effects of fluid extract of ipecac include diarrhea, cardiac arrhythmias, peripheral vascular collapse and death. The fluid extract is 14 times more concentrated than the syrup. Syrup of Ipecac U.S.P., the desired form, contains 2% alcohol and 7% ipecac in a glycerin vehicle. Ipecac is derived from the dried root of either Cephaelis ipecacuanha or Cephaelis acuminata, and its active principles are the alkaloids emetine and cephaeline. Of these alkaloids, cephaeline is the more toxic and causes more nausea and vomiting, whereas emetine is primarily cardiotoxic. It is available over-the-counter in 1 oz. bottles. Many persons with small children keep syrup of ipecac on hand. Ipecac acts by local irritation of the stomach and, when its active alkaloids are absorbed in adequate amounts, by stimulation of the hemoreceptor trigger zone of the medulla.

In dogs which were experimentally administered barium sulfate, ipecac syrup was 62%, 44%, and 30% effective in recovering the barium sulfate when administered immediately, 30 minutes, or 60 minutes, respectively, after barium ingestion. A decrease in the recovery rate of ingested material has also been demonstrated in dogs given sodium salicylate where a 30-minute delay in inducing vomiting resulted in a 44% recovery rate. This was in contrast to the observed recovery rate of 39% if vomiting was further delayed. Syrup of ipecac-induced emesis was superior to gastric lavage in recovering salicylate from the stomach of children in one study.

**The dose of syrup of ipecac for dogs is 1 - 2 ml/kg.** Only if the lower dose is used may the dose be repeated, and then only once. Note: Cats have been experimentally dosed with syrup of ipecac as either a 50% solution (diluted with water) or an undiluted solution. Doses with the 50% solution were 2.2 and 6.6 ml/kg (equivalent to 1.1 and 3.3 ml/kg if undiluted) and vomiting was reliable at all the doses. At the lower doses, however, vomiting was delayed. After the lowest dose (1.1 ml/kg), the mean time to emesis was unacceptably long (40-63 minutes: mean of 52 minutes). At the intermediate dose (3.3 ml/kg), vomiting occurred in 5 out of 5 cats after a latent period of from 11 to 34 minutes: mean of 23 minutes). Emesis did occur faster with the highest (6.6 ml/kg of undiluted syrup of ipecac) dose (range of 9 - 17 minutes, mean of 11 minutes], but the cats displayed a reduction in activity and salivation which persisted for several hours. In spite of mentioning these effects, the author stated that "no signs of depression" were seen. The **dose of syrup of ipecac, presently being recommended for cats**,
is 3.3 ml/kg of body weight. In instances in which otherwise healthy cats have ingested potentially lethal doses of a toxicant, the use of the higher dose (6.6 ml/kg) of syrup of ipecac seems well justified, unless activated charcoal or another effective adsorbent can be relied upon to effectively bind the toxicant in question.

The preferred way of administering syrup of ipecac to cats is to dilute it 50/50 in water so that a total volume of 6.6 ml/kg (3.3 ml/kg of undiluted syrup of ipecac) can be administered via a No. 12 French rubber urethral catheter using a mouth gag. Cats may object to oral administration and the dilution in water also facilitates passage through a nasogastric or stomach tube. The dose is administered once. Even syrup of ipecac well beyond the expiration date (at least up to a few years) may be used. Activated charcoal adsorbs and therefore should not be used concurrently with ipecac at least until after emesis or apparent failure of the emetic.

As mentioned above, when administering any emetic, the veterinarian must realize that "you can't squeeze an empty balloon". In other words, stomach contents must be of sufficient volume to allow vomiting, but when administering an emetic that relies upon gastric irritation or absorption, such as syrup of ipecac, too much dilution may decrease gastric irritation, reduce the rate of absorption, and therefore diminish the efficacy of induction of vomiting. Thus, water at 5 ml/kg is indicated immediately after emetic administration if the animal has a nearly empty stomach. The administration of milk with syrup of ipecac has been associated with a delay in the onset of emesis. It has been postulated that the ingestion of antiemetic compounds (e.g., phenothiazines, anticholinergics, and tricyclic antidepressants) would produce a diminished response to emesis induced by syrup of ipecac. In humans, however, the time to onset of emesis as well as percentage responding to syrup of ipecac was not diminished in patients which had ingested an antiemetic. Use of an emetic would not be recommended for agents like benzo diazepines and tricyclic antidepressants due to their rapid onset and risk of aspiration. The major concern about ipecac toxicity is that of cardiotoxicity. In humans receiving emetine therapy, reversible EKG abnormalities were observed. Cardiotoxicity is not anticipated from the recommended doses of ipecac syrup.

**Hydrogen peroxide** - H₂O₂ (3%) is easily administered orally especially using a syringe or plastic squeeze bottle inserted between the teeth. It may be effective alone or may be used with apomorphine on the infrequent occasions when the former is initially ineffective. The dose of 3% hydrogen peroxide is 5 to 15 ml per 10 pounds body weight, and this can be repeated up to two times if emesis does not occur within five to ten minutes after dosing. Also, 3% H₂O₂ has been suggested for use as an emetic in swine. The dose may be given via the external nares. Concentrated hydrogen peroxide, such as the kind used in hair bleach should not be confused with 3% solutions and should not be given to animals.

**Xylazine** - Xylazine is somewhat effective as an emetic in cats. The pharmacologic effects are not reversible with a narcotic antagonist. Xylazine may aggravate respiratory depression and cause parasympathetic slowing of the heart. The dosage of xylazine to induce emesis in cats is 1.1 mg/kg (0.5 mg/lb) IM or SQ. The α-2 adrenergic blocking agent yohimbine has been used in a number of species to reverse the central nervous system depression that results from xylazine's actions on α-2 adrenergic receptors. A dosage of 0.1 mg/kg IV yohimbine in dogs and cats reverses CNS depressant, bradycardic, and hypotensive effects of xylazine in dogs. At dosages of yohimbine greater than 0.5 mg/kg, excitement, tachycardia, and hypertension may develop. Yohimbine has also been reported to shorten ketamine-induced anesthesia in cats through an unknown mechanism.

**Liquid Dish Detergent and Liquid Emetic Agent (LEA)** - LEA is an experimental detergent-based, strawberry flavored oral emetic, which is rapid and effective. LEA consists of sodium tripolyphosphate (12%), tetrapotassium pyrophosphate (8%), sodium saccharin (2.5%), and a strawberry flavoring. The drug induces vomiting even when chlorpromazine has been administered, suggesting a local effect by LEA. Because of economic and legal concerns, LEA is not likely to be made available commercially. Orally administered liquid dish detergent is also somewhat effective as an emetic as demonstrated in experimental trials in children in which doses of 30 ml and greater were used and may be effective when ipecac or hydrogen peroxide is not available. When tried in a small number of cats, liquid dish detergent was not particularly effective.

**Copper Sulfate** - Copper sulfate is an emetic exerting its effect by direct gastric irritation. The agent must be made up fresh each time just prior to administration. In the past, copper sulfate was used as an emetic for children in a dose of 150 - 250 mg dissolved in 30-60 ml of water. The emetic action of copper sulfate was reliable (93 of 100 children vomited). The time to induce vomiting ranged from 0 - 40 minutes with a mean of 6.9 minutes. Although ceruloplasmin and serum copper levels increased, no obvious hemolysis or liver dysfunction was apparent. However, increased urinary excretion of copper, proteinuria, and renal and hepatic damage have been reported. The potential for copper poisoning has precluded widespread application of copper sulfate as an emetic. Copper sulfate and zinc sulfate induce emesis in dogs even after surgical ablation of the chemoreceptor trigger zone. The gastric reflex afferent nerves, which stimulate the vomiting center and are responsible for copper sulfate induced emesis, are
not completely blocked by sectioning the vagus nerves. As little as 40 mg of copper sulfate given orally will induce emesis in the dog.

**Lobeline** - Lobeline sulfate is an effective emetic drug that has been evaluated in dogs at a dose of 10 mg/kg SQ. Unfortunately at 12 mg/kg, a very slightly higher dose, dogs developed hyperactivity and convulsions. The margin of safety is obviously far too low to recommend.

**Dry Powdered Mustard** - When added to warm water, one of the glycosides of mustard is hydrolyzed to liberate the volatile oil (allyl isothiocyanate). Black mustard (from *Brassica nigra*) is richer in the volatile oil than is the yellow variety. All prepared mustards are ineffective as emetics. The dose of dry powdered mustard is "1 to 4 teaspoons in 1 cup of warm water". It is not highly recommended for it is largely ineffective. The mechanism of action is reported to be gastric irritation.

**Prostaglandin F2-α** - Prostaglandin F2-α has been evaluated in a single study as an agent to stimulate vomiting and defecation in the dog. At a dose of 0.111 mg/kg (presumably SQ, route not stated in the paper), defecation consistently occurred without vomiting. At a dose of 0.444 or greater, both vomiting (87.5%) and defecation (75%) usually occurred in a single episode which ended within approximately 15 minutes. No studies of the efficacy of gastric emptying by this method as compared to apomorphine are known. Prostaglandin F2-α causes increases in respiratory rate and airway resistance, such that animals with respiratory disease may be at an increased risk of complications if this agent is used.

**Salt** - The emetic mechanism of dry salt is pharyngeal stimulation. **NaCl is not a reliable emetic and may result in salt poisoning in small animals.** Saline solutions have been shown to be only 25% as efficacious as ipecac in inducing vomiting in humans. The development of hypernatremia has been reported to occur in humans in which salt had been used as an emetic. Secondary to the development of severe hypernatremia will be the development of cerebral shrinkage as water is drawn out of the brain tissue. Intracranial blood vessels expand and secondary intraventricular and brain hemorrhage has been reported in human patients. Terminally, cerebral edema has been documented in sodium toxicosis of animals. Clinical signs of salt intoxication can include weakness, vomiting, seizures, tachycardia, and pulmonary edema. **Note:** Ingestion of 1 tablespoon of salt (contains 250 mEq of sodium) by an animal with a 10-liter total body water (e.g., 15-kg dog) can result in an increase in serum sodium by 25 mEq/l. Salt water has also been recommended but is probably even less effective and is far too dangerous to recommend.

### Hazards of Salt as an Emetic - Summary of Reported Deaths in Man

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Drug Ingested</th>
<th>How Salt was Administered</th>
<th>Did Vomiting Occur</th>
<th>Maxim. Na</th>
<th>Serum Cl</th>
<th>Time Until Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>M</td>
<td>60 mg perphenazine/750 mg imipramine</td>
<td>1 T/300 ml water x2</td>
<td>yes</td>
<td>174</td>
<td>152</td>
<td>32 hr</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>F</td>
<td>5000 mg thioridazine</td>
<td>3000 mEq/4000 ml water x1</td>
<td>?</td>
<td>184</td>
<td>150</td>
<td>8 days</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>M</td>
<td>250mg propoxyphene</td>
<td>4 T/8 oz water x 4</td>
<td>yes</td>
<td>189</td>
<td>156</td>
<td>9 days</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>M</td>
<td>2900 mg aspirin</td>
<td>? amt x2</td>
<td>no</td>
<td>188</td>
<td>160</td>
<td>28 hr</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>F</td>
<td>? mg chlordiazepoxide</td>
<td>?</td>
<td>?</td>
<td>214</td>
<td>-</td>
<td>18 hr</td>
</tr>
</tbody>
</table>

Based on the evidence at hand, salt water is too dangerous to recommend for use either at home or in the emergency room.

**Gastric Lavage**

Emesis vs. lavage: whenever the patient's condition allows emesis to be induced, the greater efficacy of vomiting in removing stomach contents, the greater ease of administering an emetic, and the more satisfactory removal of sizable amounts of particulate matter or tenacious mucus by vomiting, all favor emesis over lavage. In dogs which were administered barium sulfate orally, emesis (ipecac, apomorphine) was equally effective as gastric lavage (mean of 78%, 62% vs. 54% recovery rates, respectively) when administered immediately. However, a significant difference was noted if these procedures were delayed. If delayed 30 minutes, recovery rates were apomorphine 64%, ipecac 44%, and lavage 26%. By 60 minutes postingestion, lavage was only 8% effective. Research by others has demonstrated that gastric lavage is less effective than emesis in recovering toxicant whether administered immediately or following a delay after ingestion.
Proponents of gastric lavage suggest that in many of these studies lavage was performed incorrectly. To adequately perform gastric lavage, **large bore gastric lavage tubes** (e.g., foal stomach tube could be substituted) and **copious amounts of lavage fluid** are required. Other factors that influence the efficacy of lavage are: 1) lavage fluid temperature (tepid water preferred, colder water increases gastric emptying time), 2) agent ingested, and 3) frequency of lavage. Increased gastric emptying time could be desirable in some situations (i.e., toxicant in stomach not absorbed from stomach but from GI). When potent toxicants have been ingested and vomiting has not been intense, lavage may be worthwhile. Lavage may also be indicated in the ingestion of agents in which delayed gastric emptying is anticipated (e.g., tricyclic antidepressant ingestion). Of course gastric lavage is used in many cases in which the patient cannot safely be made to vomit as previously mentioned; for example, if the patient is comatose and a toxicant ingestion is suspected. Gastric lavage is **contraindicated** in the ingestion of caustic materials and for seizing animals unless the animal has been anesthetized and will be continuously monitored.

**Technique for Gastric Lavage**

Note - Minimal pressure should be used since the stomach wall may be weakened. The procedure is performed on unconscious or lightly anesthetized animals (watch fingers). An **endotracheal tube (cuffed)** is inserted and inflated to avoid aspiration of stomach contents. A 2 - 4 foot-long clear plastic tube with as large a diameter as possible and having the end fenestrated with one or two oblong holes is used. A smaller tube or loop ended wire is handy to clean out stomach tubes after they have been removed from the animal. It may also help to alternate stomach tubes, one in use, one being cleaned out. One also needs to have available funnels, buckets, aspiration bulbs for extremely small animals and a drench (bilge) pump for all others.

The tube is inserted to a length equivalent to the distance from the tip of the nose to the xiphoid cartilage. After the stomach tube is in place, the mouth should be kept lower than the chest (tilt table). A watery activated charcoal suspension is recommended for the lavage fluid **after the initial washings have been collected** for analysis. Gently creating turbulence by pumping the fluid in under slight pressure as from a bilge pump, mixes the contents near the end of the tube allowing gradual removal by gravity flow. Several cycles (perhaps 15 - 20) of 50 - 200 ml (5 - 10 ml/kg) each may be required to thoroughly rinse out the stomach. The last few washings should be clear. The end of the tube should be closed as the tube is removed in order to prevent aspiration. A thicker activated charcoal suspension is instilled after either gastric lavage or cessation of vomiting.

**Enemas**

Enemas may be occasionally indicated in cases where absorption has not been completed in the upper GI tract. Enemas also facilitate the effects of cathartics. A solution of warm water and castile soap (available at many groceries, pharmacies) is sometimes recommended. Patients with an increased potential for renal failure should not receive phosphate enema solutions because of the possibility of precipitating acute renal failure. Such solutions have sometimes been recommended for oral administration as a saline cathartic or to precipitate ingested iron. In addition, hypertonic phosphate enemas (e.g., fleet enema) when used in cats and small dogs may result in severe toxicosis due to rapid electrolyte (hyperphosphatemia, hypernatremia, hypocalcemia, hypomagnesemia) and acid-base (metabolic acidosis) disturbances.

**Enterogastric Lavage**

This technique may be used to remove the entire contents of the gastrointestinal tract. However, it is not regarded as practical and has not been demonstrated to be safe or effective (and hence is not recommended) for animals with highly modified, high volume digestive tracts such as ruminants, horses, rabbits and swine (spiral colon). First, an emetic is used if not contraindicated, then minimal anesthesia is induced and a standard gastric lavage performed, leaving the endotracheal and gastric tubes in place. Second a moderately high, warm water enema is used. Mild digital pressure is then applied around the enema tube at the anus and water is administered slowly using a colon tube with a faucet adaptor and low pressure to cause retrograde filling of the intestine. The water is gradually added until it is clear as it flows from the gastric lavage tube. By the time that fluid comes from the stomach tube, the intestinal loops may be substantially enlarged by the water. Activated charcoal may be instilled at the end of the procedure.

**Rumen Lavage and Rumenotomy**

Rumen lavage is much more rapid and far less work then rumenotomy, however to be efficient, access to tap water is almost essential. The procedure is usually performed on conscious, standing animals. A head stanchion should be used if possible. The use of a chute is **not** recommended because when cattle lie down, as they often do when in a chute, you cannot accurately judge rumen distension. Excessive distention of the rumen can compromise ovement of the diaphragm resulting in sudden death. If possible, place the animal on a sloped incline so that the head is below the body. A large stomach tube is passed with a mouth gag. A slightly smaller tube, such as a garden hose with or without a nozzle, that just fits inside the
A stomach tube is used as a connection to the water faucet. Water flowing rapidly from the smaller tube is directed into the large tube by slipping the smaller one inside for just a few seconds. The water is then allowed an opportunity to run back out. Often the first infusion or two will not be returned. However, by the time distension of the paralumbar fossa is evident, water should be running back out after each administration. This is continued until the water is clear, then activated charcoal is administered. Toxicoses involving ingestion of coarse toxic plant material (e.g., Taxus, Rhododendron) will probably required rumenotomy. In situations in which few animals are poisoned and in which rumen lavage cannot be performed and in situations in which activated charcoal is unavailable or unlikely to be successful, rumenotomy may be considered. An alternative to the use of rumen lavage or rumenotomy is the use of a large bore (3/4") diameter trochar which is inserted into the rumen at the level of the stifle. A hose is employed as in rumen lavage, and rumen contents exit the rumen via the trochar. The trochar is left in place for at least 5 days in order to allow the rumen to form an adhesion to the body wall resulting in a decreased risk of peritonitis. This technique has been used clinically in the management of acute grain overload in cattle.

Gastrotomy
On rare occasion, a gastrotomy may be required in order to remove foreign bodies from the stomachs of small animals. Examples of cases in which gastrotomy should be considered include metal ingestions (e.g., lead weights, pennies, zinc bolts, etc.) or rarely large quantities of ingested drugs which form coalesced masses (e.g., meprobamate). Although this method is effective, if used should be considered heroic and reserved only for cases where more conservative methods have failed or are likely to fail. An alternative to gastrotomy would be endoscopic retrieval, use of an endoscope and appropriate probes to disrupt masses or remove foreign bodies from the stomach may be preferred.

Note - any of these techniques must be weighed against the stress associated with both the necessary restraint and the actual detoxification procedure.

Osmotic Cathartics
Sodium Sulfate or Magnesium Sulfate (Saline Cathartics) - The effectiveness of sodium sulfate and magnesium sulfate have been attributed to their poor or slow rate of absorption which results in osmotically induced fluid retention within the intestinal tract. The laxative effect results from reflex stimulation of motility caused by the increased intraluminal fluid volume. The sulfates of both sodium sulfate and magnesium sulfate are, however, absorbed to a greater extent than generally recognized. It is also known that, in the presence of renal disease, sufficient magnesium may be absorbed to produce clinical signs of hypermagnesemia, including muscle weakness and depression of the central nervous system. The concurrent use of a cathartic with activated charcoal has not been demonstrated to decrease absorption of an agent over the effect of activated charcoal alone. In evaluating whether a saline cathartic should be administered, several factors should be considered: 1) saline cathartics should not be administered if the ingested agent will have similar cathartic effects (e.g., laxative ingestions); 2) some formulations (e.g., enteric coated, microencapsulated) may have decreased bioavailability if a cathartic is administered; 3) activated charcoal may cause constipation and cathartics may minimize this effect. Magnesium (in magnesium citrate) and sulfate are poorly absorbed to activated charcoal and are not thought to interfere with its adsorptive capacity.
Sodium sulfate (Glauber's Salt) is a more efficient saline cathartic then magnesium sulfate (Epsom Salt). Also the magnesium ion can depress the CNS. Magnesium sulfate is, however, more widely available and for some toxicoses the depressant effects of the magnesium ion may be of no harm or even of benefit. Using the contents of an ordinary teaspoon (the kind used to eat, not to measure) the following weights were derived for level teaspoons.

<table>
<thead>
<tr>
<th>Weights determined in grams for &quot;level teaspoons&quot; of</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium sulfate (Glauber's Salt)</td>
<td>9.12</td>
</tr>
<tr>
<td>Magnesium sulfate (Epsom Salt)</td>
<td>7.11</td>
</tr>
<tr>
<td>8.32</td>
<td>6.98</td>
</tr>
<tr>
<td>8.03</td>
<td>6.43</td>
</tr>
</tbody>
</table>

The dose of sodium or magnesium sulfate for dogs and cats is therefore 1/4 teaspoon (approx. 1.75 - 2 grams) per 10 pounds (4.54 kg) of body weight (this is approximately equivalent to 385 - 440 mg/kg BW). It is administered per os preferably by
stomach tube as a 20% (or more dilute) solution in water. One of the principle benefits of sodium sulfate is mixing of the gastrointestinal contents when administered concurrently with activated charcoal. The combination is far more effective than the cathartic alone and may be significantly better than the charcoal alone. If charcoal is to be given repeatedly, the first two doses are generally accompanied by either a saline or osmotic cathartic.

Magnesium Hydroxide or Magnesium Citrate - Other osmotic cathartics include magnesium hydroxide (Milk of Magnesia) and magnesium citrate. Although not proven of benefit, magnesium hydroxide is recommended for animals that have ingested zinc phosphide. Dosages are shown in Table I-8.

Sorbitol - Sorbitol is sometimes used as a cathartic. At the present time, a product called Superchar-vet® is marketed in liquid form for small animals. The product contains a highly activated charcoal and sorbitol.

<table>
<thead>
<tr>
<th>Table 2. The following total doses for cathartics have been recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horse</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
</tr>
<tr>
<td>Sodium sulfate</td>
</tr>
<tr>
<td>Magnesium oxide</td>
</tr>
<tr>
<td>Magnesium hydroxide susp.</td>
</tr>
<tr>
<td>Mineral oil</td>
</tr>
<tr>
<td>Sorbitol (70%)</td>
</tr>
</tbody>
</table>

Bulk Cathartics
Metamucil® (psyllium), a hydrophilic mucilloid-based laxative is sometimes of value for animals exposed to toxicants or physical agents that may need some bulky material to gently encourage their passage (e.g., lead objects, fiberglass insulation, sand, etc.). Forms of the laxative that do not contain sugar are preferred for this purpose.

Oily Cathartics
Oily cathartics including mineral oil and olive oil are not clearly indicated for organochlorine insecticides and other organic compound ingestions, since they are often less effective than other measures, such as the use of activated charcoal with a saline cathartic, with regard to diminishing the toxicant's absorption. Oils are nevertheless, still recommended for preventing the absorption of certain other toxicants. Mineral oil is recommended for phosphorus toxicosis, but it must be carefully administered to avoid aspiration. Mineral oil administration may be followed by a saline cathartic. Surfactants such as the stool softener dioctyl sodium sulfosuccinate (DOSS) may be contraindicated with mineral oil administration as emulsification of the oil may contribute to its absorption and therefore accumulation of the indigestible oil in the liver. Castor oil is likely to pass through the intestine more rapidly than mineral oil and in some toxicoses has been more effective than mineral oil in reducing absorption.

Irritant or Stimulation Cathartics: These agents are not recommended for poisoned animals.

c. Trapping the Poison in the GI Tract
Activated Charcoal - Activated charcoal will adsorb to many substances to prevent absorption. See Tables I-9 and I-10. Indications for the administration of activated charcoal include: 1) toxicant ingestions, 2) endotoxins, and 3) agents which may undergo enterohepatic elimination or recirculation (e.g., some topically applied pesticides). Animal studies evaluating oral and topical exposure to activated charcoal have shown a lack of toxicity of the adsorbent.
Activated charcoal is considered to be a nonspecific adsorbent. Attachment to the surface of the activated charcoal is accomplished through nonspecific weak forces. The number of drug or toxin molecules that can be adsorbed varies but sometimes is approximately proportional to molecular size.
Inactivation of a compound by charcoal is not equivalent to chemical destruction. Ionized solutes are less firmly adsorbed than neutral solutes. Nonpolar large molecules are most rapidly adsorbed. Nevertheless, even in the case of a small, uncharged, rapidly-adsorbed molecule like ethylene glycol, the addition of activated charcoal to the treatment regimen is
reportedly beneficial only when given within 6 hours after oral exposure.

### Table 3a. Efficacy of Activated Charcoal

<table>
<thead>
<tr>
<th>Substance</th>
<th>Maximal Adsorption per Gram of Activated Charcoal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercuric Chloride</td>
<td>1800</td>
</tr>
<tr>
<td>Strychnine Nitrate</td>
<td>950</td>
</tr>
<tr>
<td>Nicotine</td>
<td>700</td>
</tr>
<tr>
<td>Barbital</td>
<td>700</td>
</tr>
<tr>
<td>Phenol</td>
<td>400</td>
</tr>
</tbody>
</table>

### Table 3b. Other Compounds Adsorbed by Activated Charcoal

<table>
<thead>
<tr>
<th>Acetaminophen</th>
<th>Ergotamine</th>
<th>Paracetamol (Acetaminophen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aconitine</td>
<td>Ethchloryvynol</td>
<td>Parathion</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Glutethimide</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Hexachlorophene</td>
<td>Phenolphthalein</td>
</tr>
<tr>
<td>Antimony</td>
<td>Imipramine</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>Iodine</td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Ipecac</td>
<td>Phenylpropanolamine</td>
</tr>
<tr>
<td>Aspirin (salicylate)</td>
<td>Isoniazid</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Atropine</td>
<td>Kerosene</td>
<td>Phosphorus</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Lead</td>
<td>Potassium Permanganate</td>
</tr>
<tr>
<td>Bromethalin</td>
<td>Malathion</td>
<td>Primaquine</td>
</tr>
<tr>
<td>Camphor</td>
<td>Mefenamic Acid</td>
<td>Probenecid</td>
</tr>
<tr>
<td>Cantharides</td>
<td>Meprobamate</td>
<td>Propantheline</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Mercury</td>
<td>Propoxyphene</td>
</tr>
<tr>
<td>Chlorazepine</td>
<td>Methyl Salicylate</td>
<td>Quinacrine</td>
</tr>
<tr>
<td>Chloridone</td>
<td>Methylene Blue</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Morphine</td>
<td>Quinine</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>Muscarine</td>
<td>Salicylamide</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Nicotine</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Narcotics</td>
<td>Selenium</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Nortriptyline</td>
<td>Silver</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Opium</td>
<td>Strammonium</td>
</tr>
<tr>
<td>2,4-Dichlorophenyl-</td>
<td>Organophosphorus</td>
<td>Strychnine</td>
</tr>
<tr>
<td>Oxyacetic Acid</td>
<td>Insecticides</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Organochlorine</td>
<td>Tin</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>Insecticides</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Diphenylhydantoin</td>
<td>Oxalates</td>
<td>-</td>
</tr>
</tbody>
</table>
Activated charcoal is created through 2 general steps: pyrolysis followed by controlled oxidation. The activated charcoal should be of vegetable origin and not be mineral or bone charcoal. The initial processing of activated charcoal produces a product with large pore size. Further "activation" increases pore number and surface area. Acceptable brands (manufacturer) include: Norit A (American Norit Company), Nuchar (West Virginia Pulp and Paper Company), Darco 60 (Atlas Chemical Company and Fischer Scientific), Carbo Med (Merck), and Toxiban (Vet-A-Mix). The latter product is 70% activated charcoal, 8% kaolin, and 22% wetting and dispersing agents to facilitate administration. Recently, a new superactivated charcoal (Superchar-Vet), the small animal version of which contains an osmotic cathartic (sorbitol), has become available. This product has about a 3 times greater adsorptive capacity than other activated charcoals. Burnt toast is essentially inert and should not be used as a substitute for activated charcoal.

Maximum prevention of toxin absorption occurs when a sufficient amount of charcoal is administered and the time interval between toxicant ingestion and administration of charcoal is brief. Activated charcoal powder as a suspension in water is administered orally or by nasogastric (gastric, rumen) tube. Charcoal tablets or universal antidotes are not as effective. Charcoal tablets are approximately 25% less absorptive than powders. The so-called "universal antidote", long suspected of being an irrational mixture is, in fact, less effective than activated charcoal alone. The mixture contains 2 parts activated charcoal, 1 part magnesium hydroxide and 1 part tannic acid. It is entirely irrational to combine activated charcoal with an oily cathartic, such as mineral oil, which greatly diminishes the adsorptive capacity of the charcoal. Administration of milk or flavoring agents should be avoided when activated charcoal is given.

The dosage for most activated charcoals for cattle is 1 kg per 500 kg of body weight. Bulk sources are needed where herds of animals are involved. Although the cost of some activated charcoals is prohibitive for large animals, DARCO S-51 (ICI Americas, Wilmington, DE) costs approximately $1.00/kg when purchased in ton quantities. Depending upon the toxicant involved, therapy may need to be repeated every 6 hours, daily, or every other day. Activated charcoal may sometimes be mixed into the feed of large animals. The Superchar® and Toxiban® formulations are conveniently made up as a liquid for small animals and in powdered form for large animals. Of the two, the former is likely to be more effective.

The dosage of activated charcoal for small animals is 1 - 4 gm/kg of body weight in 50 - 200 ml of H2O or 5 heaping teaspoons in 200 ml water for a 30 pound dog. Twenty to thirty minutes following the administration of the charcoal (if there is not an osmotic cathartic present as in the Superchar small animal product) a saline cathartic is often administered. After using charcoal, emetics must be administered parenterally.

Activated charcoal given repeatedly may be of benefit in interrupting enterohepatic recycling of certain xenobiotics. Its use is seldom if ever economically practical for causing depletion of tissue residue from food animals. There is also a possibility of "gut dialysis", which suggests that, by means of repeated activated charcoal administration, the lumen can act as a "sink" or trap with the toxicant passing across the mucosa to be bound by the adsorbent. Evidence for diminished bioavailability exists in humans in which the half-life and volume of distribution of intravenously administered digoxin was decreased by oral administration of activated charcoal.

The half-life of phenobarbital is decreased from 100 hours to less than 20 hours with the repetitive administration of activated charcoal during a 24 - 72-hour time period. Similar reductions have been reported for humans poisoned by digitoxin (highly excreted in the bile-unlike digoxin), nortriptyline, carbamazepine, phenylbutazone, and caffeine.

Clay or Bentonite - Kaolin, a clay, is hydrated aluminum silicate. Pectin is a purified carbohydrate from acid extraction of citrus fruit rinds or apple pomace. The combination is dissolved in 70 parts water as kapectate. Kaolin is also an ingredient, with activated charcoal, in Toxiban®. Bentonite is colloidal hydrated silica. Like kaoline, bentonite is a simple clay. Kaolin-pectin (kapectate) has been used as a demulcent and adsorbent in the treatment of some toxicoses. Kapectate is generally dosed at 10 - 50 ml/dog. In general, activated charcoal is far superior to clays as an adsorbent although clays are better adsorbents than activated charcoal for paraquat.

Ion Exchange Resins - A primary pharmaceutical use of certain members of this group is to lower blood cholesterol by binding bile acids in the intestine lowering cholesterol absorption. Similarly the absorption of other fat soluble substances such as certain organochlorines is reduced. Some of the more widely used ion exchange resins also bind other acidic anions. Acidic drugs or toxins bound in the resin are then lost in the feces. Neutral or basic compounds are less firmly bound. Ion exchange resins are not truly adsorbents since the binding of agents to their available binding sites is by ionic bonds (vs.

Note - Many other substances also adsorb to activated charcoal.

<table>
<thead>
<tr>
<th>Compounds with Little or no Absorption</th>
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<tr>
<td>Alkali</td>
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<td>Boric Acid</td>
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weak nonspecific forces involved with charcoal adsorption). The powdered products are mixed with water before use, and may be mixed in food. Their use may result in constipation (severe if used excessively). Oral fluids and a bulky diet are therefore encouraged to prevent constipation.

The ion exchange resins may delay or reduce the absorption of phenylbutazone, warfarin, chlorothiazide, tetracycline, phenobarbital, thyroid preparations and digitalis glycosides. One product, cholestyramine resin (Cumid® and Questran®) has been successfully employed to interrupt the enterohepatic recycling and to shorten the half-life of digitalis in poisoned patients. Cholestyramine is the cation exchanged salt of a basic anion exchange resin. Cholestyramine must be mixed with water or other fluids before ingestion, it should not be administered in the dry form. Doses of 200 - 300 mg/kg have been suggested for humans and extrapolation to animals from this dose may be reasonable. Potential side effects of cholestyramine include hypochloremic acidosis (overdose), steatorrhea, loss of fat-soluble vitamins, constipation, and hypoproteinemia. Another ion-exchange resin is cholestipol HCl (Colestid®). Kaexolate® is an ion exchange resin used to reduce excessive serum potassium by binding potassium in the gut in exchange for sodium.

Bismuth Subsalicylate - Bismuth compounds are demulcents and weak adsorbents and will bind to ulcerated mucosae. Bismuth subsalicylate (in Pepto-Bismol®) is also reported to have antiprostaglandin effects. These compounds' main benefit is in the treatment of diarrhea produced by enterotoxigenic organisms. Bismuth compounds may have some benefits as a symptomatic therapy for poisoned animals (but should be avoided if antiprostaglandin agents, e.g., aspirin, nonsteroidal anti-inflammatory drugs, have been ingested). A common dosage recommendation for Pepto-Bismol® is 1 ml/kg. Salicylate toxicosis (hyperventilation, hyperthermia, acidosis) is of concern for the salicylate in Pepto-Bismol® is absorbed (cat especially sensitive).

Formation of Insoluble Complexes in the Gut - Oral magnesium or sodium sulfate treatment for lead or barium exposure causes formation of insoluble lead sulfate or barium sulfate thereby preventing absorption. Note: Soluble salts of barium are highly toxic. Calcium solutions may be given orally for soluble oxalic acid or oak which contains gallotannins (gallic and tannic acids). sodium bicarbonate lavage solutions may be used in iron poisoning since sodium bicarbonate converts ferrous ion to ferrous carbonate which is poorly absorbed. Sodium formaldehyde sulfoxylate has been recommended in mercuric chloride ingestions since mercuric salts are reduced to less soluble metallic mercury.

Alkaloid Inactivation - Tannic acid has been previously recommended for certain alkaloid toxicoses but not for cocaine, nicotine, physostigmine, atropine, or morphine. When administered, tannic acid must not be left in the stomach; it is removed by catharsis or emesis. A previously recommended dose of tannic acid for small animals is 200 - 500 mg in 30 - 60 ml of water. It is becoming more widely accepted that the risk of tannic acid toxicosis may sometimes outweigh the benefit derived. Tannic acid causes centrilobular necrosis of the liver. The previously recommended dose in large animals was 5 to 25 gm in two to four liters of water. Potassium permanganate (1:5,000 to 1:10,000) is therefore, preferred for lavage and/or administration after alkaloid ingestion. For many alkaloids, however, activated charcoal can be substituted and it is much more often available.

d. Removal of Poisons after Ocular or Topical Exposure
For ocular exposure, have the client flush the eyes with copious amounts of warm water. Caution regarding restraint of the animal is mandatory for the owner's protection. Irrigation of chemically damaged eyes should never be delayed. Water or physiological saline solutions are first choices. The use of neutralizing agents is not recommended. A minimum of 20 - 30 minutes of irrigation is recommended. The animal should be examined as soon as possible thereafter. Following adequate irrigation, chemical burns to the eye are treated with lubricant ointments and lid closure techniques (e.g., third eyelid or conjunctival flap) to protect the damaged surface. atropine may be considered as a cycloplegic agent. Close follow-ups are required since epithelial damage may be delayed (especially with alkali burns).Corticosteroids should be used only if the corneal epithelium is intact.

For dermal exposures of small animals or individual large animals, start with a liquid dish detergent for oily substances (e.g., insecticide preparations). Repeat baths until the insecticide odor is reduced as much as possible or eliminated. Rinse very thoroughly with copious amounts of water. Rubber gloves and plastic aprons should be used to avoid exposure of the person bathing the animal. Avoid greasy topical medications as they may act as a vehicle to enhance absorption. Solvents may do more harm than good as they disperse the chemical, increase the exposed surface area and alter the permeability of the skin.

To remove asphalt or sticky traps used to control or monitor insect and rodent populations, polysorbate 80 containing cremes may be used, but butter may be equally effective and much less expensive. Alternatively, a mechanic's hand degreaser (e.g., Goop®) may be quite effective. These agents may also be effective in removing oil-based paint from animals. Naturally, this
is followed by a thorough bath. For dermal exposures of significant numbers of large animals, crowding the animals together in a small pen is followed by wetting with a power sprayer or high-pressure hose. This is followed by the use of one of the less irritating powdered laundry detergents and a subsequent thorough rinse. The following has been recommended for deodorizing the skunk-affected pet: 1 quart 3% hydrogen peroxide, 1/4 cup baking soda (sodium bicarbonate) and 1 teaspoon liquid soap. The bath should be followed by a tap water rinse. The animal should not be allowed to swallow the mixture. Do not use near heat source or open flame due to the release of oxygen.

6. Facilitating Removal of Absorbed Toxicants
The next concern is the systemic poison that has already been absorbed. Active methods for the removal of absorbed toxicants would include methods to: 1) enhance metabolism to less toxic forms, 2) increase excretion rates of toxin, or 3) direct removal of a toxicant from the affected animal (e.g., hemofiltration). Enzyme-inducing drugs such as phenobarbital take at least a couple of days to significantly increase mixed function oxidase activity. Therefore, they have been recommended for use in reducing residues of persistent xenobiotics in tissues but, comparative studies have failed to demonstrate significant economic benefit. More importantly, for most acutely poisoned animals, the enzyme-inducing effect is often too late. A concern also exists if enhanced microsomal enzyme activity may lead to increased metabolism of compounds activated by mixed function oxidases. Specific antidotal therapies (e.g., alcohol dehydrogenase inhibitors with ethylene glycol) are occasionally employed to modify the metabolism of a toxicant. As a result of the limited role for enhanced metabolism, attention must be focused on ways of promoting excretion. The urinary tract and biliary tract represent the two principle routes by which exogenous chemicals are most commonly removed. Interrupting enterohepatic recirculation with periodic administration of activated charcoal or ion exchange resins has already been mentioned.

a. Forced Diuresis
Clinical indications for measures to promote renal elimination of absorbed toxicants include: 1) presence of serious clinical toxicosis with clinical signs (e.g., severe hypotension, coma, arrhythmias), 2) potentially lethal dose has been ingested, 3) impairment of normal route of excretion (e.g., organ injury, concentration-dependent elimination rates), 4) progressive deterioration of an animal's clinical condition in the face of intensive therapy. The use of forced diuresis may be associated with the following complications: 1) pulmonary edema, 2) cerebral edema, 3) metabolic acidosis or alkalosis, 4) electrolyte imbalances (e.g., hyponatremia, hypokalemia), and 5) water intoxication. For these reasons, vigorous attempts at forced diuresis should be limited to situations in which benefit can be expected. Promotion of renal excretion of toxicants is frequently very beneficial to the patient and is heavily relied upon in the management of many toxicoses. However, diuresis is of benefit only for compounds which are present in significant concentrations in the plasma. In general, organic acids are present in plasma in greater concentrations than organic bases due to the fact that, the plasma is slightly alkaline compared to the intracellular environment, which results in partitioning. Nonpolar compounds which tend to resist biotransformation, such as dieldrin or kepone are present in plasma in such low concentrations that diuresis is of little benefit for increasing their excretion. The composition of urine is determined by the combined processes of: 1) ultrafiltration, 2) active tubular secretion, and 3) passive tubular reabsorption. In the glomerular tufts, toxicants which are not bound to albumin will be ultrafiltered. Active transport systems are present in the proximal convoluted tubules which can transport some drugs or toxicants. Separate transport systems exist for basic and acidic agents. Tubular reabsorption of foreign substances is limited to unionized lipid-soluble agents and is largely passive. Indirectly, however, this passive migration is a consequence of the active tubular transport of sodium chloride. This is because the tubular fluid (glomerular filtrate) tends to become concentrated with respect to all solutes not actively resorbed during this process. In general, excretion of toxic substances is promoted by taking steps necessary to minimize passive tubular reabsorption of toxic solutes. The effect of administration of water (water diuresis) on the excretion of most substances is minimal. An increased water load inhibits ADH secretion, but the principle effects of ADH are on the volume and flow in the distal tubules and collecting ducts. Most passive resorption occurs in the proximal tubules.

b) Osmotic Diuretics
Osmotic diuretics reduce water resorption in the proximal convoluted tubules and prevent the concentration of passively resorbed substances at this site. This reduces renal toxicity and promotes excretion.

Mannitol - Mannitol is one of the most commonly used osmotic diuretics. It does crystallize and is sometimes hard to dissolve (immerse in hot water). Therefore, it is wise to store unopened vials away from cold walls, etc. Mannitol is infused intravenously as a 20% solution at a rate not to exceed 0.5 grams per kg the first hour. This should increase urine flow. The
diuresis should continue with 5% mannitol in Ringer's solution since mannitol diuresis also increases the excretion of sodium and potassium. Supplementation of Ringers with potassium could be considered. If either glomerular or tubular function is too severely compromised, mannitol will not increase urine flow. Mannitol should not be administered to anuric animals. Infusion of 5% mannitol at a rate of approximately 10 ml/kg/hour should at least triple urine flow. Urinary output and body weight should be measured to avoid overhydration and pulmonary edema. Mannitol has also been recommended to reduce the pressure and volume of the cerebrospinal fluid. Mannitol is distributed in the extracellular fluid. Administration is therefore accompanied by an expansion of the extracellular fluid volume. In the patient with cardiac decompensation, this represents an undesirable hazard. Marked pulmonary congestion or edema, dehydration, and intracranial hemorrhage are additional contraindications to the use of mannitol.

Urea - Urea may be used as an osmotic diuretic at a dose rate one-half that of mannitol.

50% Dextrose - Concentrated dextrose is also effective, inexpensive and provides a small amount of energy to the animal. Provided it is kept free of bacterial contaminants, it is one of the safest osmotic diuretics. With any osmotic diuretic, fluids are required to maintain hydration.

c) Water Loading and Other Diuretics

In large animals such as cattle and horses, when it is difficult to obtain the large volumes of solutions necessary for infusion it is sometimes practical to pump fairly large volumes of water or nonsterile electrolyte solutions into the rumen or stomach. This will increase urine flow and, in this circumstance, the judicious use of potent diuretics such as furosemide may enhance diuresis. In other toxicoses, in which renal shutdown does not respond to osmotic diuresis, a single dose of furosemide may also be warranted.

d) Ion Trapping

The basic premise of ion trapping is that ionized compounds do not readily traverse cell membranes and are therefore not resorbed by the renal tubules. Many chemicals, particularly drugs, are weak acids or weak bases. Note the ratio of nonionized to ionized drug is calculated from the Henderson-Hasselbach equation; \( pH = pK_a + \log [\text{salt}] / [\text{acid}] \). At a pH equal to the pKa, an agent will be 50% ionized and 50% nonionized. If the urinary pH favors the ionized form, an agent becomes "trapped" in the tubular fluid and is more likely to be excreted. Acidic compounds such as aspirin remain ionized in alkaline urine and alkaline drugs such as amphetamines are ionized in acidic urine. Generally alkaline urine therefore favors increased excretion of acidic drugs and vice versa.

For an agent to respond to pH manipulation of the urine, the following criteria must be met:

1) the toxicant or its toxic metabolite(s) must be significantly eliminated by the kidneys in an unconjugated form, 2) the agent or its toxic metabolite(s) must have a pKa (acidic or basic) that is in the range of common urinary pHs, and 3) the agent must not be extensively protein bound and is not highly lipophilic. Ammonium chloride (100 mg/kg in dog or 20 mg/kg in cat, BID) or chlorethamine are used orally to acidify the urine. Administration of ammonium chloride requires monitoring of metabolic status and is contraindicated if hepatic or renal insufficiency is present. Acidification of the urine is also contraindicated if severe rhabdomyolysis or myoglobinuria is present. The nephrotoxicity of myoglobin is considered to be enhanced in acid urine. Ammonia intoxication can also develop and is most often manifested by depression and coma. Plasma potassium and urine pH should be monitored frequently. Acid diuresis of human patients is presently limited to amphetamine (pKa = 9.9), phencyclidine (pKa = 8.5), guanine (pKa = 8.4), strychnine (pK1 = 6.0, pK2 = 11.7), and fenfluramine (pKa = 9.9) overdoses. A urine pH of 5.5 - 6.5 is usually maintained. Forced alkaline diuresis is generally achieved with sodium bicarbonate at 1 - 2 mEq/kg administered intravenously every 3 - 4 hours. The goal in man for urine pH is 7.0 or greater. Carnivores tend to have more acidic urines, however, and excessive attempts to increase urinary pH to this point may result in metabolic alkalosis. The use of alkalinization may require the correction of associated potassium and chloride deficits. Bicarbonate is of considerable benefit in ethylene glycol toxicosis. To alkalinize urine, one must exceed the renal threshold for bicarbonate of 24 mEq/liter. It is suggested that blood bicarbonate be increased by 40 - 50%. This would require 2.0 mEq HCO3/kg. Sodium bicarbonate should be infused intravenously at a very slow rate or, better, may be added to fluids for infusion. The administration of lactated Ringer's solution, to which mannitol or urea is added is effective for enhancing excretion of barbiturates. The addition of bicarbonate would be expected to further enhance excretion. Alkalinization of the urine has been used successfully to treat salicylate, phenobarbital, and 2,4-dichlorophenoxy acetic acid (2,4-D) poisonings.

Note: Strong bases (pKa greater than 8.0) and strong acids would tend to be already charged in the glomerular filtrate and therefore readily excreted by the kidney without modifying the pH.

Principles of Ion Trapping
Principles of Ion Trapping (Continued)

Ion trapping of a Weak Acid

Bicarbonate
\[ \text{Na}^+ \text{HCO}_3^- \rightarrow \text{HCO}_3^- + \text{H}^+ \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2 \]

- Excreted in urine

Ammonium chloride
\[ \text{NH}_4\text{Cl} \rightarrow \text{NH}_3 + \text{HCl} \rightarrow \text{H}^+ + \text{Cl}^- \]

- Expired in air

\[ \text{NH}_4^+ \text{ excreted in urine} \]

\[ \text{100\% \ -COO-} \]

\[ \text{pH} \rightarrow \text{pK}_a \]

\[ \text{50/50} \]

\[ \text{100\% \ -COOH} \]

Capillary lumen

- COOH \[ \rightarrow \text{-COO-} \]

Alkalizing blood (bicarbonate) decreases [H⁺]

- COOH (in tissues)

\[ \text{50/50} \]

\[ \text{100\% \ -NH}_2 \]

- NH₂ \[ \rightarrow \text{-NH}_3^+ \text{ or} \]

\[ \text{> NH} \rightarrow \text{> NH}_3^+ \]

Acidifying blood (ammonium chloride) increases [H⁺]

\[-\text{NH}_3^+ \text{ or } > \text{NH}_3^+ \text{ (may tend to stay in tissues)} \]

Tissues Normally More Acid than Blood

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Principles of Ion Trapping (Continued)
e) Dialytic Techniques for Toxin Removal

Dialysis is used to describe the movement of an agent across a semipermeable membrane. The effectiveness of a dialytic technique depends upon the toxin's size (smaller sized more easily dialyzed), lipid solubility, protein binding, volume of distribution, and the presence of a concentration gradient, in addition to blood flow rates and dialysate characteristics.

**Dialysis should be considered if renal failure is present** or if large quantities of a toxicant are present.

**Peritoneal Dialysis** - In peritoneal dialysis the large surface area of the peritoneum serves effectively as a membrane for exchange of diffusible substances of varying molecular weight. Fluid placed within the peritoneal cavity becomes an extension of the extracellular fluid compartment and at equilibrium will have an identical composition of solutes as present in the blood perfusing the abdominal viscera. Six hours of peritoneal dialysis may be equivalent to 12 hours of hemodialysis using an artificial kidney. The most common indication for the use of this procedure is detoxification of anuric animals suffering from primary renal failure. Peritoneal dialysis may also be used to remove xenobiotics, hydrate dehydrated animals, dehydrate over-hydrated individuals, or correct hypothermia if warmed dialysates are used. Peritoneal dialysis must be used repeatedly to be of much value. The technique should be learned before the emergency arises. Ion trapping the toxicant in the dialysate may be used where it will not aggravate acidosis or alkalosis.

Bilaterally nephrectomized dogs have been kept alive for up to 111 days by peritoneal dialysis. The most serious complications are peritonitis and penetration of the abdominal viscera during insertion of the trochar or cannula. Attention must also be directed toward avoiding overhydration and loss of protein and electrolytes. Peritoneal dialysis is sometimes the detoxification method of choice in small animal practice. These instances include situations in which: a) a significant quantity should be in the plasma water or rapidly equilibrate with it; b) the degree of toxicosis should be directly related to the blood concentration and duration of exposure to the poison; c) the rate of clearance of the toxicant from the blood is much greater than the normal rate in the absence of renal failure; and d) the amount of poison dialyzed must add significantly to the normal mechanisms for disposal of the toxin under the physiological circumstances of the patient. Highest clearance rates can be achieved with small molecular weight molecules.

**Technique for Peritoneal Dialysis** - Dialysate--contains dextrose (1.5 - 4.25%) to induce osmotic fluid removal from the animal. Dialysate should be prewarmed. Commercially available dextrose dialysate bags are preferred (Dianed 137 with 1.5% dextrose-viaflex). A disc peritoneal dialysis catheter (Purdue column catheter) is placed into the lower abdominal quadrant. These are reported available from Henry Schein at (800) 537 - 2980. The disc is placed firmly against the parietal peritoneum and a routine closure of the abdomen performed with the catheter exiting through an adjacent stab incision.
Dialysate is instilled into the abdomen until mild abdominal distension is noted. Fluid is left in the abdomen for 45 - 50 minutes. Dialysis cycles may be repeated hourly until clinical improvement (or decreased uremia) occurs. Complications of peritoneal dialysis include peritonitis.

Peritoneal dialysis has been effectively utilized in human patients with barbiturate, ethylene glycol, lithium, theophylline, salicylate, and quinidine toxicosis. Other approaches which may eventually become more widely employed in veterinary medicine include Hemodialysis and hemoperfusion, using newer, less expensive, and even back-pack artificial kidneys. Hemodialysis was introduced experimentally in 1913 in an evaluation of the ability to remove salicylate from dog's blood. The first successful clinical experiences were reported in the mid 1950s in human patients with severe salicylate poisoning. Several hemodialysis techniques are available, including: 1) aqueous hemodialysis (most commonly used for toxicoses), 2) lipid hemodialysis, and 3) ultrafiltration dialysis. The driving force in conventional hemodialysis is the concentration gradient of unbound ultrafilterable solute between the plasma and the dialysate employed. Hemodialysis equipment employs a blood delivery system, dialyzer, and dialysate. Additionally, Hemoperfusion using activated charcoal, ion-exchange resins, or lipid aqueous phase columns may be used. Hemoperfusion was introduced in human clinical toxicology in 1965 for treatment of acute barbiturate toxicosis. During hemoperfusion, blood is pumped through an extracorporeal circuit containing a filtering cartridge. Cartridges may contain activated charcoal or resins (XAD-4) which will absorb the toxicant. Hemoperfusion has become the method of choice for the treatment of life-threatening human poisoning from a wide variety of toxicants and drugs. The use of both hemoperfusion and hemodialysis do not replace more commonly employed methods of decreasing a toxicant's action. These techniques are, however, being employed (e.g., one study reported that approximately 0.15% of all overdose patients in the United States undergo hemodialysis or hemoperfusion) in some human hospitals. At the present times due to the expense and technical difficulties in performing these techniques, their use in animals is experimental.

f) Drug Antibodies
Attempts have been made to employ the use of specific FAb drug antibody fragments for the treatment of severe digoxin poisoning in man. FAb fragments bind to the specific drug (antigen) with high specificity and result in "neutralization." Immunopharmacological techniques are largely experimental at the present time; however, as clinical experience is gained with these methods, their use may increase in the future. Specific antibodies have been developed and found to be effective in experiments evaluating animals exposed to digitalis glycosides and the mycotoxin T-2 toxin. These techniques are already being used routinely in some human hospitals.

7. Use of Antidotes
Antidotes are best considered with individual toxicants and are not discussed herein. Some antidotal information on the labels of commercial products is out of date. When in doubt contact the National Animal Poison Control Center.

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