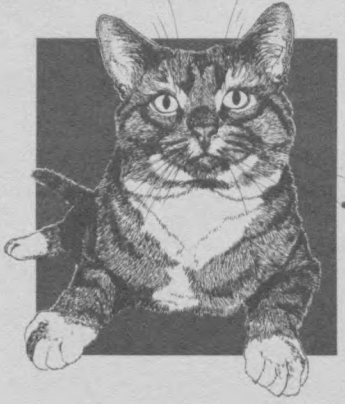

Cornell Feline Health Center
Veterinary News
Summer 1984

Cats and Pharmaceuticals

Nina Shoulberg, D.V.M., M.S. and Wayne S. Schwark, D.V.M., Ph.D.

With the increasing popularity of cats as housepets, it is inevitable that the veterinary practitioner will have occasion to use drugs in a greater number of feline patients in the future. Considering the cat's unique deficiencies in capacity for drug metabolism, it is essential that cats not be thought of as simply "small dogs" when medicated. It is the aim of this article to discuss certain compounds which are considered to be relatively safe in other species but which are toxic to cats. These drugs are some of the most potentially dangerous because an unsuspecting practitioner who has had little trouble with the drug in a dog might be tempted to use it without caution in a cat.

Because the pharmacological and toxicological effcts of a chemical substance are usually directly proportional to the concentration of that compound in the animal's body fluids and tissues, pharmacokinetic factors are of primary importance in determining responses to exogenous chemicals. The concentration of a given compound in an animal's body fluids and tissues is determined by its dosage and pharmaceutical form, as well as the absorption, distribution, biotransformation, and excretory properties of the drug.

It has become increasingly apparent that cats differ markedly from other species in the rate at which they biometabolize compounds and that this often accounts for their unique sensitivity to many drugs and chemicals. Biotransformation is usually a two-step process involving oxidation, reduction or hydrolysis followed by conjugation of a compound. These processes occur for the most part in the liver, utilizing enzymes associated with the smooth endoplasmic reticulum of the hepatocyte. Metabolites are formed which may have activities similar to or markedly different from that of the parent compound. These drug metabolites tend to be more polar and less lipophilic than the original drug and hence are more readily excreted from the body. Among the common domestic animals, cats are unique in that they have low levels of hepatic glucuronyl transferase, an enzyme essential for the conjugation of compounds such as alcohols, phenols, carboxylic acids, amines, amides, and thiols with glucuronic acid. Examples of drugs representing these groups of compounds include morphine, acetaminophen, acetylsalicylic acid, and chloramphenicol. Hence, a decreased ability to convert these drugs into inactive, readily excretable metabolites explains, at least in part, the observed accumulation and toxicity of drugs such as these in cats.

Analgesics

Acetylsalicylic acid (aspirin), an over-the-counter pharmaceutical, is a common cause of poisoning in the cat. Daily administration of less than one-half of an adult human aspirin (2 grains) can produce intoxication within one to two days in cats. Clinical signs include anorexia and depression progressing to vomiting after approximately the fourth dose. Higher levels of the drug produce more intense toxic effects, such as hematological disorders, fever, dyspnea, acid-base

(Continued on page 3.)

Feline Advisory Council Welcomes New Members

Six new members have been appointed this year to the Cornell Feline Health Center Advisory Council, contributing a broad spectrum of interests and perspectives to the development of feline programs. We are happy to welcome Joan M. Arnoldi, D.V.M., President of the American Association of Feline Practitioners; Nancy A. Bull, President and Managing Publisher of Veterinary Practice Publishing Co.; Roger Caras, noted author and Special Correspondent on Animals and the Environment for ABC News; Mark L. Morris, Jr., D.V.M., Trustee and Research Vice President of the Morris Animal Foundation; Mordecai Siegal, TV talk show personality and award-winning author of numerous books and columns on pets; and Joan Wastlhuber, President of the Robert H. Winn Foundation for Cat Research.

They join fellow members George W. Abbott, D.V.M., and Jean Holzworth, D.V.M., of Angell Memorial Animal Hospital; John M. Brentlinger, Jr.; Sally Faile El-Sayed; Hazel Lindstrand, Cat Fanciers Association Shorthair Judge; Rosemonde Peltz, M.D.; Theodore A. Rude, V.M.D., Assistant to the President of Salsbury Laboratories; and Ellen Yanow, Executive Director of Tree House Animal Foundation.

The Annual Meeting was held in June. Pictured from left are Dr. Arnoldi, Ms. Yanow, Ms. Bull, Ms. Wastlhuber (seated), Mr. Siegal (seated), Dr. Rude, and Dr. Morris.

Correction

The dose of pancuronium listed in "A Guide to Feline Anesthesia," on page 7 in the Spring 1984 issue of "Veterinary News," should have been 0.03 mg/lb. IV, rather than 0.3 mg/lb. IV.

In many cases, a tenfold error in the administered dose of a drug will produce a serious threat to the well-being of the animal receiving it; fortunately, this does not appear to occur with pancuronium use in cats. Although the dose required to produce neuromuscular blockade in most anesthetized cats is 0.03 mg/lb., much higher doses are tolerated without toxic effects as long as ventilatory support is provided. This high margin of safety, along with the reversibility of the drug, would seem to make pancuronium the drug of choice for producing neuromuscular blockade in the cat.

Cornell Feline Health Center
Veterinary News

A publication for veterinary professionals

The ultimate purpose of the Cornell Feline Health Center is to improve the health of cats everywhere, by developing methods to prevent or cure feline diseases, and by providing continuing education to veterinarians and cat owners. All contributions are tax-deductible.

Director: **Fredric W. Scott, D.V.M., Ph.D.**
Editor: **Joyce Tumbelston**
Secretary: **Sheryl A. Bronger**
Special Consultant: **Leo A. Wuori, D.V.M.**

Pharmaceuticals

disturbances, possibly convulsions, and death.

Treatment of aspirin intoxication is basically supportive. Fluid therapy is complicated by the fact that the cat may be either in respiratory alkalosis or, as the intoxication progresses, in metabolic acidosis. A practitioner can circumvent the uncertainty of acid-base status by using a Harleco apparatus to determine the metabolic state of the animal. If aspirin ingestion is relatively recent, emesis or enterogastric lavage may be indicated. Alkalinizing the urine to a pH greater than 8 will hasten the excretion of the aspirin and help correct the metabolic acidosis which is most commonly present.

Analgesics even more dangerous to cats are acetaminophen (Tylenol®) and phenacetin (a compound which is converted to acetaminophen in the liver). One Extra Strength Tylenol® (500 mg) or two Regular Strength Tylenol® capsules (325 mg) given four hours apart may produce toxicity in cats with clinical signs such as depression, anorexia, shallow respiration, pale cyanotic mucous membranes, icterus, vomiting, limb and facial edema, and dark, chocolate-colored urine. Methemoglobinemia, as evidenced by chocolate-colored blood, is a common factor of this toxicity. If the toxicity is left untreated, death may occur within three days post-administration.

Treatment of acetaminophen intoxication is supportive, possibly entailing the use of blood transfusions. Additionally, acetylcysteine has been advocated as a specific antidote. The rationale for the use of this drug relates to the feline's deficient glucuronyl transferase system. Due to the cat's inadequacies in conjugating acetaminophen metabolites with glucuronide, a larger proportion of a toxic reactive metabolite, N-acetyl-p-benzoquinone, is formed. This metabolite is subsequently inactivated by conjugation with endogenous hepatic glutathione by an alternate enzyme system. When the glutathione is depleted, cellular damage ensues due to the unbound reactive metabolite. Acetylcysteine, a compound similar in structure to glutathione, is given in an effort to provide an exogenous substrate for the metabolite. It is available to the practitioner as Mucomyst® and is provided as a 20% solution. The recommended treatment regime for acetaminophen intoxication is 0.7 ml/kg orally given on admission, followed by a similar dosage at four, 12, and 20 hours thereafter.

Clinical experience indicates that phenylbutazone is also more toxic in cats than in other species. Acceptable treatment regimes with this drug as well as other newer nonsteroidal antiinflammatory drugs such as flunixin meglumide (Banamine®) have not been established in the feline.

Fortunately, acceptable narcotic analgesics are available for the management of acute pain situations in the feline. Morphine, when given at the dosage suitable for dogs (1 mg/kg), may produce severe CNS stimulation in cats. However, when administered at a reduced dosage, morphine is an effective, safe analgesic in the cat. The recommended dosage of 0.1 mg/kg SC will produce analgesia for over four hours. Dextro-propoxyphene hydrochloride (Darvon®), a synthetic narcotic similar to methadone, given at 2.2 mg/kg IM, also produces acceptable, safe analgesia within two hours, with a duration of greater than four hours. Meperidine (Demerol®), with a plasma half-life of only 0.7 hours, produces acceptable analgesia two hours following IM injection of 11 mg/kg (this dose being comparable to that used in a dog). Unfortunately the analgesic effects of meperidine are short-lived and by four hours pain sensation returns. Finally, a newer semisynthetic narcotic analgesic, oxymorphone (Numorphan®), at a dosage of 0.4 to 1.5 mg/cat SC, IM, or IV, produces satisfactory analgesia. An obvious disadvantage of these narcotic compounds is the fact that they are controlled substances; however, they do represent effective choices for acute pain management in the cat.

Antibiotics

Controversy has long existed over the use of chloramphenicol in cats. The rare, idiosyncratic, nondose-related agranulocytosis and aplastic anemia seen in human patients has not been reported in the feline. However, cats are susceptible to the dose-dependent bone marrow depression and blood dyscrasias reported in other species because this drug is highly dependent on hepatic biotransformation for elimination from the body. Perhaps a more significant clinical consequence of chloramphenicol administration is anorexia. In an already debilitated patient, this may be life-threatening. Hence, it is desirable (if chloramphenicol must be used) that a minimum acceptable regime of therapy be employed with regard to both dosage and total duration of therapy. A dosage of 13 to 20 mg/kg orally B.I.D. (versus the recommended dose of 20 mg/kg T.I.D.) has been shown to produce therapeutically effective plasma chloramphenicol levels and may represent an acceptable treatment regime.

Streptomycin and dihydrostreptomycin may produce neurotoxic effects in cats. Respiratory failure due to neuromuscular blockage may be induced by high doses (150 mg/kg IV) of streptomycin. Repeated smaller doses (50 mg/kg) given IM produce ataxia, gait and postural alterations, and disappearance of the normal rotational nystagmus; hearing is also reported to be affected. It should be noted that all aminoglycoside antibiotics (streptomycin, dihydrostreptomycin, kanamycin, neomycin, and gentamycin) have been shown to cause either vestibular lesions or renal tubular damage in dogs and cats when used for prolonged periods of time. Veterinarians should use this group of antibiotics cautiously in both species, particularly when any degree of renal impairment is present, for these drugs are eliminated by direct renal excretion.

Antiparasitics

Clinical impressions indicate that cats are highly sensitive to organophosphates. In acute organophosphate intoxication, signs referrable to acetylcholine accumulation are produced: miosis, frequent defecation and urination, salivation, vomiting, muscle fasciculations, convulsions, and death due to respiratory paralysis. Signs may be seen from minutes to in excess of 24 hours post-exposure. Additionally, cats appear to be more susceptible to the delayed form of neurotoxicity, in which minimal exposure to an organophosphate results in axonal degeneration days to weeks later. The degeneration and consequent signs of paresis and paralysis begin peripherally and progress toward the central nervous system. It is not known why cats are more susceptible than most other domestic animals to this form of toxicity. Finally, dichlorvos-impregnated flea collars have been reported to cause contact dermatitis in cats and should be used with particular caution in debilitated cats.

Treatment of acute organophosphate intoxication is supportive and may entail the use of enterogastric lavage. Additionally, atropine at 0.1 to 0.2 mg/kg given slowly IV is a specific antidote. To avoid ventricular fibrillation, atropine should not be given to a cyanotic patient; rather resuscitative efforts should be instituted first. In more serious cases of poisoning, IV 2-PAM at 20 mg/kg should be given in conjunction with atropine.

Malathion is one organophosphate approved for use in cats and considered safe and efficacious for the treatment of ectoparasites. Its rapid metabolism in mammals compared to insects may account for the increased safety relative to other organophosphates.

Cats appear to be very sensitive to chlorinated hydrocarbons, thus their use is contraindicated. Chlordane, lindane, dieldrin, aldrin, and endrin cause apprehension, belligerence, hyperesthesia, hypersalivation, convulsion, and death in cats. These signs may occur from minutes

to weeks post-exposure and the clinical course of the intoxication may be prolonged, for these compounds are readily stored in fat depots. Treatment entails washing the product off the fur and/or enterogastric lavage. Additionally, sedation with diazepam and housing the animal in a dark, quiet environment are recommended to control seizure activity. Because chlorinated hydrocarbons are excreted by the kidneys, it is important that adequate urine production be maintained.

Miscellaneous Drugs

Griseofulvin induces teratogenic effects when given to pregnant queens; therefore its use in these animals is not recommended. Animals are particularly vulnerable during the first trimester of pregnancy, when multiple malformations including cleft palate, cyclopia, and exencephaly are produced. Treatment during the third or fourth week of gestation may result in weak or stillborn festuses; however, treatment during the last half of pregnancy is apparently without ill effects on the fetus.

Urinary antiseptics containing methylene blue may cause a severe Heinz body hemolytic anemia and concurrent pallor, icterus, dyspnea, depression, and death if left untreated. Blue urine and feces may be one of the presenting signs. Methylene blue causes an irreversible oxidation of the hemoglobin molecule leading to the formation of Heinz bodies in the red blood cells. These cells then undergo intravascular hemolysis to produce the observed clinical signs.

Phosphate-containing enemas (e.g., Fleet®) may produce profound depression, collapse, violent vomition, hypersalivation, tachycardia, cyanosis, hypothermia, muscle fasciculations, and tetany within 20 minutes post-administration; their use is an absolute contraindication in cats. Serum electrolyte analysis at the time of presentation will show a severe hypocalcemia, hyperphosphatemia, and hypernatremia. Treatment is aimed at restoring the serum calcium levels to normal. Initially, a 10% solution of calcium gluconate should be administered slowly IV. Given until the tetany and muscle fasciculations have ceased, this approximates a dose of 1.5 ml/kg. Concurrent EKG monitoring is advised during calcium administration. The cat should then be put on a maintenance drip of 5% dextrose in water supplemented with 10% calcium gluconate. Serum calcium levels should be monitored daily and the drip discontinued when calcium levels return to normal.

A decreased ability to conjugate phenols with glucuronic acid and the subsequent buildup of toxic quinones explains the cat's generalized sensitivity to phenol-containing compounds. One example of such a product is hexachlorophene. Used in germicidal soaps (e.g., Septisol®), hexachlorophene may be potentially toxic if incorporated into enemas or used as a surgical scrub. Because it is readily absorbed from the skin and digestive tract, it may cause the following clinical signs: vomiting, depression, ataxia, patellar hyperreflexia progressing to hyporeflexia, anuria, and flaccid paralysis. Treatment is supportive and may entail gastric lavage or administration of a saline cathartic. In addition, management of cerebral edema may be necessary.

Finally, benzyl alcohol, used as a preservative in many solutions for parenteral administration, may be toxic to cats if given in excessive amounts. Small amounts can be conjugated by the cat's glucuronyl transferase system but quantities such as those involved in fluid replacement therapy cannot be effectively eliminated. A toxic metabolite, benzoic acid, accumulates and causes the central signs of ataxia, hyperesthesia, muscle fasciculations, and depression. Overzealous use of solutions containing benzyl alcohol as a preservative should therefore be avoided in cats.

Much research needs to be done to

(Continued on page 8.)

Feline Diagnostic Services at Cornell

Guidelines for Submission of Samples to the Diagnostic Laboratory

Cheryl A. Stoddart, M.S.

Many practitioners contact the Cornell Feline Health Center for advice on problematic cases, most frequently feline leukemia, feline infectious peritonitis, chronic upper respiratory disease, gastrointestinal disorders, reproductive problems, and kitten mortality. In response, we often recommend that specific diagnostic tests be performed to determine the cause and facilitate treatment. Unfortunately, not all veterinarians are aware of the correct procedures for collection and submission of samples for these specific tests and, as a result, they may neglect to have these crucial tests performed, incur unnecessary delays, or obtain false results. This article is an attempt to familiarize readers with the proper procedures for collection and submission of samples, and to encourage practitioners to more fully utilize the Diagnostic Laboratory at Cornell.

Before submitting samples the most important step is to write or call the Diagnostic Laboratory to obtain 1) their Policy and Fee Schedule, 2) a pad of submission forms, and 3) supply request forms (all available free of charge). The Policy and Fee schedule lists the currently available tests and contains detailed information concerning sample submission for each individual test. By using the supply request form, you can order (for nominal fees) most of the items needed for proper sample submission. Such available items mentioned in this article are denoted with an asterisk (*).

Sample Collection

Choose samples judiciously according to the nature of the disease: serum samples for antibody, feline leukemia virus, and hormone baseline/response tests; conjunctival, pharyngeal, and nasal swabs (upper respiratory disease) and vaginal and uterine swabs (reproductive problems) for isolation of bacteria and viruses; fecal samples and intestinal scrapings (gastrointestinal disorders) for parasite examination, bacteria culture, and electron microscopy; and tissue samples (from biopsy or necropsy) for histopathology and virus isolation.

Serum: Allow the blood sample to clot at room temperature (two hours) and for greatest serum yield, place it in the refrigerator overnight. The clot will then retract. Aseptically transfer the serum (approximately 1 ml per test) to a sterile vial*. (If a centrifuge is available, spin down the clot; if not, carefully remove the serum from around the clot with a pipette). Refrigerate the vials and ship in a styrofoam blood-tube mailer* or in a styrofoam "biomailer"* with cold-packs. (Save the cold-packs from vaccine shipments for this purpose). In the case of antibody tests for cats which show clinical signs, it is helpful to submit paired serum samples obtained three to four weeks apart; active infection is demonstrated when a marked (fourfold or more) increase in titer occurs over time. The first sample must be collected as early in the acute phase of the disease as possible and the second during convalescence. To avoid confusion, freeze the first sample and retain it until the second sample is obtained, at which time both can be submitted together. For healthy cats of unknown prior infection status, a test on a single sample will provide useful information. Additionally, a very high titer on a single sample, when consistent with clinical signs, is supportive of the presumptive diagnosis.

Swabs: Place swabs for bacteria cul-

ture in sterile vials containing the transport medium specific for the organism to be isolated, i.e.; Amies transport medium* or "culturettes" for aerobic bacteria, mycoplasma, and ureaplasma; anaerobic bacteria transport medium*; and chlamydia transport medium*. Refrigerate the vials and send them in a biomailer* with cold-packs situated in such a manner that the samples do not freeze. A separate set of swabs can be submitted for virus isolation in a viral transport medium.* If these are to be shipped overnight, they should be sent with cold-packs. If there is to be a delay in shipment, they should be frozen and shipped frozen. Use of dry ice (difficult to obtain but sometimes available from ice cream companies) in the biomailer will ensure against thawing of samples. If dry ice is used, seal vials in Ziploc® bags to prevent the CO_2 from inactivating the virus. Remember: DO NOT use virus transport medium for swabs submitted for bacteria culture or for chlamydia, and DO NOT use bacteria transport medium for virus isolation, because this will preclude successful isolations.

Fecal samples: For bacteria and virus culture, place 1 to 5 gm fresh feces in a sterile wide-mouth sealed container* and send on cold-packs without preservative or fixative. Samples for electron microscopy (2 gm) should also be sent cold but not frozen. If feces are liquid and a delay in transport is anticipated, several drops of 10% formalin can be added. For parasite screen, feces can be preserved by adding 3 to 5 gm to 10 volumes of 10% formalin. (Formalin can be obtained from a veterinary supplier or pharmacy.) Fecal samples should be collected within 24 hours of the acute phase of disease and not after two to three weeks of unsuccessful treatment.

Tissues: Collect <u>fresh</u> samples 0.5 to 2.0 cm thick from tissues demonstrating macroscopic lesions, including the periphery of the lesion as well as some surrounding normal tissue. If lesions are not evident, as is usually the case with kittens dying from "fading kitten syndrome," a variety of tissues should be obtained (thymus, lung, heart, liver, spleen, kidney, lymph node, intestine, etc.). If tissues are to be submitted for both virus isolation and histopathology, you MUST submit DIFFERENT SETS of tissues for each because of drastically different submission procedures. The set for histopathology must not be frozen and should be placed in a wide-mouth jar* containing at least 10 times the tissue volume of 10% neutral-buffered formalin. Refrigeration and fast delivery are not necessary but be sure to seal the jars tightly to prevent evaporation and leakage. The set of tissues for virus isolation and immunofluorescence (FA tests) MUST NOT be fixed in formalin. Place each tissue in individual, labeled containers or plastic specimen bags. For FA tests, the tissues also should not be frozen, but shipped cold, with overnight delivery if possible. Tissues for virus isolation that are shipped for overnight delivery can be sent unfrozen with cold-packs. If lengthy delays are anticipated, tissues for virus isolation should be frozen and shipped to arrive frozen.

Sample Submission

Packaging: Label each sample with the names of the animal, the owner, and veterinarian, the date obtained, and the nature of the sample or tissue. Make sure containers are tightly sealed. Fill out the submission form completely, including a detailed history, and specify the tests requested on each sample. If given the history, the Diagnostic Laboratory will be able to provide a more meaningful interpretation of the test results.

Shipping: Affix a Diagnostic Laboratory mailing label* or write the correct address on the box. In order to assure prompt attention to your sample, send it directly to the Diagnostic Laboratory, not to the Cornell Feline Health Center or any other department. The Feline Health Center is not directly associated with the Diagnostic Laboratory, and mislabeling of packages has resulted in lengthy delays in sample processing. It is also important

that the samples for various isolations be shipped early in the week by the fastest means possible, i.e., hand delivery or overnight mail. DO NOT send the samples on Friday or before a holiday. Refrigerate or freeze them, whichever is appropriate, until the beginning of the next week and then send them.

It is hoped that these brief instructions will enable you to obtain satisfactory service through proper preparation and handling of specimens. For more information or to obtain a Policy and Fee Schedule, necessary forms, and supplies, contact:

Diagnostic Laboratory
N.Y.S. College of Veterinary Medicine
at Cornell
P.O. Box 786
Ithaca, NY 14851
(607) 256-6541

Cheryl A. Stoddart (M.S., Cornell '83) is working toward a Ph.D. in Veterinary Virology, continuing her studies of feline infectious peritonitis. She was assisted in writing this article by Drs. Richard Jacobson, Edward Dubovi, Thomas Reimers, and Alfonso Torres, specialists at the Diagnostic Laboratory.

Pharmaceuticals

further our understanding of the cat's unique sensitivities to drugs. The ability to design rational dosage regimes with drugs depends on information provided by sophisticated pharmacokinetic studies, which are now becoming more commonplace in veterinary medicine. It behooves the practitioner to maintain careful scrutiny of veterinary journals for reported intoxications and to limit his or her armamentarium to those drugs and dosage regimes which have been shown to be safe and efficacious in cats.

Nina Shoulberg is a 1984 graduate of the College of Veterinary Medicine, Cornell University. She obtained her master's degree in immunology at Purdue University prior to entering veterinary school, and is currently an intern at the Animal Medical Center in New York City.

Wayne S. Schwark completed his D.V.M. at Ontario Veterinary College, Canada, in 1965 and his Ph.D. in pharmacology at the Medical College of the University of Ottawa, Canada, in 1970. An Associate Professor of Pharmacology at Cornell, he was given the Norden Distinguished Teacher Award in 1983.

Cornell Feline Health Center
Cornell University
College of Veterinary Medicine
Ithaca, New York 14853

ADDRESS CORRECTION REQUESTED