associated with wound healing in tissues that have been exposed to high concentrations of corticosteroids are exaggerated by a ventral weight-bearing incision. In addition, the large amount of abdominal fat found in patients with Cushing's syndrome, coupled with the location of the adrenals dorsal and medial to the kidneys, makes the ventral midline approach difficult.

The paracostal retroperitoneal approach to adrenalectomy provides adequate exposure of the adrenal gland on that side of the abdomen. This approach avoids the wound-healing problems on a weight-bearing ventral midline incision as well as the difficulties of traversing an abdomen filled with fat. Also, the adrenals, which are dorsolateral to the vena cava and aorta, are more accessible by way of the paracostal approach. Marked disadvantages of the paracostal approach include only being able to explore one adrenal bed (exploration of the opposite side requires closure of the first incision and a second surgical procedure) and inability to evaluate the liver and the balance of the abdomen for metastasis.

Regardless of the surgical approach, an attempt should be made to remove an adrenal tumor as one mass. This is not always possible because of mass friability, and care must be taken to remove small tumor pieces. If a tumor is deemed to be inoperable at surgery, an attempt should be made to debulk the mass as much as possible. Such attempts have resulted in patient improvement.

Patient Management During Surgery. At the time of anesthesia, IV fluids (saline or Ringer's solution) should be administered at a maintenance rate. When the adrenal tumor is recognized by the surgeon, dexamethasone is placed in the IV infusion bottle at a dose of 0.05 to 0.1 mg/lb of body weight.[39, 78] This dose is given over a 6-hour period and repeated four times a day for 2 days before beginning oral prednisone therapy. Alternatively, an infusion of hydrocortisone hemisuccinate can be used (625 μg/kg/h). The hydrocortisone should have both glucocorticoid and mineralocorticoid effects, although we have not been impressed that hydrocortisone provides adequate mineralocorticoid effect. The blood pressure and BUN, serum electrolytes, and blood glucose concentrations should be closely monitored. Adrenal tumors cause decreased secretion of pituitary ACTH, and this causes some atrophy of all three zones of the adrenal cortex. When an adrenal tumor is excised, acute hypoadrenocorticism may result. If hyperkalemia and/or hyponatremia is identified, desoxycorticosterone pivalate (DOCP; 1 mg/lb IM) or oral fludrocortisone acetate (0.01 mg/lb) should be administered.

Although some investigators have recommended treating surgical patients with corticosteroids for 1 or 2 days before the procedure, this protocol is unnecessary and actually potentially harmful. The iatrogenic steroids predispose the patient to fluid balance problems (overhydration) and an increased risk of thromboembolic episodes.

Once the dog is eating and drinking on its own, it should receive 1 mg/lb of prednisone PO twice a day for 2 days. The dosage is then tapered over a period of 2 to 4 months. Fludrocortisone acetate or DOCP is continued if the serum electrolyte concentrations (hyperkalemia ± hyponatremia) indicate that it is needed (40 per cent of the dogs have needed this medication). Its dosage is then tapered similar to that of the glucocorticoid. Glucocorticoid and mineralocorticoid medication must meet individual requirements; "cookbook" approaches must be avoided. ACTH stimulation tests can be used as adjuncts to therapy in determining when to discontinue medication. Any time a patient becomes listless, anorectic, or ill during the tapering process, the glucocorticoid dose may need to be raised and serum electrolytes monitored. If the dog has a normal ACTH stimulation test result, medication is no longer needed.

Results (Prognosis). Of 102 dogs we have diagnosed with functioning adrenocortical tumors, 98 had a unilateral tumor and 63 of those underwent surgery. Four dogs were euthanized at surgery with an inoperable mass. Eighteen dogs died during surgery or soon after as a result of direct complications from the surgery (hemorrhage) or postoperative problems of sepsis or thromboembolism. Forty-one dogs underwent successful surgery—24 had carcinomas and 17 had adenomas. The dogs that underwent successful surgery have a good prognosis if metastasis has not occurred and if they survive the 1- to 4-week postsurgical period. Medical therapy was used in some of the dogs that had surgery (because of recurrence) as well as in those not undergoing surgery. The average life expectancy after surgery is about 46 months. Dogs with adenomas, logically, have a better prognosis. Although the dogs with adenomas do live longer as a group, the tumors in some dogs have been misdiagnosed (adenomas ultimately diagnosed as carcinomas and vice versa). As previously discussed, endocrine tumors are notorious for being difficult to correctly identify and classify. This makes rigid statements to owners unwise.

Inoperable Mass, Poor Anesthetic Risk, or Obvious Metastasis. Surgery cannot be considered for some dogs with Cushing's that have adrenocortical tumors. The reasons for avoiding surgery include finding a large, obviously inoperable mass on radiographs, ultrasound, or CT scan; finding metastatic lesions in the lungs, liver, or other tissue; having a patient that is so debilitated that surgery probably would be harmful; and having an owner who refuses surgery. In these dogs, medical therapy should be considered.

Pituitary-Dependent Hyperadrenocorticism

Hypophysectomy. Surgery to remove the pituitary gland, and thus the source of ACTH in PDH, has been successfully performed in the dog. The procedure has been described,[79-81] but it is not commonly performed.

Adrenalectomy. Removal of both adrenals results in complete resolution of signs attributed to Cushing's. This surgery involves the risk of putting an ill animal with a compromised immune system and poor wound healing through a difficult procedure. As with hypophysectomy, experience minimizes these risks, but such dogs must be permanently treated for hypoadrenocorticism. Because "medical adrenalectomy" is relatively easy to accomplish in dogs with *o,p'*-DDD, the risk of surgery seems unwarranted.

TREATMENT—MEDICAL MANAGEMENT OF CUSHING'S USING *o,p'*-DDD

Pituitary-Dependent Hyperadrenocorticism

Initial Chemotherapy Using *o,p'*-DDD

Background. Since the treatment protocol first suggested by Schechter and others in 1973, chemotherapy with *o,p'*-DDD has become the most common method of treating PDH in dogs. The systemic effects of *o,p'*-DDD, a chemical derived from the insecticide DDT, were first reported in 1949 by Nelson and Woodard. The drug causes severe, progressive necrosis of the zona fasciculata and zona reticularis. Subsequent studies by Kirk and Jensen in 1975 also demonstrated partial or complete necrosis of the zona glomerulosa. The only other major pathologic processes involved the liver,

including moderate to severe fatty degeneration, moderate centrolobular atrophy, and congestion.

Normal dogs given *o,p'*-DDD appear clinically resistant to the adrenocorticolytic effects of the drug. In the 1940s study, four dogs received 50 mg/kg 5 days per week. Two of the four died after 20 and 21 months of therapy, respectively. The third dog was euthanized after 21 months of therapy, and the fourth dog was alive after 38 months on the drug. In the 1975 study, 10 dogs were treated at a dosage of 50 mg/kg/day. One dog died after 124 consecutive days of treatment, and a second died after 147 days. The remaining eight dogs were clinically healthy at the time of euthanasia, after 36 to 150 consecutive days of drug therapy. These dogs, however, had biochemical evidence of decreased adrenocortical reserve and adrenocortical destruction after only 3 to 10 days of therapy. These reports should remind veterinarians of the potent effects of *o,p'*-DDD, that the drug must not be used indiscriminately, and that dogs with Cushing's are more sensitive to the drug than are normals.

A dog diagnosed as having PDH, requiring more than 21 consecutive days of *o,p'*-DDD therapy, must be carefully reevaluated. Possible explanations for resistance are the dog is not receiving or absorbing the drug (it should be administered after meals); the dog has an adrenocortical tumor; the diagnosis is incorrect; and the dog may have a resistant form of PDH.

Initiating Therapy—Loading-Dose Phase. Therapy is begun at home with the owner administering *o,p'*-DDD at a dosage of 50 mg/kg/day, divided and given twice a day (Fig. 118–26). The drug must be administered immediately after the meal has been consumed to enhance absorption.[82] Glucocorticoids are not advised, but the owner should have a small supply of prednisone tablets if an emergency should arise. During this phase of treatment, the dog should be fed one-third of its normal intake twice daily. This decrease in food allotment should enhance the dog's excessive appetite and make it easier for the owner to monitor the pet. The owner should receive thorough instructions on the actions of *o,p'*-DDD and have specific instructions on when the drug should be discontinued. *o,p'*-DDD administration should be stopped when the dog demonstrates reduction in appetite (this might mean just pausing slightly during meal consumption, stopping to drink some water, or stopping in response to the owners voice); the polydipsic dog consumes less than 60 ml/kg/day of water; vomiting occurs; diarrhea occurs; or the dog is unusually listless.[19] The first two indications for stopping the medication are strongly emphasized because they are common. The occurrence of any of these signs strongly indicates that the end point in therapy has been achieved.

Because of the potency of *o,p'*-DDD, the veterinarian is encouraged not to rely on the instructions given to an owner. An owner should not be provided with more than an 8 day supply of *o,p'*-DDD initially. This drug is highly successful in eliminating the signs of Cushing's because of its potency coupled with close communication between owner and veterinarian. Either the veterinarian or a technician should call the owner every day during the loading-dose phase, beginning with the second day of therapy. In this way, the owner will be impressed with the veterinarian's concern and will observe the animal closely. It is wise for the owner to feed the dog two small meals each day, as previously described. The dog's appetite should be observed before each administration of *o,p'*-DDD. If food is rapidly consumed (with or without polydipsia), medication is warranted. If food is consumed slowly or not at all, medication should be discontin-

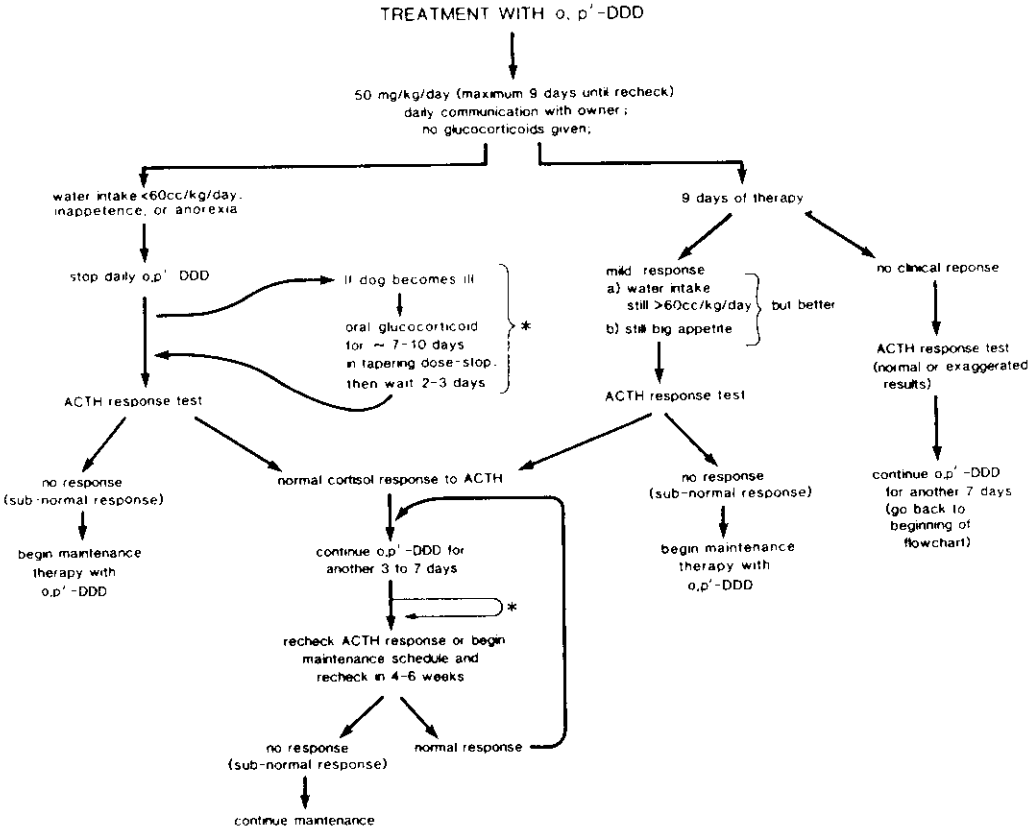

Figure 118–26. Flow chart for the management of hyperadrenocorticism using *o,p'*-DDD. Asterisks indicate similar treatment protocols.

ued until the veterinarian is consulted. The initial loading-dose phase usually is complete when a reduction in appetite is noted or after water intake approaches or falls below 30 ml/lb/day.

If a dog diagnosed with Cushing's syndrome is not polyphagic, the diagnosis and the advisability of treatment must be questioned. The most important monitoring guide in these dogs is their appetite. We do not treat dogs that fail to exhibit excellent to ravenous appetites. Reduction in appetite in a dog receiving *o,p'*-DDD is an indication that overdosage is imminent.

The water intake in polydipsic dogs may decrease to the normal range (less than 30 ml/lb/day) in as few as 2 days or in as long as 35 days (average, 5 to 16 days). Owners should continue to monitor water intake daily until it falls to or below this level. Water intake usually begins to diminish within days of initiating *o,p'*-DDD treatment, but it usually does not become normal until after some reduction in appetite is obvious.

A small percentage of dogs demonstrate mild gastric irritation or systemic signs of illness from the *o,p'*-DDD 1 to 3 days after medication has been started. These signs, in addition to anorexia, include vomiting, diarrhea, weakness, and lethargy. If any of these signs are observed, the medication should be discontinued until the veterinarian can evaluate the dog. If the signs are the result of drug sensitivity and not because the treatment is complete, dividing the dose further may be helpful; discontinuing the medication for a few days may be necessary. It is recommended that *o,p'*-DDD treatment be initiated on a Sunday, so that if illness develops after just a few days, the veterinarian should be available during a regular work week.

Veterinary Monitoring. In addition to making daily telephone calls, the veterinarian should see the dog 8 to 9 days after beginning therapy. At this time, a thorough history and physical examination should be performed and a recheck of the ACTH response test obtained. A recheck of the BUN, serum sodium, and potassium concentrations may be warranted, although these test results are seldom abnormal. Regardless of the clinical response, *o,p'*-DDD should be withheld until the ACTH response test results can be evaluated (see Fig. 118–26).

Goal of Therapy. The goal of therapy is to achieve an ACTH response test result suggestive of hypoadrenocorticism. In our laboratory, successful response to *o,p'*-DDD is indicated by pre- and post-ACTH plasma cortisol concentrations less than 5 μg/dl. Whenever the appetite has declined or the water intake declines below 30 ml/lb/day, the ACTH response test results typically correspond by being dramatically improved.

A dog that has a normal or exaggerated response to ACTH before therapy and a normal response to ACTH after the initial phase of therapy is likely to continue exhibiting some clinical evidence of Cushing's. This is due to the continuing presence of an abnormal pituitary-adrenal axis (see Fig. 118–5). *o,p'*-DDD therapy has no effect on the pituitary abnormality. Mild to severe excesses in ACTH secretion continues, causing the excess cortisol secretion for much of each 24-hour period.[65]

To Continue or Not Continue o,p'-DDD at the Loading Dose. If the dog with Cushing's has a normal or exaggerated response to ACTH after the initial 8 to 9 days of *o,p'*-DDD therapy, medication should be continued. It usually is continued for 3 to 7 additional consecutive days, the shorter period being used for dogs that have shown some significant (albeit inadequate) response. Repeat ACTH response tests are continued every 7 to 10 days until a low post-ACTH plasma cortisol response is achieved. Numerous repeat tests usually are not necessary because most dogs have responded during the initial 5 to 9 days of medication and almost all have responded by the 14th day of therapy.

Average Duration of Daily Loading-Dose o,p'-DDD Therapy. Most dogs with PDH respond within 5 to 9 days (average, 6.4 days). Some dogs respond in as little as 2 or 3 days, and a few have required more than 21 consecutive days of therapy. More than 80 per cent of our patients respond in the initial 5-to-9-day period. Each dog must be treated as an individual. There is no reliable method of predicting the length of time a dog will need to respond or the amount of *o,p'*-DDD necessary to destroy enough of the adrenal cortex for response to be seen.

Concomitant Glucocortoids During the Loading-Dose Phase. The veterinary literature recommends two distinct protocols for the induction or loading-dose phase of *o,p'*-DDD therapy: no concomitant glucocorticoids versus administration of both glucocorticoids and *o,p'*-DDD. Neither method is wrong, and there are advantages and disadvantages with each.

NO GLUCOCORTICOIDS. The advantages of not administering glucocorticoids are as follows: (1) Close communication between veterinarian and client, plus an understanding of when to discontinue medication, clinically, has been successful. (2) If a dog receives glucocorticoids, it is not possible for an owner or a veterinarian to know if and when an adequate amount or too much *o,p'*-DDD has been administered. (3) Because the end point cannot be seen clinically, the clinician must rely on the ACTH stimulation test. To perform this test, all glucocorticoid therapy must be withdrawn for 1 or 2 days to avoid having the cortisol assay detect the oral rather than the dog's glucocorticoid concentrations. (4) If glucocorticoids are needed because of *o,p'*-DDD overdosage, a crisis may develop after their withdrawal. (5) Simultaneous administration of glucocorticoids did not eliminate clinical signs of cortisol deficiency in many dogs treated with both drugs. (6) It seems easier to determine if glucocorticoid therapy is needed during treatment. The incidence of *o,p'*-DDD overdosage with clinical signs is less in dogs that do not receive simultaneous glucocorticoids than in dogs that do receive the drug because the owners can appreciate mild clinical changes early in therapy and stop the medication before the problem becomes severe. Transient need for glucocorticoids has occurred in only 5 per cent of our dogs (versus 35 per cent in glucocorticoid-treated dogs) and permanent Addison's, in only 2 per cent of our dogs (versus 5.5 per cent of glucocorticoid-treated dogs). If signs of cortisol deficiency do develop, the clinician can be certain that the end point in therapy has been achieved. An ACTH response test may be performed immediately and the dog then placed on glucocorticoids. Response to glucocorticoid medication would also be diagnostic of surpassing the desired end point of therapy.[79,83]

GLUCOCORTICOIDS. The advantages of using glucocorticoids are as follows: (1) Use of both glucocorticoids and *o,p'*-DDD has been quite successful. (2) The number of dogs with one or more adverse effects to *o,p'*-DDD is significant, and administration of glucocorticoids minimizes or eliminates these signs. (3) Resolution of clinical signs was obvious to owners despite the glucocorticoid therapy. (4) Oral glucocorticoids do not interfere with assays if discontinued the day of testing.[83]

Need for Glucocorticoids. If signs of anorexia, vomiting, diarrhea, weakness, or listlessness develop, glucocorticoid therapy is warranted. If the dog has received no glucocorticoids during the initial phase of *o,p'*-DDD therapy, they

should be started. If the dog has been treated with glucocorticoids, the dose needs to be increased. This is true during the maintenance phase of therapy and if the well-controlled dog undergoes major stress (e.g., illness, trauma, elective surgery). Prednisone is administered at 1 mg/lb/day for 2 days. If signs have developed as a result of *o,p'*-DDD overdosage, the dog usually shows clinical improvement within hours of initiating prednisone therapy. If oral therapy is not possible because of vomiting, parenteral steroids are warranted. After 2 days of therapy, the prednisone dosage is tapered over 1 to 3 weeks and then stopped. Recurrence of signs demands reinstitution of therapy or raising the dosage.

Planned Induction of Permanent Hypoadrenocorticism. Favorable results associated with accidental induction of permanent hypoadrenocorticism have prompted the suggestion that all dogs with hyperadrenocorticism undergo a treatment schedule aimed at the complete destruction of the adrenal cortices. Substitution therapy for the ensuing adrenocortical insufficiency would continue for the life of the dog. The treatment protocol involves 25 consecutive days of *o,p'*-DDD in a dose of 50 to 75 mg/kg daily and as much as 100 mg/kg daily for toy breeds. The daily *o,p'*-DDD dosage is divided into three or four administrations per day with food to minimize neurologic complications and ensure good intestinal absorption. Lifelong cortisone (0.5 mg/lb twice a day) and mineralocorticoid (Chapter 119) substitution is begun on the 3rd day of *o,p'*-DDD administration. The cortisone dosage should be tapered after the 25-day *o,p'*-DDD schedule has been completed.[84, 85]

There are several disadvantages to this protocol. First, about 33 per cent of dogs so treated relapse with Cushing's within the first year alone, suggesting that periodic ACTH stimulation testing is necessary, just as with traditional modes of treatment. This treatment protocol would be considerably more expensive than long-term treatment with *o,p'*-DDD because treatment of Addison's disease is usually expensive. Finally, the dog with well-controlled Cushing's receiving *o,p'*-DDD several times a week or month is not in danger if medication is not given, whereas the dog with hypoadrenocorticism must receive its medication to live.

Need for Both Glucocorticoids and Mineralocorticoids. *o,p'*-DDD is reported to spare the zona glomerulosa and, therefore, mineralocorticoid secretion. Dogs that develop signs of weakness, anorexia, and/or vomiting without electrolyte imbalances require immediate glucocorticoid therapy. Electrolyte disturbances suggestive of deficient mineralocorticoids (hyperkalemia and/or hyponatremia) have resulted from *o,p'*-DDD administration; these dogs require both glucocorticoid and mineralocorticoid therapy (Chapter 119). This finding is extremely rare (seen in less than 2 per cent of our closely monitored dogs). Glucocorticoid deficiency usually is transient in *o,p'*-DDD–treated dogs. Addison's disease (deficiency of both glucocorticoids and mineralocorticoids) in *o,p'*-DDD–treated dogs usually is permanent.

Time Sequence for Improvement in Signs and Biochemical Abnormalities. Dogs with *o,p'*-DDD–treated PDH usually respond quickly. The most obvious and rapid response is the reduction in appetite, water intake, and urine output seen during the first 5 to 9 days of therapy. Many owners comment that they see an increase in activity during the 1st or 2nd week of treatment. Other signs take longer to dissipate. Muscle strength improves within weeks, as does reduction in the potbellied appearance.

Alopecia, thin skin, acne, calcinosis cutis, and panting often take 3 to 6 months for significant improvement to be noted. Dogs with hair coat abnormalities may go through a phase of severe seborrhea associated with a terrible hair coat or worsening alopecia and pruritus that may last for 1 or 2 months before the hair coat shows significant improvement. Some dogs go through a phase of "puppy hair coat" before the normal adult coat returns. A few dogs have dramatic changes in coat color after successful therapy (Fig. 118–27). Female dogs may begin an estrous cycle within 1 or 2 months of completing successful treatment.

The external appearance of a dog with Cushing's syndrome improves with therapy before internal changes are noted. The liver enzymes and cholesterol may take 6 to 18 months to improve. These two parameters may not improve, however, because of the mild but continuing effects *o,p'*-DDD has on the liver (resulting in abnormal serum enzyme activities) and because in people, *o,p'*-DDD has been demonstrated to cause increases in serum cholesterol concentration.[86, 87] Six to 18 months may be required for return of normal blood pressure. Urinary tract infections may resolve quickly or linger because of pyelonephritis, bladder retention of urine, calculi, or other problems.

Failure to Respond to o,p'-DDD. It is uncommon for *o,p'*-DDD to fail to help a dog with PDH. The drug is potent, and its effect on destroying the zona fasciculata and zona reticularis is consistent. There are several reasons for apparent treatment failures. (1) A dog thought to have PDH may indeed have an adrenocortical tumor (adenoma or carcinoma). Adrenocortical tumors are relatively resistant to the cytotoxic effects of *o,p'*-DDD. (2) The drug itself may not be potent, and replacing the owner's tablets with *o,p'*-DDD obtained from a new or different bottle may solve an appar-

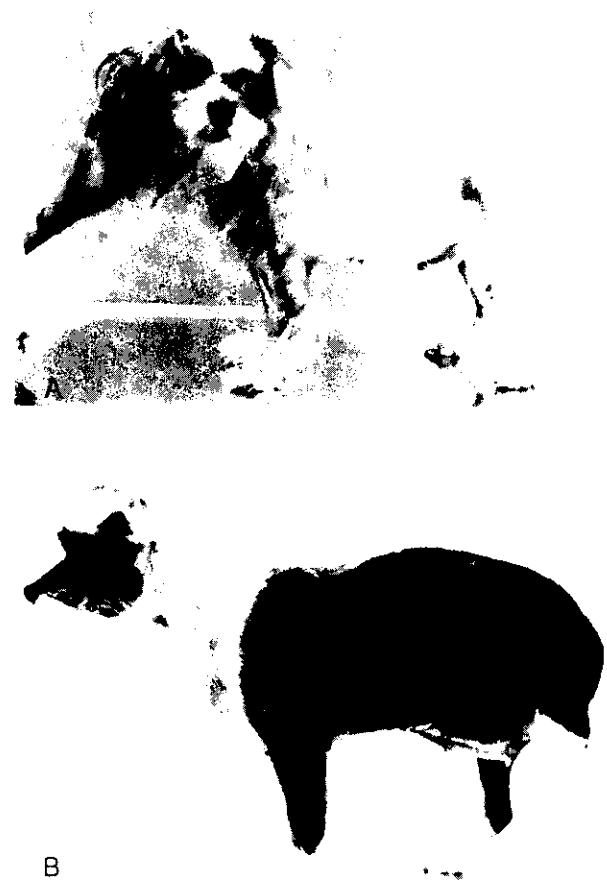

Figure 118–27. Small mixed-breed dog with PDH before therapy (*A*) and 2 months after *o,p'*-DDD therapy, showing dramatic hair coat color change (*B*).

ent treatment failure. (3) The drug may not be given with food, and absorption may be adversely effected (fatty meals improve absorption the most, but when given with any food, absorption is enhanced). (4) There may be concern about a treatment failure after 14 days without response, but a small percentage of dogs require 30 to 60 consecutive days of therapy, or 100 to 150 mg/kg/day rather than the usual initial dosage of 50 mg/kg/day. (5) Dogs that are diagnosed incorrectly fail to respond. (6) The dog may have iatrogenic Cushing's syndrome.

The various causes of an apparent treatment failure must be considered before abandoning the use of *o,p'*-DDD. If treatment failure has occurred, the 25-day induction of hypoadrenocorticism, ketoconazole therapy, or bilateral adrenalectomy should be considered. Other medical therapies can also be considered (each is described later in this chapter).

Therapy of Concurrent Diabetes Mellitus and Cushing's Syndrome

INITIAL DIAGNOSIS AND TREATMENT. If both diagnoses are suspected at initial examination, insulin therapy should be initiated while completing the diagnostic evaluation for Cushing's. Most of these dogs require large doses of insulin. Those that need a conservative or low dose of insulin are the best candidates for no longer needing insulin after *o,p'*-DDD therapy. Attempts at extremely good control of the diabetes should not be undertaken until the Cushing's is controlled or until that diagnosis is refuted.

o,p'-DDD DOSAGE. These dogs should be treated in the same manner as any dog with PDH (*o,p'*-DDD at 50 mg/kg/day and no glucocorticoids). It is recognized, however, that Cushing's results in insulin antagonism. Therefore, successful reduction in the circulating cortisol concentrations should reduce insulin requirements. Failure to recognize this effect could result in hypoglycemic reactions.

TREATMENT AND MONITORING PROTOCOL. The complicated nature of treating this combination of diseases should be carefully explained to the owner. Both owner and veterinarian must be aware that as the dog receives *o,p'*-DDD, the Cushing's should progressively resolve, and the diabetes management usually changes as well. Owners should be asked to catch a small amount of urine for glucose monitoring at least three times daily from their pet during the loading-dose phase of *o,p'*-DDD therapy. Any time a urine sample is found to be negative for glucose, the subsequent insulin dose should be reduced by at least 10 to 20 per cent. The hyperadrenocorticism in most of these dogs is controlled in the expected 5 to 9 days.

The ACTH stimulation test should be rechecked within 7 days of initiating the *o,p'*-DDD to recognize the end point and to avoid overdosage. The recheck protocol for these dogs should proceed as follows: (1) owner feeds pet at home; (2) dog brought to veterinary hospital in the morning (7 to 9 A.M.); (3) blood glucose measured and owner observed as he or she administers insulin; (4) blood glucose monitored every hour throughout the day; (5) 1 to 2 hours before owner is to pick up the pet in the late afternoon, ACTH stimulation test is begun and completed. This protocol provides an opportunity to answer two critical questions: What effect has *o,p'*-DDD therapy had on diabetes control (blood glucose, insulin dosage), and what effect has it had on the hyperadrenocorticism?

PROGNOSIS. About 10 per cent of these dogs require no insulin after successful therapy. An additional 60 to 70 per cent require significantly less insulin and their diabetes mellitus is easier to control. The insulin requirement in the remaining dogs may not be reduced by control of the PDH, but that insulin should be more effective in lowering blood glucose concentrations. If none of these three results are observed, the original diagnosis of hyperadrenocorticism must be questioned.

o,p'-DDD Therapy of Dogs with Functioning Adrenocortical Tumors

Background. The ideal treatment for a dog with a functioning adrenocortical tumor causing hyperadrenocorticism is surgical removal of the tumor, curing the dog. It is appreciated, however, that some of these dogs have inoperable tumors, some have metastases at the time of diagnosis, some are too debilitated for this type of major surgery, and some have owners who will not allow surgery for any of a variety of reasons. *o,p'*-DDD treatment of dogs with PDH was compared with that in dogs with adrenocortical tumors. Using similar doses of *o,p'*-DDD (50 mg/kg/day initially), it was demonstrated that dogs with adrenocortical tumors were relatively resistant to the adrenocorticolytic effects of the drug (Fig. 118–28).[88] Some dogs with adrenocortical tumors, however, respond to the traditional doses, and those that appear resistant often respond to higher dosages.[89]

Protocol. The recommended treatment of dogs with adrenocortical tumors with *o,p'*-DDD would be to follow the protocol for PDH, using the same initial dose of 50 mg/kg/day. If, after the initial 7 to 10 days of treatment, the ACTH response test result demonstrates improvement but not values in the ideal less than 5 μg/dl range, the original 50 mg/kg/day schedule should be continued. This second 7-to-10-day phase should again be assessed with an ACTH stimulation test.

Lack of significant improvement in ACTH response testing after the initial 7-to-10-day loading-dose phase would indicate a need for continuing the *o,p'*-DDD at twice the dosage for an additional 7 to 10 days. Duration of the loading-dose phase and dosage requirement would then be determined on an individual basis.

Results. Using this protocol, 43 per cent of 32 dogs had abnormally exaggerated ACTH response test results after the first 10 to 14 days. Despite concurrent glucocorticoid therapy, 60 per cent suffered adverse effects sometime during treatment as a result of direct drug toxicity associated with high-dose *o,p'*-DDD or low cortisol concentrations or both. More than 60 per cent of the *o,p'*-DDD–treated dogs with adrenocortical tumor were considered to have a good to excellent response.[89]

***o,p'*-DDD Resistance and Histologic Evaluation.** There is little doubt, from clinical response to therapy, that adrenocortical tumors are relatively resistant to *o,p'*-DDD compared with the adrenocortical hyperplasia associated with PDH. This concept is supported with review of histologic findings from these two groups of dogs. Histologically, the adrenal cortices, specifically the zona fasciculata, of dogs with *o,p'*-DDD–treated PDH demonstrates collapse, necrosis, and hemorrhage, with fibrosis, atrophy, and degeneration in dogs that received the drug chronically. In the latter group, hyperplastic nodules occasionally are noted. In many, adrenocortical destruction is noted and hyperplasia is presumed to have been present.

Dogs with adrenocortical tumors similarly treated with *o,p'*-DDD, by contrast, usually have a clear description of tumor histology. The pathologist usually provides an impression with respect to the malignant potential of the tumor (adenoma or carcinoma).[88, 89] Most of these evaluations con-

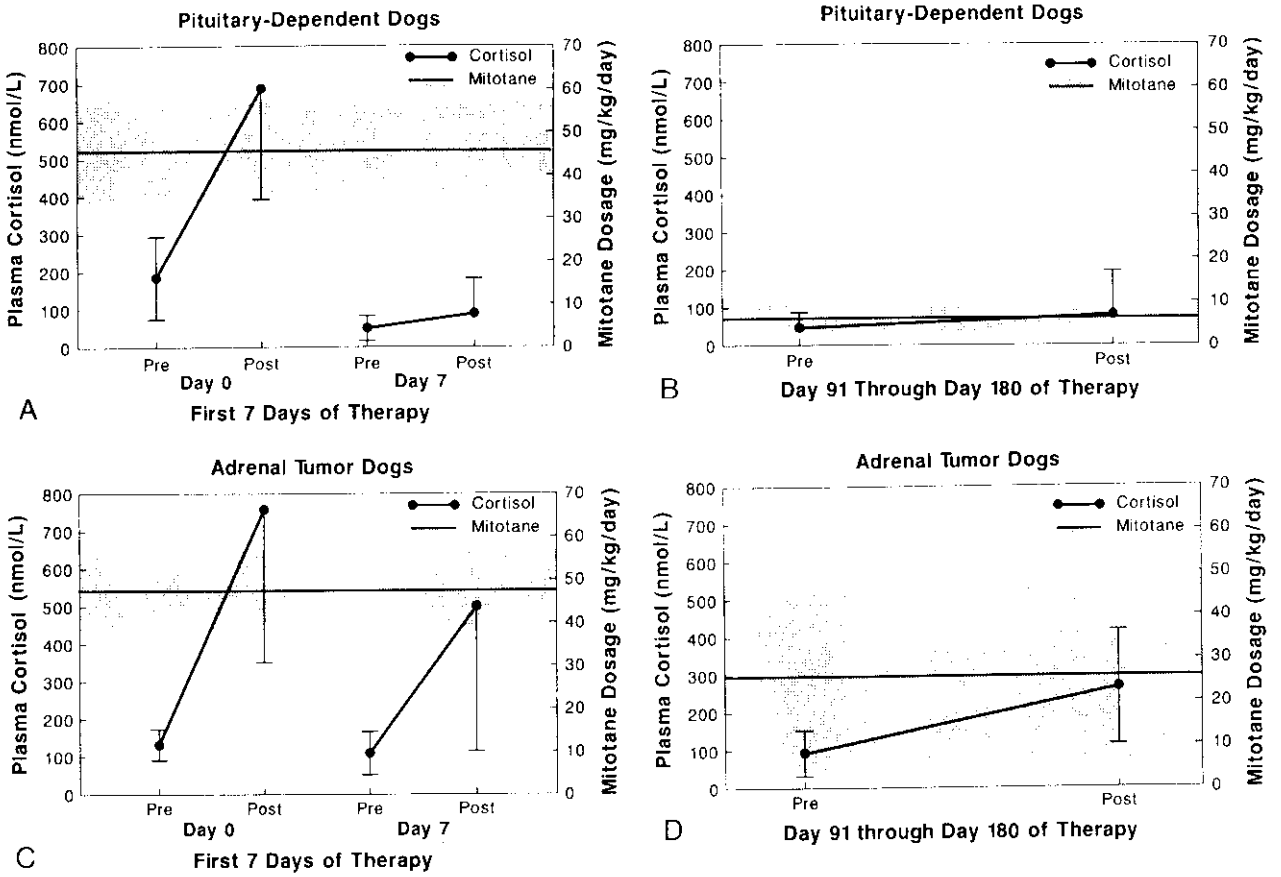

Figure 118–28. ACTH response test results from a group of 12 dogs with PDH before and after 7 days of *o,p'*-DDD treatment (*A*) and again after 180 days of treatment (*B*) compared with results of the same tests from a group of 12 dogs with hyperadrenocorticism resulting from adrenocortical tumors that were matched for age, body weight, and dose (*C* and *D*). The results show that dogs with PDH are more sensitive to *o,p'*-DDD than are dogs with adrenocortical tumors.

tain no mention of adrenal destruction or necrosis, support to the concept that these tumors are more resistant to the lytic effects of the drug.

Maintenance (Long-Term) Therapy with o,p'-DDD

Background. Once the initial daily protocol with *o,p'*-DDD completes adequate destruction of the adrenal cortex, as determined by clinical signs (reduced appetite and water intake) and/or ACTH stimulation test results, maintenance therapy should begin. In dogs with PDH, *o,p'*-DDD has not affected the abnormal pituitary, and excessive ACTH secretion continues or becomes exaggerated.[65] Failure to continue *o,p'*-DDD therapy will result in regrowth of the adrenal cortices and return of clinical signs. This exacerbation of the disease usually occurs within 3 to 24 months of stopping therapy, although some dogs demonstrate recurrence within weeks.

Protocol. Maintenance therapy involves choosing a regimen and altering that regimen as required. Dogs that respond to daily *o,p'*-DDD therapy within 9 days or that have a post-ACTH plasma cortisol concentration less than 2 μg/dl are classified as sensitive and begin a maintenance schedule of 25 mg/kg of *o,p'*-DDD every 7 days. Those that initially require more than 10 days of therapy or with a post-ACTH plasma cortisol concentration greater than 5 μg/dl are classified as resistant and receive 50 mg/kg every 7 days. In either situation, the dosage is divided into two to four treatments per week.

An ACTH response test is performed 1 and 3 months after beginning the maintenance therapy. If the plasma cortisol concentration after ACTH administration begins to rise to or above 4 to 5 μg/dl, the *o,p'*-DDD dosage is increased. Some dogs remain stable for months or years on conservative dosages, whereas others receive rather large doses. It is important to tailor treatment to the needs of each dog. Return of clinical signs suggestive of hyperadrenocorticism should be managed by performing an ACTH stimulation test to confirm disease exacerbation, followed by raising the dose of *o,p'*-DDD. Obvious recurrence of Cushing's should be managed with daily *o,p'*-DDD after ruling out other diseases with signs that mimic Cushing's, such as kidney disease and diabetes mellitus (see Table 118–6).

Long-Term Monitoring. Many dogs treated with *o,p'*-DDD remain stable on maintenance treatment. It is recommended that these dogs be rechecked with an examination and an ACTH response test every 3 to 4 months. Test results allow the veterinarian to adjust maintenance dosages if subclinical problems are occurring. Whenever the post-ACTH plasma cortisol concentration exceeds 5 μg/dl, the dose of *o,p'*-DDD should be increased. Whenever listlessness and anorexia are associated with low plasma cortisol results, the *o,p'*-DDD should be transiently discontinued or the dose should be reduced.

Stress or Illness. Dogs receiving *o,p'*-DDD and undergoing stress (illness, trauma, elective surgery) should be treated with glucocorticoids. The adequately treated dog with PDH has sufficient adrenal reserve for day-to-day living but not enough to handle major stress.

o,p'-DDD Overdosage

Overdosage with *o,p'*-DDD is common. Most overdosed dogs (20 to 50 per cent of treated dogs) have mild and transient signs, especially after glucocorticoid treatment. A minority of dogs (less than 2 per cent) develop permanent Addison's disease. Permanent disease usually is associated with hyperkalemia, hyponatremia, and low plasma cortisol concentrations before and after ACTH. Most of these dogs require both mineralocorticoid and glucocorticoid treatment for life.

In the more typical and mild forms of overdosage, the *o,p'*-DDD–treated dog becomes weak, anorectic, lethargic, ataxic, or develops vomiting and/or diarrhea. Serum chemistry profiles, CBC, and urinalysis from these dogs often are unremarkable. The easiest method of confirming the diagnosis is to treat the dog with prednisone. Clinical improvement in 1 to 3 hours (sometimes 6 to 12 hours are required) confirms that an overdosage of *o,p'*-DDD has occurred. Treatment with *o,p'*-DDD is withheld. The prednisone is initially administered to effect (to eliminate all signs). The prednisone dose is then slowly tapered over 2 to 6 weeks. As long as the dog needs prednisone, *o,p'*-DDD is withheld. When the prednisone is discontinued and the dog is stable on no treatment for an additional 2 to 4 weeks, *o,p'*-DDD should again be given but at a lower dosage.

Prognosis—o,p'-DDD–Treated Dogs with PDH

Pituitary-dependent hyperadrenocorticism is a serious disorder. We have been able to monitor more than 500 treated dogs. Of the dogs that have died, the life expectancy averaged 29.7 months. These included dogs that lived only days and several that lived longer than 10 years. It appears that good owner observation improves the prognosis. Relapses were common. More than 40 per cent of the dogs had at least one period in which signs of hyperadrenocorticism recurred, requiring a brief repeat of daily *o,p'*-DDD therapy or an increase in the maintenance dose. Forty-five per cent of the dogs that died had a problem that could have been or was related to the hyperadrenocorticism (e.g., thromboembolism, congestive heart failure, infection, pancreatitis, diabetic ketoacidosis, growing pituitary tumor). Episodes of *o,p'*-DDD overdosage were also common. Five per cent of the dogs were mildly overdosed during the induction phase of therapy. A total of 32 per cent were overdosed sometime during therapy. Death from overdosage was seen in less than 2 per cent of the dogs.

TREATMENT—MEDICAL MANAGEMENT WITH KETOCONAZOLE

Background

Ketoconazole (Nizoral), an imidazole derivative, is an orally active broad-spectrum antimycotic drug. At high dosages, the drug also affects steroid biosynthesis. The endocrine potencies of the substance result from an interaction of the imidazole ring with the cytochrome P-450 component of various steroidogenic enzyme systems. *In vivo*, the administration of low doses of ketoconazole leads to a significant reduction in serum androgen concentrations, whereas at higher doses, cortisol secretion is suppressed.[90] This inhibitory effect of ketoconazole on steroid biosynthesis has led to its therapeutic use in the treatment of advanced prostatic cancer, hirsutism, precocious puberty, and Cushing's syndrome.[91]

Protocol in Canine Cushing's Syndrome

The drug is administered initially at a dose of 5 mg/kg twice daily for 7 days. If no problems with appetite or icterus are noted, the dose is increased to 10 mg/kg twice daily. After 14 days, an ACTH response test should be completed, in addition to a complete history and physical examination. If the Cushing's is not controlled, the dosage is increased to 15 mg/kg twice daily. We have not used larger doses. Some dogs can be maintained at the 10 mg/kg, b.i.d., dose and others at the 15 mg/kg dose indefinitely. Dose requirement is determined from owner opinion, physical examination results, blood chemistries, and ACTH stimulation test monitoring. The goal in ACTH stimulation results are pre- and post-ACTH plasma cortisol concentrations less than 5 μg/kg. Most dogs do not achieve clinical remission at doses less than 30 mg/day.

Results

We have evaluated the use of this drug in more than 50 dogs with naturally occurring hyperadrenocorticism, including dogs with pituitary-dependent disease as well as dogs with adrenocortical tumors. Laboratory data demonstrate that about 80 per cent of treated dogs have a rapid reduction in serum cortisol concentration and cortisol responsiveness to ACTH (Fig. 118–29). In the dogs treated for more than 2 months, there has been significant improvement in their clinical condition, as evidenced by a reduction in water intake, urine production, appetite, panting, and other signs. Regrowth of hair and return of muscle strength are also noted. Signs of toxicity seldom have developed. Signs of overdosage usually are due to hypocortisolism.[92]

It appears that 20 to 25 per cent of dogs fail to respond to the drug as a result of poor intestinal absorption. Although this is true for some dogs that fail to improve, other explanations must be entertained because some dogs demonstrate a paradoxical increase in pre- and post-ACTH plasma cortisol concentrations when receiving ketoconazole. Plasma cortisol concentrations return to pretreatment levels when the drug is discontinued. The major drawbacks (Table 118–7) to the use of this drug are its expense and failure to respond and the fact that it must be administered twice daily indefinitely.

Indications

Ketoconazole, with its low incidence of toxicity and negligible effects on mineralocorticoid production, may be an attractive (albeit expensive) alternative in the medical management of canine hyperadrenocorticism (see Table 118–7). Ketoconazole is readily available, and because effect is a result of enzyme blockage, it is completely reversible. It may be used as an alternative to *o,p'*-DDD in the medical management of dogs with malignant, large, or invasive adrenal tumors if surgical intervention is not an option but palliative therapy is desired. We use ketoconazole most frequently in the preoperative stabilization and improvement of surgical candidates. Some dogs (extremely rare in our experience) do not tolerate *o,p'*-DDD at any dose, and ketoconazole can be tried. Despite the number of screening tests for hyperadrenocorticism, the clinician may use response to therapy as a diagnostic aid. In this situation, ketoconazole is an enzyme blocker with no long-term effects. One can assess its effect without causing tissue damage.