GLUCOCORTICOIDS
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For good reasons, glucocorticoids (GLs) have been the cornerstone of immunosuppressive therapy in humans and animals. Their impact on immunomodulation reflects inhibition at every stage of the immune response, including innate, acquired, and cell-mediated responses; the humoral response, however, is minimally directly affected. However, understanding their safe and effective use is complicated by their complex physiologic effects. They are among the most important hormones in the body, responsible for normal support and support during times of stress.

Molecular Mechanism of Action: In the future, new glucocorticoids are apt to be “designer” drugs. The design reflects changes in drug structure that will cause them to be more selective in directing their effects. An understanding of the current mechanism of action is necessary to appreciate potential changes. The effects of GLs are generally recognized to be dose dependent. GLs must pass through target cell membranes where they bind to intracellular receptors which are also complexed with heat shock proteins in the cytoplasm of the target cell. Binding of the GL to the receptors causes the receptor to dissociate from the heat shock protein; the GL and receptor then move into the nucleus where the GL binds to specific DNA sequences or receptors called GL responsive elements (GRE). The GL can now influence gene expression. Binding to GRE in the promoter regions of GL-regulated genes (positive GRE) facilitates gene expression (transactivation) whereas binding negative GRE (nGRE) represses genes and their expression (referred to as transrepression). The GL receptor (GR) generally has a lower affinity for nGRE compared to pGRE. Transactivation generally involves binding to specific DNA recognition leading to direct transcription; accordingly, these activities are also referred to as cis. This is in contrast to repressive activities which tend to involve (indirect) protein-protein couplings that then modulate other transcription factors (eg, NFk-B, AP-1, STAT-5α or NF-AT) such that their activity is modified; these activities are referred to as trans. The largely undesirable metabolic effects associated with long-term GLC therapy appear to be mediated by transactivation or cis activities, whereas desirable anti-inflammatory and immunomodulatory effects appear to reflect transrepression or trans activities through n-GREs. Because GL-nGRE interactions appear to occur at lower concentrations compared to p-GRE effects, limiting GL use to lower doses should decrease undesirable side effects. Alternative pathways increasing trans effects can be expected to be specifically targeted by “designer or dissociative GLC” that are more potent for transrepression rather than other actions. Dexamethasone and prednisolone are examples of a “symmetrical” GLC, characterized by equal binding affinity for both cis and trans actions (or trans repression and activation). In contrast, medroxyprogesterone acetate is predominately transrepressive.

Glucocorticoid Resistance: Human patients may fail to respond to GLs. Causes include poor compliance and poor bioavailability as well as GL resistance (both familial and iatrogenic). Resistance may reflect decreased receptor number (e.g., down-regulation) or affinity. Reversible down-regulation is a documented sequel to GL treatment (demonstrated in T-lymphocytes of humans receiving GL to treat host-versus-graft rejection). This type of resistance might be avoided by higher doses of GL, including pulse dosing. A relative imbalance of GL receptor isoforms may also be responsible: the α isoform binds to GLs, DNA and transcription factors, thus modulating transcription, whereas the β isoform binds to DNA, but not other ligands and fails to activate transcription, thus potentially interfering α isoform actions. Some human patients with severe IBD that fail to respond to high doses of GLs have poor antiproliferative response by blood T-lymphocytes whereas responders completely inhibit. A similar situation has been demonstrated for other chronic allergy-based diseases, such as asthma or rheumatoid arthritis, and renal allograft rejection. Other factors that may contribute to poor response to GLC include overexpression of the
multidrug resistance gene (MDR1 polymorphism), which might be reversible by co-administration of cyclosporine, an inhibitor of P-glycoprotein.

**Physiologic effects of glucocorticoids.** Glucocorticoids support the body in times of stress (think flight or fight). The metabolic effects of glucocorticoids are particularly profound and help explain the typical presentation of a patient with spontaneous or iatrogenic hyperadrenocorticism. The goal of corticosteroids in general is to maintain the body for stress, including fight or flight. For glucocorticoids, a major role is maintaining plasma glucose to assure that the brain receives the energy it needs to function. The CNS is the only organ that does not require insulin for glucose to enter the cell. As such, the body, through glucocorticoids, makes sure the CNS is fed. Protein will be broken down (a peripheral catabolic effect). Muscle atrophy occurs, the skin becomes thin, and wounds do not heal. However, in the liver, the deaminated protein will be converted to glucose (which is released) and glycogen (which is stored for later release). As such, glucocorticoids are anabolic in the liver. Carbohydrate formation (glucose) increases while tissue utilization of glucose is impaired (an anti-insulin effect). Hyperglycemia and glycogen storage in the liver occur. Lipids are also impacted: although not directly converted to glucose, they are used to generate energy. They also are redistributed: animals often have fat pads develop on their hind end; the pendulous abdomen reflects not only weakened abdominal muscles, but also accumulation of belly fat. Triglycerides and cholesterol may be increased. Contributing to flight or fight is an increased red blood cell mass. This reflects increased production as well as a decrease in RBC phagocytosis (part of the normal life span of the red blood cell; inhibiting this effect is particularly important in patients with immune-mediated hemolytic anemia). Typical of glucocorticoids, whether endogenous or exogenous, is the stress leukogram: neutrophilia which reflects demargination of neutrophils into the blood, and redistribution of lymphocytes and eosinophils out of the circulating blood.

Critically important to the flight or fight response are the permissive effects of glucocorticoids which occur at physiologic (as well as pharmacologic) doses. A physiologic dose is low and is more likely to mimic endogenous secretions. The permissive effects of glucocorticoids largely reflect the ability to facilitate the response of the body to adrenergic signals. These include alpha mediated peripheral vasoconstriction, which maintains vascular tone (while distributing blood to skeletal muscles in anticipation of flight), increasing cardiac output through increased heart rate and contractility (beta one effects) and increasing oxygenation of tissues by assuring bronchodilation (beta 2 effects). These effects do not rely on synthesis of effect proteins and as such occur rapidly. These effects, for example, are the reason that asthmatic cats should be treated with glucocorticoids simultaneously with bronchodilators and why patients with hypoadrenocorticism, or relative adrenal insufficiency (i.e., critical care patients) must receive physiologic concentrations of glucocorticoids to avoid cardiovascular collapse. Other organs impacted particularly by glucocorticoids include the **respiratory tract**, with the permissive effects on bronchodilation critical. The impact of glucocorticoids on normal **cardiovascular physiology** is just as important as the impact of mineralocorticoids on sodium and water retention. In the face of deficiency, the loss of vascular tone will result in cardiovascular collapse which will be exacerbated by loss of cardiac efficiency in terms of rate and contractility. An important side effect of glucocorticoids reflects their permissive effects combined with mineralocorticoid effects: patients with early congestive heart failure may develop clinical failure, or their disease may worsen due to increased afterload (vasoconstriction) and, if mineralocorticoid effects, increased sodium and water retention. The latter might be offset by using an aldosterone antagonist (i.e., spironolactone) diuretic, and the use of angiotensin converting enzyme inhibitors might be indicated. Dexamethasone may have less risk of cardiac abnormalities because it does not cause sodium retention. A potentially under-recognized impact of glucocorticoids is on thrombosis. As a specific Cox-2 inhibitor, glucocorticoids will inhibit prostacyclin, which otherwise would offset the thrombogenic effects of Cox-1 mediated thromboxane. In the presence of high glucocorticoids, prostacyclin is maximally inhibited, which may allow thromboxane mediated platelet aggregation to go unchecked, leading to thrombosis. The effects of glucocorticoids on **bone** include direct chondrocyte death, and can lead to cartilage destruction.
particularly with long term use. The effects of glucocorticoids on blood glucose and CSF production were discussed. However, an important CNS effect not previously mentioned is the euphoric effect that is evident when glucocorticoids are administered. The euphoria is associated with increased appetite (which is among the reasons they have been used in “ADR” patients). These responses, however, can mask clinical signs of disease, misleading the owner into thinking the patient is doing well. In the gastrointestinal tract, glucocorticoids (by virtue of their effect on cyclooxygenase) can increase the risk of GI ulceration. This is more likely to occur in patients that already are at risk or in patients that have had a spinal injury that results in altered blood flow to the GI tract. However, glucocorticoids are not as ulcerogenic as NSAIDs. The impact of glucocorticoids on calcium and sodium/chloride in the GI tract were previously discussed. In the reproductive tract, glucocorticoids induce parturition or cause abortion in a variety of species, particularly cows and horses, and as such, should be avoided in pregnant animals.

**Endocrine**: Glucocorticoids are anti-insulin. Patients in a state of hyperadrenocorticism are more apt to develop diabetes mellitus (which may not resolve with discontinuation of therapy), are largely resistant to insulin treatment, and will disrupt diabetic control in previously controlled patients.

**Electrolytes**: Glucocorticoids cause loss of water. This reflects an anti-antidiuretic hormone effect at the level of the collecting tubule, but also centrally. Part of this latter effect reflects centrally-mediated increased water consumption. If the glucocorticoid has mineralocorticoid effects, sodium and water retention will occur in the kidney, ileum and ciliary body of the eye and probably CSF. Serum calcium also is impacted by glucocorticoids which act to deplete the body of calcium by preventing its absorption, mobilizing it from bone and increasing urine excretion. This can cause osteoporosis (a primary human problem because of the long time it takes to develop) but can be of therapeutic benefit in states of life threatening hypercalcemia, such as might accompany a secondary hyperparathyroidism state accompanying some neoplasias.

**Inflammation and immunomodulation**: For lymphocytes, GLs cause up or down regulation of up to 2000 genes involved in the regulation of the immune response, targeting both early and late phases of inflammation. GLs 1. reduce circulating lymphocytes; 2. alter lymphocyte response to mitogens and antigens (T lymphocytes are inhibited to a greater degree than B lymphocytes); 3. alter white blood cell function; 4. inhibit edema, fibrin deposition, leukocyte migration, phagocytic activity, collagen deposition, and capillary and fibroblast proliferation (generally through inhibition of lymphokines and other soluble mediators of inflammation); 5. induce annexin I, which inhibits phospholipase 2, thus blocking the release of arachidonic acid and its subsequent conversion to eicosanoids (i.e., prostaglandins, thromboxanes, prostacyclins, and leukotrienes); 6. preferentially inhibit transcription of cyclooxygenase 2, the inducible form of cyclooxygenase, thus decreasing the risk of toxicity. 7. induce protein MAPK phosphatase 1, which, through various actions activates a number of proteins important in the signaling of cytokines; 8. inhibit transcription of NF-k-B. **Effect on immune cells**: GL 9. inhibit release of tumor necrosis factor and interleukin-2 (IL-2) from activated macrophages. 10. inhibit release of platelet-activating factor from leukocytes and mast cells; 11. inhibit macrophage migration-inhibition factor, (macrophages migrate away from the affected area); 12. block IFN- released from activated T cells (needed to facilitate antigen processing by macrophages). 13. inhibit synthesis and release of IL-1 by macrophages thus, suppressing activation of T cells, and IL-2 synthesis by activated T cells. 14. inhibit bactericidal and fungicidal actions of macrophages; 15. alter synthesis of and biologic response to collagenase, lipase, and plasminogen activator. 16. Inhibit the inducible form of nitric oxide synthase (iNOS). Interestingly, despite their effective immunosuppressant effects, glucocorticoids have been associated with allergic reactions, including type I acute anaphylaxis.

**Central Nervous System**: GL: 1. Maintain adequate plasma concentrations of glucose for cerebral functions, maintain cerebral blood flow, and influence electrolyte balance; 2. Decrease formation of cerebrospinal fluid; 3. influence mood (including "euphoria"), behavior, and brain excitability. 4. regulate neuronal excitation; 5. induce glutamine synthetase in both the central and peripheral nervous systems.
Increased glutamate has been associated with CNS pathology. Among the effects of some glucocorticoids in the CNS is a protective effect against oxygen radical formation that commonly accompanies CNS trauma or hypoxia. This reflects the ability of selected drugs to insert themselves in the lipid component of the cell membrane, thus stabilizing it when the membrane is damaged. Damage puts into play a cascade of mechanisms that generates the oxygen radicals. Methylprednisolone may be more able than other steroids to decrease the negative impact of CNS damage on oxygen radical formation.

**Glucocorticoid Preparations.** Close to 50 different generic corticosteroid products are approved for human use and several for (small) animal use. They differ in their routes of delivery, but also in their duration of action, mineralocorticoid activity, and anti-inflammatory potency; As the anti-inflammatory potency of a particular agent increases, its biologic half-life and duration of action also increase. For example, dexamethasone is 30 X and prednisolone 4 X as potent as hydrocortisone in impairing glucose metabolism (da Silva 2005). With current drugs, anti-inflammatory properties parallel the effects on carbohydrate and protein metabolism, but mineralocorticoid effects can be altered independently by changing the molecular structure of the steroid. The 4,5 double bond and the 3-ketone are necessary for mineralocorticoid and GL effects. Synthetic modifications of cortisol increase the anti-inflammatory activity, decrease protein binding, and decrease hepatic metabolism, thus prolonging activity. First generation glucocorticoids were formed with the addition of a 1,2 double bond increased the ratio of GL to mineralocorticoid effects (prednisolone, prednisone and methylprednisolone). The second-generation steroids were fluorinated at the C-9 position, increasing potency. Methylation at the C-16 position eliminates mineralocorticoid activity (dexamethasone, betamethasone and triamcinolone). Third generation glucocorticoids will more specifically target trans versus cis activities.

The structure-activity relationship of the corticosteroids influences potency and mineralocorticoid activity. This slide demonstrates the order of glucocorticoid potency, which also is in reverse order of the amount of mineralocorticoid activity for each of the drugs. We will also see in a bit that the most potent drugs also have a longer half-life and duration of action. As potency for glucocorticoid activity increases, the relative dose decreases and the amount of mineralocorticoid activity decreases.

The clinical use of corticosteroids, and particularly glucocorticoids, is complicated by the presence of endogenous steroids. Glucocorticoids in particular cause a feedback inhibition that will ultimately result in decreased adrenal gland hormone synthesis and adrenal atrophy. This effect will occur regardless of whether the glucocorticoids is endogenous or supplied exogenously. This secretion is influenced by stress and is characterized by a diurnal rhythm (or perhaps nocturnal in cats). The impact of normal endogenous glucocorticoid secretion influences the clinical use of glucocorticoids, which is designed to minimize their impact on endogenous secretion. The longer the glucocorticoid is used therapeutically, the more important it becomes to give the body (adrenal glands) an opportunity to re-adapt to the absence of the drugs. Several approaches are used to minimize this impact. Short acting glucocorticoids that have an effect less than 24 hrs will allow endogenous adrenal secretion to occur. Likewise, using a physiologic dose will minimize the impact and as such, the dose will be tapered as soon as possible to alternate day use. Morning
administration will more likely mimic normal secretion in the dog. Finally, as the drug is finally discontinued, the dose will be gradually tapered to allow the body to adjust to the declining presence of the drug. The duration of the taper should reflect the duration of therapy.

**Disposition:** The disposition of glucocorticoids contributes to clinical differences in response. Those available for oral administration are well absorbed orally in some but not all species. Cats and horses do not appear to absorb prednisone well; indeed, some dogs may absorb less prednisone compared to prednisolone, warranting use of the latter drug in non-responders. Prednisone and its ketone hydroxylated active metabolite, prednisolone, are not truly equivalent in cats: both area under the curve (AUC) and maximum drug concentration (Cmax), parameters that measure oral bioavailability, are decreased substantially for prednisone when the same dose is given compared to prednisolone. This probably reflects oral absorption rather than metabolism because prednisone also does not show up in the blood of cats when given orally. Absorption of parenteral glucocorticoids is manipulated through the addition of R groups. Esters must be hydrolyzed by esterases in the muscle (or plasma) and the rate of hydrolysis is impacted by the specific esterase. Succinate esters are very rapidly released (including in the plasma) versus acetates which are very slowly released. Acetate products thus are “depo” preparations and even if an “intermediate” or “short” acting glucocorticoid active pharmaceutical ingredient is administered, if the ester is only very slowly released, the drug is not short acting. Further, if a drug with a depo ester is administered IV, emolization of this drug in the lungs can be lethal. If it is white, do not give IV. Pivvalate is added to desoxycorticosterone, rendering it a slow release mineralocorticoid that might be given monthly. Glucocorticoids might also be given topically to minimize systemic exposure and subsequent suppression of the hypothalamic pituitary adrenal axis (HPAA). However, do NOT assume that sufficient drug will not be absorbed: studies have demonstrated sufficient absorption, particularly when applied to inflamed skin, or joints, etc., that the HPAA axis is impacted.

In an attempt to minimize the systemic effects of glucocorticoids applied topically in humans, manufacturers have again manipulated drugs. The term “soft” glucocorticoids has been applied to those administered locally with the intent to avoid systemic side effects. These include ocular, inhalant and gastrointestinal. Such drugs must be potent, which precludes the systemic drugs. Inhalant drugs may still be orally absorbed as they travel up the mucociliary tract and drugs in the GI tract may be absorbed orally. One manipulation that has minimized systemic side effects of such drugs is first pass metabolism. Examples include beclomethasone or fluticasone (commonly used in asthmatic cats) available in metered device inhalers (MDA), and budesonide, available in oral capsules. However, studies have demonstrated that in animals, the drugs must not be entirely metabolized with first pass because side effects may occur. Interestingly, demodectic mange of the muzzle has been reported in cats receiving inhalant glucocorticoids. Likewise, topical effects of budesonide (because of its potency) in the GI tract may increase the risk of GI ulceration, which might not have occurred with other systemic glucocorticoids.

As a reminder, based on duration of action, drugs can be divided into short acting, generally less than 12 hrs, intermediate, generally 12 to 36 hrs (including prednisolone) and long acting, generally greater than 36 hrs, represented by dexamethasone. The intermediate acting, particularly the preds, may be short acting enough that once daily therapy (and especially alternate day therapy) is sufficient to minimize suppression of the HPAA axis. As a reminder, as duration of action increases, so does potency, anti-inflammatory effects, and side effects.

Most patients for which glucocorticoid therapy is implemented will require prolonged therapy. Ideally, because of their side effects, use will be limited to life- or organ-threatening diseases. It is important to start with a high enough dose and to maintain it long enough to avoid resistance. Once remission is achieved, the dose should then be tapered to a minimum effective dose. Morning dosing with a short acting drug, going to alternate day therapy, and tapering withdrawal have been discussed. The dose as indicated before varies with the potency, but also with the intent: ideally ultimate doses will be physiologic but as disease is forced into remission, the highest dose might be a “shock dose” (which is rarely
indicated), followed by an immunosuppressive dose, followed by an anti-inflammatory dose.

**Drugs:** Room precludes describing all GL used in dogs or cats; discussion will be limited to important points. **Prednisolone versus Prednisone:** Prednisone is rapidly metabolized by the liver to prednisolone (C-11 ketol reduction). Prednisone and prednisolone generally are (inappropriately) considered equivalent in terms of therapeutic use in veterinary medicine; veterinary dosing formularies generally make no distinction between the two. Yet, in the cat, the AUC for prednisolone was 3230.55 ng/mL/h and Cmax of 1400.81 ng/mL with a half-life for excretion of 1 h. This compares to a prednisolone AUC of 672.63 ng/mL/h and Cmax of 122.18 ng/mL following oral administration of prednisone; interestingly, a portion of the AUC reflected a half-life which was much longer at 2.46 h. In cats, a 3 to 5-fold dose should be given; in dogs, a 2-fold increase should be sufficient. **Methylprednisolone** has greater antioxidant activity, that has been shown to be beneficial in the treatment of experimental spinal cord trauma in cats and experimentally induced *E. coli* bacteremia. **Dexamethasone phosphate** offers a more rapid movement into the cell and is indicated for acute situations.

Inhalant metered devices. **Inhalant glucocorticoids** generally are delivered by metered device inhalers which are intended to deliver high concentrations locally, that is, at the site of action. For asthma, the preferred route in humans with mild disease is low-dose inhaled glucocorticoids. Beclomethasone was among the first aerosol glucocorticoids developed for inhalant therapy. Examples of corticosteroids marketed as inhalant metered devices (MDIs; see later discussion) in the United States include beclomethasone dipropionate (Beclovent), triamcinolone acetonide (Azmacort), flunisolide (Aerobid), budesonide (Pulmicort), fluticasone propionate (Flovent), and mometasone (Asmanex). Corticosteroid delivery of MDIs has been improved by the advent of hydrocarbon fluoroalkyl (HFA)—propelled MDI. Beclomethasone dipropionate delivery to peripheral airways increases from 5% to 15% for the chlorofluorocarbon—propelled preparation to 50% to 60% with the HFA propellant. Not only is total lung delivery increased, but the depth of penetration also is enhanced, which is critical to successful therapy. Although side effects are minimized compared to systemic delivery using MDI, up to 90% of an inhaled dose is still deposited on the oral mucosa or pharynx and swallowed in humans. Because animals cannot be directed to inhale, a similar or greater proportion of drug deposition might be anticipated in animals. Multiple methods have emerged to reduce adversities associated with glucocorticoids administered by MDI without decreasing efficacy. Differences in pharmaceutical (delivery) and pharmacokinetic properties largely determine variable responses to inhaled glucocorticoids. Characteristics that can be manipulated to influence efficacy or safety include potency (the amount of drug or number of molecules that impart a target response), thus allowing use in a MDI; retention at the site of action, thus prolonging local effect, and rapid metabolism, thus decreasing systemic effects. Corticosteroids marketed in MDI vary up to fivefold or more in potency. The relative potency of drugs marketed as MDI roughly follows the following order: mometasone, which exceeds both fluticasone and budesonide, which, in turn, are 2 to 3 times more potent than beclomethasone; triamcinolone is the least potent of these drugs. While potency does allow administration of a small dose, it does not predict clinical efficacy of inhaled glucocorticoids. Despite sixfold differences in potencies among inhaled glucocorticoids, comparative clinical trials in humans have failed to demonstrate differences in efficacy when drugs are administered at equipotent dosages. Further, dose response curves for inhaled glucocorticoids tend to be flat, indicating that increasing doses is not likely to enhance efficacy. Among the mechanisms whereby undesirable side effects of GLCs can be minimized is topical administration of drugs that are potent for the glucocorticoid receptor (GR) but also rapidly metabolized should the drug be absorbed into systemic circulation via the oral route. These efforts generally reflect manipulation of chemical groups on the D ring of the GLC. The term “soft glucocorticoids” has been used to refer to these drugs. Examples include beclomethasone, budesonide, and fluticasone propionate, steroids designed specifically for use in inhalant metered doses. Their potency when inhaled varies in clinical trials, with fluticasone propionate being most potent and budesonide and beclomethasone dipropionate approximately equipotent. Time of onset in humans for budesonide is approximately 10 hours.
based on evidence of clinical improvement at that time. Improvement can be expected over the next 1 to 2 days, with maximum effects potentially not being evident until 2 weeks after therapy has begun. Drugs have been manipulated to prolong local presence. Inhaled corticosteroids generally are delivered as microcrystals, which must dissolve in the epithelial mucosal fluid. Crystals must be water soluble to ensure local delivery before the mucociliary tract removes the drug. However, alteration of dissolution times may also affect local delivery and thus local effects. For example, the dissolution time for budesonide is 6 minutes compared with beclomethasone dipropionate (5 hours) and fluticasone (8 hours). Lipophilicity of the drug enhances uptake and the duration of local effects. The addition of a halogen increases tissue retention compared with nonhalogenated drugs. Lipophilicity is greatest for beclomethasone and fluticasone followed by budesonide, with triamcinolone followed by dexamethasone and, finally, prednisolone as the least lipophilic. Not surprisingly, the most lipophilic of the drugs also is associated with the greatest number of side effects, including suppression of the hypothalamic pituitary adrenal axis. In humans, fluticasone is both the most potent and most lipophilic glucocorticoid. As such, it is characterized by the greatest evidence of systemic side effects. Recommendations for humans are that high-dose fluticasone propionate (>500 mg twice daily) be used only on the order of a physician and that the dose be titrated down to the lowest effective dose. Budesonide offers an example of a different type of manipulation that may allow longer dosing intervals while minimizing side effects. Because of its structure (a free C21 hydroxyl group) (see Chapter 30), excess intracellular budesonide complexes with long chain fatty acids. The complex is inactive but probably allows persistence of the drug at the site, much as a depot form would, with reversible esterification occurring as receptors are depleted of active drugs. Other drugs with a free C21 hydroxyl include triamcinolone, flunisolide, and ciclesonide, although long-chain fatty acid esterification has not been determined for them. Neither fluticasone, nor beclomethasone dipropionate, and probably mometasone, form fatty acid esters.

**Therapeutic Considerations:** Unless one is administering GLs for replacement therapy in a deficiency state (i.e., hypoadrenocorticism), GL therapy is not directed at the inciting agent. GL therapy is intended to reduce the physiologic processes that are activated in response to the disease. Despite the adverse events associated with their use, GCL continue to be heavily used in veterinary medicine, and potentially at doses that exceed that recommended. Indeed, in human medicine, the use of GLC clearly exceeds that recommended in text books and review papers. The advantages of low versus high doses have been previously discussed and are addressed again in Adverse Reactions. In general, an anti-inflammatory dose is considered to be 10 times the "physiologic" dose, and immunosuppressive doses are twice the anti-inflammatory dose. Shock doses of GLs have been reported at 5 to 10 times the immunosuppressive dose; however, the disadvantages of this high dose and the advantages of low dose therapy in shock patients are discussed below. When treating a patient for an immediately life-threatening condition such as immune-mediated hemolytic anemia, therapy should be aggressive, with a minimum effective dose determined after response has been achieved. Because high doses of GLs are often required to adequately treat immune-mediated diseases, adverse effects are likely to occur and should be anticipated. Tapering of doses not only helps avoid side effects associated with long term therapy but may also avoid antibody rebound that has been associated with abrupt withdrawal of glucocorticoids in human patients treated for prevention of graft versus host transplant rejection (REF). Dose reduction in patients with autoimmune diseases should be conducted gradually. The reduced dose should be continued for at least 2 weeks before the next attempted dose reduction, and the actual dose should be decreased by no more than half. It is essential to assess the patient's status frequently for recurrence of clinical signs. Concurrent administration of additional immunosuppressive (azathioprine, cyclophosphamide, chlorambucil) or anti-inflammatory drugs (antihistamines, omega fatty acids, pentoxifylline, leukotriene receptor antagonists) may allow the GL dose to be decreased (“dose sparing” effect). High-dose pulse therapy has been reported in human patients with acute relapse of chronic graft-versus-host disease. Using an open design, patients either receiving no immunosuppressive therapy or patients which failed (a median of 2 failures) current therapy (mean
prednisolone dose of 0.2 mg/kg/day, range of 0.2-2.5 mg/kg/day) were treated with methylprednisolone at 10 mg/kg IV or PO for 4 days. The rationale behind the high dose is based on the lympholytic properties of this dose, thus causing destruction of lymphocytes that otherwise would cause irreversible organ damage. The high dose is assumed to target the (non-genomic) metabolic processes necessary for sustained activity of lymphocytes, as opposed to the low (genomic) doses which target lymphocyte replication. Additionally, the high dose is considered to overcome GL receptor saturation associated with GL therapy, causing significant GL down regulation. Induction of T-lymphocyte apoptosis may also occur. Antiviral and antimicrobial therapy (sulfonamides) accompanied high dose GL therapy. During a 2-year follow-up, patients tolerated the therapy well, with no major life-threatening effects occurring in the first 3 post treatment months. However, three patients developed infections after completion of the therapy, suggesting profound immunosuppression. Yet, the median time to progression of disease was 2 years after treatment, leading the authors to conclude that high-dose pulse steroid therapy is an effective and well tolerated treatment for progressive graft-versus-host disease. Side effects of GLs can occur if withdrawal of a GL occurs too rapidly. In human patients receiving GLs, the most frequent problem encountered with rapid withdrawals is recrudescence of the underlying condition for which the GL was indicated.

**Side Effects/Adverse Effects** Glucocorticoids in particular can influence clinical pathology results. The stress leukogram was previously discussed. Hyperglycemia and increased BUN reflect the formation of glucose from protein, and increased cholesterol and triglycerides demonstrate their impact on lipid mobilization and metabolism. Increases in hepatic transaminases (SALT, SAST) might reflect a glycogen storage type of response or direct effect, but this is should not generally be considered a hepatopathy. Likewise, glucocorticoids are potent inducers of serum alkaline phosphatase, and a history of glucocorticoid therapy should be sought in patients with high SALKP and no other indicators of disease. The PU/PD effects (central and renal) cause hyposthenuria (dilute urine), which contributes to poor immune function in the urine. As such, it is not unusual for patients to have bacteria; this may not represent true infection and may not necessarily need treatment. Finally, if the HPAA axis is negatively impacted, the thyroid axis also might be inhibited. The side effects of glucocorticoids should largely be predictable based on their physiologic effects. Note that the euphoria can be profound. Immunosuppression cannot be avoided by use of anti-infectious drugs; these should not be used to “cover” a patient receiving glucocorticoids. Note that while iatrogenic hypoadrenocorticism is unusual (because of proper dose tapering), iatrogenic hyperadrenocorticism is not, although it may not be severe.

Among the possible side effects of glucocorticoids in horses is laminitis, perhaps because of glucocorticoid induced vasoconstriction and altered blood supply to the hoof. As such, inhalant drugs might be better for treatment of chronic respiratory disease. Fat redistribution is not a serious side effect. The risk of GI ulcers is greater with potent, “topical” drugs compared to less potent systemically-intended drugs; and of course, in patients receiving NSAIDs. The hepatopathy associated with glycogen storage generally does not present a risk to the patient. The risk of pulmonary thromboembolism may be a reason to avoid using these drugs in patients at risk for thromboembolic events or with bleeding disorders.

A number of contraindications exist for glucocorticoids. Again, understanding their physiologic effects allows most of these to be predicted. Their impact in pancreatitis is not really understood. Renal disease may be worsened if the poorly compensated kidneys are subsequently exposed to larger amounts of blood urea nitrogen. With chronic therapy, glucocorticoids in particular may lower seizure threshold, increasing the risk of epilepsy.