researcher interested in a specific disease. Dermatopathologic findings are needed for appropriate interpretation of antibody findings and are also used to determine the exact type of antibody testing performed. A logical approach to cases suspected of having an autoimmune or immune-mediated disease is careful selection and procuring of representative skin specimens and the forwarding of those specimens to a knowledgeable dermatopathologist. We recommend collecting serum from dogs and cats when they are initially seen and saving it in the freezer. After other test results are reviewed, and with the recommendation of the pathologist, the indirect immunofluorescence test may still be performed by an appropriate commercial or research laboratory. This sample may also be used at a later date as a pretreatment sample for some serum biochemical parameters. By identifying these diseases accurately, we will be able to determine whether the variants described in humans also exist in dogs and cats, and whether their differentiation leads to prognostic or therapeutic value.

**CLINICAL MANAGEMENT OF IMMUNE-MEDIATED SKIN DISEASES**

As a group, all immune-mediated dermatoses are characterized by an inappropriate immune response that, to be adequately controlled, may require use of potent immunosuppressive and immunomodulating drugs. In the past, this primarily meant high levels of glucocorticoids, and when this failed, addition of other drugs such as cyclophosphamide or azathioprine. These initial attempts at treatment, although often successful, led to many side effects (see Chap. 3). Recent studies of pemphigus foliaceus treatment have shown that there can be wide variations in success and that many failures are due to euthanasia, often related to treatment side effects. In recent years, however, a variety of different therapeutic approaches have been evaluated, and now more options are available to the clinician for managing some of these diseases. The goals of therapy have also been modified to try to improve outcome by having fewer animals euthanized for reasons other than poor disease response. Table 9-1 presents key principles and rationales that have been adapted from recommendations for the treatment of pemphigus foliaceus.

**PHASES OF TREATMENT OF IMMUNE-MEDIATED DERMATOSES**

Immune-mediated diseases are not all treated in the same way, and some are partially or more responsive to certain drugs such as tetracycline/niacinamide. For example, tetracycline/niacinamide is more effective in discoid lupus erythematosus than pemphigus foliaceus. Immune-mediated dermatoses also have different prognoses, so it is important for the clinician to make as specific a diagnosis as possible. Drugs used to treat immune-mediated skin diseases are generally called immunosuppressive agents. However, the exact mechanism of some of these drugs is unknown. They may act in methods different from those of the more classically used immunosuppressive agents. They are considered together here because whatever their mechanism of action, they share the feature of being beneficial in managing immune-mediated skin diseases. Most immune-mediated skin diseases require more, stronger, or a combination of drugs to put them into remission, and less to keep the disease in remission. The long-term goal is to keep the animal lesion-free off medications. Four main phases one typically goes through when treating immune-mediated dermatoses have been recognized: (1) induction of remission, (2) transition, (3) maintenance, and (4) determining cure (Table 9-2).

**INDUCTION PHASE**

The initial therapy used in treating immune-mediated dermatoses should stop inflammation and suppress the immunologic response against the skin. Higher doses of drugs are usually needed for this phase of therapy. If induction therapy is not effective in a timely manner for the chosen class of drugs and the disease, treatment should be immediately changed. For example, if a case of canine pemphigus foliaceus being treated with prednisolone 1.1 mg/kg every 12 hours or 2.2 mg/kg every 24 hours is not responding within 7 to 10 days, a different induction treatment should be selected. Patients treated with azathioprine alone should show a good response within 4 weeks. Some clinicians use one high dose of intravenous or subcutaneous glucocorticoid then immediately go to a transition level.
<table>
<thead>
<tr>
<th>Phase</th>
<th>Typical Duration</th>
<th>Key Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Days to weeks</td>
<td>Avoid bad side effects.</td>
</tr>
<tr>
<td>Transition</td>
<td>Weeks to months</td>
<td>Get to lowest effective dose.</td>
</tr>
<tr>
<td>Maintenance</td>
<td>6 months to years</td>
<td>Maintain dose for duration of disease, with monitoring to avoid side effects.</td>
</tr>
<tr>
<td>Determining Cures</td>
<td>One to several attempts</td>
<td>Stop drugs after complete remission has been maintained, and observe for recurrence of disease.</td>
</tr>
</tbody>
</table>

**TRANSITION PHASE**

The transition phase involves tapering the drugs used to minimize the long-term side effects, risks of adverse reactions, and cost. When combinations of medications are prescribed, the first drugs to be tapered are those with greater likelihood of adverse effects. When control of the disease and side effects have reached levels acceptable to both the client and clinician, tapering of more expensive drugs or drugs that require greater monitoring expense can begin. All medications are slowly tapered until there is a recurrence of clinical signs. If no recurrence is seen, the case may be cured.

**MAINTENANCE PHASE**

Maintenance is reached after recurrence or exacerbation of the disease occurs in the transition phase. Once recurrence is noted, medication doses are raised again sufficiently to reduce remission, then doses are maintained at the level reached prior to recurrence. Thus, maintenance doses are the lowest doses that result in a stable degree of disease that is acceptable to the client and clinician. After 1 year of maintenance therapy, tapering is repeated, and some cases may remain cured even though they had flared at the end of the transition phase.

**DETERMINING CURES**

Immune-mediated dermatoses that have been put into remission, treated with maintenance therapy, then do not recur off medication may be considered “cured.” Cure may be achieved at the end of the transition phase or after the maintenance phase has persisted for a period of time. Dogs that have been on maintenance therapy for 8 to 12 months should have a trial off medication. If recurrence is significant and remission is harder to achieve, discontinuing the maintenance phase should not be attempted again.

**DRUGS FOR IMMUNE-MEDIATED DERMATOSES**

As already noted, the drugs used to treat immune-mediated skin diseases are generally called immunosuppressive agents, and the exact mechanism of some of these drugs is unknown. The more commonly used drugs will be discussed individually, but most often, except for glucocorticoids, combinations are used. Some drugs are only effective in certain diseases and in particular combinations. Other therapies such as antimalarials, chrysotherapy, dapson, intravenous immunoglobulins, monoclonal antibodies targeting immune regulatory factors, plasmapheresis, and sulfasalazine are rarely used, experimental, or currently unrealistically expensive for general use. Alternative infrequently used or newer treatments are available if a dog or cat does not respond to the more common treatments discussed here. In those situations, referral or consultation with a specialist is warranted.

Glucocorticoids are the most common class of drugs used as immunosuppressive agents. They are discussed in Chapter 3. A special use of glucocorticoids for initial treatment of some severe immune-mediated dermatoses is pulse therapy, which is especially designed for use in inducing remission; 11 mg/kg methylprednisolone sodium succinate given intravenously over 1 hour for 3 consecutive days was used to induce remissions in cases of canine pemphigus that had not responded to oral glucocorticoids. This therapy is expensive and not without complications (see Chap. 3).

Cyclosporine (Atopica [Novartis]) is also discussed in Chapter 3 and is commonly used in immune-mediated diseases. It can be tried as sole therapy, but is most effective when used in combination. It has been used most extensively with systemic glucocorticoids, but has also been used with glucocorticoids and azathioprine.

**AZATHIOPRINE**

Azathioprine (available as generic and Imuran® [Prometheus]) is a synthetic modification of 6-mercaptopurine that can be given orally or by injection. The drug antagonizes purine metabolism, thereby interfering with DNA and RNA synthesis. However, for skin diseases, the oral (PO) route is usually used. It is metabolized in the liver to 6-mercaptopurine and other active metabolites. 6-Mercaptopurine is then metabolized by three enzyme systems. Xanthine oxidase and thiopurine methyltransferase (TPMT) produce inactive metabolites. Humans and possibly dogs that have absent (homozygous) or low (heterozygous) TPMT activity are more likely to experience myelosuppression; cats have lower levels, making them more susceptible to toxicity. Ten percent of the normal dogs sampled had low (heterozygous) TPMT activity (9.1-3 U/mL RBC; normal, 15.1-26.6).

Azathioprine primarily affects rapidly proliferating cells, with its greatest effects on cell-mediated immunity and T lymphocyte-dependent antibody synthesis. Primary antibody synthesis is affected more than secondary antibody synthesis. Azathioprine is preferred over 6-mercaptopurine because it has a more favorable therapeutic index and 6-mercaptopurine is less effective when given orally to humans.

Even so, azathioprine is a potent drug with potential toxicities that include anemia, leukopenia, thrombocytopenia, vomiting, hypersensitivity reactions (especially of the liver), pancreatitis, elevated serum alkaline phosphatase concentrations, rashes, and alopecia. The most common significant side effect is diarrhea, which may be hemorrhagic. This often responds to dose reductions or temporary discontinuation of the drug. More than 90% of patients experience anemia and lymphopenia, but usually not to the degree that treatment needs to be discontinued. It has also been suggested that patients not responding to therapy, not lymphopenic, and otherwise tolerating the drug very well should have their dose of azathioprine increased. Long-term therapy is associated with development of demodicosis, recurrent bacterial pyoderma, or dermatophytosis in at least 10% of cases. Pancreatitis may occur, but this has been primarily reported in dogs also receiving glucocorticoids. Experimentally it does effect the canine pancreas when used alone but did not induce inflammation. We have diagnosed pancreatitis in a few dogs and, in some cases, azathioprine could be continued when the glucocorticoid was discontinued, without further episodes of pancreatitis. Hepatoxicity may occur in dogs on combinations of glucocorticoid...
and azathioprine; in some cases this will not resolve without discontinuing the azathioprine.

Patients should be monitored initially every 2 weeks with complete blood cell counts (CBC) and platelet counts. Since changes in medications and doses are determined by trends and not just absolute blood values, it is helpful to organize the test results in a way that trends are easily seen. Figure 9-3 presents an easy-to-use form for tracking changes in test results during the three treatment phases for immune-mediated diseases. After the patient’s condition is stable, monitoring can be tapered to once every 4 months. If other symptoms occur, after 8-12 weeks then at least biannually, a chemistry panel should also be run. Hepatitis and pancreatitis are the major conditions to monitor with chemistry panels.

In small animals, azathioprine has been found to be one of the most beneficial immunosuppressive drugs for treatment of any immune or autoimmune disease that warrants its use. Azathioprine is usually not used alone but combined with systemic glucocorticoids. In combination with glucocorticoids, it has been described as the treatment of choice for canine pemphigus foliaceus. In humans, it was shown to be a better steroid-sparing drug for treating pemphigus vulgaris than cyclophosphamide and mycophenolate mofetil. There is often a lag phase, with clinical improvement occurring in 3 to 6 weeks. After remission is achieved, the dosages of both drugs are tapered, but initially (unless side effects are a problem) the glucocorticoid dosage is tapered to levels approaching 1 mg/kg every 48 hours or less. The oral dosage of azathioprine for dogs is 50mg/m² though some use 1.5-2.5 mg/kg every 24 hours (generally towards higher dose range in dogs under 23kg and heavier dogs receive lower dose range) until clinical response is achieved, and then it is continued every other day.

| Date | WBC | RBC | HCT | Neuts | Lymphs | Mono | Eosin | PLT | TP | Albumin | GlobulIn | AST | ALT | Alk Phos | GGT | T. Bili | BUN | Creat | Phos | Glucose | Calcium | Na | K | Cl | Amylase | Lipase | CPK | T4/T4ed | TSH | PPT4 | ACTH Pre | ACTH Post | HWT | FELV | FIV |
|------|-----|-----|-----|-------|-------|------|-------|-----|----|---------|----------|-----|------|---------|-----|--------|-----|-------|-----|--------|--------|----|----|---|---------|--------|-----|------|-----|       |--------|-----|------|-----|

**FIGURE 9-3** Form for tracking changes in test results during the three treatment phases for immune-mediated diseases.
for a month or longer. Slow tapering to as little as 1 mg/kg every 72 hours may be achieved. Slow tapering to the lowest dose possible decreases side effects and the expense of therapy. Glucocorticoids can be given on the alternate days when azathioprine is not given. If this combination has not been effective, addition of cyclosporine may be effective. Another option is to continue to increase the azathioprine dose if the CBCs are relatively normal, especially if the patient is not lymphopenic.

Cats are susceptible to azathioprine toxicity (including fatal leukopenia and thrombocytopenia), and this drug should be used very cautiously if at all in this species.

**CHLORAMBUCIL**

Chlorambucil (Leukeran® [GlaxoSmithKline]) is an orally administered alkylating agent derived from nitrogen mustard. Its cytotoxic effect is due to cross-linking of DNA. Compared with other alkylating agents, it is slow acting and less toxic. Although serious toxicity is rare at usual doses, myelosuppression is possible. Consequently, patients should initially be monitored with hemograms every 2 to 4 weeks. Anorexia, vomiting, and diarrhea have been reported at daily dosages but often resolve with alternate-day therapy. Alopecia and delayed hair growth after clipping have been reported, and poodles and Kerry blue terriers are reported to be at greater risk. Neurotoxicity is seen in humans, but it has only been reported once in a cat that developed myelosuppression. Chlorambucil is available in 2mg and 5mg tablets, making it most useful in small dogs and cats.

Chlorambucil may be useful in the pemphigus complex, bullous pemphigoid, discoid and systemic lupus erythematosus, immune-mediated vasculitis, and cold agglutinin disease, as well as in lymphocyte and plasma cell malignancies. It is especially helpful in cats because they do not tolerate azathio-
prine as well as dogs; feline pemphigus foliaceus has been effectively treated with chlorambucil. Chlorambucil is most commonly combined with a glucocorticoid and occasionally with azathioprine (dogs only!). It may be used to replace cyclophosphamide if hemorrhagic cystitis develops during use of that drug. The oral dosage in dogs and cats is 0.1 to 0.2 mg/kg every 24 to 48 hours, and at least during the induction phase, it is most commonly used in conjunction with a glucocorticoid. It may take several weeks for a beneficial effect to appear, but once it does, chlorambucil can be tapered to every other day or less during the maintenance phase.

**COLCHICINE**

Colchicine (Colcrys® [URL Pharma] and other brands available online) was a very old plant-derived drug used for many years to treat gout. It is believed to have a variety of antiinflammatory and antifibrinolytic properties. It is an alkaloid that suppresses neutrophil chemotactic and phagocytic functions via disruption of microtubule assembly and elongation, increasing cellular cyclic adenosine monophosphate (cAMP) levels and inhibiting lysosomal degranulation. It also inhibits immunoglobulin secretion, interleukin (IL)-1 production, histamine release, and human leukocyte antigen (HLA)- DR expression. It inhibits cell division during metaphase by interfering with sol-gel formation and the mitotic spindle. Exciting, Colchicine has been useful for the treatment of humans with leukocytoclastic vasculitis, epidermolysis bullosa acquisita, linear immunoglobulin (Ig)A bullous dermatosis, dermatitis herpetiformis, relapsing polychondritis, and pemphigus folia-
ceous. In dogs it has been used in combination therapy to treat epidermolysis bullosa acquisita, junctional epidermolysis bullosa, amyloidosis and Shar-Pei fever syndrome. The main side effects are gastrointestinal. It was recently approved by the U.S. Food and Drug Administration (FDA) for treating gout and familial Mediterranean fever, and the price significantly increased as the drug became patent protected for at least 3 years. It is usually given at 0.03 mg/kg every 24 hours, and there are concerns about concurrent nonsteroidal antiinflammatory drug (NSAID) use and bone marrow suppression. It also should not be used with azathioprine or chlorambucil. In humans, it is contraindicated or used cautiously with cytochrome P450 enzyme inhibitors and P-glycoprotein pump inhibitors. It is available only in 0.6mg tablet size, making dosing problematic.

**CYCLOPHOSPHAMIDE**

Cyclophosphamide (Cytoxan [Bristol-Myers Squib] and other brand names available) is a nitrogen mustard alkylating agent that is metabolized to agents that inhibit mitosis by interfering with DNA replication and RNA transcription and replication. Lymphocytes are especially sensitive to cyclophosphamide. The drug is immunosuppressive to both the humoral and cell-mediated immune systems, but it is more effective against B cells than T cells. Cyclophosphamide suppresses antibody production. Maximal effect occurs if the drug is given shortly after the antigenic stimulus, when it suppresses primary and secondary humoral responses. Major toxic sequelae include sterile hemorrhagic cystitis (decreased with concurrent furosemide therapy), bladder fibrosis, teratogenesis, infertility, alopecia and poor hair growth, nausea, inflammation of the gastrointestinal tract, increased susceptibility to infections, and depression of bone marrow and hematopoietic systems. Cats may lose their whiskers. Hemorrhagic cystitis occurs in up to 30% of dogs on chronic therapy of more than 2 months’ duration.

Cyclophosphamide is used alone or in combination with other chemotherapeutic agents for the treatment of various neoplasms, as well as for its immunosuppressive activity in nonmalignant diseases and organ transplantation. In the past, this drug was recommended for immune-mediated skin diseases, but it is now rarely used; immune-mediated skin diseases typically require months of therapy, and cyclophosphamide has more side effects and greater associated risks with longer use. Additionally, its efficacy for this use has been questioned. When used, it is typically in the induction phase of treatment.

**MYCOPHENOLATE MOFETIL**

Mycophenolate mofetil (CellCept [Genentech] generics available online) is a drug that inhibits de novo purine synthesis and suppresses both T and B lymphocytes. In humans it has been used to prevent organ transplant rejection and a variety of autoimmune and immune-mediated diseases. Use in the dog and cat has been limited, with most studies related to preventing allograft rejection; use for canine autoimmune diseases has also been reported. Mycophenolate mofetil is reportedly effective in 50% of canine pemphigus foliaceus cases, with some dogs weaned completely off prednisone, whereas others required concurrent glucocorticoids. A comparative treatment study in dogs with myasthenia gravis showed it had no benefits compared to the standard treatment group.

Mycophenolate mofetil is a prodrug of the antiproliferative agent mycophenolic acid (MPA). It specifically and reversibly inhibits inosine monophosphate dehydrogenase, thereby inhibiting synthesis of guanine nucleotides, blocking synthesis of purine, and preventing maturation of T and B lymphocytes. It also has other effects such as inducing T-lymphocyte apoptosis and dendritic cell maturation, and can induce human monocyte-macrophage cell line differentiation, decreasing the expression of IL-1 and enhancing expression of the IL-1 receptor antagonist.

It is available in 250-mg and 500-mg tablets; generics are available, making it more cost-effective. A wide range of
dosages have been used, from 2 mg/kg every 24 hours to 13 mg/kg every 8 hours. Though some evidence suggests every 8 hours would be optimal, the most common dose range appears to be 10 to 20 mg/kg every 12 hours. Since in humans and dogs it is synergistic with cyclosporine in prevention of acute graft-versus-host disease (GVHD) and has a steroid-sparing effect, its use as a combination agent should be evaluated further.72,73 The every-12-hours and lower doses are more often used when the drug is used in combination. Principal side effects include bone marrow suppression, nausea, vomiting, diarrhea, and increased incidence of infections. Other side effects were minimal, but the most common included pyoderma, Malassezia infection, diarrhea, and leukocytosis.95 Gastrointestinal side effects are more common when the drug is given as a sodium enteric-coated tablet.74

**TETRACYCLINE AND NIACINAMIDE**

The drugs tetracycline and niacinamide, alone or together, are either beneficial or have steroid-sparing effects for over 20 inflammatory skin diseases.75 There are also reports of beneficial effects in human immune-mediated diseases, particularly bullous pemphigoid and pemphigus.75-78 As a result, the combination was tried in dogs.79 The exact mechanism of action of either drug or the combination for treating inflammatory or immune-mediated disease is unknown.79,80 Tetracyclines possess various antiinflammatory and immunomodulatory properties, including suppression of in vitro lymphocyte blastogenic transformation and antibody production, inhibition of matrix metalloproteinases, downregulation of cytokines, suppression of in vivo leukocyte chemotactic responses, inhibition of the activation of complement component 3, inhibition of lipases and collagenases, and inhibition of prostaglandin synthesis.79-80 Niacinamide or nicotinamide have been shown to block antigen IgE-induced histamine release in vivo and in vitro, prevent degranulation of mast cells, act as photoprotectants from inducing immunologic damage, act as a cytoprotectant that blocks inflammatory cell activation and apoptosis, inhibit phosphodiesterases, and decrease protease releases.81,82,83 There is little documentation of what these two drugs do in combination and whether they have additive or synergistic effects.

The combination of tetracycline and niacinamide has been recommended for the treatment of discoid lupus erythematosus, pemphigus erythematous, and pemphigus foliaceus in dogs, with some being retained in remission long term with just this therapy.81,82,83,84,85 Reported results are variable, but 25% to 65% of cases have an excellent response. It has been used for a variety of diseases, many with unknown pathogenesis that may involve immunologic mechanisms. The diseases described include sterile histiocytosis, idiopathic onychodystrophy, vesicular cutaneous lupus erythematosus, lupoid onychitis (onychodystrophy), German shepherd dog metatarsal fistulae, sterile panniculitis, sterile granulomatous/pyogranulomatous dermatitis, and vasculitis.86

The initial dosage for dogs weighing more than 10 kg is 500 mg of tetracycline and 500 mg of niacinamide given every 8 hours. If response is favorable, the dosage may be decreased to every 12 hours and then to every 24 hours. Anecdotal reports exist that this combination may have shown benefit when used concurrently with vitamin E or glucocorticoids as well as prednisone and azathioprine. It was also reported that tetracycline alone may be beneficial in treating discoid lupus erythematosus. Doxycycline has been recommended in place of tetracycline, although no studies or reports of its relative efficacy are available. Because of its longer half-life, a lower dose and longer interval (5 mg/kg every 12 hours) is acceptable.51 Side effects are uncommon, although vomiting, anorexia, lethargy, and diarrhea have been reported. Two cases were reported of anorexia with increased liver enzyme activity that resolved with discontinuation of therapy.86 In some cases, tetracycline administration was continued, suggesting that the niacinamide was responsible for the adverse reactions. Another author (KLC) has observed an increased frequency of seizures in epileptic dogs following treatment with niacinamide and no longer prescribes niacinamide to dogs with a history of seizures.

**AUTOIMMUNE DISEASES**

**THE PEMPHIGUS COMPLEX**

The pemphigus complex is a group of uncommon autoimmune skin diseases that affect dogs, cats, and horses, with individual cases also reported in goats.86 They are classically characterized by acantholysis, which is the breakdown of the epidermal intercellular desmosomal connections, with separated keratinocytes becoming rounded up as darkly staining acantholytic cells. The two major subsets of pemphigus in animals, as in man, are pemphigus foliaceus (PF) and pemphigus vulgaris (PV), with the latter occurring relatively much less frequently in animals than in man. Uncommon or rare variants are pemphigus vegetans (PVeg), paraneoplastic pemphigus (PNP), and pemphigus erythematosus (PE). In man, drug eruptions can be a cause of pemphigus, and it is believed this may be responsible for some cases in dogs and cats. However, as discussed later, a cause-and-effect relationship is very difficult to establish. The term pemphigus foliaceus-like pemphigus has been proposed to encompass cases in which acantholysis with a neutrophilic and/or eosinophilic infiltrate occurs throughout the epidermis, as seen in the descriptions of some cases of PVeg and PE.84 However, this term has not found general usage, in that many of the described cases could be considered variants of PF.85

**AUTOIMMUNITY IN PEMPHIGUS**

In the great majority of cases of human pemphigus, intercellular deposition of antibody within the epidermis is demonstrable, and circulating autoantibody is detectable employing indirect immunofluorescence on cultured keratinocyte sections of normal skin.85 The antibody binds to the interdesmosomal cell membrane and also within the desmosomes themselves.86,87 Indeed, clinicians are reluctant to make a definitive diagnosis in the absence of such evidence, and a specific diagnosis is achieved in some 90% of cases of human pemphigus by determination of the autoantibody profile.87,88 The desmosomal antigens reportedly targeted are desmoglein 1 (Dsg1) in PF, and Dsg3 in PV with predominantly mucosal involvement, and additional activity against Dsg1 where there is significant cutaneous involvement.89 In general, localization of the lesions parallels the ultrastructural distribution of the respective antigens within the epidermis.90 However, other desmosomal antigens may be targeted in man, including desmocollin 3 in PV,90 and the plakin family antigens envoplakin and periplakin in PNP.91

Although the clinical and pathologic spectrum of the pemphigus diseases in animals is quite well defined, the classical immunologic abnormalities are not always evident. Thus in an early study, immunoglobulin deposits were seen in only 56% of 45 cases in which a final diagnosis of pemphigus was made based upon a combination of clinical signs, direct immunofluorescence, histopathology, and subsequent clinical course.92 In two later studies involving 37 and 18 cases of PF, intercellular deposits were seen in 66% and 88%, respectively.93,94 In one third of the cases in the latter study, deposits were primarily restricted to the outer layers of the epidermis. Subclass-specific staining in another study revealed that the deposits in some cases were restricted to the IgG2 and/or IgG4 subclasses.95