

Endemic pemphigus foliaceus (fogo selvagem).

I. Clinical features and immunopathology

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Endemic pemphigus foliaceus is an autoimmune disease that has remarkable features. Endemic foci are found in characteristic environments within the interior of Brazil. The epidemiologic data strongly suggest that an environmental factor initiates the autoantibody response in the host. As such it is an important disease for in-depth study. A group of interested investigators in both Brazil and the United States has been formed to attempt to do just that. As part of the overall effort, this Cooperative Research Group for the Study of Fogo Selvagem presents a definition of the disease, a proposed clinical classification for various forms of the disease, and an outline of what is currently known of its immunopathologic characteristics. (*J AM ACAD DERMATOL* 1989;20:657-69.)

The term *pemphigus* refers to a group of diseases that are characterized by the presence of cutaneous or mucosal blisters and erosions and antiepidermal autoantibodies.^{1,2} Table I shows the clinical forms of pemphigus. With one exception all forms of pemphigus are rare and occur sporadically throughout the world. This exception is endemic

Table I. Clinical variants of pemphigus

Pemphigus vulgaris
Pemphigus vegetans
Cazenave's pemphigus foliaceus
Endemic pemphigus foliaceus (fogo selvagem)
Pemphigus erythematous (Senear-Usher syndrome)
Drug-induced pemphigus

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pemphigus foliaceus (fogo selvagem), which is seen primarily in Brazil, and of which there are more than 15,000 cases registered and very likely many more that are unrecorded.

The most characteristic feature of all forms of pemphigus is the presence on histologic examination of epidermal cell-cell detachment, which results in intraepidermal vesicle formation (acantholysis). It is now clearly established that acantholysis is the result of the binding of IgG autoantibodies to an antigen present on the cell surface of differentiating keratinocytes.²

The Cooperative Research Group for the Study of Fogo Selvagem has been established to coordinate clinical and basic studies of this disease. Its members, who are the authors of this article, present here their understanding of current infor-



Fig. 4. Farmer from the state of Goiás with a 3-week history of bullous, pustular, and erosive lesions of the central body. The face shows confluent crusted and erosive lesions.

mation concerning the disease. It is hoped that their classification of the disease will become an accepted standard to facilitate reporting among clinicians.

DEFINITION OF ENDEMIC PEMPHIGUS FOLIACEUS (FOGO SELVAGEM)

Fogo selvagem is similar to the pemphigus foliaceus that is seen in North America and Europe and that was originally described by Cazanave.³ Both diseases are characterized by superficial blistering and erosive lesions that affect the skin but rarely involve mucosal surface.^{4,5} Both are characterized by acantholysis involving the subcorneal layers of the epidermis, and in both forms circulating autoantibodies in the patients' sera recognize desmoglein I glycoprotein.⁶ The major factors that distinguish the two diseases are epidemiologic features, including their geographic distribution and age distribution.⁷⁻⁹

Another widely used term applied to fogo selvagem is *Brazilian pemphigus foliaceus*. It is agreed by the Cooperative Research Group that this term is not as useful as the term *Endemic pemphigus foliaceus* because clusters of cases of this disease currently are being reported in Colombia, El Salvador, Paraguay, and Peru, as well as in Brazil.⁹

The disease occurs in areas of Brazil that are being agriculturally developed, and historically, occupations related to development have been associated with susceptibility to the disease. As patterns of settlement change, however, the foci of endemic pemphigus also change. Early in the twentieth century when the state of Sao Paulo was being developed, there were so many cases in the region that a referral hospital in the city of Sao Paulo was constructed specifically for the care of affected persons. Now that the city houses an urban population of about 15 million and the state is more urbanized, the disease is rare in the area, and the foci of new cases have moved farther into the developing interior of the country. The states that have the largest numbers of cases are Goias, Mato Grosso do Sul, Parana, and Sao Paulo (Fig. 1). Significantly, a major focus of disease currently is found in the state of Goias, where relocation of the country's capital to Brasilia has produced extensive new development in this rural area. The manuscript of a detailed historical study of the

epidemiology of the disease has been submitted for publication.¹⁰

The population at risk includes farmers predominantly, but any persons who live and work in endemic areas can be affected. The most common occupations that predispose to development of the disease are agricultural work, work involving road construction or clearing land for agriculture, and other rural labor. No racial or ethnic group is exempt from development of the disease; the incidence of fogo selvagem relates solely to occupation and location. It is not safe to say that the disease "never" develops in persons who live in cities and do not travel into the countryside, but these cases are extremely rare. Unfortunately there is no clear idea of how long an exposure to the environment is required for the disease to develop, but affected persons' histories frequently indicate that they lived or worked in the endemic areas for months or years. Anecdotally, we have seen several persons in whom fogo selvagem has developed within 6 months of moving to an endemic areas. One of these patients was a prospector who was panning for gold in rural areas of the state of Goias. There is also one incident in which fogo selvagem developed in a dentist from Brasilia after a 3-week fishing trip on an isolated river in the state of Goias. This is the shortest exposure we have heard of, but we have not interviewed the dentist to verify the history. It should be stressed that Brazilian dermatologists do not believe that short exposures to the environment put one at risk.

The disease affects children and young adults frequently, and the peak incidence is in the second and third decades of life. This evidently is different from the age distribution observed in Cazenave's pemphigus foliaceus.³ It is possible that this age distribution may be partially a result of exposure because those in this age group are most commonly employed in the kind of work that puts them at risk for the disease.

Both forms of pemphigus foliaceus are easily differentiated from pemphigus vulgaris and its variants such as pemphigus vegetans. In pemphigus vulgaris the lesions usually first appear on mucosal surfaces, acantholysis is suprabasilar rather than subcorneal, and the patients' autoantibodies recognize a different epidermal glycoprotein.¹¹ The salient features of the disorders are summarized in Table II.

Table II. Pemphigus syndromes: Differential features

Differential features	Fogo selvagem	Pemphigus foliaceus (Cazenave)	Pemphigus vulgaris
Distribution	Endemic in Brazil	Sporadic	Sporadic
Cause	Environmental?	Unknown	Unknown
Age	Children and young adults	Elderly	Adults
Familial cases	Frequently observed	None	Rare
Skin lesions	Superficial, subcorneal	Superficial, subcorneal	Deeper, suprabasilar
Mucosal lesions	Rare	Rare	Common
Passive transfer	Subcorneal disease in mice	?	Suprabasilar disease in mice
Antigens	Desmoglein I	Desmoglein I	135-kilodalton glycoprotein
Pregnancy	Normal neonates	?	Neonatal pemphigus
Prognosis	Variable	Variable	Guarded

Table III. Fogo selvagem classification

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| <p>A. Clinical presentation</p> <ol style="list-style-type: none"> 1. Localized (<i>forme fruste</i>) 2. Generalized forms <ol style="list-style-type: none"> a. Bullous-exfoliative b. Exfoliative-erythrodermic c. Disseminated keratotic plaques 3. Hyperpigmented forms: inactive disease (in remission) <p>B. Clinical evolution</p> <ol style="list-style-type: none"> 1. Acute 2. Chronic 3. Relapsing or recurrent 4. Inactive or cured cases |
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CLINICAL PRESENTATION, CLASSIFICATION, AND EVOLUTION

The clinical appearance of patients with fogo selvagem is similar to the more familiar form of Cazenave's pemphigus foliaceus. The primary cutaneous lesion is a superficial vesicle that may resemble lesions of impetigo. These lesions rupture easily, leaving superficially denuded areas. Lesions always occur in the head and neck area and then spread acraly (Fig. 2). Mucosal blisters or erosions rarely are observed, even in advanced cases. The striking distribution of lesions in sun-exposed skin, the "burnt" appearance of the patient, and a painful burning sensation in lesions were responsible for the popular name used by lay people to describe the disease—fogo selvagem, which is Portuguese for "wild fire." In a large number of patients the cutaneous lesions of fogo selvagem are altered by superimposed infection and incomplete treatment with systemic steroids. In all clinical

forms, when the disease is active a Nikolsky's sign can be elicited. In contrast to pemphigus vulgaris, neonatal pemphigus has not been observed in babies born to mothers with active fogo selvagem.*

In the majority of patients the disease begins gradually, with cutaneous lesions evolving during a period of several weeks or months. On rare occasions fogo selvagem is acute and fulminant, with extensive bullae erupting during a period of 1 to 3 weeks. Members of the Cooperative Research Group agree on the clinical classification of fogo selvagem as it is discussed in the text and summarized in Table III.

Clinical presentation

Localized form (*forme fruste*). The lesions are distributed on seborrheic areas of the face and trunk. Individual lesions appear as round or oval keratotic plaques with a yellow-brown surface; some lesions may be violaceous or hyperpigmented (Fig. 3). The localized lesions of fogo selvagem may resemble the lesions of discoid lupus erythematosus in their distribution and clinical appearance; however, the plaques of fogo selvagem lack follicular prominence (the "carpet tack" sign) or the atrophy and hypopigmentation observed in lesions of lupus erythematosus.¹² The resemblance of these lesions to those of lupus erythematosus had prompted many clinicians in the past to label this form *Senear-Usher syndrome* because of its close

*Proenca NG, Proenca YM, Guedes M. Gravidez em doentes com penfigo foliaceo Sul-Americano (fogo selvagem). Ann Brasil Dermatol 1979;54:239-44.



Fig. 5. Patient in Fig. 4. Closeup photograph of the arms shows extensive vesiculopustular lesions typical of this form of the disease.

Figs. 6 and 7. Lesions of fogo selvagem on the trunk and face. The punctate and hemorrhagic lesions of the mid portion of the face are those of herpes simplex. These patients have the often concomitant complication of Kaposi's varicelliform eruption that frequently is fatal despite treatment with acyclovir.

Fig. 8. Exfoliative erythrodermic form of fogo selvagem. This man, 27 years of age, living in the state of Parana, demonstrated confluent crusted lesions of fogo selvagem that affected most of his body surface area, excluding the palms, soles, and mucous membranes.

resemblance to pemphigus erythematosus.* Patients with fogo selvagem, however, have no evidence of lupus in biopsy specimens or on the basis of serologic studies; thus this terminology is not included in the proposed clinical classification.

Generalized forms. The case of a patient with generalized fogo selvagem may fall into three clinically distinct syndromes. (1) The bullous-exfoliative form affects patients with acute, aggressive disease, with a predominance of bullous lesions and a minor component of chronic erosive lesions resembling an exfoliative dermatitis (Figs. 4 and 5). In some of these patients fever, arthralgias, and general malaise are associated with the onset of the vesicular eruption, but bacteremia or sepsis are not found. This form of fogo selvagem may develop into life-threatening Kaposi's varicelliform eruption if affected patients are exposed to the herpes simplex virus (Figs. 6 and 7). Other superimposed infections such as dermatophytosis, scabies, and warts also are reported to complicate generalized fogo selvagem.¹³ The vesicular lesions are superficial, and in patients with active, untreated disease many of the blisters will be pustular. On occasion the vesicles form circinate or annular patterns, which, after rupturing, produce exfoliation that resembles tinea imbricata. (2) The second clinical form affects patients in whom typical exfoliative erythroderma develops. In these patients, confluent superficial erosions with crusting and serum exudate are the prominent lesions. This form affects both children and adults (Fig. 8). (3) The third generalized form affects those patients in whom keratotic plaques and nodular lesions, similar to those seen in chronic localized forms of the disease, are generalized (Fig. 9).

Hyperpigmented forms. It is interesting to note that hyperpigmentation syndromes are seen in patients undergoing remission.¹² The hyperpigmentation may be restricted to areas of previous lesions or may be diffuse and involve previously unaffected skin. Brazilian dermatologists who worked with these patients in the presteroid era thought that hyperpigmentation was the early indicator of a remission or cure of fogo selvagem (in Portuguese, *aurora da cura*). Their studies documented that clinical remission caused dramatic changes in their patients' skin color; for example, Caucasians looked like mulattoes, mulattoes became black, and

the skin of black patients acquired a deep gray-blue color.

Clinical evolution

For epidemiologic and statistical analysis of patients it is important to classify fogo selvagem in acute, chronic, relapsing, and inactive or cured cases. The following classification is proposed. (1) *Acute cases* involve those patients with a disease duration of fewer than 6 weeks. (2) *Chronic cases* involve those patients with a disease duration of more than 6 weeks. (3) *Relapsing cases* involve patients with chronic disease who have only a partial disease remission after therapy and experience a subsequent reactivation of the disease. (4) *Cured cases* are those in which a person is considered "cured" if neither active cutaneous lesions nor positive serologic findings occur for a period longer than 12 months.

Two of these clinical variants are more commonly observed in endemic pemphigus foliaceus than in Cazenave's pemphigus foliaceus. (1) It is not uncommon to encounter aggressive disease that quickly evolves into an exfoliative erythroderma that involves the entire body surface, which rarely is seen in Cazenave's pemphigus foliaceus. (2) Chronic disease with persistent verrucous nodules or plaques that resemble lesions of prurigo nodularis is a feature frequently observed in fogo selvagem.

Other curious complications of the disease are as yet unexplained.⁹ First, when children are affected with the disease, their normal growth becomes arrested, and if the disease persists for long periods they may suffer from dwarfism. If they are treated with oral corticosteroids, paradoxically, their growth will resume and they achieve near-normal stature. Second, azoospermia also has been observed in adult patients who had the disease as children. Finally, there may be some permanent changes in personality that accompany the disease. Many persons seem to become emotionally withdrawn; they are quiet, isolated, uncommunicative, and introverted, and they appear chronically depressed. The relationship of these symptoms to the cutaneous disease is not known.

HISTOPATHOLOGIC FINDINGS AND ULTRASTRUCTURE OF CUTANEOUS LESIONS

The cardinal histologic feature of fogo selvagem is the presence of an acantholytic intraepidermal vesicle located in the subcorneal region of the

*Silva JR, Peryassu D. Síndrome de Senear-Usher. Ann Bras Dermatol Sifilol 1938;13:63-4.



Fig. 9. In this form of fogo selvagem, chronic and persistent lesions that consist of hyperkeratotic nodules and plaques, which resemble those seen in prurigo nodularis, are present. This condition may occur in localized areas only, or it may be generalized.

Fig. 10. This woman had fogo selvagem throughout her pregnancy, with chronic lesions on the facial malar area and trunk. The titer for pemphigus antibodies was 1:320. She was delivered of a normal child who was free from cutaneous lesions. This course is typical of fogo selvagem inasmuch as neonatal pemphigus has never been reported to occur. In contrast, pemphigus neonatorum has been described several times in pemphigus vulgaris.

Fig. 11. Typical "pemphigus country" in the state of Parana in 1987 shows representative housing and landscape of patients. In the subtropical countryside, agricultural activity involves soybeans, corn, and cotton. The climate allows the harvesting of two crops per year. Most houses have outdoor plumbing, and infestations of rodents and insects are pervasive.

Fig. 12. Typical environment for children in the endemic areas. They are exposed to numerous biting insects, including the black fly, *Simulium pruinsum*, and numerous other parasites and vermin. To identify any single agent to which they are exposed that may precipitate the disease will be a substantial task.

epidermis. Acantholysis occurs only immediately above or below cells of the stratum granulosum. Some of these vesicles may be filled with neutrophils, and eosinophilic spongiosis may be present in some biopsy specimens.^{12,14,15} Similar features also may be seen in bullous impetigo and subcorneal pustular dermatosis, so that immunofluorescence studies are required to differentiate these conditions with certainty.²

Verrucous or vegetating plaques frequently are observed in the localized or chronic cases of fogo selvagem. Histologic examination reveals acanthosis, hyperkeratosis, parakeratosis, and papillomatosis. Acantholysis also is present in these lesions.^{12,14,15}

In cases in which there is hyperpigmentation, such as disease in remission, although there is melanocytic proliferation within the epidermis and a consequent increase in epidermal pigment, pigment incontinence with melanin accumulation in dermal phagocytes is the primary abnormality.¹⁵

The ultrastructural features of the epidermal lesions of fogo selvagem have been well documented.^{8,16} Although by light microscopy there is acantholysis only of suprabasilar cells, by electron microscopy the cell-cell adhesion of all layers is affected to varying degrees. There is documentation in several studies that there is partial cell-cell detachment on the lateral surfaces of the basal cell layer that extends outward toward the stratum spinosum and granulosum. The cell-cell detachment is more prominent in the upper layers of the stratum spinosum, and acantholysis is finally observed in the cells of the granular layer. The stratum corneum forms the roof of the vesicle and the stratum spinosum the floor. It is also documented that as the cell-cell detachment increases, there is a progressive loss of desmosomal structures.* The gradual loss of desmosomes is associated with perinuclear retraction of tonofilaments and rounding up of the keratinocyte.

Immunoelectron microscopy shows that pemphigus autoantibodies bind diffusely on the cell surface of the keratinocytes, and there is no restriction of antibody binding to desmosomes.¹⁶ This point is relevant because, as mentioned later, the pemphigus foliaceus antigen has been isolated from desmosomal preparations.

*Barros C. Ultraestrutura da lesão bolhosa e do sinal de Nikolski no penfigo foliaceo [Thesis]. Sao Paulo, Brazil: Faculdade de Medicina da Universidade de Sao Paulo; 1972.

IMMUNOLOGIC ABNORMALITIES IN FOGO SELVAGEM

A consistent feature of the disease is the presence of high titers of autoantibodies against the cell surface of keratinocytes, demonstrable by immunofluorescence in lesional skin and circulating in the serum.*, †, ^{2,17} The fluorescence pattern produced by fogo selvagem autoantibodies is identical to that produced by pemphigus vulgaris antibodies. There is no preferential binding of IgG in the subcorneal layers of the epidermis on biopsy or in superficial cells of skin or monkey esophagus when serum is examined. Although mucosal lesions do not occur in this disease, it is surprising to note that the majority of patients have in vivo bound pemphigus autoantibodies in the intercellular spaces of the oral and esophageal mucosa.‡ It is interesting to speculate why these antibodies may bind to mucosal epithelium but do not produce lesions.

We have personally obtained and examined biopsy specimens of 19 patients with the disease by direct immunofluorescence and have performed indirect immunofluorescence assays on the serum of 196 patients, 138 relatives of these patients, and 95 unaffected persons who live in endemic areas of Brazil. Positive direct immunofluorescence staining for IgG on cell surface of affected epidermis was present in all 19 biopsy specimens. Circulating antibodies were found in all patients with active disease, and there was a good correlation between a high titer of antibody and extensive disease. Of the 138 relatives examined, none had circulating pemphigus antibodies, and none of the indirect immunofluorescence results of the 95 controls from unaffected, unrelated Brazilians showed positive findings. This study indicated that pemphigus antibodies are highly specific for the disease and are not present in other persons living in the endemic regions. It is important to note that indirect immunofluorescence assays for pemphigus foliaceus antibodies are much more reliable and

*Rivitti EA. Eletroforese, imunoeletroforese, antiestreptolisina "O" e anticorpos antiepitélio, no penfigo foliaceo Sul-Americano. Estudo evolutivo [Thesis]. Sao Paulo, Brazil: Faculdade de Medicina da Universidade de Sao Paulo; 1972.

†Odo MEY, Rodrigues RL, Miyauchi L. Imunofluorescência direta em biópsia de pele no penfigo foliaceo. *Ann Brasil Dermatol* 1981;56:131-4.

‡Takahashi MDF. Imunopatologia do penfigo foliaceo Sul-Americano. Estudo por imunofluorescência direta e imunofluorescência indireta [Thesis]. Tese, Sao Paulo, Brazil: Faculdade de Medicina da Universidade de Sao Paulo; 1981.

have better detection of antibody if calcium is incorporated into the buffer.¹⁸

A significant contribution in understanding the pathogenesis of the acantholytic lesions of pemphigus has been the demonstration that the antiepidermal autoantibodies produced by patients with pemphigus vulgaris and fogo selvagem are pathogenic to the epidermis of experimental animals. Passive transfer of these autoantibodies into neonatal mice reproduces the clinical, histologic, ultrastructural, and immunologic findings of the human disease, establishing that they play a primary role in inducing the disease in human beings.^{19,20} The notable finding in these studies demonstrated that fogo selvagem antibodies infused into neonatal mice specifically cause acantholysis only within the granular cell layer of the epidermis. On the other hand, antibodies from patients with pemphigus vulgaris produce suprabasilar acantholysis under the same conditions. This shows that the lesions produced by passive transfer of human fogo selvagem and pemphigus vulgaris autoantibodies are as distinct in the animal model as they are in the humans from whom the antibodies are obtained. In view of the success of these experiments, it is curious that neonatal pemphigus caused by placental transfer of maternal autoantibodies has been reported in pemphigus vulgaris²¹⁻²² but does not occur in fogo selvagem even in cases where the mother of the newborn child had extensive and active disease (Fig. 10).*

There are only a handful of human autoimmune diseases in which binding of autoantibodies to the target tissue alone have been shown to produce all the features of the disease. The list now includes fogo selvagem, pemphigus vulgaris, Goodpasture's syndrome, myasthenia gravis, and Lambert-Eaton syndrome.²³⁻²⁵ Thus these two dermatologic diseases join the rare group of human autoimmune diseases in which passive transfer of human autoantibodies reproduce the features of the human disease in recipient animals.

The molecular mechanisms of acantholysis in fogo selvagem are not clear. It is tempting to speculate that the pemphigus foliaceus antigen is a molecule that is critical to normal cell-cell adhesion in the granular cell layer of the epidermis. Binding of the antibody to this antigen may interfere with

its normal function, and the cells fall apart. It is unlikely that this simple hypothesis can explain the pathophysiologic findings completely. Recent studies^{26,27} seem to indicate that complement activation may be implicated in the epidermal cell-cell detachment. This observation is based on in vitro studies that demonstrate that fogo selvagem autoantibodies potentiate their role in epidermal cell detachment in the presence of complement. In addition, the role of plasminogen activator, a protease whose production is stimulated after pemphigus antibody binding, may be important in the development of acantholysis.²⁸

Recent studies by Stanley et al.⁶ provide substantial data regarding the identity of the antigen to which these autoantibodies bind. Their data show the following. The keratinocyte surface antigen recognized by fogo selvagem sera appears to be a desmosomal core glycoprotein that has been named *desmoglein I*, a term derived from *desmo*, which refers to the desmosomal origin of the protein, and *glein*, which translates as *glue* and refers to the proposed function of the antigen as a cell adhesion molecule. Desmoglein I also is recognized by sera from patients with Cazenave's pemphigus foliaceus, which underscores the fundamental similarities between these two forms of the disease. Only ~30% of patients' autoantibodies will bind desmoglein I when immunoblotting techniques are used, which by necessity employs antigen denatured by exposure to an ionic detergent, sodium dodecyl sulfate (SDS). Essentially, however, all patients' sera will recognize this glycoprotein when nondenatured antigen (by an immunoprecipitation technique) is incubated to antibody in the presence of calcium. This would seem to provide the biochemical basis for what our laboratory observed in indirect immunofluorescence tests. That is, the antibody in some patients recognizes an epitope, or region, of the glycoprotein that requires the presence of a calcium ion to express its antigenicity. In summary, both Cazenave's pemphigus foliaceus and endemic pemphigus foliaceus autoantibodies seem to be directed against a calcium-dependent epitope on the desmosomal glycoprotein, desmoglein I.

We have identified two other interesting immunologic abnormalities in fogo selvagem. The first abnormality is the elevation of serum levels of the thymic peptide, α_1 -thymosin,²⁹ and the second is the identification in these patients' sera of autoantibodies highly specific for the 59-kilodalton acidic

*Proenca NG, Proenca YM, Guedes M. Gravidez em doentes com penfigo foliaceo Sul-Americano (fogo selvagem). *Ann Brasil Dermatol* 1979;54:239-44.

murine keratin and its 56.5-kilodalton human counterpart.³⁰

α_1 -Thymosin, a peptide produced by thymic epithelium, promotes maturation of T cells. Elevation of serum levels of α_1 -thymosin has been reported to occur in viral diseases such as acquired immunodeficiency virus,³¹ influenza, and other infectious diseases. We found that patients with fogo selvagem have extremely elevated levels of serum α_1 -thymosin and that these elevations were not observed in relatives or unaffected persons from endemic areas. This observation provides circumstantial evidence for a putative infectious cause for the disease.

The observation that some patients may also have high-titer antibody specific for a single human or murine keratin also may be relevant.³⁰ Autoantibodies against intermediate filaments, for example, keratins and vimentin, are found in rheumatic diseases³¹⁻³³ and viral infections such as measles, viral hepatitis, and infectious mononucleosis.³⁴ Certain viral antigens may share a certain degree of homology with intermediate filaments, which may be responsible for production of cross-reactive antibodies.³⁵ The relevance of the antikeratin autoantibodies detected in the serum of approximately 20% of patients with fogo selvagem to the cause or pathogenesis of the disease is not clear, but it is an additional piece of what is becoming substantial circumstantial evidence for an environmental or infectious cause for the disease.

A study published several years ago³⁶ showed that patients with fogo selvagem have a 30% reduction in the total peripheral T lymphocyte counts, when compared with controls (32% vs 46%) and depletion of T lymphocytes from the paracortical areas of lymph nodes. The numbers of B lymphocytes were found to fall within the normal range. It also has been reported that the sera of patients with fogo selvagem contain high titers of antistreptolysin antibodies, which, however, showed no correlation with either disease activity or the titers of pemphigus autoantibodies.*

Studies searching for evidence of other autoantibodies, such as antinuclear antibodies (ANA), anti-nDNA antibodies, or precipitin antibodies against Sm, nRNP, SSA/Ro, and SSB/La, have all showed negative findings.³⁷

*Rivitti EA. Electroforese, immunoelectroforese, antistreptolisina "O" e anticorpos antiepitelio, no penfigo foliaceo Sul-Americano. Estudo evolutivo [Thesis]. Sao Paulo, Brazil: Faculdade de Medicina da Universidade de Sao Paulo; 1972.

TREATMENT AND PROGNOSIS

The cutaneous eruption of the great majority of patients with fogo selvagem responds to treatment with systemic corticosteroids alone. In a few patients, however, despite the use of steroids, the disease runs a chronic course, and all the side effects of the therapy, for example, Cushing's syndrome and osteoporosis, occur. These patients usually demonstrate verrucous plaques on the trunk and extremities, which are extremely resistant to therapy.*

It is thought that local fluorinated steroids may promote the healing of some lesions and are used as an adjuvant to systemic therapy. It is the experience of Brazilian dermatologists that systemic triamcinolone (usual starting dose, 48 mg/day) is superior to prednisone in the treatment of fogo selvagem because they believe that the incidence of steroid side effects is lower with this preparation. Immunosuppressive agents³⁸ and gold compounds† also have been used with moderate to good success. Other modalities employed in the past and reported to induce remissions of the disease include the use of a tar plus benzoic acid paste (Jamarsan) and antimalarial agents.‡,39

The mortality rate of fogo selvagem was radically altered after the advent of systemic steroids. Approximately 40% to 60% of patients died of their disease in the 1930s and 1940s.^{12,14} Presently less than 10% of the patients die, often as a result of complications of the steroid therapy, such as superimposed bacterial infection. In addition, Kaposi's varicelliform eruption is a frequently fatal complication.¹³

Spontaneous remission of fogo selvagem was expected in approximately 20% of cases reported by Vieira^{12,14} before steroids were available for treatment. Such remissions also were observed in both localized and generalized forms of the disease. Aranha-Campos⁴⁰ calculated that less than 7% of the generalized cases of fogo selvagem may go into remission (40 of 604 patients included in his series). A notable example of spontaneous remission occurred in the wife of a Seventh-Day Adventist

*Proenca N, Nanni ME, Castro RM. Estudo clinico das lesoes resistentes a corticoterapia em doentes de penfigo foliaceo sul-americano. *Dermatol Ibero Latino-Am* 1971;13:213-22.

†Auad A, Auad T, Auad A, Auad P. Terapeutica coadjuvante no tratamento do penfigo foliaceo sul-americano com auranofina. Estudo duplo-cego. *Ann. Bras. Dermatol.* 1986;61:131-4.

‡Lemos-Torres U. Penfigo foliaceo. *Arq Med Municipais* 1956;8:75-176.

priest and was the subject of a popular book, *Savage Fire*.⁴¹ We had the opportunity to examine this patient some 40 years after her clinical remission; she was in good health, and her serum was negative for pemphigus autoantibodies. This patient was treated with tar plus benzoic acid. After her recovery she had more children, all of whom are in good health.

It is frequently observed by Brazilian dermatologists that many patients move to the city to receive treatment and enter into a stable remission. If, while they are being maintained on therapy, those persons return to the area from which they came, the disease will recur and fail to respond to therapy. On their return to the city the disease will again be much easier to control. This is additional "soft" evidence for an environmental factor that may stimulate the autoimmune response.

ETIOLOGY

Substantial epidemiologic evidence exists that fogo selvagem may be precipitated by an environmental factor, but that factor has not yet been identified.¹⁰ As mentioned earlier, most affected persons live and work in a characteristic environment (Figs. 11 and 12). The vast majority live on or close to rivers and streams. The peak incidence of new cases of fogo selvagem occurs at the end of the rainy season, when insects are most abundant. Most affected persons report massive exposures to biting insects, including a black fly called *borrachudo* (*Simulium pruinsum*). The distribution of *S. pruinsum* is the same as the distribution of endemic areas. On the Atlantic coast of Brazil where fogo selvagem does not occur, a different species of black fly, *S. pertinax*, is found. From personal observation, it is, however, obvious that these affected persons are exposed to many environmental agents. They usually live in poor housing with infestations of rodents, many biting insects, fleas, and occasionally other insect vectors such as reduviid bugs (Figs. 11 and 12). They have pets and domestic animals, and sanitation is primitive. To identify a single agent that may precipitate the disease amidst this state of "biologic pollution" will be a formidable task.

Although there are numerous cases where more than one household member may be affected, there has never been a reported case of transmission of the disease to hospital personnel or transmission through blood products or bodily fluids. There have been numerous attempts to isolate an infectious

agent, all of which were either unsuccessful or nonreproducible. Blood, serum, and blister fluid from patients have been injected into animals and cell cultures, and no viral agents have been found in these cultures.^{12,14,42} The studies on viral isolation must, however, be repeated with the use of modern techniques.

Both pemphigus vulgaris and pemphigus foliaceus have been reported to occur in domestic animals in North America, including cats, dogs, goats, horses, and baboons,⁴³⁻⁴⁵ but there have been no observations of a pemphigus foliaceus-like disease affecting either domestic or wild animals in the endemic regions of Brazil.

Strong circumstantial evidence exists that certain drugs may induce pemphigus foliaceus or a pemphigus foliaceus-like cutaneous disease. Recent reports implicate penicillamine,^{46,47} captopril,⁴⁸ and rifampin⁴⁹ as the causative drugs in many of these cases. Patients affected with fogo selvagem generally are not taking any drugs, and there is no evidence that they are exposed to chemical toxins or pollutants that may precipitate the disease.

There is also some evidence that genetic factors may play a role in the development of pemphigus. Although pemphigus vulgaris occurs in all ethnic and racial groups, there is a higher incidence in Jews, in whom there is an increased prevalence of the human leukocyte antigen (HLA)-DRw4 phenotype.⁵⁰⁻⁵¹ Recently, the authors of a study of the genetics of pemphigus vulgaris by restriction fragment length polymorphism analysis reported striking results.⁵² They confirmed that almost all affected persons have the HLA phenotype DR4 or DRw6. In addition, using cDNA probes for the HLA-DQ α and β genes of the major histocompatibility complex, they found a unique and specific HLA-DQ β restriction fragment in almost all patients with pemphigus vulgaris that was not detected in the control groups. The specificity of this finding suggests that there may be genes within the major histocompatibility complex that confer susceptibility for autoimmune disease to the host. Potentially, it may be possible to define precisely the gene that predisposes persons to development of pemphigus vulgaris and subsequently for pemphigus foliaceus.

Rarely, pemphigus has been associated with other autoimmune disorders such as lupus erythematosus (Senear-Usher syndrome), rheumatoid arthritis, myasthenia gravis, pernicious anemia,

Hashimoto's thyroiditis, and benign thymomas,⁵³⁻⁵⁴ which may corroborate the frequently observed tendency of multiple autoimmune diseases to occur in certain kindred.⁵⁵

In a study of 2686 patients with fogo selvagem, there were 485 cases in which more than one household member was affected.* In these cases 93% occurred in genetically related members of the household (e.g., father, son, and siblings), and only 7% of cases occurred in unrelated household members (e.g., husband and wife). These data seem to indicate that genetic predisposition to development of the disease may be an important factor in its cause. Studies to define the frequency of extended HLA haplotypes have not been performed in patients and relatives with fogo selvagem, largely because the disease occurs in rural parts of Brazil, where the money to pay for such studies and the technical expertise required to perform them do not exist. In 1980 Patrus† examined fogo selvagem patients for the frequency of HLA-A and B loci and found a significant increase of HLA-B16 in patients under 2 years of age, and HLA-A26 and A24 in older patients.

SUMMARY

It is the hope of the members of the Cooperative Research Group for the Study of Fogo Selvagem that this article will provide (1) a proposed clinical classification for standardizing a description of the disease, (2) a brief summary of current knowledge about histologic and immunologic abnormalities observed in these patients, and (3) a brief summary of what is known about the putative agent(s) that may precipitate this disease, presumably in genetically predisposed persons.

We hope that ongoing studies involving more careful and prospective epidemiologic studies in Brazil, as well as basic investigations performed in both Brazil and the United States, may provide insight into the actual cause of this remarkable human autoimmune disease.

*Auaud A. Penfigo foliaceo Sul-Americano no Estado de Goias. *Rev Patol Trop* 1972;1:293-346.

†Patrus ORA. Antigenos de histocompatibilidade, imunocomplexos e complemento no penfigo foliaceo [Thesis]. Minas Gerais, Brazil. Faculdade de Medicina, Universidade Federal de Minas Gerais; 1980.

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