The past few years has borne witness to an increased realization of the importance of pulmonary hypertension (PH), and schistosomiasis-associated PH, one of the most common causes of PH worldwide, is likely driven by the host response to parasite antigens. More than 200 million people are infected with schistosomiasis, the third most common parasitic disease, and approximately 1% of those chronically infected develop PH. Acute cutaneous infection causes inflammation at the site of parasite penetration followed by a subacute immune complex-mediated hypersensitivity response as the parasite migrates through the lungs. Chronic schistosomiasis infection induces a granulomatous inflammation around ova deposited in the tissue. In particular, *Schistosoma mansoni* migrates to the portal venous system and causes preportal fibrosis in a subset of individuals and appears to be a prerequisite for PH. Portal hypertension facilitates shunting of ova from the portal system to the pulmonary arterial tree, resulting in localized perivascular pulmonary granulomas. The pulmonary vascular remodeling is likely a direct consequence of the host inflammatory response, and portopulmonary hypertension may be a significant contributor. However, therapies available for PH have not been widely tested in patients with schistosomiasis and often are unavailable for those infected in resource-poor areas of the world where schistosomiasis is endemic. Furthermore, the current PH therapies in general target vasodilation rather than vascular remodeling and inflammation. Further research is needed into the pathogenic mechanism by which this parasitic infection results in pulmonary vascular remodeling and PH, which also may be informative regarding the etiology of other types of PH.

**Schistosomiasis-Associated Pulmonary Hypertension**

Brian B. Graham, MD; Angela Pontes Bandeira, MD; Nicholas W. Morrell, MD; Ghazwan Butrous, MD; and Rubin M. Tuder, MD

Inflammation is likely a critical underlying etiology in many forms of severe pulmonary hypertension (PH), and schistosomiasis-associated PH, one of the most common causes of PH worldwide, is likely driven by the host response to parasite antigens. More than 200 million people are infected with schistosomiasis, the third most common parasitic disease, and approximately 1% of those chronically infected develop PH. Acute cutaneous infection causes inflammation at the site of parasite penetration followed by a subacute immune complex-mediated hypersensitivity response as the parasite migrates through the lungs. Chronic schistosomiasis infection induces a granulomatous inflammation around ova deposited in the tissue. In particular, *Schistosoma mansoni* migrates to the portal venous system and causes preportal fibrosis in a subset of individuals and appears to be a prerequisite for PH. Portal hypertension facilitates shunting of ova from the portal system to the pulmonary arterial tree, resulting in localized perivascular pulmonary granulomas. The pulmonary vascular remodeling is likely a direct consequence of the host inflammatory response, and portopulmonary hypertension may be a significant contributor. New specific therapies available for PH have not been widely tested in patients with schistosomiasis and often are unavailable for those infected in resource-poor areas of the world where schistosomiasis is endemic. Furthermore, the current PH therapies in general target vasodilation rather than vascular remodeling and inflammation. Further research is needed into the pathogenic mechanism by which this parasitic infection results in pulmonary vascular remodeling and PH, which also may be informative regarding the etiology of other types of PH.

**CHEST 2010; 137(6)(Suppl):20S–29S**

**Abbreviations:** BMPR2 = bone morphogenetic protein receptor type 2; IL = interleukin; IPAH = idiopathic pulmonary arterial hypertension; PH = pulmonary hypertension; PZQ = praziquantel; RELM-a = resistin-like molecule a; TGF-ß = transforming growth factor ß; Th-2 = T-helper2

1% and 5% of patients with COPD or interstitial pulmonary diseases develop severe PH characterized by mean pulmonary artery pressures in excess of 40 to 45 mm Hg. Pulmonary vascular injury due to inflammation remains the most probable cause in the...
enlargement (Fig 1).

She was born and grew up in a small town outside Recife, in a region where schistosomiasis is endemic, and she had worked as a sugar cane farmer for 25 years. She had a history of multiple unexplained syncopal episodes beginning at age 17. At the time of presentation, she complained of significant progressive shortness of breath with minimal exertion (World Health Organization functional class III), palpitations, and intermittent chest pain. She had never smoked or used anorexigens. She was born and grew up in a small town outside Recife, in a region where schistosomiasis is endemic, and she had worked as a sugar cane farmer with multiple exposures to fresh water.

On physical examination, the patient was thin and in respiratory distress. Her BP was 100/70 mm Hg, and heart rate was 56 bpm. She had prominent jugular venous distention, and cardiac auscultation revealed a regular rhythm with an S3, a loud P2, and a loud systolic murmur at the lower left sternal border. Her lungs were clear. The liver was enlarged at 8 cm below the right costal margin, and the spleen was enlarged at 6 cm below the left costal margin. Peripheral edema was present. Her electrocardiogram showed evidence of right atrial and right ventricular enlargement (Fig 1A). Chest radiographs demonstrated a very enlarged heart (Fig 1B). Echocardiography revealed severe enlargement of the right ventricle and right atrium, severe tricuspid regurgitation, and an estimated tricuspid valve pressure gradient of 121 mm Hg (Figs 1C, 1D). The patient was able to ambulate 338 m in 6 min.

The patient was started on an oral phosphodiesterase type 5 inhibitor (sildenafil), and her 6-min walk distance improved to 385 m. A right-sided heart catheterization was later performed, which found a right atrial pressure of 28 mm Hg, right ventricular pressure of 110/22 mm Hg, and a pulmonary artery pressure of 110/43 mm Hg, with a mean of 71 mm Hg. Three years later, she developed recurrent dyspnea, and an oral endothelin receptor antagonist (bosentan) was added. Four months after that, she represented with worsening dyspnea and dizziness and was found to be hypotensive, requiring treatment with vasoactive medications. An emergent atrial septostomy was performed, resulting in an increase in the patient’s cardiac output. Unfortunately, she then developed nosocomial urosepsis and died. On autopsy, the patient had an enlarged liver and heart. Histology of her lung tissue showed characteristic findings of PH (Figs 1E, 1F).

THE GLOBAL IMPACT OF SCHISTOSOMIASIS

Schistosomiasis is the third most common parasitic disease after malaria and amebiasis, affecting about 200 to 300 million people in 74 countries, 85% of whom live in sub-Saharan Africa. Almost 500 to 800 million people are at risk for acquiring the infection that accounts for >250,000 deaths per year. It causes up to 4.5 million disability-adjusted life year losses annually due to factors such as anemia, pain, diarrhea, exercise intolerance, and undernutrition that results from chronic infection. The infection imparts a major health burden in endemic areas, mostly in developing countries, largely because of reinfection of individuals allied to poor sanitary conditions, new economic development such as the construction of dams, and natural disasters such as flooding. In spite of the availability of therapies such as praziquantel (PZQ), which is a single-dose monotherapy used worldwide in community-based programs to control schistosomiasis (see “PH and Schistosomiasis-Specific Treatment Options” later in this article), significant social and economic hurdles make the total control of this disease a very difficult task and make drug treatment alone inefficient.

SCHISTOSOME, THE PARASITE

Schistosomiasis is an ancient and chronic disease of humans, nonhuman primates, other mammals, and birds. It is also known as bilharzia, or snail fever, and is caused by several species of the genus Schistosoma.
These parasites are flatworm flukes of the trematoda class. The main species to infect humans is *Schistosoma mansoni* (also known as Manson blood fluke or swamp fever). The worm has two hosts in its life cycle (Fig 27) and involves many steps. Snails of the *Biomphalaria* genus are the preferential intermediate host in the asexual cycle. *Schistosoma japonicum* is endemic in China and Southeast Asia, where it uses snails in the *Oncomelania* genus as its intermediate host, ultimately affecting the intestinal and hepatic circulatory system, preferentially the superior mesenteric veins. *Schistosoma mekongi*, found in Cambodia and Laos, affects both the superior and inferior mesenteric veins. *S mekongi* is related to *S japonicum* but has smaller eggs, a different intermediate host, and a longer preclinical period in the mammalian host. *Schistosoma hematobium* (also known as bladder fluke) is endemic in Africa, the Middle East, India, and East Asia. The adult worm resides in the venus plexus of the bladder, but it also can be found in the rectal venules. Their intermediate host is of the *Bulinus* genus.

The sexual cycle of *Schistosoma* occurs in vertebrates. Both male and female worms are separate organisms (diecious), which after mating, produce many thousands of eggs for up to 30 years. The female separates from her mate to migrate to the venules of the organ specific to the species to deposit her eggs.
such as the lumen of the intestine (S. mansoni and S. japonicum) or the bladder and ureters (S. hematobium). Adult worms have a 2- to 4-mm thick natural outer tegument, which is believed to enable the worm to evade the host immune system and therefore explain the prolonged longevity of the worm in the host bloodstream.

The eggs are eliminated by the urine (in the case of S. hematobium) and feces (in the cases of S. mansoni and S. japonicum) into the water. Under favorable environmental conditions, the eggs hatch within 30 min, releasing a ciliated larva, called miracidia, that swim and penetrate the specific snail intermediate hosts within 1 to 24 h. Within the snail, the miracidia undergo various transformations with asexual multiplication into primary and secondary saclike structure called sporocytes. The sporocytes migrate to the snail hepatopancreas and start to divide again, producing large numbers of new parasitic forms known as cercariae. Cercariae are 1 mm long and have a characteristic forked tail. Over several weeks, thousands of cercariae may be released from an infected snail, often following a daily circadian rhythm coinciding with the moon or early sunlight, a time in which there is human-water contact activity. In S. hematobium, 4 to 8 weeks elapse from the penetration of the miracidia to the liberation of cercariae, whereas in S. mansoni, under optimum conditions, only 4 weeks are necessary. The cercariae remain swimming in fresh water, using a whip-like tail, for a
maximum of 48 h. They can penetrate the skin of people working or bathing in the infected water in 3 to 5 min using proteolytic enzymes. The most common way of contracting schistosomiasis in developing countries is by direct contact with infected water. Daily activities such as walking, bathing, and swimming or even just foot contact with shallow water may suffice to allow infection to occur. (For a general review, see Lewis, Ross et al, Mahmoud, and Davies and McKerrow. In this context that schistosomiasis constitutes a major health burden worldwide.

**ACUTE SCHISTOSOMIASIS INFECTION**

After penetration, the cercariae may remain in the skin for 1 to 2 days. At the site of penetration, the parasite leaves behind an itchy punctate rash, called cercarial dermatitis, that self-resolves after the parasite leaves. The cercaria accesses the bloodstream through the postcapillary venules and undergoes transformation into schistosomulum prior to becoming an adult worm. Migration through the venous system continues, and the parasite reaches the lungs. At this stage, schistosomiasis infection causes a subacute and self-limiting illness known as Katayama fever. Cercarial dermatitis and Katayama fever particularly occur in people infected for the first time, such as tourists, rather than in chronically and recurrently infected residents of endemic regions. Katayama fever is an immune complex-mediated hypersensitivity response to the parasite antigens. The illness is characterized by fevers, chills, dyspnea, a dry cough, fatigue, and GI symptoms, including diarrhea and abdominal pain, lasting about 4 to 6 weeks. The symptoms are reminiscent of the flu and often are misdiagnosed unless an astute clinician connects the clinical scenario with potential exposure to contaminated water. Chest radiograph can show diffuse infiltrates, and laboratory studies will reveal peripheral eosinophilia.

Once in the lungs, the parasite undergoes another developmental change within 1 week to enable subsequent migration to the systemic circulation toward the targeted organ. The parasite begins to feed and find a mate, with the female worm residing in the gynaecophoric channel of the male. They begin to produce eggs (about 300 eggs/day for *S. mansoni*) and may produce up to 3,000 eggs/d (for *S. japonicum*). Mature eggs are capable of passing through tissues (possibly through the release of proteolytic enzymes), and the majority reach the urine or stool. Some eggs, however, become trapped in the small venules, where the antigens can elicit a vigorous immune response, resulting in the cellular pathology classically associated with schistosomiasis.

Much of the immunologic etiology for the host response to schistosomiasis infection has been determined using murine models. The initial reaction to schistosomiasis infection is a T-helper 1 (Th-1) response mediated by type 1 lymphocyte subset CD4+ helper T cells. The stimulation of this specific subset is likely due to the antigens released by schistosomules (adult worms) and then the ova, and during acute infection, the host has elevated serum levels of tumor necrosis factor-α, interleukin (IL)-1, IL-6, and interferon-γ. However, as the infection becomes more chronic and the main antigenic exposure transitions to ova antigens, the immunologic response becomes dominated by type 2 lymphocyte subset CD4+ helper T cells (T-helper 2 [Th-2]).

**PORTAL FIBROSIS: A POTENTIAL PRECURSOR TO CHRONIC PULMONARY DISEASE**

A minority of the eggs released by the reproducing adult worms remain within the host. For *S. mansoni* and *S. japonicum*, the retained ova remain within the portal venous system, either in the intestinal mucosa or in the small portal veins within the liver. Within the liver, the ova become niduses for periovular epitheloid granulomatous reactions as the immune system attempts to encapsulate the parasite. Although these lesions result in eventual egg destruction, they also lead to tissue destruction due to progressive fibrosis. The granulomas are complex and dynamic, beginning with eosinophils and neutrophils, effec- tively forming periova microabscesses. The lesions then transition to contain more lymphocytes and macrophages, particularly alternatively activated macrophages that contribute to the Th-2 response, and fibrocytes appear located around the periphery of the lesions. Collagen deposition then becomes predominant, and the granulomas are replaced with fibrotic lesions, which may be around the remnants of disintegrated ova. Cytokines that are stimulated are those of a Th-2 immunologic response, including IL-4, IL-5, IL-10, IL-13, and resistin-like molecule α (RELM-α). IL-4 and IL-13 in particular appear to be associated with the granulomatous response, whereas IL-13 regulates the transition to hepatic fibrosis. IL-5 drives the recruitment of eosinophils, which in turn contribute IL-13.

Five percent to 10% of patients chronically infected with schistosomiasis develop the hepatosplenic form of the disease. In this severe form of schistosomiasis infection, periovular granulomas in periportal spaces result in periportal fibrosis associated with vascular changes, which leads to a characteristic pathology.
called Symmers pipestem fibrosis. Chronicity, reinfection, and coinfection; poor nutrition; altered immunologic status; coexisting viral hepatitis infection; environmental factors; and genetic factors may predispose certain individuals to overt liver disease. In patients with hepatosplenic disease, this fibrosis results in progressive portal venous system destruction, leading to the appearance of small vessels sprouting from the largest portal veins within portal triads. The consequence of hepatosplenic disease is portal hypertension and the opening of portosystemic shunts that allow the embolization of ova to the lungs. Other clinical complications of portal hypertension include esophageal varices, ascites, hepatomegaly, and splenomegaly. However, cirrhosis historically suppresses Smad2 and Smad3 signaling, which are destroyed more rapidly and more completely in the lungs than in the liver.

About 10% to 20% of patients with hepatosplenic disease and pulmonary granulomas also develop a concurrent progressive pulmonary arterial vasculopathy. The vasculopathy is diffuse but heterogenous, and the precise anatomic relation (if any) to perivascular granulomas or Schistosoma antigen is unclear. The vascular changes include increased thickness of the arterial media, thrombus, perivascular inflammation, and intimal remodeling (see the pathology from the case example in Fig 1). Intimal remodeling is the manifestation of localized endothelial cell proliferation, and pathologic forms of this remodeling include concentric lesions, dilated lesions, and plexiform lesions. These vascular pathologic transformations are strikingly reminiscent of the pathology of idiopathic pulmonary arterial hypertension (IPAH), leading to the most recent clinical PH classification to include schistosomiasis-associated PH within class I, the same class as IPAH. The actual burden of ova in the lungs is heterogenous, and embolic obstruction alone likely is only a minor contributor to the increased pulmonary vascular resistance.

Although the etiology of schistosomiasis-induced vascular remodeling and PH remains unclear, the cytokines released by cells within the granulomas may act as triggers or enhancers of the pulmonary vascular disease. A unifying hypothesis may link these disease-specific events (ie, Th-2 responses to schistosoma eggs) to signaling pathways shown to be relevant in pulmonary arterial hypertension, particularly in IPAH. Specifically, many of the cytokines that are upregulated as a consequence of schistosomiasis infection are known to be important in other clinical and experimental models of vascular remodeling and PH. Current hypotheses of severe pulmonary arterial hypertension have highlighted that abnormal cell proliferation with impaired cell death may underlie the pulmonary vascular pathobiology. Many of these events resemble neoplastic processes, including the recent observation of somatic mutations in lungs of patients with IPAH and clonality within IPAH plexiform lesions. Whether similar events account for schistosomiasis-associated PH remain to be determined.

Following the bone morphogenetic protein receptor type 2 (BMPR2) paradigm in which loss-of-function mutations are present in many cases of familial as well as sporadic IPAH, alterations in the downstream signaling mediators of BMPR2 also may be present in schistosomiasis infection. BMPR2 normally suppresses Smad2 and Smad3 signaling, which are both downstream mediators of the transforming growth factor beta (TGF-β) signaling pathway. This observation is consistent with the findings of increased TGF-β expression in lungs from patients with schistosomiasis-associated PH.

### Pulmonary Periovular Granulomas and Vascular Remodeling: What Is the Link?

In patients with portal hypertension, Schistosoma eggs embolize into the lungs where they lodge in small muscular arteries and induce isolated granulomas. Andrade and Andrade reported that among 78 persons with hepatosplenic schistosomiasis, 72% had periovular granulomas. One-third had numerous periovular granulomas involving the alveolar tissue and the pulmonary arterioles. The cellular components of the pulmonary granulomas include eosinophils, macrophages, leukocytes, and fibroblasts as well as the residual components of the vessel that has been infiltrated by inflammation (smooth muscle cells and endothelial cells) and remnants of the pulmonary parenchyma (type 2 alveolar cells) that have been occupied by enlarging inflammation. These lesions are Th-2 driven, including cytokines IL-4, IL-13, and RELM-α. There is evidence that eggs are destroyed more rapidly and more completely in the lungs than in the liver.

The present evidence indicates that portal hypertension appears to be an important contributor to the pathogenesis of pulmonary disease because most cases of PH associated with schistosomiasis develop in the setting of portal fibrosis. However, an alternative hypothesis is that portal fibrosis is an indicator of a more severe form of the host immune response to schistosoma antigens, as suggested by the presentation of PH in the absence of significant portal hypertension. Currently, it is unclear whether portal hypertension causes schistosomiasis-associated PH, but portosystemic shunting may be considered an important pathogenic mechanism for the development of the disease. Moreover, some patients with schistosomiasis also develop hepatopulmonary syndrome, which is seen in other contexts in patients with advanced liver disease, including liver cirrhosis.

**www.chestpubs.org**

**CHEST / 137 / 6 / JUNE, 2010 SUPPLEMENT**

25S
growth factor β (TGF-β) receptor. In human IPAH, there is evidence of increased Smad2 signaling in plexiform lesions, and TGF-β signaling is upregulated in monocrotaline and chronic hypoxia rat models of PH. Consistent with these findings, we have observed in mice infected with schistosomiasis that the pulmonary perivascular granulomas have significant expression of phosphorylated Smad2 (the active form) (Fig 3A), suggesting enhanced TGF-β signaling potentially in the context of BMPR2 suppression.

Furthermore, Th-2-specific signaling may lead to the release of mediators of pulmonary vascular remodeling. RELM-α, also called hypoxia-induced mitogenic factor, is upregulated by hypoxia and is necessary for the development of PH in the rat chronic hypoxia model. Upregulating RELM-α expression alone in the absence of hypoxia also causes PH. We have found an increase in RELM-α expression within the pulmonary granulomas of schistosomiasis-infected mice (Fig 3B). This expression is IL-13 dependent and could be contributing to the widespread vascular remodeling and resultant PH.

Given the relatively high incidence of schistosomiasis-associated PH (approximately 1% of all persons with chronic infection or between 10% to 20% of patients with the hepatosplenic form), it is conceivable that the disease is rather heterogeneous with regard to severity and pathogenesis, with mild and more severe forms. Investigations into whether the severe forms require additional genetic events compared with mild forms may provide key data for potential diagnosis and treatment.

The overall course of events leading to PH in the context of this common parasitic infection is complicated and remains largely unclear. A hypothesized paradigm for the pathogenesis of schistosomiasis-associated PH is presented in Figure 4.

**PH and Schistosomiasis-Specific Treatment Options**

It is apparent that schistosomiasis relies on persistent, recurrent, high-egg-burden chronic infection. The cycle can be interrupted with sanitation and education measures to prevent fresh water exposure to infectious cercariae. However, several cultural and economic hurdles prevent the successful implementation of these preventive measures. These difficulties underlie the global impact of schistosomiasis. Furthermore, patients with recurrent hemoptysis due to hepatosplenic disease in resource-poor settings often undergo surgical portocaval shunt placement to decrease the severity of portal hypertension, which unfortunately can dramatically worsen PH due to facilitated transfer of ova to the lungs.

For persons already infected, the best option is to target the egg burden. On the one hand, inroads into the treatment of the portal fibrosis also are predicted to combat the complication of PH. On the other hand, persons who already have an initiated process of pulmonary vascular disease rely on drugs that have been tested and validated in related diseases such as IPAH or scleroderma-associated PH.

Several medications are available to treat schistosomiasis infection. The primary medication is PZQ, an antihelmintic that is extremely effective against mature parasites, usually only requiring a single dose, and has minimal side effects. However, PZQ is not effective against immature parasites, and consequently, two doses several weeks apart are given in the setting of acute infection. In addition, due to the acute release of antigen with the death of the parasites, PZQ often is given concurrently with a course of corticosteroids. Arthemeter, an antimalarial with activity against schistosomiasis as well, is effective against the juvenile parasites but less effective for adult worms.
Consequently, artemether may be more effective for acute infection and can prevent Katayama fever. However, a prospective study of combination therapy with PZQ and artemether for acute infection found that the combination was safe but not more effective than PZQ alone.\textsuperscript{55}

In the setting of chronic infection, there is still a role for PZQ in newly diagnosed schistosomiasis-associated PH. Treatment will kill the adult worms that are releasing eggs, decreasing the ova burden and resulting in a lower antigenic load, all of which will decrease the signaling cascade resulting in vascular remodeling. However, the vascular remodeling appears to have a point of no return beyond which antiparasitic treatment alone will be ineffective in preventing further progression. Curative treatment can promote reversal of the perivascular granulomatous lesions formed in the alveolar tissue, but changes in the arterial and arteriolar lesions are defectively repaired, and the segmental vascular fibrosis, narrowing, and angiomatoid changes persist after treatment.\textsuperscript{56}

Medical treatment of schistosomiasis-associated PH specifically has not been well studied. Case reports and small series suggest that the treatments for PH studied in patients with other forms of PH can be reasonably extrapolated to schistosomiasis-associated PH.\textsuperscript{57} Unfortunately, however, these treatments often are not available to those infected with schistosomiasis in resource-poor areas. The only treatment with a mortality benefit for PH in a prospective trial is prostacyclin, which requires a continuous infusion due to the extremely short half-life.\textsuperscript{58} Inhaled iloprost is an alternative. Endothelin receptor antagonists antagonize vasoconstriction and block a pathway, promoting smooth muscle cell proliferation.\textsuperscript{59} Phosphodiesterase type 5 inhibitors effectively increase the activity of endogenous nitric oxide by inhibiting the breakdown of cyclic guanosine monophosphate, the nitric oxide mediator of pulmonary vasodilatation.\textsuperscript{60} Phosphodiesterase inhibitors may be of benefit in patients with schistosomiasis-associated PH, as evidenced by a study of seven patients demonstrating reversal of right ventricular hypertrophy and clinical improvement after 3 months of treatment.\textsuperscript{61}

Another study of 13 patients with severe schistosomal pulmonary hypertension showed a significant increase in functional class and 6-min walk distance after treatment with sildenafil for 6 months.\textsuperscript{62}

Future treatments specific for schistosomiasis-induced PH may include therapies designed to block the signaling pathways either in the inflammatory response or the resulting vascular remodeling. These therapies may include inhibitors of Th-2 signaling, such as IL-4 or IL-13 antagonists or TGF-β inhibitors. By extrapolation, these approaches also might have therapeutic potential in other forms of pulmonary arterial hypertension in which inflammation plays a major role. Other therapies that may prevent or reverse the vascular pathology in multiple forms of PH include antiproliferative therapies such as tyrosine kinase inhibitors or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors.\textsuperscript{63}

**ACKNOWLEDGMENTS**

**Financial/nonfinancial disclosures:** The authors have reported to CHEST the following conflicts of interest: Dr Bandeira has received speaking fees from Pfizer, Dr Butrous owns Shares in Pfizer Ltd and has participated in speaking activities and industry advisory committees. Drs Graham, Bandeira, Morrell, Butrous, and Tuder have disclosed that they are affiliated with the Pulmonary Vascular Research Institute.

**REFERENCES**


