
The Rise and Fall of Bilharzia in Puerto Rico: Its Centennial 1904-2004

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Its discovery in Egypt in 1851. Bilharzia (=schistosomiasis=esquistosomiasis=bilharziasis) is a chronic disease of humans in Africa, the Caribbean, South America and Asia caused by a parasite of the genus *Schistosoma*.

T. Bilharz first described it in Cairo on May 1st 1851 in an autopsy in which he found numerous flukes in the portal veins of the liver (Bilharz, 1853). The description noted a pair of clear flukes with the female inside the male "like a sword in its scabbard." The eggs were oval and pointed (with a spine) towards the end (i.e. terminal spine). Bilharz named this fluke *Distomum haematobium* (later designated *Schistosoma haematobium* as the schistosome with eggs having terminal spines).

Schistosomiasis is an ancient disease. Ruffer (1910) found calcified ova of *S. haematobium* in the kidneys of two Egyptian mummies from the XXth Dynasty (1184-1087 B.C.).

Bilharzia at the beginning of the XXth Century in Puerto Rico. Isaac Gonzalez Martinez established definitively the existence of human schistosomiasis in Puerto Rico in 1904 when he reported the discovery of fluke eggs in feces from two teenagers who had lived all their lives in the environs of Mayaguez, P.R. in the western part of the island (Gonzalez-Martinez, 1904). What he found were "huevos de bilharzia con espiculo lateral" and he identified it as *Bilharzia hematobia*. Gonzalez Martinez stated in his message that it was imported "durante la epoca vergonzosa de la esclavitud con los africanos, que los infames negreros nos importaron del Congo, Angola y Cafreria". He correctly observed the fact that in Puerto Rico schistosomiasis was in the intestinal form (the species with the oval egg with lateral spine) as compared with the genito-urinary form (the species harboring the oval egg with terminal spine). These eggs were shown to Drs. Ashford, Muñoz, & Hernandez in San Juan, Dr. Malaret from Yauco, Dr. Entenza from Cuba. In August, 1904 he performed an autopsy of a patient who "died of intense uncinariasis complicated by intestinal bilharziosis,

extracting from the trunk of the portal vein 219 schistosome flukes." By December 1904, Gonzalez-Martinez had identified 59 cases of 1321 fecal samples examined (4.5 % positive rate) and in 1905 he reported a single case from a patient from Santo Domingo, Dominican Republic. (see Gonzalez Martinez, 1916). "The first Anemia Commission of Porto Rico recorded 21 cases out of 5,000 anemia patients examined by them" (0.4 % positive). In 1913 the Institute of Tropical Medicine of Porto Rico recorded 320 cases from 10,140 patients for 3.16 % positives. By then, he reported that schistosomiasis prevails on the coasts of the Island and in those lowlands and valleys of the interior where cane is cultivated, but not in the mountain regions with the exception of Utuado, "founded in a damp valley crossed by two large rivers contaminated by human dejections" (Gonzalez-Martinez, 1916). It should be pointed out that the fecal examinations done were a relatively insensitive thin smear.

A major agricultural shift in Puerto Rico about 1905 from coffee to sugar was also influential. For example, in 1906, fecal samples from 600 individuals were examined for parasite eggs at the Guayama substation of the Anemia Commission. In these samples eggs of many common parasites were found, but no schistosome eggs. By 1909 over 2600 individuals had been examined with no schistosome eggs found in their feces. In 1914, an irrigation system for sugar cane had been constructed in the South Coast Irrigation System between Guayama and Patillas with an ensuing spread of schistosomiasis to this region reaching estimated highs of infection of 25 % between 1930 and 1950. Thus it is thought that sugar cane production spread the snails and infection via the irrigation systems in Puerto Rico with Guayama the "classic" example (Jobin, 1980).

Unfortunately, in terms of identifying a new parasite, in 1902 Sir Patrick Manson had described in England a single case of intestinal bilharziasis from a patient from the Caribbean island of Antigua finding oval eggs with lateral spines. Because of this observation, he suggested that there were possibly two different species of bilharzia, one with lateral and the other with terminal spines. Sambon (1907) gave the name *Schistosoma mansoni* to the bilharzia species that had oval eggs with lateral spines, in memory

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of Manson. The other species with terminal spine, found in Egypt but not in the Western Hemisphere, was the urinary tract schistosome, *S. haematobium*.

The 1920s. On September 22, 1926 the School of Tropical Medicine was formally inaugurated in San Juan, Puerto Rico. The architect of the classical building was Gonzalo Fernos (Ashford, 1934, p. 363). Coincidental with the School was *The Puerto Rico Journal of Public Health and Tropical Medicine* "Published Quarterly...of Each Year by the Department of Health of Puerto Rico and the School of Tropical Medicine of the University of Puerto Rico under the auspices of Columbia University." This was the first scientific journal in Puerto Rico. It should be noted that each article was printed back to back both in English and in Spanish. This frequently imposed on the Editors the need to adopt for translation new scientific concepts appearing in one or the other language. With the opening of the School of Tropical Medicine, there was renewed interest in schistosomiasis mansonii in the Island. Among many studies, Hoffman showed experimentally in 1927 that (*Helisoma*) *Planorbina guadeloupensis* (later denoted as *Australorbis glabratus*, and now as *Biomphalaria glabrata*) was the snail intermediate host. The pathological report for the first 3 years of the School of Tropical Medicine (1926-1929) showed that 30 of 225 (13.3 %) autopsies performed, mostly from the vicinity of San Juan, showed the presence of *S. mansonii* infection (see Faust, 1933b).

The 1930s. In a special article in the journal *Science* (1933a), E.C. Faust outlined the intensive studies to be undertaken in Puerto Rico by cooperative efforts of the School of Tropical Medicine of the UPR under the auspices of Columbia University and the Dept. of Tropical Medicine of Tulane University. These eight seminal, classical studies beginning with history, then on biological, pathological, clinical, and epidemiological aspects of schistosomiasis done for the most part in the 1930s are summarized below.

Hoffman and Faust (1934) used the gross thin smear technique as well as a more sensitive stool concentration method combining sieving and centrifugation to detect *S. mansonii* infections in the human population. Although the total population studied was not stated, they did find then that schistosomiasis was an important public health problem in Puerto Rico and defined 9 endemic areas: (1) Guayama, Arroyo, Patillas, (2) Humacao, (3) Caguas, (4) Rio Piedras, (5) Aibonito, Barranquitas, Comerio, (6) Utuado, (7) Mayaguez, Añasco, (8) Lajas, and (9) the Island of Vieques, this last one with 12 % prevalence, notwithstanding the fact that the streams in this last one were brackish, the salinity apparently not affecting the snails nor the emerging infectious cercariae.

As to prevalence and comparative frequency of severe cases, # 1 above was highest due to the extensive irrigation system for sugar cane. In Guayama the prevalence was 20-30 % primarily schoolchildren, but in Colonia Vives (Esperanza) of this district the prevalence was 56 % which they attributed to slowly moving waters into irrigation channels. They concluded that two principal types of environment are responsible: (1) the pools from streams, and (2) the irrigation system south of the principal mountain range. Both coexist in the irrigated regions of the south, while only the first is known in other areas. Interestingly they believed that schistosomiasis was spreading in the northwestern part of the island, since snails were common in the limestone sinks as well as in recently established irrigation systems.

In a stool survey of 1003 persons from Trujillo Alto and environs, Caguas, Guayama, Utuado and Mayaguez, Faust, et al. (1934) found 12.2 % positive for *S. mansonii*, and considered this a fair estimate of infection in Puerto Rico. But its actual distribution is spotted in that much higher prevalences were found in Caguas (30.7 %) and Utuado (41 %).

Studies of the schistosomes in the extra-mammalian, snail intermediate host, and a discussion of the genus and species names, then denoted *Australorbis glabratus* (Say) were done by Faust and Hoffman (1934).

A thorough study of the mammalian phase of the schistosome life cycle followed in Faust, et al. (1934). They reported "the ordinary uneducated person in parts of Puerto Rico, exposed to *S. mansonii* infection refers to the accompanying pruritus as piquiña, and that of 'ground itch' as mazamorra..." (caused by the hookworm larva).

Koppisch (1937) described the pathology of experimental schistosomiasis in rabbits and rats, beginning with the penetrating cercariae and migration to lungs and eventually mesenteric veins, including the host responses to the parasite. He found that eggs trapped in the finer venules were enveloped by the proliferation of vascular endothelium. Then, the granulomatous process of pseudotubercle formation occurs and the vein becomes occluded.

This was followed by the clinical studies of Pons (1937) of 150 cases observed in the University Hospital and from a survey of public schools in Barranquitas. He concludes (p. 175) "We have been impressed from the very beginning by the frequency with which the intra-hepatic portal circulation becomes seriously involved, to the point, in fact, where the consequent hepatosplenic pathology and symptomatology dominate the pathologic and clinical pictures, the intestinal lesions and manifestations remaining, unimportant, in the background. While many cases of Manson's schistosomiasis are purely intestinal

in their clinical manifestations, so much is the hepatosplenic pathology a part of the disease caused by the *S. mansoni* that we can find no justification for it being termed 'intestinal schistosomiasis'." Among the elementary school children from Barranquitas "where they have easy access to an infective stream", 33 % of fecal samples voluntarily submitted were positive for *S. mansoni*, with first infection usually taking place when they were in their 4th and 5th grades. Of 44 children returning questionnaires, 68 % reported "dysenteryiform" manifestations, which increased as reinfections took place with time. Five of 13 children had hepatosplenic involvement. He concluded that this disease was responsible for much ill health among the school population, high absenteeism from school, and was a legitimate public health problem.

The series concludes with the 8th and last article on the human pathology studies by Koppisch (1940). He studied 147 cases of schistosomiasis from 1009 (14.6 % positivity) consecutive autopsies performed on native Puerto Ricans, 72 % of the positives were 21-50 years old. The majority (64.6 %) of the autopsy cases presented no clear cut clinical manifestations of schistosomiasis or gross pathologic changes of diagnostic import. Twelve cases (8.1 %) represented schistosomiasis in its last stages and of earlier, very heavy infections with death directly ascribable to this disease in all but one. Simple smears of feces were positive for *Bilharzia* ova only in half of these cases. Periportal fibrosis of the white clay pipe-stem variety was evident in all 10 cases with cirrhosis. He summarized that the fundamental histopathologic unit of this disease was the pseudotubercle developing around the ova that, with time, revolutionizes into a fibrous body. From the beginning, the disease is primarily hepatic and colonic, with pathologic changes occurring by the deposition of ova in the tissues. In the colon it leads to colitis and in the liver to periportal cirrhosis. Splenomegaly develops, at least in part secondary to portal obstruction.

Schistosomiasis was a known entity by Puerto Ricans and infections by the poor, undernourished, country people, the jibaro. Emilio S. Belaval wrote in 1934-36 "...situar los flacos cuerpecillos de jibaritiños, entre todos los saltos de agua o los líquenes empozados de las quebradas. Esta vez los que rompieron a aplaudir, fueron los caracolitos conductores de las bilharzias, soñando con la suculenta ración de hígado tierno que le depararía."

The 1940s. The largest stool survey for schistosomiasis and other helminths in Puerto Rico's history was reported by Weller & Dammin. (1945). The study group consisted of 19,139 Puerto Rican Selective Service registrants between the ages of 18 and 38, who had passed the army induction examination. One gram from a single stool sample

was concentrated and examined. The overall "incidence" found was 10 %. The true overall prevalence was probably much higher since these army recruits were "relatively healthy and well-educated adult males with proportionately few laborers from the sugar, tobacco, and coffee-farming areas." Both the 1934 Hoffman and Faust study (see above) and the 1945 Weller and Dammin study defined the same nine endemic areas of human schistosomiasis in Puerto Rico. Curiously, the island of Vieques had 21 % positive of 219 examined. In a 1911 P.R. Anemia Commission report to U.S. Congress they found in Vieques 14 % positive of a group of 801 patients using a less sensitive thin smear test (in Weller and Dammin, 1945).

Numerous articles on the biology of the *S. mansoni* egg and its miracidium in its mammalian host, in stools, free-swimming in water, and penetrating their snail intermediate host was reported by J. F. Maldonado in the 1940s and 1950s (see his monograph, 1967).

Thousands of articles on experimental schistosomiasis *mansoni* state that they are using the "Puerto Rican strain of *S. mansoni*." The Puerto Rican *S. mansoni* isolate has undoubtedly been used for research purposes on a greater scale than any other single isolate. Historically, there have been two PR isolates widely used, but the differences between them (at least as far as snail infectivity) are marginal, and there is the possibility of their being mixed in the distant past. The so-called NMRI isolate was obtained from Puerto Rican school children in the Washington DC area in the mid-1940's and maintained at the Naval Medical Research Institute (hence NMRI). in Bethesda, MD. The PR-1 isolate was obtained from infected snails in Arecibo, PR in 1950. The use of both these PR isolates has driven greater progress in the field of experimental schistosomiasis than any other geographic isolate (Fred Lewis, Biomedical Research Institute, Rockville, MD., personal communication).

The 1950s. In August, 1950, the new UPR School of Medicine admitted its first class with Adan Nigaglioni as Dean and Jaime Benitez, Chancellor. This supplanted the previous UPR School of Tropical Medicine.

Also in 1950, the Puerto Rico Journal of Public Health and Tropical Medicine came to an end in the December issue, Vol. XXVI, No. 2. The Editors wrote on p. 176: Upon the establishment of "a school of general medicine, the more specialized School of Tropical Medicine will become a minor subdivision of the former."

The successful control of schistosomiasis in the national level in the past involved a sustained effort over a long period of time that in democracies meant changes in government and its priorities, organization and personnel. Transmission of the parasite must be monitored in large human populations over decades. The Puerto Rico Health

Department initiated a program to control schistosomiasis in 1953 using limited chemotherapy and snail control by environmental, biological and chemical means as well as sanitation and health education. At the same time, extensive programs of improved water supply, health education, and free latrine distribution were underway throughout the island. In the pilot projects, chemotherapy involved the use of Fuadin from 1954 to 1957 when chemotherapy was discontinued because of drug-related deaths. The principal chemical for snail control was sodium pentachlorophenate. Biological control of the snail intermediate host, *Biomphalaria glabrata* was begun in 1958 with the ampullarid snail *Marisa cornuaretis*, especially in irrigation reservoirs, farm ponds, and the major lakes. Swamp drainage, and ditching and channeling of streams were also used to supplement the chemical and biological efforts at snail control. In addition to the snail control activities by the Health department, there was an independent program throughout the island consisting of improved water supply and sewerage systems, constructed and operated by the P.R. Aqueduct and Sewer Authority (Negron and Jobin, 1979). Among educational tools, in 1954 staff from the P.R. Department of Health and the P.R. Field Station of the U.S. Communicable Disease Center (now San Juan Laboratories, Centers for Disease Control and Prevention) created a set of black and white slides titled "Hay Bilharzia"! as a tool for community education as part of the control efforts in the human population. It also delineates the dismal living conditions widely prevalent in Puerto Rico in the 1950s (Rigau-Perez and Pereira Diaz, 1996).

Also in 1954 the P. R. Health Department, with technical assistance from the U. S. Public Health Service, initiated a program for the control of schistosomiasis mansoni in 6 municipalities, including Vieques Island. The control program was based primarily on two techniques: control of snails with sodium pentachlorophenate and treatment of all infected persons with sodium antimony tartrate (Fuadin®). The Vieques Island study was of special interest because the island was drained by 36 creeks, with only 5 of them continuing to flow during the dry season. At the beginning of the study 6.7 % (11 of 231) of 6-year old children were positive, dropping to 0 in 1963. The *Biomphalaria* snail populations were virtually eliminated in the first 2 years, but colonies continued to reappear at various sites, despite intensive efforts at eradication. Thus here chemotherapy diminished infection even in the presence of the snail intermediate host. However, in the untreated "control" watershed of Caguas, human infections were also decreasing, in the 6-year old children group from 11 % in 1954 to less than 1 % in the first half of the 1960s. This was probably due to general increase in

standard of living and improvement in public water supply with the elimination of habitats for the snail intermediate hosts (Ferguson, *et al.*, 1968). What is not stated is the fact that the U. S. Navy purchased 2/3 of the island during World War II and was using half of their lands for war exercises via troop landings and air bombings. What was the effect of these activities on the infective streams was neither stated nor discussed (Note: the Navy withdrew all activities from Vieques Island on May 1, 2003 and pulled out of the Roosevelt Roads Base in eastern Puerto Rico on May 1, 2004).

The PR Health Dept. also supported a "Bilharzia Clinic" in the P. R. Medical Center with faculty from the UPR School of Medicine. This clinic was initiated by Ramos Morales in the 1950s and significantly expanded by Zoilo Sotomayor in the 1960s, followed by Guillermo Vazquez in the period 1979 through 1995. Many promising anti-schistosomal drugs were tested in this clinic.

In 1980, the PR Health Department shut down the bilharzia control program (see the Boqueron Schistosomiasis Project, below).

Parallel experimental studies on biological and chemical control of snails were being conducted in the 1950s and 1960s by Lyman P. Frick and Lawrence S. Ritchie first at the U.S. Army Tropical Research Medical Laboratory in Puerta de Tierra, San Juan, shut down by the U.S. Department of Defense in 1966, and later at the PR Nuclear Center in the PR Medical Center in San Juan; and Fred Ferguson at the CDC San Juan Laboratories, and extensive field studies were ongoing by Henry Negron and William Jobin (1979, cited above).

The circumoval precipitin (COP) test was described by Oliver-Gonzalez in 1954 as a schistosome egg-specific test "which may be of diagnostic and prognostic value." Its elegance resides in its simplicity requiring only a microscope, microscope slides and cover-slips, serum or plasma and schistosome eggs. This classic work showed that the largest reactions observed with human schistosomiasis mansoni sera occurred in fully embryonated eggs, that all human infection sera tested developed precipitins around the eggs, and that the test was immunologically specific in that similar reactions did not occur around *Ascaris*, hookworm, *Trichuris*, or *Fasciola* eggs. (Note: The vast contributions to immunoparasitology by Oliver-Gonzalez, a world-class scientist who authored over 130 articles and reviews over a 38-year career almost completely at the UPR School of Medicine, must be recognized. He passed away in January, 2004).

A quarter of a century later (see also the Boqueron Project, below) a two part study compared the sensitivity and specificity of 9 serologic tests for the immunodiagnosis

of infection with *S. mansoni* using results from 3-6 stool examinations as a reference standard of humans living in an schistosomiasis endemic area, Parcelas de Boqueron near Las Piedras, PR. In that study the COP test was found to have a sensitivity of 95 % and specificity of 96 %, reaching a level of 100 % sensitivity at average egg excretion levels of 10 or more eggs per gram (Ruiz-Tiben, *et al.*, 1979; Hillyer, *et al.*, 1979).

Two important classic articles by Diaz-Rivera and coauthors of the UPR School of Medicine examined acute schistosomiasis mansoni and the pathogenesis of Manson's schistosomiasis. In the first (Diaz-Rivera, *et al.* (1956), 12 cases of acute schistosomiasis in males 8-16 years old were studied in detail. Incubation times from first exposure to clinical onset varied from 21-42 days, averaging 28 days. Exposure to infested streams varied from a few minutes to several hours daily for as long as 16-25 consecutive days in 5 cases. Immediate cutaneous manifestations were mild itching and urticaria appearing in 4 cases and lasted from 10 minutes to 2 hours. Clinical onset was characterized by its explosiveness and dominated by chills, fever, profuse diaphoresis, generalized body aches and pains, headache, anorexia, severe watery diarrhea, non-productive cough and rapid weight loss. All of the patients were acutely and severely ill when first seen. The authors stated that "The severity of the clinical manifestations in acute Manson's schistosomiasis depends in part upon organ hypersensitivity. The symptoms are mainly referred to the gastrointestinal tract, liver and lungs. The degree of severity of the allergic state may be measured by the eosinophilic response." In other words, acute schistosomiasis is an allergic disease. They concluded: "Acute Manson's schistosomiasis is the self-limited phase of infection which follows the first or several exposures to the cercariae of *S. mansoni*. It is characterized by a variable asymptomatic incubation period, infrequent early cutaneous manifestations, an explosive onset with severe constitutional manifestations indistinguishable from those of an acute infectious disease (typhoid fever), and symptoms and signs dominated by gastrointestinal, hepatic and pulmonary dysfunction."

The second seminal article dealt with 13 case reports from an analysis of 400 cases studied over a 12 year period (Diaz-Rivera, *et al.*, 1957). In their study population they observed a high incidence of 15-20 % with schistosomiasis in their hospital population and "very frequent deaths with but not from Manson's schistosomiasis." In fact, they stated that "There is enough clinical evidence to suggest that Manson's schistosomiasis is mainly an intestinal disorder, and that, although the lungs and liver seldom escape involvement, extensive hepatic and

pulmonary alterations are rather uncommon in Puerto Rico." Heavy infections were another matter. Here "the picture may be dominated by portal hypertension with fragile esophageal varices and congestive splenomegaly with signs of hypersplenism...In some cases the prominent feature is chronic *cor pulmonale*, with pulmonary hypertension."

One manifestation of human schistosomiasis mansoni is portal hypertension. This occurs because schistosome eggs are laid in the venules of the mucosa and submucosa of the colon and rectum, from where some of them are swept into the portal venous system and, as they lodge in the intrahepatic portal venules, multiple and extensive portal venous embolism occurs leading to typical lesions that, if extensive, produce portal hypertension. The patient may then die of exsanguination due to bleeding esophageal varices. Garcia-Palmieri, *et al.* (1959) showed that communication between the portal vein and the vena cava established surgically relieved portal hypertension and hemorrhage from esophageal varices in 31 patients, and all subsequently remained free from esophageal bleeding. This established for the first time that portacaval shunt is the ideal procedure to treat this type of patient even in the presence of splenomegaly and hypersplenism.

A stool survey of 11,690 schoolchildren in the first 12 grades (5 to 18 years old) comprising 17 municipalities in P. R. in 1953 showed an overall schistosomiasis prevalence of 10 %. Municipalities with highest prevalence (20-30 %) included Jayuya, Ceiba, Rio Piedras, Patillas, Guayama, and Caguas (White, *et al.*, 1957). Interestingly, with few exceptions, the results of this study were comparable to Weller and Dammin (1945) even though the surveys were made at different times and with different age and sex groups (see above). In general, the abundance of the snail vector (*B. glabrata*) was related directly to the incidence of human schistosomiasis. It should be noted that multiparasitism was a common feature of this population, viz.: hookworm (17 %), *Ascaris* (20 %), *Trichuris* (93 %).

The 1960s. Jose F. Maldonado (1966) published a comprehensive 119 page monograph on "Schistosomiasis in America."

Garcia-Palmieri and Marcial-Rojas (1962) presented a new scheme for the clinico-pathologic classification of human schistosomiasis mansoni. Of 1,804 cases seen at the UPR clinics, 25 % were asymptomatic. The clinical manifestations of the illness, as seen in Puerto Rico, "occur after oviposition has started, and its intensity and the type of clinical syndromes depend upon the tissues affected, the severity of the infestation, the degree of damage to the tissues, and the condition of the host." In addition to the asymptomatic "illness", they reported on "the acute phase of the disease, the gastrointestinal

picture, the presence of portal hypertension secondary to intrahepatic venous obstructive phenomena, the pulmonary arterial obstructive phenomena, the pulmonary arterial obstructive syndrome with associated cor pulmonale, and the different granulomatous manifestations." Special emphasis was given to the immunological and vascular components of the disease.

Ramos-Morales, *et al.* (1968) reported on the clinical analysis of 1,845 untreated patients with confirmed *S. mansoni* infection in Puerto Rico. Manson's schistosomiasis was seen more often in males than in females at a 3:1 proportion. 76 % (1407) were 15 years of age or younger. Despite careful interrogation by the physician, 25 % of the patients denied any symptoms. The symptoms in descending order were: abdominal pain (51 %), weakness (25 %), anorexia (24 %), and history of severe diarrhea (30 %), dyspepsia (19 %), and history of bloody diarrhea (16 %), fever following initial exposure (6 %). The most common physical finding in their patients was an enlarged liver, which was usually smooth and non-tender in one third of the cases and splenomegaly in 12 %. The duration of the illness was less than 10 years in 65 % of the cases. The authors concluded that the disease in Puerto Rico seems to be milder than in other areas of the world.

During the 1960s and 1970s three large island-wide surveys were done using intradermal skin test reactions. The reactions in the 3rd survey differed markedly from the 1st two surveys and are discussed in Negron-Aponte and Jobin (1979) and in Hiatt, *et al.* (1978). In an extensive evaluation of the test, Hiatt, *et al.* (1978) concluded that "it is well established that the sensitivity and specificity of the intradermal-test results vary with sex, age, site of injection, and geographic location... We believe that the many sources of variability involved and the unsatisfactory sensitivity and specificity of the test in any case limit its epidemiologic usefulness."

The 1970s. Raul Marcial-Rojas published his authoritative reference work on the Pathology of Protozoal and Helminthic Diseases (1971).

The Boqueron Schistosomiasis Project, carried out by San Juan Laboratories, Centers for Disease Control in Puerto Rico, B. L. Cline, Director, was a prospective community-based study of *S. mansoni* infection after the interruption of transmission by non-chemotherapeutic control measures in an area with high (37 %) prevalence of schistosome infection. Snail control was begun in early 1973 with molluscicides and habitat modification. Despite a low rate of transmission, prevalence only decreased from 37 % to 34 % over a 5-year period and the population geometric mean fecal egg output did not substantially change in a cohort of 528 individuals examined in each of

6 annual surveys (Hiatt, *et al.*, 1980). The conclusion was that the half-life of *S. mansoni* in this population was more than 10 years. More importantly, regarding control of schistosomiasis in Puerto Rico and elsewhere, the findings of this study imply that unless control programs are prepared to continue and properly maintain mollusciciding for extremely prolonged periods, success in permanent interruption of *S. mansoni* transmission is unlikely. They stated: "The length of the life of the adult worm effectively sets the control timetable. If mollusciciding is continued for a period less than the life span of the parasite, and if snails themselves cannot be eliminated, then the cycle of transmission can be re-established." (Hiatt, *et al.*, 1980). It should be noted that the same year of this report, the PR Health Department stopped its schistosomiasis control program that was based primarily on snail control via mollusciciding.

The Boqueron Schistosomiasis generated much useful data on the natural infection of schistosomiasis, and served as a model for a similar study in Qalyub, Nile Delta, Egypt (see Cline, *et al.*, 1989). It also generated valuable serum samples for future studies. Two that evaluated 8 different serodiagnostic assays were reported above (Ruiz-Tiben, *et al.*, 1979; Hillyer, *et al.*, 1979).

The last comprehensive study of acute schistosomiasis studying 26 Puerto Rican patients was by Hiatt, *et al.* (1979). As expected, clinical severity differed widely. However, they demonstrated that the clinical severity of acute schistosomiasis was closely correlated with the intensity of *S. mansoni* infection as measured by the concentration of eggs in the stool. Moreover, in individual cases heavy infections may not be necessary for the classic acute syndrome described above in Diaz-Rivera (1956). Additionally, the earliest phase of the acute syndrome can be initiated by parasite antigens present before oviposition (schistosomule antigens?). Elevations of IgG, IgM, IgE, and of titers of antibody in serum indicated that the illness was associated with intense immune activity. And lastly, the fact that the intensity of infection as measured by fecal egg counts remains elevated despite the disappearance of symptoms indicated that the host modifies (modulates) its response to schistosome antigens.

In 1976, Hillyer reported that mice and hamsters vaccinated with antigenic extracts of *Fasciola hepatica* acquired immunity to challenge infection with *S. mansoni*. He furthermore purified the *F. hepatica* antigens which bound to antibodies to *S. mansoni* and demonstrated that the protective antigens were those that linked; those that did not link were not protective. Thus, the cross-protection observed had an immunologic basis. Similarly, mice infected with *F. hepatica* for 9 weeks developed significant resistance to challenge infection with *S. mansoni*.

The 1980s. In 1982, Hillyer co-edited a reference work on trematode and arthropod zoonoses. His schistosomiasis chapter has extensive lists of species of mammals infected with different human schistosome species.

Also in 1982, the *Puerto Rico Health Sciences Journal* began publication. This, as *The Journal of the University of Puerto Rico Medical Sciences Campus*, at the time Norman Maldonado, Chancellor, is the premier scientific publication in Puerto Rico, and is included in *Index Medicus* and in *MEDLINE*.

In 1980, the P.R. Health Department shut down its schistosomiasis snail control program due to the reason that it was "costly and ineffective". The workers were transferred to a dengue mosquito control program. By this time oxamniquine and praziquantel were available for chemotherapy of human schistosomiasis *mansoni*, both of which had been evaluated in the Bilharzia Clinic. Little was known about the status of human schistosomiasis in Puerto Rico.

Some of the ongoing research at UPR focused on defining the nature of the COP reaction. For example, Demaree and Hillyer (1981) showed by transmission electron microscopy that schistosome eggs had pores and that soluble egg antigen inside the egg would exit via the pores and react with the antibody immunoglobulin, forming the characteristic and diagnostic precipitations outside the egg shells. Dunne, *et al.* (1988) showed that an anti-COP serum reacted with a cationic egg fraction and that this fraction in ELISA could be used to predict cure in patients, albeit slowly, with 50 % seroreverting to negative by 2 years post-chemotherapy and 100 % seroreverting 5 years after cure. With the advent of HIV-1/AIDS in Puerto Rico, it was shown that persons with schistosomiasis and dying with HIV-1 infection/AIDS developed antibodies to schistosome eggs as seen in the COP reaction, but failed to develop T-cell granulomatous responses against eggs (Hillyer and Climent, 1988).

In 1992, a recombinant *Fasciola/Schistosoma* cross-reactive, cross-protective antigen was shown to have high homology with a *Schistosoma mansoni* fatty acid binding protein (Rodríguez-Perez, *et al.*, 1992). The native molecule was shown to also protect against *F. hepatica* in mice and calves. Both the *Fasciola* and *Schistosoma* FABPs have been shown to be dual-purpose molecules in that they have been shown to protect against both the homologous and the heterologous genera.

The end of the XXth Century and early beginning of the XXIst. With virtually no research on the status of schistosomiasis *mansoni* in the Puerto Rican population, the Secretary of Health appointed in 1994 George V. Hillyer Chair of a Bilharzia Commission. The purpose was to use

modern technologies to see if one could predict the current status of schistosomiasis on the island. Hillyer asked the Division of Parasitic Diseases of the CDC/NCID (1994) for assistance. The decision was made to use high (99 %) sensitivity/specificity assays by screening for antibodies to *S. mansoni* microsomal antigens by a FAST-ELISA and confirming by the detection of a 30 kDa glycoprotein by Western Blot. In the first systematic island-wide survey for schistosomiasis in Puerto Rico in 40 years, we screened 2,955 plasma samples from healthy blood donors obtained randomly from the Red Cross in March and April, 1995 and covering the 76 municipalities of the island of Puerto Rico (Tsang, *et al.*, 1997). Overall confirmed positivity was 10.6 %, ranging from 0 to 38.5 %, with the highest seroprevalence concentrated in only 17 municipalities that accounted for 48 % of all seropositive samples. However, these 17 municipalities contained only 18 % of the total population of Puerto Rico supporting the contention that schistosomiasis has been transmitted in a focal fashion during the past approximately 20 years. An additional finding was that 10 % of the confirmed positive samples were from individuals 25 years or younger and were for the most part residents from the high seroprevalence municipalities.

In the second study (Hillyer, *et al.*, 1999) we used serum samples from 766 individuals 25 years or younger who had donated a blood sample from 1991 through 1995 to the Centers for Disease Control and Prevention San Juan Laboratories for the determination of antibodies to dengue viruses. Overall confirmatory positivity was only 1.8 %, but with a clear age-specific decrease: 4.7 % in those 21-25 years of age, 2.6 % in the 16-20 year group, 1.2 % in the 11-15, 0.7 % in the 6-10, and 0 % in the 0-5 age group. These results support the concept that there had been little transmission of *S. mansoni* in Puerto Rico during the first half of the 1990s and confirmed anecdotal comments of local physicians who have not seen new infections during this same period.

This approach in using highly sensitive and specific immunodiagnostic approaches to defining the status of schistosomiasis in areas of the world where elimination is occurring caught the attention of the World Health Organization and they had a meeting in London in April, 2000 on "Schistosomiasis in low transmission areas: control strategies and criteria for elimination."

All recent trends suggest that human schistosomiasis is disappearing from Puerto Rico. The Veterans Administration Center in San Juan recently had 3 phases of requests for antibody tests for schistosomiasis, with an aging population of veterans, in fact, those expected to harbor "old" infections: 1988-91 had 84-56 requests, 1992-95 with 31-13 requests, 1996-98 with only 3 requests, with

the number of positives highest in 1988 (n=14), and decreased to 4 or less from 1992-95, and none since then (Table 1). The decrease in the requests for antibody testing was due to the absence of clinical findings related to schistosomiasis in these veterans.

A second patient population from Caguas and

Table 1. Detection of antibodies to *Schistosoma mansoni* egg antigens (COPT) in patients at The Veterans Administration Hospital, San Juan, PR

Year	COPT		
	# Positive	Total	% Positive
1988	14	64	21.8
1989	10	84	11.9
1990	4	56	7.1
1991	10	60	16.6
1992	4	31	12.9
1993	3	14	21.4
1994	4	27	14.8
1995	2	13	15.3
1996	0	0	—
1997	0	3	0
1998	0	0	—
1999	0	0	—
2000	0	0	—

eastwards is younger, and here also showed a gradual but continuous decrease in seropositive individuals from 21 % in 1993 to 12 % in 1996, with a precipitous decrease to 5 % in 1997 and in the 4.1-7 % range through 2003 (Table 2). The positives from 2000-2003 were overwhelmingly 50+ years of age, suggesting old infections. Interestingly, 4 patients from which at least two serum samples were obtained one or two years apart always had lower antibody reactions in the latest sample. When querying the physician we found that the patients with positive COP reactions were treated with praziquantel. Thus we discovered that the COP test could also be used to predict success of chemotherapy based on a decrease in % egg reactors and/or the size of the precipitations emanating from the egg pores (Hillyer and Soler, 1999). Thus, chemotherapy of antibody positive individuals is a method for the gradual elimination of infection in areas of low transmission such as is the case of Puerto Rico. It is significant that no new cases have been found in 2004 and through September, 2005 (Table 2). Clearly, serodiagnosis is a powerful adjunct to follow changes of infection and cure in low intensity, low transmission schistosomiasis endemic areas evolving towards elimination of schistosomiasis.

P. R. Health Dept. reports also suggest that schistosomiasis is disappearing. As shown in Table 3, for example, from 1990 through 26 Sept. 2005 only 21 cases in

Table 2. Detection of Antibodies to *Schistosoma Mansoni* Egg Antigens (COPT) in Patients from Borinquen Laboratory

Year	Males			Females			Totals		
	#Pos	Total	%Pos	#Pos	Total	%Pos	#Pos	Total	%Pos
1993	19	67	28	3	37	8	22	104	21
1994	7	63	11	15	58	25.8	22	121	18
1995	9	61	14.7	6	42	14.3	15	103	14.6
1996	11	72	15.3	3	46	6.5	14	118	11.8
1997	1	45	2.2	4	54	7.4	5	99	5.05
1998	4	61	6.6	1	48	2.1	5	109	4.6
1999	3	43	6.9	0	29	0	3	72	4.1
2000	6	47	12	0	23	0	6	70	8
2001	2	25	7	0	19	0	2	45	4
2002	1	29	3	3	31	9	4	60	6
2003	4	28	14	1	23	4	4	51	7
2004	0	31	0	0	24	0	0	55	0
2005	0	9	0	0	8	0	0	17	0

Sept 20, 2005

single digits yearly were reported by the Epidemiology Division of the PR Health Dept. In fact, the decrease was striking with 9 cases in 1990, 4 in 1991, 2 in 1992, and 0 or 1 case yearly from 1993 through 2005. Only 4 of the cases were female and only 3 were from Mayaguez and 1 from Jayuya; the rest were from a line North-South from San Juan-Caguas eastwards. The last, single case was in 2005, a 69 year old male from the city of Ceiba, on the east coast of Puerto Rico, this probably being an "old" case. (Note: special thanks to Yanire Garcia Guadalupe from Div. of Epidemiology, PR Health Dept. for information on the past three years).

So, why has human bilharziasis been decreasing in

Table 3. Cases of Schistosomiasis Reported to the Division of Epidemiology, Puerto Rico Department of Health from 1973 Through 2005.

Year	No. Cases	Year	No. Cases	Year	No. Cases (Municipality, Sex, Age)
1973	59	1984	4	1995	0
1974	29	1985	99	1996	1 (San Lorenzo, M, 40)
1975	32	1986	3	1997	1 (Canovanas, M, 64)
1976	16	1987	11	1998	0
1977	8	1988	14	1999	0
1978	6	1989	7	2000	1 (Humacao, M, 46)
1979	5	1990	9	2001	0
1980	5	1991	4	2002	0
1981	1	1992	2	2003	1 (Caguas, M, 36)
1982	10	1993	0	2004	0
1983	2	1994	1 (Juncos, F 38)	2005	1 (Ceiba, M, 69) thru 26 Sep 2005

Puerto Rico during the last half of the XXth Century? Some scientists claim that biological snail control with introduced competitor snails such as *Marisa* and *Taeribia* were factors. Chemical snail control was probably

ephemeral in nature because snails escaping the chemicals would rebound, repopulating the freshwater sources. That is why the P. R. Health Dept. eliminated this program as a method of snail control. Chemotherapy has not been instituted on a comprehensive, island-wide basis. However, increases in economic well-being and improvement in housing and piped water that has occurred in Puerto Rico during the last half of the XXth century clearly means less exposure to infected waters.

For the immediate future an insidious danger is lurking: contaminated water. Hunter and Arbona (1995) reported on Puerto Rico having a landfill crisis, a heritage of toxic dumps, and an advancing tide of pollution. Rivers and reservoirs are nearly ubiquitously affected and ground waters, long thought to be naturally protected, show evidence of increasing contamination. More recently, in addition to the ubiquitous fecal coliforms that are evidence of water contamination, heavy metals such as arsenic, mercury and copper are being found in the rivers and streams of Puerto Rico (Rivera Santos, 2004). It should be noted that heavy metals kill snails.

So what should we do in Puerto Rico, an area of low (or no) transmission island-wide? In the absence of significant, active transmission and little or no evident morbidity, chemotherapy of serologically positive cases with follow-up to monitor decrease of antibody levels post-chemotherapy is probably the most cost-effective means. The Vieques model has shown that human transmission can be stopped even in the presence of snails. Hopefully, soon we will have a bilharzia-free Puerto Rico, for a variety of reasons, but nevertheless bilharzia-free.

In the meantime we should not forget that there is some bilharzia still in Puerto Rico and transmission is possible. It is low transmission, be it because competitor snails displaced or eliminated *Biomphalaria* snails from our waters, be it because of chemical pollution killing snail intermediate hosts and limiting humans with water contact, be it that, except for hurricanes that destroy fresh water distribution to the population, and short term means an increase in water contact and possible infection, all roads point towards elimination of schistosomiasis from humans in Puerto Rico. There will come a day when we can say with confidence: "No hay bilharzia aqui."

Finally it should be stated that faculty and staff at the UPR, the PR Health Dept., and the San Juan Laboratories of the CDC with UPR and/or the PR Health Dept. all have made serious, long-term and costly commitments towards defining the status of schistosomiasis in Puerto Rico and its control during most of the XXth century. Their work done in Puerto Rico was international in scope and our professors and scientists were major players in this field of science and medicine. We are grateful and proud of their excellent contributions.

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Figure 1. Map of the island of Puerto Rico delineating its 78 municipalities including the offshore islands of Culebra and Vieques.

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