By the turn of the present millennium, parasites had already acquired a prominent position on the list of agents that can cause kidney disease. Their importance stems not only from their clinical and epidemiologic importance in the tropics, but also because of their incremental spread into the industrialized world through travel and immigration. In addition, they can pose clinical challenges in immunocompromised patients at large,1 many of whom are within the domain of nephrology.

There are 342 known parasites that may cause disease in humans, and about 20 of these may lead to kidney disorders (Fig 1).2 However, the majority can cause merely subclinical or mild and self-limited disease that usually passes unnoticed, particularly if masked by more substantial extrarenal manifestations.3 Only 4 have attained significant clinical or epidemiologic importance, namely schistosomiasis, malaria, filariasis, and leishmaniasis. It took humankind more than 5,000 years to build up enough knowledge to link those sundry disorders and understand how they channel into a relatively narrow range of kidney injury. This review is an attempt to track the story of these 4 parasites from their early beginnings all the way to our present knowledge and understanding.
of the respective clinical syndromes was not reported until the Middle Ages and Renaissance by European and Persian philosophers.

**Schistosomiasis**

The first written document on this disease is the Ebers papyrus (1550 BCE), which is thought to be copied from more ancient papyri dating back to 3000 BCE. The Ebers and subsequently the Edwin Smith (1500 BCE) papyri contain an accurate description of “ââ“ (bloody urine disease), with a “worm” pinpointed as its causative agent, and recommendations for its prophylaxis and treatment. The identification of ââ“ as urinary schistosomiasis was confirmed many centuries later when schistosomal ova were recovered from the bladders of Egyptian mummies dating 2000-1000 BCE. Interestingly, ova also were found in contemporary mummies from China, which suggests the undocumented existence of the disease in Asia since ancient times. Its geographic limitation to Africa and Asia may explain the lack of further description of the disease during the Middle Ages and Renaissance.

**Malaria**

Paroxysmal febrile episodes associated with splenomegaly, typical of malaria, were described in the Nei Ching Chinese medical literature, dated as far back as 2700 BCE. Similar episodes also were alluded to in ancient Sumarian, Egyptian, and Indian texts. The identity of the disease was elaborated in the Hippocratic Collection (460-377 BCE) and Avicenna’s Canon of Medicine (1025 CE). It was so highly prevalent in Italy that it initially was known as “Roman fever” and may have even contributed to the decline of the Roman Empire. Its current name is derived from Medieval Italian language, being composed of “mala” and “aria,” referring to malus (bad), and aeris (air), thought to result from exposure to “poisonous air rising from marshes.”

**Filariasis**

The first known record of lymphatic filariasis is a statue of Pharaoh Mentuhotep II (2000 BCE) that renders him with irregularly swollen legs, suggestive of elephantiasis. Another typical feature of the disease, the “hanging...
“scrotum,” was depicted in artifacts from the Nok civilization in West Africa (500 BCE). However, the first written document on filariasis was in 1590, when the Dutch merchant and historian Jan Huygen van Linschoten mentioned in his writings that natives in Goa, India, were “all born with one of their legs and one foot from the knee downwards as thick as an elephants leg.”

Leishmaniasis

Skin lesions were recognized many centuries before visceral involvement in leishmanial infection. They were displayed on tablets dating back to the 7th century BCE at the time of the Assyrian King Ashurbanipal. It is believed that some of these were derived from texts as old as 1500-2000 BCE. Detailed description of cutaneous leishmaniasis was provided in the 10th century CE by Avicenna, who gave the lesions the name “Balkh sore.” Further description of such sores came from South America, India, and Africa and were given many names, including “oriental sore” and “white leprosy.” Systemic illness was associated with such sores in the mid-18th century, being known as “valley sickness” or “Andean sickness” in South America and “Dumdum fever” or “black fever” (kala-azar) in India.

### PHASE 2: DISCOVERY OF THE PARASITES AND THEIR LIFE CYCLES

The second half of the 19th century witnessed the discovery of most parasites. The main players were European clinicians and scientists working in the tropics during the era of political and military colonization.

#### Schistosomiasis

By 1825, when Antoine Clot, the French surgeon-in-chief of the Egyptian army, established the first organized medical service in the country, schistosomiasis had become so endemic that hematuria was considered a “sign of mal-

### Figure 2. Timeline of the key discoveries in the story of parasitic kidney diseases. Abbreviations: EBV, Epstein-Barr virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NS, nephrotic syndrome.

<table>
<thead>
<tr>
<th>Phase I: Old Documentation</th>
<th>Phase II: Paraspore Discovery</th>
<th>Phase III: Kidney Disease</th>
<th>Phase IV: Coinfection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ill-defined papyri</td>
<td>1852: Discovery of parasite</td>
<td>1911: Discovery of ova in mummies</td>
<td>1992: HCV coinfection</td>
</tr>
<tr>
<td>Ebers and Smith papyri</td>
<td>1893: Discovery of life cycle</td>
<td>1945: Urinary schistosomiasis</td>
<td></td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>1910: Discovery of parasite</td>
<td>1960: Salmonella coinfection in urinary schistosomiasis</td>
<td></td>
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<tr>
<td>Nei Ching scripts</td>
<td>1880: Discovery of parasite</td>
<td>1964: Schistosomal glomerulopathies</td>
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<tr>
<td>Hippocratic collections</td>
<td>1884: Blackwater fever described</td>
<td>1975: Salmonella coinfection in glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td>1025: Avicenna’s Canon of Medicine</td>
<td>1884: Malarial Bright disease described</td>
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<tr>
<td>Malaria</td>
<td>1897: Discovery of transmission</td>
<td></td>
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<tr>
<td>Mentuhotep II statue</td>
<td>1905: Discovery of transmission by sandfly</td>
<td></td>
<td></td>
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<tr>
<td>Nok artefacts</td>
<td>1590: Written description of elephant-like legs</td>
<td></td>
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<tr>
<td>Filarisis</td>
<td>1878: Discovery of adult worm</td>
<td>1973: Filarial glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td>1590: Written description of elephant-like legs</td>
<td>1900: Discovery of life cycle</td>
<td>1986: Schistosoma coinfection</td>
<td></td>
</tr>
<tr>
<td>1025: Black sore described</td>
<td></td>
<td>2002: Wolbachia coinfection</td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>1835: Kala-azar described</td>
<td>1980: Schistosoma coinfection</td>
<td></td>
</tr>
<tr>
<td>1889: Discovery of parasite</td>
<td>1901: Donovan bodies described</td>
<td>1987: HIV coinfection</td>
<td></td>
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<tr>
<td>1905: Discovery of parasite</td>
<td>1903: Discovery of microfibril</td>
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<tr>
<td>1900: Discovery of life ciclo</td>
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<tr>
<td>1971: Discovery of glomerulonephritis</td>
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<tr>
<td>1986: Schistosoma coinfection</td>
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<td></td>
</tr>
<tr>
<td>1992: HCV coinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998: HIV coinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006: Schistosoma coinfection</td>
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</tbody>
</table>
rity” in teenagers. It was not uncommon for a father to take his son to the doctor if he did not “menstruate” by the age of 20! Clot imported young physicians from Europe to teach in the military medical school in the outskirts of Cairo. Among those was the German surgeon Theodor Bilharz, who eventually discovered the worm responsible for endemic hematuria. The parasite initially was called after his name, “Bilharzia haematobia,” until it acquired the formal name Schistosoma haematobium in 1858. Its life cycle was characterized 3 decades later, thus paving the road for understanding schistosomal pathogenicity, prevention, and management. Other schistosomal species subsequently were discovered in humans, apes, cattle, and domestic animals. Of 21 known species, 7 were identified to infect humans, which differ in their geographic distribution and target-organ affinity.

Malaria

The parasite ultimately called plasmodium was first reported in the red blood cells of infected patients by the French physician Charles Laveran while working in Algeria in 1880. For this discovery, he was awarded the Nobel Prize for Physiology or Medicine in 1907. As early as the 7th century BCE, the Indian physician Susruta had suggested that mosquitoes probably were responsible for the transmission of malaria. However, this hypothesis was not confirmed until the late 1800s by Scottish physician Sir Ronald Ross, also in India, for which he received the second Nobel Prize for discoveries in malaria in 1902. Many species have been identified, and the following cause disease in humans: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, and Plasmodium malariae.

Filariasis

In 1863, French surgeon Jean-Nicolas Demarquay first described microfilariae in hydrocele fluid, and Brazilian physician Otto Wucherer described them in urine in 1868. Ten years later, while working in Brisbane, Australia, the British parasitologist Joseph Bancroft discovered the adult worm, which subsequently acquired the composite name Wuchereria bancrofti. The role of mosquitoes in parasite transmission and completion of the life cycle was established by George Carmichael Low in 1900. Seven other filarial nematodes were discovered in the following years, of which 3 are human pathogens; namely, W bancrofti, Loa loa, and Onchocerca volvulus.

Leishmaniasis

The Russian military surgeon Peter Borovsky was the first to discover the causative parasite of “Sart sore,” as it is called in Russian, and published his observations in a local journal in 1898. This publication was overlooked for many years and not acknowledged until Borovsky’s death in 1932. The credit went to William Leishman, a Glaswegian doctor who served with the British Army in India, who discovered the parasite in splenic aspirates from a patient with Dumdum fever in 1901. It took him 2 years to publish his findings, just a few weeks before Charles Donovan published similar observations on a patient with kala-azar. The identity of the organism in both discoveries was confirmed, hence the composite name “Leishman-Donovan bodies.” Subsequently, the official name of the parasite became Leishmania donovani.

The succeeding decades witnessed the discovery of 30 species of Leishmania, of which 21 infect humans, the best known being L donovani, Leishmania tropica, and Leishmania braziliensis. They are transmitted by 30 of the 500 known sandflies of the genera Phlebotomus and Lutzomyia. The disease is transmitted to humans from dogs or (rarely) cats in the Mediterranean region and China, rodents in Africa, and foxes in Brazil and Central Asia, whereas humans may serve as a reservoir for transmission in India and possibly other parts of the world where kala-azar is prevalent.

PHASE 3: DISCOVERY
OF PARASITIC
KIDNEY DISEASES

Identification of almost the full spectrum of kidney disease attributed to parasitic infection took about a century, starting with the description of malarial nephropathy in the late 1800s and ending with the documentation of leishmanial kidney disease in humans in the mid-20th century.

Schistosomiasis

{\textit{S haematobium}}

Egyptian pioneers in the early 1900s and Sudanese and Nigerian clinicians later on identified the lower urinary manifestations of \textit{S haematobium} infection and their upstream sequelae. These were documented in Professor Naguib Makar’s seminal monograph in which the bladder lesions were illustrated by detailed hand paintings, at a time when color photography was not available.
The “granuloma,” formed around single or multiple ova or worms, was soon identified as the basic histologic lesion throughout the urinary tract. Although active granulomas were blamed for some of the early manifestations of schistosomiasis, it was the healed lesions that induced peak morbidity, particularly by affecting the lower ureters. To the latter are attributed the upstream obstructive manifestations, infection and end-stage kidney disease.15,16

An epidemiologic study from Upper Egypt documented the occurrence of a transient immune-mediated acute glomerular injury in patients exposed to new *S haematobium* infection.17 The same also was reported in sporadic cohorts,18 which seems to indicate that *S haematobium* glomerulopathy is relatively uncommon compared to *Schistosoma mansoni* (discussed later), of little clinical significance, and self-limited.

A unique complication of urinary schistosomiasis, documented since those early descriptions, is bladder cancer. A cause-and-effect relationship had been proposed initially through postmortem observations in 40 Egyptian patients.19 This subsequently was confirmed on the basis of statistical association, characteristic clinicopathologic features, and the demonstration of ova within the neoplasm. The histopathologic pattern of “bilharzial cancer,” as it often is called, has changed during the past half century from predominantly squamous cell20 to transitional cell carcinoma.21

### Table 1. Modified AFRAN Classification of Schistosomal Glomerulopathies

<table>
<thead>
<tr>
<th>Class: Histology</th>
<th>Immune Deposits</th>
<th>Biologic Agent</th>
<th>Prevalence</th>
<th>Clinical Picture</th>
<th>Treatment of Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Mesangiocapillary proliferative, exudative</td>
<td>IgM, IgA, IgG, IgA, C3, S. mansoni</td>
<td><em>S. mansoni</em></td>
<td>7%-20% of asymptomatic pts; 80% of pts with overt kidney disease</td>
<td>Hepatosplenomegaly &amp; NS, HTN, progressive CKD</td>
<td>None effective</td>
</tr>
<tr>
<td>II: Diffuse proliferative, exudative</td>
<td>IgG, IgA, C3, <em>S. haematobium</em> antigens</td>
<td><em>S. haematobium/S. mansoni</em>, and <em>Salmonella</em></td>
<td>11%-38%</td>
<td>Unknown</td>
<td>Combined antiparasitic and anti-Salmonella treatment</td>
</tr>
<tr>
<td>III: Membranoproliferative (mesangiocapillary)</td>
<td>IgM, IgG, IgA, C3, <em>S. haematobium</em> antigens</td>
<td><em>S. mansoni</em>, <em>S. haematobium</em></td>
<td>7%-20% of asymptomatic pts; 80% of pts with overt kidney disease</td>
<td>Hepatosplenomegaly &amp; NS, HTN, progressive CKD</td>
<td>None effective</td>
</tr>
<tr>
<td>IV: Focal segmental glomerulosclerosis (mesangio-proliferative)</td>
<td>IgM, IgG, IgA, C3, <em>S. mansoni</em></td>
<td><em>S. mansoni</em> and <em>S. haematobium</em></td>
<td>11%-38%</td>
<td>Unknown</td>
<td>Combined antiparasitic and anti-Salmonella treatment</td>
</tr>
<tr>
<td>V: Amyloidosis</td>
<td>IgG, IgA, IgM, C3, <em>Salmonella</em> protein</td>
<td><em>S. mansoni</em> and <em>S. haematobium</em></td>
<td>7%-20% of asymptomatic pts; 80% of pts with overt kidney disease</td>
<td>Hepatosplenomegaly &amp; NS, HTN, progressive CKD</td>
<td>None effective</td>
</tr>
</tbody>
</table>

Abbreviations: AFRAN, African Association of Nephrology; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; HCV, hepatitis C virus; HTN, hypertension; Ig, immunoglobulin; NS, nephrotic syndrome; pts, patients; *S. haematobium*, *Schistosoma haematobium*; *S. mansoni*, *Schistosoma mansoni*.

The role of *S mansoni* in causing kidney disease was discovered half a century later. The spark was a thesis submitted in 1964 at the
Universidade de Minas Gerais in Brazil, where M. Lopez reported the association of hepatointestinal schistosomiasis with significant proteinuria and histologically documented glomerular lesions. This was confirmed by subsequent clinical, histopathologic, postmortem, and experimental observations in the same country. Similar observations were made in Egypt by Sabbour et al., who introduced the term “schistosomal nephritis.” The clinical significance of schistosomal glomerulopathy, as it was called in later publications, subsequently was confirmed during the same decade by clinicopathologic studies in Africa and Central America. Its burden was estimated in both Brazil and Egypt to range from 15%-20% of those with hepatointestinal schistosomiasis and to account for 3%-5% of patients undergoing regular dialysis in Egypt.

Many glomerular lesions were described in this context. In order to categorize the lesions into distinct clinicopathologic entities, a 5-tier classification was initially introduced and acknowledged by the African Association of Nephrology (AFRAN) as its official classification. This was subsequently modified by adding a sixth tier to accommodate coinfection with hepatitis C virus (Table 1; Fig 3).

**Malaria**

During 1884, malarial kidney disease was independently described for the first time in 2 geographically distant regions. Thus, P. falciparum was held responsible for acute kidney injury (AKI) in South East Asia, whereas P. malariae was held responsible for chronic kidney disease in West Africa.

**P falciparum**

The Sierra Leonean doctor John Farrell Easmon was the first to relate kidney disease to malaria by describing “blackwater fever.” Passage of black urine and subsequent anuria were attributed to massive intravascular hemolysis, mostly in patients treated with quinine. When the use of quinine was abandoned in 1950, blackwater fever became exceedingly rare and reappeared with the use of the drug in recent years for the treatment of multidrug-resistant malaria. Less commonly, blackwater fever was reported later in patients treated with chloroquine or artemether compounds.

The role of falciparum malaria in causing AKI by its own right, regardless of any treatment, was disclosed during the years of withholding quinine therapy. Many reports estimated the incidence at ~1% of infected patients. This suggests a global incidence of 4 million per year, based on the World Health Organization prevalence estimates.

The work of Thai physicians during the last few decades of the 20th century attributed malarial acute renal failure to a combination of renal ischemia due to pooling of blood in the peripheral capillaries, interstitial kidney injury, and intravascular hemolysis. The main reason for the key hemodynamic perturbation turned out to be increased adhesiveness of parasitized red blood cell membranes.
due to surface expression of multiple parasite-related proteins.31

Acute immune-mediated glomerular lesions had been described later,32 mainly in patients who developed nephrotic syndrome as the sole manifestation of *P falciparum* nephropathy or after malarial acute renal failure.

**P malariae**

Malarial glomerulonephritis (GN) was first described by the American pathologist I.E. Atkinson, who introduced the term “Bright’s disease of malarial origin” in Nigerian children with quartan malaria.33 Similar reports were published from the same region in succeeding years, before G. Giglioli34 published his comprehensive clinical monograph in 1930 on the renal manifestations of malaria in British Guiana. The disease was described as a progressive steroid-resistant nephrotic syndrome in children. The usual histologic pattern was immune-complex mediated mesangiocapillary GN with the formation of large intramembranous “lacunae” that were considered pathognomonic by some authorities (Fig 4).35,36

Although the identity of quartan malarial nephropathy has been acknowledged for many decades, it recently was challenged on the basis of discrepancies in the pattern of glomerular injury in different geographic regions and the inconsistency of demonstrating malarial antigens in many studies.37

**P vivax**

During the past 2 decades there has been a growing trend of *P vivax* causing malarial acute renal failure38 or acute GN in India and China.39 According to several clinical reports, the disease seems to be more common in children and is associated more often with thrombocytopenia and pulmonary complications compared with *P falciparum* disease.

**Filaria**

The English physician William Prout was the first to describe chyluria in 1849. He ascribed this condition to “the passage of lymph in urine,”40 which was attributed later to obstruction of the central lymphatics by filarial worms. The occurrence of proteinuria in such patients traditionally has been considered an expression of lymphatic leakage. Even hematuria, reported in some cases, was attributed to capillary rupture into the dilated lymphatics.41 It remained until the late 1970s for typical mesangiproliferative GN to be histologically documented in filarial infection,42 later attributed to deposition of immune complexes containing worm antigens.43 Although subsequent reports confirmed these observa-
tions, glomerular disease remains relatively rare in bancroftiasis compared with other filarial species.

A fairly wide spectrum of glomerular lesions has been described since the early 1970s with *L. loa* infection. The most consistently reported is membranous nephropathy. Mesangio proliferative GN and focal segmental glomerulosclerosis also have been associated with this infection.

Mesangio proliferative GN associated with onchocercosis was described sparingly during the following years. It often was associated with severe chorioretinitis ("river blindness"), highly prevalent in inhabitants near the stagnant rivers where mosquitoes grow.

**Leishmaniasis**

Kidney involvement was unknown in leishmaniasis for almost a century after the discovery of kala-azar. It initially was suggested in 1961 by a French team working in West Africa who attributed nephrotic syndrome in a local child to *L. donovani* infection. A decade later, GN became well known in naturally infected dogs. Subsequent reports from endemic areas unveiled a wide spectrum of kidney disease in humans as well, with an overall incidence of up to 60% of infected patients in a Brazilian cohort. The variety included AKI, acute and chronic interstitial nephritis, mesangiocapillary GN, and renal amyloidosis.

**PHASE 4: COINFECTION**

For the sake of scientific accuracy, almost all early experimental studies of parasitic kidney diseases intentionally were restricted to single-agent infections. In relevant clinical reports, patients coinfected with another parasite, bacteria, or virus were legitimacy excluded. Although this served in defining the specific impact of a particular parasite, it did not necessarily address what occurs in actual life, where such coinfections are common. Our relatively recent clinical awareness of coinfection may be attributed to the following: (1) better reporting from underprivileged communities in which such multiple infections dominate, (2) actual increase due to the discovery of new agents such as HIV (human immunodeficiency virus) and hepatitis C virus (HCV), and (3) growing knowledge from translational research.

Although a lot of information in this area has accrued from experimental models, I allude mainly to clinical reports. It must be emphasized that many data are conflicting and explanations are imprecise, which tells that much remains to be learned about the complex immunologic interactions involved.

**Schistosomiasis**

Perhaps the first reported of such coinfections relevant to kidney disease is that between *Schistosoma* and *Salmonella* species. The impact of this coinfection was recognized in the mid-1960s, when chronic enteric infection was documented to confound the urinary manifestations of hematobiosis and the intestinal manifestations of mansoni as. Nephrotic-range proteinuria was reported with the latter coinfection in Egyptian patients. Kidney biopsy showed an exudative mesangio proliferative GN (AFRAN class II).

Soon after the discovery of HCV, its association with *S. mansoni* infection became well recognized. This was attributed to acquisition of the viral infection through the unhygienic ambiance supervening in mass treatment of schistosomiasis by intravenous injections. However, the demonstration of HCV in schistosomal cercariae in vitro may suggest that coinfection is acquired simultaneously. It has been shown that HCV aggravates the clinical course and significantly modifies glomerular lesions in schistosomal nephropathy, thereby acquiring specific recognition under an appended class VI in the AFRAN Classification (discussed later).

Since the late 1980s, HIV coinfection with *S. haematobium* and with *S. mansoni* was reported from several sub-Saharan African countries, where both conditions are common. Most studies agree that schistosomal infection augments the replication of HIV, hence increased transmission and rapid progression of the disease. HIV does not seem to change the clinical course of schistosomiasis, although it may increase the frequency of reinfection after successful treatment.

Schistosomal infection was shown to modify the host response to other parasites, including plasmodia, filariae, and leishmanias. The effects of these coinfections are discussed with the individual parasitic infections (discussed later).
malaria.\textsuperscript{62} Mansoniasis has the set of symptoms, and milder ill-
ness, which correlates with the egg count in stools.\textsuperscript{63} It appears that the reported difference in reaction relates to the host’s immune status in response to the helminthic infection upon acquiring malaria (discussed later). None of these observations has been reported to date to reflect on kidney disease associated with either parasite.

**Filariasis**

Bacterial coinfection has been known to be of pathogenetic significance in elephantiasis. Staphy-
lcocci and certain streptococci often were implicated in the pathogenesis of glomerular lesions. More recently, the rickettsialike bacteria called Wolbachia were discovered within filarial nematodes and found essential for their growth.\textsuperscript{64} They were incriminated in the pathogenesis of filarial GN in dogs.\textsuperscript{65} However, it remains to be elucidated if Wolbachia have a pathogenetic role in filariasis in humans.

HIV coinfection with all human-pathogenic filariae has been reported from Africa since the mid-
1990s, whereas a lot of experimental work recently has been conducted in the United States. \textit{W bancrofti} has been quoted most frequently in this respect. Most clinical and experimental data suggest that although the course of filariasis is not significantly affected, the rate of HIV replication, transmission, and disease progression are augmented.\textsuperscript{66}

Clinical observations of the association of schistosomiasis with filariasis suggest a deleterious effect of the former on the acute and chronic clinical manifestations of filariasis. However, the presence of prior filarial infection modulates the severity of schistosomal hepatosplenic disease.\textsuperscript{67} No specific reflection has been reported on kidney disease associated with either parasite.

**Leishmaniasis**

The association of kala-azar with HIV initially was reported only 4 years after discovery of the virus.\textsuperscript{68} It subsequently was shown that viral replication is considerably accelerated in patients with kala-azar, leading to augmentation of all HIV-related kidney diseases. In particular, this coinfection has been blamed for the development of renal amyloidosis.\textsuperscript{52}

Experimental infection with leishmania following established mansoniasis in mice is associated with rapid multiplication of amastigotes and extensive tissue injury.\textsuperscript{69} Clinical reports from East Africa and South East Asia suggest that recovery from leishmania-
asis is delayed in patients with chronic schistosomiasis.\textsuperscript{70} There are no data for the renal manifestations of this coinfection.

**TREATMENT MILESTONES**

Although antiparasitic chemotherapy has been among the most fruitful medical achievements in history, its impact on the treatment of parasitic kidney disease remains limited to acute disorders. Impressive success was accomplished with the 2 protozoal diseases causing AKI, namely \textit{P falciparum} and \textit{L donovani}. The Jesuits had conveyed the cinchona bark alkaloid quinine from Peru to Italy, where it was used for the treatment of malaria as early as 1631.\textsuperscript{71} Newer effective and less toxic agents have radically changed the outcome of malarial acute renal failure.

Pentavalent antimony was the mainstay of kala-azar treatment since 1950. By the time AKI was identified as a complication of the disease, antimony preparations were already falling out of use because of increasing resistance and significant adverse reactions. Clinical experience with leishmanial AKI thus is limited to treatment with the more recently introduced antibiotic amphotericin, which proved effective in immunocompetent and immunocompromised patients despite its nephrotoxicity.

Early schistosomal granulomata have been known to respond to the antimonial preparation tartar emetic since 1918,\textsuperscript{72} with reversal of most acute morbidity. Similar outcomes subsequently were reported with more modern antischistosomal treatments, notably praziquantel.

The currently available antiparasitic agents seem to be effective in treating early proliferative glomerular lesions associated with many...
parasites. However, no controlled randomized trials have excluded the possibility of spontaneous resolution. However, chronic kidney disease attributed to any of the parasites addressed in this review does not respond to specific therapy, perhaps due to the confounding effect of multiple pathogenetic mechanisms (discussed later).

PATHOGENETIC INSIGHTS

Serious work on immunity to parasitic infections began only after World War II in several high-status US institutions, such as the University of Chicago, Johns Hopkins University, and the Rockefeller Institute. In the simplest terms, all studies agree that innate immunity is responsible for getting rid of the main load of infectious organisms. This phase is followed by an adaptive immune response that progresses from phases involving helper T cell types 1 (TH1) and 2 (TH2), and with certain parasites, a state of tolerance may be achieved, compatible with prolonged survival of the parasite as with schistosomiasis (Fig 5). Associated clinical syndromes have been linked to these stages in almost all parasitic infections. The kidney manifestations are excellent examples of such linkage.

We now know that the acute phases of parasitic disease are associated mostly with a TH1 response, whereas late and chronic complications occur during the TH2 phase. Cell-mediated responses are characteristic of certain disorders such as schistosomal granulomata, whereas most of the glomerulopathies are attributed mainly to immune complexes involving circulating parasitic antigens and different classes of host immunoglobulins. The earliest glomerular deposits usually contain immunoglobulin M (IgM) and complement, whereas IgG dominates in late deposits. There are specific settings in which this scenario is modified, as in schistosomal hepatosplenic disease, for which progressive glomerular lesions were associated with IgA deposits.

The observation that parasitic antigens usually are displayed only in early glomerular lesions has led to the discovery of several confounding factors, such as autoimmune, coinfection, and impaired macrophage function. The latter has been blamed for progres-
sion of glomerular lesions in schis-

tosomiasis,81 as well as for the development of amyloidosis.82

Almost a whole century has elapsed since the first milestones of immunity against parasites were reached. A lot has been learned, particularly with relevance to prevention, vaccination, and disease pathogenesis. However, there is still a lot to discover, particularly in the era of coinfections in which multiple infections may synergize, antagonize, or modify the immune response in every detail.

FORECAST

Although the actual burden of parasitic kidney disease is unknown, merely 4 parasites constitute a huge reservoir that threatens kidney health in almost a billion human beings, particularly in the poorest nations. It is for their huge epidemiologic impact that the World Health Organization has included schistosomiasis, filariasis, and leishmaniasis on their list of neglected tropical diseases.83 In 2012, a massive international campaign was established to support the London Declaration on Neglected Tropical Diseases to control, eliminate, or eradicate 10 of these diseases with an initial budget of $785 million, with the plan “to bring these diseases to their knees” by 2020.84 Given the gigantic numbers of infected individuals in the tropics, the impact of this initiative on the prevalence of kidney disease may match that of the control of diabetes in the industrialized world. Would this be the happy end of our 5,000-year story?

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