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A glimpse of fever, bites, and stings from bed to the bench: A journey through decades

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The past is buried. Epidemics of fevers hit hard the rural villages of Ceylon till the early 20th century causing deaths and famine. Survivors abandoned the settlements and migrated to new locations. Local authorities or headmen erected boundaries called "epidemic fence" or "wasangatha weta" to warn travelers where fevers were rampant. Nature took its toll. One such fever was malaria then named "jungle fever" which led to a higher death rate than the birth rate in the 1920s. The famous poet Wimalaratne Kumaragame observed protruding abdomen of poverty-stricken village children in the 1940s in poetic verses while he was working in remote North Western province. Shaking chills and rigors coming in repeated attacks in the latter 1960's seeded my interest in infections. Similarly, my inquisitiveness about environmental hazards built my interest in snakes and other creatures. During my 5-year stint in General Hospital Anuradhapura from 1994, malaria was rampant in the region, mostly very complicated falciparum infection. The Department of Parasitology, Faculty of Medicine, Colombo, conducted research on malaria and a doctor from Myanmar read for PhD with my assistance. For the first time, I detected quinine-resistant severe falciparum infection with multiple organ failure where I had to use artemisinin to save the patient. Whilst facing major outbreaks of Japanese encephalitis, viral hepatitis, typhoid, and leptospirosis, the first case of dengue infection was detected in 1997 at Anuradhapura. Chronic kidney disease (CKD) was in full swing by 1994 and a ward-based audit showed more than 100 deaths due to CKD in 1995. Poisoning was a common occurrence where yellow oleander (Kaneru) seed poisoning caused cardiac complications and needed daily transfer of patients to the Cardiology Unit, Colombo for pacing. In 1995, a team from Oxford, UK headed by Prof David Warell and a team from the Faculty of Medicine, Colombo came to do a clinical trial on an antivenom developed against local Russell's viper ("Polonga Tab") and I was the research site collaborator. A team from the Faculty of Medicine, Peradeniya conducted neurophysiological studies on snakebite and agrochemical poisoning. Anuradhapura was a treasure of research materials and the hub of research of that era. Some of those data were published as conference abstracts and journal publications, but a vast pool of data remained unpublished leading to data aging and perishing.

Rickettsioses

Observation of fever and rash suggestive of rickettsioses in the Base Hospital, Nawalapitiya in 1991 was serendipity. Until such time, such infections were considered alien to Sri Lanka. However, a thorough literature search revealed a few publications of scrub typhus fever published from 1939-41 from Southern Ceylon.[1] Before that Dr. Lucian De Zilwa, the first Ceylonese gynecologist wrote in his autobiography that in 1935, he suffered from a life-threatening illness with fever lasting over three weeks which was serologically confirmed as tropical typus. Since the 1940s, there was hardly any authentic literature on typhus in Sri Lanka giving the impression of its non-existence in the island. A clinical study done in the Teaching Hospital, Peradeniya included 118 cases of probable rickettsial infection over two years from 1999, and of them, 60 serum samples were tested in Japan and

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Thailand to confirm the diagnosis. This study detected a high prevalence of spotted fever rickettsial infections in the hilly Central region of Sri Lanka and was the first report of its kind.[2] Since then a regular database has been maintained for over two decades resulting in many collaborative clinical studies and laboratory studies. The researched questions addressed were as follows.

1. Distribution of spotted fever group (SFG) rickettsioses in the central region
2. Reasons for re-emergence of rickettsioses
3. Description of the clinical features in detail
4. Detection of atypical manifestations and complications
5. Identification of the causative rickettsial agents
6. Identification of the vector (tick species) and the mode of transmission

Establishments of collaborations and diagnostics:

1. Faculty of Veterinary Medicine and Animal Science, University of Peradeniya
2. Faculty of Science, University of Peradeniya
3. Faculty of Medicine, University of Kelaniya
4. CDC, Atlanta, USA

The diagnostics such as Indirect Fluorescent Antibody Test (IFA) and molecular test (PCR) were established in the Department of Veterinary Pathobiology, University of Peradeniya with assistance from CDC, Atlanta. Research grants were obtained from NSF and NRC and produced 2 MPhils and one PhD.

Some of the vector studies were done in collaboration with Department of Zoology, University of Peradeniya obtaining research grants from NSF and NRC producing a MPhil on otoacariasis and one ongoing PhD about zoonosis and human infection identifying SFG agents.

I observed rickettsioses as a re-emerging infection in Sri Lanka considering increasing notification from all districts. Improved awareness of the clinicians about the infection and the contribution of other research groups helped to understand the distribution of the infection in Sri Lanka. Accordingly, mite-borne scrub typhus is distributed in the coastal belt and the dry zone of the island, whilst tick-borne SFG is prevalent mainly in the central hilly region. I defined an SFG belt that extends from Nawalapitiya to Kegalle on the western slope of the central hills. There is a high prevalence of SFG in the Kadugannawa valley around Hemmathagama.

Even though, scrub typhus existed in 1940 in down south of the island, there is no literature to support the existence of SFG until the recent discovery. Being zoonotic infections, rickettsioses have animal reservoirs. The postulation is that the changing ecology over the last decades and increased wild pig population and rodents, and their habitation close to human dwellings may be contributing to the emergence and transmission of the disease. To support this hypothesis, we carried out an extensive molecular analysis of collected ticks from different locations in Sri Lanka from dogs, goats, tortoises, cattle, pangolin and pigs in 2008 in the CDC Atlanta, USA. The molecular characterization of 847 ticks collected from flagging and animals identified tick species, their animal host and pathogenic rickettsial agents.[3] It is interesting to note, that ticks from cow, goats and dogs from Peradeniya and Hammathagama in the central hills yielded rickettsial agents.[3] Another study in dogs showed positive serology for SFG.[4]

Typical clinical presentation of SFG is high fever, prostration, maculopapular discrete skin rash, and arthritis mainly involving ankle joints.[5] We studied cutaneous manifestations of SFG and added novel descriptions of fern leaf skin necrosis to the literature. Atypical manifestation of SFG is not uncommon and often overlooked.[6] We documented a series of patients with neurological manifestations where extrapyramidal manifestations such as bradykinesia and tremors were observed in elderly patients.[7] In a series of patients with obscure lower motor facial nerve palsy with otoacariasis collected prospectively over 16 years from the ENT clinic Kandy, we found SFG aetiology. After the initial presumption of tick toxin paralysis, the approach was changed and we demonstrated that patients had positive IFA serology for rickettsia and finally molecular studies detected rickettsial DNA in a tick species collected from the ear canal.[8]

Many attempts have been made to identify circulating SFG rickettsial agents from patients in Sri Lanka. PCR-based molecular studies conducted using skin lesion biopsies from patients, successfully identified the 17-kDa spotted fever group-specific antigen.[6] Currently, NSF funded project in collaboration is investigating the SFG rickettsial agents with shared vectors, reservoir hosts, and phylogenetic affinities of the pathogen in humans. The study of 847 ticks in the CDC, Atlanta identified 5 genotypes of spotted fever rickettsial agents indicating the involvement of many spotted fever agents causing human infection.[3] Spotted fever agents are diverse and ubiquitous and so far

described over 30 agents in the world causing different clinical entities. Close scrutiny of variation of clinical manifestations in the local population suggests the involvement of many SFG agents. Therefore rickettsioses in Sri Lanka is yet to understand fully.

Dengue

The dawn of the new millennium showed dengue was replacing malaria where both infections are mosquito-borne. Dengue outbreaks were reported in many regions of the island from the year 2000. Except for WHO 1997 guideline, there were hardly any educational materials available for clinicians on dengue management. Peer communication and sharing experience helped in case management. Against this backdrop, I commenced research on dengue with the following objectives.

1. To describe clinical features and laboratory parameters
2. To demonstrate myocarditis as a manifestation overlooked
3. To conduct autopsy studies and to use molecular diagnostics to demonstrate viruses in the myocardium, liver, and other tissues
4. To do therapeutic trials and to describe treatment modalities
5. To study host genetic susceptibility
6. To disseminate knowledge

At the Teaching Hospital, Peradeniya, a prospective clinical study enrolled 404 consecutive adult dengue patients over two years from 2001 and described clinical features and the trend of evolution of parameters such as WBC, platelet count, and hematocrit. The fatal complications were identified. However, the causative serotype was not known.[9] In 2005, there was an abrupt outbreak of dengue with severe morbidity, and the causative serotype was identified as DEN 3. Cardiac manifestations were dominant and their early detection prevented deaths. In a series of 160 patients, 75 had ECG changes and unstable vital parameters accountable for myocarditis.[10-12] I maintained a regular database of dengue and witnessed two more serotype changes causing massive outbreaks, DEN1 and DEN2 in 2009 and 2017 respectively. The mortality was related to resistant profound shock, bleeding, acidosis, and multiple organ failure. Profound shock in dengue is contributed by summation of hypovolemia, haemor-rhage, cardiac dysfunction, liver failure, and sepsis. To understand the causation of deaths despite dedicated guideline-based management, revisiting the pathophysiology of dengue was a requirement. Therefore, autopsy studies were carried out and the presence of dengue virus virtually in all body tissues was demonstrated by RT-PCR. Histological studies proved myocarditis and haemorrhagic necrosis of the liver in deceased patients.[13,14] It was my impression that in the management of dengue, just fluid manage-ment alone is not adequate, but vigilant observation is necessary to look for the extended manifestation of dengue.[15] I audited treatments of successful cases and also conducted a therapeutic trial.[16] I was invited by the *BMJ* Best practice and point of care to write up a web-based chapter on dengue and later I wrote papers on the clinical management of dengue in *BMJ* and *RCP Clinical Practice Journal*.[17]

Leptospirosis

Leptospirosis is responsible for severe morbidity and mortality among the aquacultural communities of Sri Lanka. It is endemic in many regions of the island and periodic outbreaks were occurring in the Kandy district. From the latter part of 2007, there was a high incidence of leptospirosis and 2008 saw a major outbreak with very high mortality. Since then, we as a collaborative team commenced our research with the following objectives.

1. To understand the epidemiology of the outbreak
2. To identify causative serogroups and serovars
3. To introduce methylprednisolone bolus in severe leptospirosis to reduce mortality
4. To identify novel clonal groups in different geographical regions

I commenced a prospective clinical study in January 2008 with broader objectives to document epidemiology and clinical manifestations. I found most of the patients were males, and most of them have contracted the infection while cultivating abandoned paddy fields for years. It was shocking to record 17 deaths by May 2008 due to multisystem involvement particularly pulmonary and renal. Therefore, I started methylprednisolone (MP) bolus therapy for complicated patients. As the mortality rate came down, the therapy was continued. Finally, mortality rates were compared between pre-MP and post-MP periods and found a significant difference which was highly significant before the late stages of multiple organ dysfunction.[18] Currently, this treatment has been accepted for clinical practice.

In this cohort, the diagnosis of leptospirosis was based on a non-specific MAT test done at MRI-

Colombo. However, for the identification of serogroups and serovars, it needs specific MAT and molecular studies which were not available in Sri Lanka. Further studies were done in collaboration with Japan, and identified 14 serovars and 14 serogroups among our cohort of patients as causative leptospira species.[19] A recent multicentre study identified 12 clonal types of leptospira pathogen.[20] Now we understand the diversity of pathogenic leptospira species in Sri Lanka and their correlation to the severity of the disease.

Snakes and snakebites

My childhood curiosity about snakes, and a brain full of myths and legends were sorted out by lectures and demonstrations on snakes during the undergraduate years that I vividly remember today even after 4 decades. The expert committee of snakebites of SLMA was formed in 1983 and an issue of *CMJ* was dedicated to snakes and snakebites which serves as the handbook even today. Due to the dedication of the committee, public trust in the government hospital improved with time and the death rate declined. According to the Annual Health Bulletin of MOH, snakebite hospital admissions and number of deaths in 1985 were 3820 and 132 respectively compared to 2019 figures of 34239 admissions and 50 deaths. Later SLMA guideline on snakebite management was developed and the guidelines are being updated regularly, the latest was in 2022. I have been the Chairman of the committee for the last 6 years. The main thrust of my research is snakebite with over 70 publications on different objectives as follows.

1. To describe the epidemiology and clinical manifestations of all venomous snakes in Sri Lanka
2. To test methods of prevention of antivenom reactions and management of reactions
3. To describe supportive medications to reduce morbidity and mortality in snakebite
4. To develop antivenom specific to local snake species

In a prospective series of 210 patients of common krait bite over three years from 1996, I documented all clinical-epidemiology data. This is the largest clinical study of common krait in the world and the results were novel. Of the total, 48% needed assisted ventilation and 17 patients died. Eight necropsy examinations were done to understand the causes of death and found ARDS due to nasal insufflation of herbal medicine as a cause and hypoxic brain damage as another. Further, I described a state of deep coma, autonomic disturbances, hypokalemia, acidosis, anterograde memory loss, and delayed neurological manifestation with severe envenoming.[21] Meanwhile, there was a dearth of knowledge about saw-scaled viper bite due to three decades of unrest in the north. I had no idea about the pattern of snakebites in Jaffna. In a collaborative study with the Teaching Hospital, Jaffna, we studied all snakebite admissions in 2009. Most of those bites numbering 99 were due to saw-scaled viper. I visited Jaffna in 2010 and studied the habitat condition of saw-scaled viper and a glimpse of the geography and social conditions. Of 99 saw-scaled viper bites, 26 patients had come with killed specimens of offending saw-scale vipers, and those specimens were brought to Peradeniya for morphological study. There were no deaths due to saw-scaled viper bite, but 92% of patients developed coagulopathy.[22] During the same visit, I visited Kankasanthurai beach early morning to study sea snakes. It was amazing to observe hundreds of sea snakes entangled in fishing nets of boats reaching the shore. Fishermen disentangled sea snakes most of which were dead at that time. However, sea snake bites are rare among fishermen. Subsequently, I documented three cases of sea snake bites in Negombo and Chilaw where the offending snake was aggressive *Enhydrina schistosa*. One patient died and others had severe rhabdomyolysis and myoglobinuria.[23]

Antivenom is the treatment for snakebites. Currently used Indian polyvalent antivenom carries a high risk of severe anaphylaxis. Overall reaction rates are high. In 2 RCTs, I tested hydrocortisone prophylaxis given in parallel or well ahead antivenom.[24] Also, in another RCT, I tested the place of antibiotics in severe local swelling in viper bites. It was found that antibiotics did not reduce local swelling significantly.[25] Thrombotic microangiopathy is a recently described development of snakebite. This is a dreaded complication where treatment options are limited. The condition comprises a triad of acute renal dysfunction, microangiopathic haemolytic anaemia, and thrombocytopenia. The condition was very much described with hump-nosed viper envenoming.[26]

Other than the high rate of allergy and anaphylaxis, the efficacy of Indian antivenom for local species is doubtful. At the same time, it does not cover hump-nosed viper envenoming. Hump-nosed viper is a highly venomous species causing significant morbidity and mortality and it is the commonest venomous snakebite in Sri Lanka. I have been trying to develop antivenom specific to local species for the last two decades without much success. However, in 2016, a tripartite collaboration was established between the University of Peradeniya and an Indian antivenom producer named Premium serum. Serpentarium was

established at the University of Peradeniya with the permission of the Department of Wildlife, Sri Lanka. Venom was sent to India where the polyvalent antivenom has already been manufactured for 5 local species including hump-nosed viper. After successful preclinical studies, now we are about to start the clinical trial.

Stings

In a clinical-epidemiological study in the primary hospitals in the Northwestern province of Sri Lanka in 2010, we found 632 hospital admissions due to arthropod stings and bites. Offending arthropods were 357 (57%) Hymenoptera (bees, wasps, hornets), 99 centipedes, 61 spiders, and 40 scorpions.[27] This study highlights the medical importance of other environmental creatures which has been a neglected topic. Many deaths due to arthropods envenoming were unaccounted for. There is no management guideline and no specific treatment. However, these creatures are ecologically important. Because of Hymenoptera's role in pollination, trees bear fruits. Unfortunately, their existence is threatened due to human activity e.g., misuse of agrochemicals, and fogging to control mosquitos. My research objectives were,

1. To describe clinical manifestations and epidemiology
2. To identify medically important new species

I described the autopsy findings of both Giant Asian honey bee (*Apis dorsata* / Bambara) and hornet (*Vespa affinis* / Debara) fatal stinging that included bowel gangrene and severe pulmonary oedema. Acute coronary syndrome due to coronary vasospasm has been established with Hymenoptera stings.[28,29]

During my visit to Jaffna in 2010, I found stories about a new deadly scorpion species called the white scorpion. Subsequently, my collaboration with the Department of Zoology, University of Peradeniya identified it as the Indian red scorpion (*Hotantota tamulus*) with the help of the world's experts on scorpions.[30] We postulated that it had come to Jaffna with military goods in the 1980s. This was followed by a descriptive study of Indian red scorpion envenoming over one year in the Teaching Hospital, Jaffna. The clinical manifestations were due to an autonomic storm apart from severe local pain at the site of the sting. Even though there were fatalities when it was discovered, with the use of prazosin to counter autonomic storm, there were no deaths.[31] The first reported case of fatal stinging by the large carpenter bee *Xylocopa tranquebarica* was a detective story, that I initiated after reading a newspaper report in 2015. With the help of JMO Puttalam, all details were uncovered, and the offending insect was secured and identified as a wild carpenter bee, in collaboration with the Department of Zoology, University of Peradeniya.[32]

Concluding remarks

In this short essay, I provided a birds-eye view of a long journey through my career of research work. I highlighted three infections among others namely rickettsioses, dengue, and leptospirosis that I am still actively researching on. The vast amount of data remains unpublished and subjected to the process of data aging and perishing. Similarly, many aspects of snakes and snakebites are presented to provoke thoughts and the challenges faced in the development of antivenom. My interest to discover medically important creatures and their contribution to the ecological balance is another aspect. Developing collaborations with the maximum use of available resources in a resource-poor situation at a low cost is what I did so far.

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