SPECIAL ISSUE EDITORIAL

Advancing the multi-disciplinarity of parasitology within the British Society for Parasitology: Studies of host-parasite evolution in an ever-changing world

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Left running head: *Stothard* et al.

Right running head: *Exploring the multi-disciplinarity of parasitology*

SUMMARY

The study of parasites typically crosses into other research disciplines and spans across diverse scales, from molecular- to populational-levels, notwithstanding promoting an understanding of parasites set within evolutionary time. Today, the 2030 Sustainable Development Goals (SDGs) helps frame much of contemporary parasitological research, since parasites can be found in all ecosystems, blighting human, animal and plant health. In recognition of the multi-disciplinary nature of parasitological research, the 2017 Autumn Symposium of the British Society for Parasitology was held in London to provide a forum for novel exchange across medical, veterinary and wildlife fields of study. Whilst the meeting was devoted to the topic of parasitism, it sought to foster mutualism, the antithesis perhaps of parasitism, by forging new academic connections and social networks to exchange novel ideas. The meeting also celebrated the longstanding career of Professor David Rollinson, FLS in the award of the International Federation for Tropical Medicine Medal for his efforts spanning 40 years of parasitological research. Indeed, David has done so much to explore and promote the fascinating biology of parasitism, as exemplified by the 15 manuscripts contained within this special issue.

Key words: Epidemiology, Ecology, Sustainable Development Goals, COU**NTD**OWN, ZELS

INTRODUCTION TO MULTIDISCIPLINARITY OF PARASITOLOGY

It is well-known that parasitology is a broad and far reaching discipline, constantly changing in its remit and priorities, and typically set within medical, veterinary or wildlife fields of research (Stothard & Rollinson, 2018). Academic interests aside, much of the future ambition and direction of today's practicing parasitologists can be found within the 2030 Sustainable Development Goals (SDGs), especially those working on malaria and neglected tropical diseases (Engels, 2016). These goals have a strong ethos of reducing inequities in human health across the globe, alongside more sensible management of the world's finite resources (Fitzpatrick & Engels, 2016). Although parasites drain ecosystems, their presence is an inevitability, argued perhaps even as an essentiality within a healthy ecosystem (Vannatta & Minchella, 2018). Implicit in the SDGs, however, is the recognition that solving global problems typically requires multi-disciplinary teams (Bangert *et al.*, 2017). These teams seek to forge essential "cross-talk" among critical components of knowledge to assemble a holistic appraisal of a solution over and above what simple reductive reasoning within each discipline alone could achieve.

Today, fostering the multi-disciplinary approach is fashionable and a growing priority of national and international funding and development agencies (Brown *et al.*, 2015; Rylance, 2015). It may be that key individuals, as exemplified by the Victorian explorer and polymath Richard Francis Burton (1821–90), are talented enough, by themselves, to bring diverse disciplines together, coherently, e.g. anthropology, linguistics, cartography and natural history (Pettitt, 2015); more usually, however, it is the assembly of multi-disciplinary research teams that include specialist individuals who are open to cross-talk and exchange of ideas across wider perspectives. A good example of which is the implementation research consortium of COU**NTD**OWN that has brought together parasitologists, social scientists and health economists to tackle issues surrounding the scale-up of preventive chemotherapy in sub-Saharan Africa (Stothard *et al.*, 2017). Another is the multi-disciplinary programmes within the Zoonoses and Emerging Livestock Systems (ZELS) initiative, supported by several major UK funding agencies, which aim to promote and develop *One Health* concepts in which parasitology has a featured role (Blake & Betson, 2017; Kingsley & Taylor, 2017). The word cloud shown in Fig. 1 is a single snap shot of this multi-disciplinary vista.

<*please insert Figure 1 near here*>

It could be argued that much of the principles of multi-disciplinary approaches can be traced back to the wider remit of fundamental parasitology that sought to unravel the dynamic and evolutionary connections between parasites and their hosts, both in time and space, well before the concept of *One Health* was formalised. Its origins lie within the approach taken by the eminent helminthologist Robert Thomson Leiper (1881–1969) (cf. Cox, 2017a, b), although he was not well-known for his team spirit as his publication list as single author might testify (Stothard *et al.*, 2017). Nevertheless, modern parasitology has not been given the full recognition that it deserves for embracing the tools, techniques and approaches first developed in other fields, albeit in qualitative or quantitative methods, and then applying them to the study of parasites with subsequent inter-disciplinary cross-talk.

For example, parasitologists have provided insights at the molecular level, by exploring the myriad of immuno-physiological adaptations and implications of parasites' novel lifestyles and the perturbation of associated host microbial fauna (Jackson *et al.*, 2009; Leung *et al.*, 2018); or they have reconstructed deep parasite histories through analyses of DNA sequences to reveal their intricate phylogenetic pathways and connection with geological vicariances and/or ecological landscapes (Cable *et al.*, 2017; Johnson *et al.*, 2003). In an even broader perspective and sometimes speculative or predicative in manner, understanding the populational behaviours of potential or actual parasites and their hosts has been developed. An example is the related studies on the domestication of animals, with later farming and agricultural practices, which created new opportunities for parasites to exploit our altered environments for zoonoses or anthropozoonoses (Mennerat *et al.*, 2010). In addition, these changes also need to be framed within the context of global climate change (Booth, 2018)

THE ANCIENT ORIGINS OF PARASITES

It could be said that all parasites have a fascinating evolutionary history which may also provide some key clues about the histories of their host evolution. Understanding parasite associations, diversity and distributions through deep time relies almost exclusively on methods of inference and, more rarely, direct evidence from fossils. Co-phylogenetic studies, comparing and mapping host and parasite evolutionary histories, can track associations between co-diverging organismal lineages, revealing host dependencies, host switches and the origins of parasitic interactions and major evolutionary transitions (Page, 1994). Mapping (usually present day) ecological, morphological and developmental traits and geographic distributions provides a rich ground for inferring finer details of host-parasite associations and change through time (Krasnov *et al.*, 2016). Because of the indirect nature of these historical inferences they remain hypotheses. However, where direct evidence of host-parasite associations and interactions can be revealed from fossils, the opportunity to test hypotheses, calibrate phylogenies and reveal entirely novel host-parasite interactions arises. Such opportunities are becoming increasingly tractable and attractive with sophisticated tools such as diagnostic imaging and genomic analyses (De Baets & Littlewood, 2015b).

Enhanced imaging techniques, coupled to computed-tomographic (CT) reconstructions, are revealing unusual and hitherto unseen details within the animal fossil record at an increasing rate. The presence and nature of parasitic associations are also coming into relief through these methods. From small mites to larval pentastomids and isopod crustaceans, exquisite fossils of arthropod parasites have been revealed from fossilised vertebrate and invertebrate hosts (De Baets & Littlewood, 2015a); fossils of metazoan parasites date all the way back to the Cambrian (Bassett *et al.*, 2004). Amber-entombed parasites and vectors have long been a source of detailing historical records of intimate parasite interactions in terrestrial systems, but such finds are rare and are restricted to very few geological deposits (for nematodes, see Poinar, 2015).

More recent (< 10, 000 year-old) fossil evidence of parasites is becoming increasingly tractable for DNA research and is a focus of growing archaeological interest. Importantly, although not-lithified and, strictly speaking, occurring as 'sub-fossils', archaeological discoveries such as mummies, and human settlements, particularly including burial grounds or latrines, are yielding morphologically identifiable helminth egg deposits (Bouchet *et al.*, 2003), some of which have been shown to be amenable to DNA sequencing (Côté *et al.*, 2016). Identification of helminth eggs point to diet, likely infection intensities and disease, associations with domestic animals and possible trade or migration patterns of those parasitised.

A modern focus on genomics via next generation sequencing of common human helminths has assisted with ancient (a)DNA work on such deposits; complete genomes from modern isolates provide a bioinformatic reference scaffold from which to retrieve and characterise ancient human and livestock parasite sequences (Søe *et al.*, 2018). The opportunity to reveal genetic and genomic sequences in the distant past can provide direct evidence of historical baseline data, ancient genetic haplotypes, pre-intervention genetic signatures for both parasites and vectors. Little archaeological material has suitably preserved aDNA for sequencing, but the opportunity to retrace historical genetic variants directly through space and time adds context to present-day epidemiological data and links modern genomic data both analytically and evolutionarily. Ideally, tracking parasites through time provides insights into parasites origins, patterns of diversification and major transitions, until a species dies out.

Indeed, palaeontology and even planetology teaches us that species extinction is inevitable. The fossil record provides ample evidence of the existence of species no longer alive today; the process of extinction is both alive and well. Records of biodiversity over the last 200 years and present-day surveys attest to the fact that species continue to die out – increasingly so at an alarming rate as we see the impacts of the Anthropocene defining a very different natural world. Parasites are no different in this arena, although human intervention targets agents of human disease in control, elimination and eradication programmes. Whether through active intervention, as, for example, in the concerted efforts to eradicate the Guinea worm (*Dracunculus medinensis*) (Hopkins *et al.*, 2017), or more usually through the associated extinction of their hosts, or through ecological perturbations, parasites come and go (Carlson *et al.*, 2017). There is no doubt that parasites of some kind will remain on Earth long after the extinction of mankind or remain with us upon our future diaspora, either inadvertently within us or upon our contaminated itinerant machines.

PARASITOLOGY FOR TODAY AND THE FUTURE

So, what is the multi-disciplinarity of today's parasitology? Frank Cox, a former editor of this journal, once remarked that it is easier to define what parasitology isn't rather than what it actually is (Cox, 2009). Yet, the simple statement that 'a*ll living species are involved in parasitism, either as parasites or as hosts'* is a universal truth. This set the founding concept for discussions at the 2017 Autumn Symposium of the British Society for Parasitology entitled ***"The multidisciplinarity of parasitology: host-parasite evolution and control in an ever-changing world".*** Without doubt, as a way of life, parasitism is a successful evolutionary strategy, but is also part of a broader picture of symbiosis and a convenient classification of the dynamics of how organisms, big or small, interact. As a metaphor, it is tremendously powerful and is regularly used in today's language to describe significant socio-political events as societies and even nations sometimes negatively exploit others. The agenda of parasitology is exciting, challenging and globally relevant.

Like the agenda for the BSP Autumn Symposium, the grouping of the papers assembled into this special issue revolves around three themes, but these divisions blur, as they should, for we encourage cross-talk as much as possible. The '**ever changing world**' hopes to place parasitological research within the new terminology of the Anthropocene and how mankind is altering global environments which may or may not favour parasitic diseases of medical, veterinary or wildlife importance. The '**multi-disciplinarity of parasitology**' encourages synergies between molecular, ecological and social science components that link parasites and hosts into a more holistic appraisal of parasitism. The meeting closes upon '**host-parasite evolution and control**' to recognise that parasites are not simple self-replicating automata and are very able to respond rapidly to interventions waged against them. It was very fitting to discuss this aspect of parasitism at the BSP Autumn Symposium in the meeting rooms of the Linnean Society for it was at this Society that Charles Darwin (1809-1882) and Russel Alfred Wallace (1823-1913) once read their papers, nearly 160 years ago, on the origins of speciation by natural selection.

AN EVER-CHANGING WORLD

In line with the 2030 SDGs, there is a drive towards universal health access, such that the well-being of all is promoted as much as possible. Attaining well-being typically infers the absence of preventable disease, none more so than the lasting control of several neglected tropical diseases. In this light, the drive towards interruption of parasite transmission and disease elimination is important, but requires more careful orchestration of available resources within the health system. Molyneux *et al.* (2018) provide a thought-provoking review which considers the perspectives of policy makers, managers and frontline health workers and how their actions should be better integrated or harmonised on each of their targeted diseases (Molyneux *et al.*, 2018). A good example of the progress being waged against urogenital schistosomiasis in Cameroon is provided by Tchuem-Tchuenté *et al.* (2018). The well-known crater lake villages of Barombi Mbo and Barombi Kotto offer context-specific exemplars in the decline of *Schistosoma haematobium* infection. Moreover, interventions undertaken at these locations, such as exploration of better community engagement or how complementary interventions, including health education and snail control, can work alongside preventive chemotherapy approaches for more sustained reductions in schistosome transmission (Tchuem Tchuenté *et al.*, 2018).

In parallel to the battles being waged against human parasites, those against parasitic helminths in livestock have some unique challenges, especially when the economic value of farmed ruminants is considered. Vercruysse *et al.* (2018) discuss the future of worm control on farms and point out that four facets need to be considered: 1. development and application of better diagnostic tools, 2. implementation of innovative control approaches based on anthelminthic vaccines and selective breeding of resistant stocks, 3. sustainable use of existing anthelminthic drugs alongside introduction of new compounds and 4. rational integration of future control practices within a holistic information the animal production systems (Vercruysse *et al.*, 2018). The connection between human and animal health and that of farmed livestock and irrigated agriculture areas, is well exemplified by human and animal fascioliasis. Mas-Coma *et al.* (2018) highlight recent research on the liver fluke, discussing the subtleties of parasite epidemiology, including the initial infection risk of how parasite metacercariae can be ingested on a variety of foods items as well as in drinking water. The former is becoming increasing important as a burgeoning variety of freshwater wild plants are being consumed by people as often being sold in uncontrolled urban markets. The changing patterns of *Fasciola* infection is another factor adding to the increasing diversity of transmission routes of human fascioliasis across the world (Mas-Coma *et al.*, 2018).

MULTI-DISCPLINARITY OF PARASITOLOGY

With the introduction of molecular DNA methods, the detection and diagnosis of several parasitic diseases has moved away from classic parasitological sampling, such as the detection of parasite ova under the microscope to more formal use of parasite-specific genetic markers. With advances in next generation DNA sequencing, Le Clec'h *et al.* (2018) explore the use of whole genome amplification and exome sequencing of archived schistosome miracidia. Inspection of sequences retrieved by this method facilitates the transition from population genetics, using limited numbers of markers, to population genomics that offer a much wider insight into genome-wide marker associations. Analysis of these data can offer new insights into the pathogenicity of novel genetic variants and also augment the importance of museum-based collections of parasite material, such as the Schistosome Collection At the Natural History Museum (SCAN), as a collective resource for sharing across divergent research groups in future (Le Clec'h *et al.*, 2018).

The question remains, however, which detection method is optimal, and can the best method deliver meaningful results to control programmes that have to make rapid public health decisions. Al-Shehri *et al.* (2018) highlight that there is no single diagnostic method to be used for detection of *Schistosoma mansoni* infection, but rather a more carefully consideration of and application of multiple suitable methods. In particular settings, it is logical to continue with traditional parasitological methods, while in others DNA-based method should be used (Al-Shehri *et al.*, 2018). The choice and cost of which DNA assay to be used for detection of schistosomiasis and soil-transmitted helminthiasis is also discussed by Cunningham *et al.* (2018). A novel low-cost screening method, making use of multiplex high-resolution melt curve analysis, shows much promise; it can be used as a rapid screening tool to process a large number of faecal specimens, and is of particular use when infection prevalence is expected to be low (< 10%) (Cunningham *et al.*, 2018).

Using molecular markers, such as DNA barcodes, has application in environmental monitoring of schistosome infections and transmission. Using a combination of genetic loci, the detection of natural hybrids between *Schistosoma haematobium* and *Schistosoma bovis* has been evidenced in the Senegal River Basin (Séne *et al.*, 2018). With more careful sampling of miracidia obtained from infected patients, Séne *et al.* (2018) revealed many hitherto unknown, fine scale heterogeneities in transmission of schistosomes between humans and livestock. Further surprises in the transmission of schistosomiasis on Zanzibar are evidenced by Pennance *et al.* (2018); their careful molecular characterisation of schistosome cercariae shed from infected *Bulinus* on Pemba confirmed autochthonous transmission of *Schistosoma bovis* (Pennance *et al.*, 2018).

The repertoire of methods for the detection of Old World cutaneous leishmaniasis is surprisingly small, and the search for novel biomarkers continues. Subramaniam *et al.* (2018) have identified five candidate neoglycoproteins (NGPs): Galα (**NGP3B)**, Galα(1,3)Galα (**NGP17B)**, Galα(1,3)Galβ (**NGP9B)**, Galα(1,6)[Galα(1,2)]Galβ (**NGP11B)**, and Galα(1,3)Galβ(1,4)Glcβ (**NGP1B**) which are differentially detected in sera from individuals with *Leishmania major* infection (Subramaniam *et al.*, 2018). The future use of the neoglycoproteins adapted into immune-lateral flow strips, for example, holds promise for the identification of infection as well as longer term markers of treatment cure.

HOST-PARASITE EVOLUTION AND CONTROL

Unlike the well-studied genus *Schistosoma* in Africa, lung flukes of the genus *Paragonimus* have received very little attention. This is due in part because of the more isolated foci of transmission and difficulties in capturing infected hosts within the parasite's lifecycle that involves both snails, freshwater crustaceans and humans (Cumberlidge *et al.*, 2018); indeed, there are perhaps more questions than answers concerning the transmission of paragonimiasis in West and Central Africa. The importance of riverine prawns in Africa has recently received increased attention as a potential biological method of population control of intermediate host snails of schistosomiasis. Diakité *et al.* (2018) conducted a detailed ecological study to show that negative association between intermediate host snail densities and riverine prawns could occur. However, no pattern between this relationship and the prevalence of human schistosomiasis could be found (Diakité *et al.*, 2018).

While falciparum-malaria is a major blight on human health across the world, control of *all* forms of malaria should not be ignored, especially when elimination targets are proposed. Furthermore, there are still components of the lifecycle of *Plasmodium* that remain to be fully clarified. For example, gametocytes represent the sexual stage of the parasite and are indispensable for the transmission of the parasite from human to mosquito; yet, this is perhaps the least understood stage in the parasite's life cycle, and the current state of knowledge is reviewed (Beri *et al.*, 2018). In terms of the life of *Plasmodium vivax*, it is a curious fact of the evolution of the hypnozoite theory of malarial relapse is its transmogrification from theory into "fact" (Markus, 2018). However, Markus (2018) goes on to describe that relapse needs to take into account the possibility of a dual or multiple extra-vascular origin(s) of *P. vivax* in non-reinfection recurrences. This aspect raises the importance of developing better treatment schedules for patients that have putative infections who may later go on to transmit infections to mosquitoes by cryptic relapse mechanisms, perhaps recrudescing local transmission in mosquitoes.

The final paper closes this special issue upon consideration of the importance of monitoring mosquitoes themselves as a future means of shedding light on transmission patterns of lymphatic filariasis and malaria. With regard to lymphatic filariasis, xenomonitoring is recommended, particularly in the context of elimination of transmission (Opoku *et al.*, 2018). However, these authors go on to describe and compare the efficiency of collections techniques using an *Anopheles* gravid trap (AGT) against other better-known methods e.g. indoor resting collection and pyrethrum spray catches. The AGT method, as applied in Ghana, showed high trapping efficiency in collection of the highest mean number of anophelines per night as well as good trapping potential for collecting *Anopheles melas*. This latter species it notoriously difficult to catch using existing methods. The AGT method appears appropriate for xenomonitoring of lymphatic filariasis and malaria vectors (Opoku *et al.*, 2018).

<*please insert Figure 2 near here*>

CELEBRATING COLLABORATION AND A PARASITOLOGICAL CAREER

An underlying theme of the BSP Autumn Symposium on parasitism was also to explore mutualism, those biological interactions seen to benefit all players. Mutualism might be considered the antithesis of parasitism, but we should note that our Symposium was each supported in part by The Linnean Society of London, The Royal Society of Tropical Medicine & Hygiene, The London Centre for Neglected Tropical Diseases and The International Federation for Tropical Medicine (ITFM). Without too much coaxing, each society provided much more than goodwill by covering the costs necessary to run the meeting; this was a perfect example of the power of forging collaboration across groups towards the pursuit of a common good.

Strictly speaking, research collaboration(s) often begin upon finding individuals that are keen to share their wisdom and skills and mentor across the broader network and beyond. With the award of IFTM Medal at the BSP Autumn Symposium, we were able to celebrate the career of Professor David Rollinson, FLS and a former President of the BSP, who has been active in parasitological research for over 40 years, Fig. 2. David also recently received the Linnean Society Gold Medal, in recognition of his services to science. By following his example, our BSP Autumn Symposium and associated special issue volume of *Parasitology* seeks to encourage others to devote their careers and efforts into parasitological research, engendering the spirit of collaboration throughout.

ACKNOWLEDGEMENTS

We thank the British Society for Parasitology (BSP), The Linnean Society and The Royal Society for Tropical Medicine and Hygiene and Cambridge University Press for their contributions to the 2017 BSP Autumn Symposium. We gratefully acknowledge the efforts of our invited speakers, especially those who travelled from afar, our speed poster presenters as well as those participants and attendees who made this meeting convivial, and who have also contributed to this special issue. We warmly thank

Professor John Ellis for his editorial assistance and smooth management in preparing this special issue for production. We congratulate Professor David Rollinson on his receipt of the IFTM Medal and look forward for many future years in continuing his research. As Director of COU**NTD**OWN, JRS gratefully acknowledges funding from Department for International Development (DFID) that encourages multi-disciplinary implementation research.

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Figure 1. A word cloud exploring many of the topics, disciplines and activities that can be included within the study of parasites and parasitological research. The list is not exhaustive and likely has several omissions as the discipline of parasitology moves forward.

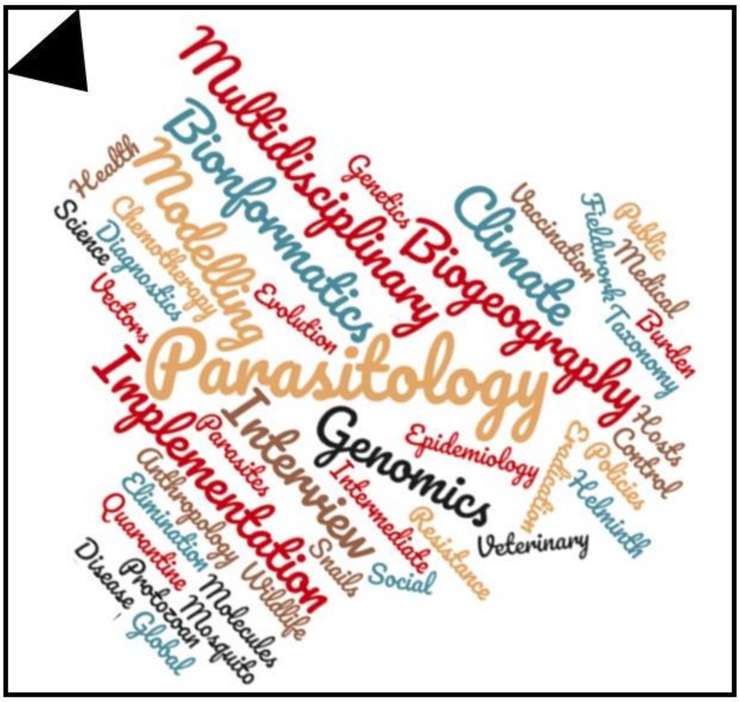

Figure 2. Celebrating the achievements of David Rollinson, FLS within multi-disciplinary parasitological research. A) David overseeing training in field malacology and parasitology in Cameroon; B) Receiving the IFTM medal at the BSP Autumn Symposium from IFTM President Santiago Mas-Coma in recognition of his longstanding career and advancing international collaborations within parasitology.