References

1 Norval, R.A.I. *et al.* (1992) *The Epidemiology of Theileriosis in Africa*, Academic Press
2 Dobbelaere, D.A.E. and McKeever, D.J. (2002) *Theileria*, Kluwer Academic Publishers
3 Shaw, M.K. (1997) The same, but different: the biology of *Theileria* sporozoite entry into bovine cells. *Int. J. Parasitol.* 27, 457–474
4 Shaw, M.K. (2002) *Theileria* development and host cell invasion. *Theileria* (Dobbelaere, D.A.E., McKeever, D.J. eds), pp. 1–22, Kluwer Academic Publishers
5 Tomley, F.M. and Soldati, D.S. (2001) Mix and match modules: structure and function of microneme proteins in apicomplexan parasites. *Trends Parasitol.* 17, 81–88
6 Miller, L.H. *et al.* (1979) Interaction between cytochalasin B-treated malarial parasites and erythrocytes. Attachment and junction formation. *J. Exp. Med.* 149, 172–184
7 Carruthers, V.B. and Sibley, L.D. (1997) Sequential protein secretion from three distinct organelles of *Toxoplasma gondii* accompanies invasion of human fibroblasts. *Eur. J. Cell Biol.* 73, 114–123
8 Håkansson, S. *et al.* (2001) *Toxoplasma* vacuoles: a two-step process of secretion and fusion forms the parasitophorous vacuole. *EMBO J.* 20, 3132–3144
9 Shaw, M.K. (1999) *Theileria parva*: Sporozoite entry into bovine lymphocytes is not dependent on the parasite cytoskeleton. *Exp. Parasitol.* 92, 24–31
10 Dubremetz, J.F. *et al.* (1998) Apical organelles and host-cell invasion by Apicomplexa. *Int. J. Parasitol.* 28, 1007–1013
11 Preiser, P. *et al.* (2000) The apical organelles of malaria merozoites: host cell selection, invasion, host immunity and immune evasion. *Microbes Infect.* 2, 1461–1477
12 Ménard, R. (2001) Gliding motility and cell invasion by Apicomplexa: insights from the *Plasmodium* sporozoite. *Cell. Microbiol.* 3, 63–73
13 Webster, P. *et al.* (1985) The entry of sporozoites of *Theileria parva* into bovine lymphocytes in vitro: immunoelectron microscopic observations. *Eur. J. Cell Biol.* 36, 157–162
14 Mordue, D.G. *et al.* (1999) *Toxoplasma gondii* resides in a vacuole that avoids fusion with host cell endocytic and exocytic vesicular trafficking pathways. *Exp. Parasitology* 92, 87–99
15 Lingelbach, K. and Joiner, K.A. (1998) The parasitophorous vacuole membrane surrounding *Plasmodium* and *Toxoplasma*: an unusual compartment in infected cells. *J. Cell Sci.* 111, 1467–1475
16 Mota, M.M. and Rodriguez, A. (2001) Migration through host cells by apicomplexan parasites. *Microbes Infect.* 3, 1123–1128
17 Shaw, M.K. (1995) Mobilization of intrasporozoite Ca^{2+} is essential for *Theileria parva* sporozoite invasion of bovine lymphocytes. *Eur. J. Cell Biol.* 68, 78–87
18 Carruthers, V.B. (2002) Host cell invasion by the opportunistic pathogen *Toxoplasma gondii*. *Acta Tropica* 81, 111–122
19 Garcia-del Portillo, F. and Finlay, B.B. (1995) The varied life styles of intracellular pathogens within eukaryotic vacuolar compartments. *Trends Microbiol.* 3, 355–368
20 Saliba, K.L. and Kirk, K. (2001) Nutrient acquisition by intracellular apicomplexan parasites: staying in for dinner. *Int. J. Parasitol.* 31, 1321–1330
21 Cudmore, S. *et al.* (1997) Viral manipulation of the actin cytoskeleton. *Trends Biochem. Sci.* 5, 142–148
22 Dramsi, S. and Cossart, P. (1998) Intracellular pathogens and the actin cytoskeleton. *Annu. Rev. Cell Dev. Biol.* 14, 137–166
23 Fawcett, D.W. *et al.* (1984) Interaction of sporozoites of *Theileria parva* with bovine lymphocytes *in vitro* I. Early events after invasion. *Tissue Cell* 16, 873–884
24 Ploubidou, A. and Way, M. (2001) Viral transport and the cytoskeleton. *Curr. Opin. Cell Biol.* 13, 97–105
25 Shaw, M.K. and Tilney, L.G. (1992) How individual cells develop from a syncytium: merogony in *Theileria parva* (Apicomplexa). *J. Cell Sci.* 101, 109–123
26 Shaw, M.K. and Tilney, L.G. (1995) The entry of *Theileria parva* merozoites into bovine erythrocytes occurs by a process similar to sporozoite invasion of lymphocytes. *Parasitology* 111, 455–461
27 Sinden, R.E. and Billingsley, P.F. (2001) *Plasmodium* invasion of mosquito cells: hawk or dove? *Trends Parasitol.* 17, 209–211
28 Heussler, V.T. (2002) *Theileria* survival strategies and host cell transformation. *Theileria* (Dobbelaere, D.A.E., McKeever, D.J. eds), pp. 69–84, Kluwer Academic Publishers
29 Shaw, M.K. *et al.* (1993) Tick salivary gland extract and interleukin-2 stimulation enhances susceptibility of lymphocytes to infection by *Theileria parva* sporozoites. *Infect. Immun.* 61, 1486–1495
30 Shaw, M.K. *et al.* (1991) The entry of *Theileria parva* sporozoites into bovine lymphocytes: evidence for MHC class I involvement. *J. Cell Biol.* 113, 87–101

Trends in teaching parasitology: the American situation

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Parasitic infections in both humans and animals are still rampant and appear to be increasing. There is a need for parasitologists, human and animal doctors to contribute toward the global eradication of communicable and food-borne diseases. The need for teaching parasitology, the recommendations and future perspectives are discussed in this article, and it is proposed that macrobiology should be recognized and taught as a subject area to include the study of eukaryotic organisms encompassing macroparasites.

Parasitology deals with the study of relationships between parasites and their biotic and abiotic environments, between parasites and their hosts, and their reactions towards each other. Parasitism is a way of life in which one species gains its livelihood at the expense of another [1–3]. Parasitic organisms range from 10 meter-long tapeworms to the enigmatic prions that appear to comprise protein, with a bewildering array in between, from prokaryotes and protists to metazoans which occupy every ecological niche imaginable [2]. In short, parasitology includes the study of microorganisms (studied as microbiology) and macroorganisms (which, logically, could and should be studied as macrobiology, as long as microbiology is used and

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identified as a field of study). Parasites have been used to develop models of basic biological phenomena. For example, in the 19th century, Von Beneden described meiosis, and Boveri demonstrated the continuity of chromosomes, both in parasitic nematodes. In the 20th century, refined techniques in physics and chemistry applied to parasites added to our understanding of basic biological principles and mechanisms. For example, Keilin discovered cytochrome and electron transport systems during his investigations of parasitic worms and insects [3].

There are far more kinds of parasitic than non-parasitic organisms in the world. Even if we exclude the viruses and rickettsias, which are all parasitic, and the many kinds of parasitic bacteria and fungi, the parasites are still in the majority [3]. The study of parasitic disease is timeless and will always be relevant to the practice of modern medicine, especially when considering how easy it is for people to travel from one place in the world to another in just a matter of hours. Inexplicably, many medical schools throughout the western world give this subject little attention in their teaching programs, if any at all [4].

Parasites on the move

Humans have suffered a great deal throughout the centuries because of parasites (malaria, schistosomiasis and trypanosomiasis, for example, have caused death to millions). Five of the six tropical diseases that the WHO wishes to eliminate are caused by parasites: malaria; trypanosomiasis; schistosomiasis; onchocerciasis; leishmaniasis; and leprosy (the only one that is bacterial). A majority of parasitic infections of humans occur in the tropical areas of the world. In the USA, some estimates place the number of children infected with worms at ~55 million. Roberts and Janovy [3] said that the notion held by the average person – that humans in the USA are free of worms – is largely an illusion created by the fact that the topic is rarely discussed because of: (1) the attitudes that worms are not the sort of thing that refined people talk about; (2) the apparent reluctance of the media to disseminate such information; and (3) the fact that poor people are the ones most seriously affected. Some parasites such as *Pneumocystis*, *Toxoplasma* and *Cryptosporidium* are among the most common opportunistic infections in patients with AIDS [3]. The number of cryptosporidiosis cases has increased from two human cases reported in the USA in 1976, to an estimated 300 000 cases reported annually. In Romania, trichinosis (trichinelliasis) has increased 17-fold since 1983 to >16 000 cases in the 1990s [5].

Parasitic infections in domestic animals of economic importance are also common in the USA [6–8]*. These are pathogenic to the animals, and some are zooanthroponotic and need to be controlled or eradicated. Sales campaigns for heartworm (*Dirofilaria immitis*) medication have increased public awareness of this dangerous pathogen of dogs [3]. There are many cases of polyparasitism and species diversity, with some animals harboring up to nine different species of parasites. Parasitologists, as well as human and animal doctors, must contribute to the global eradication of communicable and food-borne diseases.

The need for teaching parasitology

There is de-emphasis of parasitology in the medical and veterinary schools, but more so in medical schools. A survey carried out revealed that there is not a single department of parasitology in medical schools in the USA. In *Barrow's Guide to Medical and Dental Schools* of 1997, out of 122 schools and colleges of medicine listed in the USA, only two have parasitology clearly stated in their profiles or curriculum [9]. Out of 27 colleges of veterinary medicine, in 26 states of the USA, only two have parasitology spelt out and not as an independent department. In the other colleges, parasitology is taught under microbiology, pathobiology, pathology, pathobiological sciences, biomedical sciences, basic sciences and pathology.

In several medical and veterinary schools, parasitology is taught under the aegis of microbiology, and parasitologists are made to serve in the microbiology department. It appears illogical and incongruous to teach and study parasitology under microbiology, to put parasitology under the department of microbiology, instead of the other way around. The use of the terms microparasites (small parasites that multiply rapidly within the host of interest, and have a short generation time) and macroparasites (large parasites that usually do not multiply in the host of interest, have a comparatively long generation time and are spread by direct or indirect transmission) has been introduced into the literature, with microparasites including viruses, bacterial pathogens, fungal pathogens and protozoan (or prokaryotic and protistan) parasites, and macroparasites including cestodes, trematodes and nematodes in their definitive hosts, or traditionally defined parasitic helminths and arthropods [3,10]. Microbiology deals mainly with microparasites, whereas parasitology deals with both microparasites and macroparasites. Also, in terms of number and variety, parasites are more numerous than other organisms and they deserve to be given prominence.

According to Zimmer's *Do Parasites Rule the World?* [11], the study of life is for the most part, parasitology. Recent research reveals that parasites are remarkably sophisticated and tenacious, and might be as important to ecosystems as the predators. Some scientists now think that parasites are one of nature's driving forces. Every ecosystem on earth is rife with parasites, which can exert extraordinary control over their hosts, riddling them with disease, castrating them or transforming their natural behavior. Zimmer [11] made reference to the research of scientists like Lafferty, pointing to a remarkable possibility: parasites could rule the world. He observed that 'we are collections of cells that work together, kept harmonized by chemical signals. If an organism can control those signals, an organism like a parasite – then it can control us. And therein lies the peculiar and precise horror of parasites'. New research shows that parasites not only control the behavior of their hosts, they can change entire ecosystems to suit their needs. Because parasitic infections

* Craig, T.M. (1998) Epidemiology of internal parasites: effects of climate and host reproductive cycle on parasite survival. Small Ruminants for the Mixed Animal Practitioner, Western Veterinary Conference, Las Vegas, NV, USA, held 1–5 February, pp. 29–37.

Box 1. Recommendations for teaching parasitology

- Provide hands-on and/or minds-on activities, so that students could learn scientific concepts and practice the process of science
- Use parasitic models to teach. For example, use parasites to demonstrate a wide variety of concepts across diverse topics including evolution, ecology, cell biology, physiology and health
- Apply the three methods of teaching: didactic; audiovisual; and kinesthetic
- Adopt a combined disciplinary and problem-based approach
- Increase the number of lecture hours devoted to medical and veterinary parasitology. Make the time long enough for students to receive quality education in this field; to know of its importance, to appreciate parasitology and become adequately knowledgeable about parasitology
- Extra hours for instructions on clinical cases in approaches focused on animal species and/or organ diseases
- Establish a permanent committee, which should collect information and submit proposals for improvement of teaching medical and veterinary parasitology
- Stimulate students to start simple research projects in parasitology in order to grant a better role to them, to elicit and sustain their interest in parasites
- Prepare a syllabus for the teaching of medical and veterinary parasitology for adoption by various medical and veterinary schools, which could be varied slightly to allow for regional differences.

are not well addressed in the curriculum of medical education in the USA, public health care and information are suffering. The lack of knowledge on parasites of importance displayed by many physicians and veterinarians is a consequence of this apparent *laissez-faire* attitude. The following example gives cause for concern: Gauthier conducted an investigation on the knowledge and attitudes of Connecticut pediatricians and veterinarians about zoonotic helminths†. They were surveyed on their knowledge of prevention, and perceived risk of zoonotic helminth infections in children and pets. On average, veterinarians reported that they felt comfortable advising their clients about preventing transmission of zoonotic helminths, whereas pediatricians felt uncomfortable advising patients and their parents about this issue. Pediatricians were asked to name two zoonotic parasites posing a health threat to Connecticut children; a considerable proportion responded: 'don't know' (32%), or indicated that none was important (19%). There are several other such cases [12–14].

Future perspective

Parasitology needs to be taught in such a way as to sustain interest in it, bring out or emphasize its relevance (as a medical and veterinary core subject, among other fields), and to continually publicize it. Box 1 summarizes some of the ways this could be achieved.

In 1998, the Education Committee of the American Association of Veterinary Parasitologists (AAVP) sent a report to the deans of all of the veterinary schools in the USA. The report contained two sets of documents: the first set was an attempt to highlight the continued need for an emphasis in parasitology, and the second set comprised a list of learning objectives and important topics, which should be included in the core curriculum. This discussion is still ongoing. The AAVP is also working on identifying improved methods of teaching veterinary parasitology (L.R. Ballweber, pers. commun.) which is encouraging and should be supported.

Conclusion

Medical and veterinary students need to be trained to maintain the use and dissemination of parasitology during practice of their professions, and to sustain the manpower needs in these fields. It is necessary that medical and veterinary institutions in the USA reconsider their stance on the place of parasitology in their respective curriculums – to upgrade parasitology to the status of a separate subject area from microbiology, or to be named jointly as the department of microbiology and parasitology, as is the case at Georgia Veterinary School (GA, USA).

The issue of downgrading of parasitology was addressed with respect to Nigeria, a developing country where parasitic problems are intense [15]. In 1997, none of the 13 medical schools in Nigeria had a parasitology department and, up until now, the situation does not appear to have changed. This reflects a western influence, rather than a genuine conviction that human parasitic problems are minimal. The belief that there is human and animal parasitism in the USA, especially in southern part of USA, is unquestionable, and that there might be more parasitism in the future, judging from the immigration policy of the USA and importation of domestic animals, is very probable.

Parasites are a part of the ecosystem in which we live, and they will remain with us. The parasitic relationship and all that it entails is a fascinating subject in itself, but the needs of applied parasitology remain paramount. A basic comprehension of parasitology is essential to reduce significantly the detrimental effects of parasitic diseases on humans and economic animals. It is not far from the truth that parasites rule the world!

The adoption of macrobiology as a field of study and as a counterpart of microbiology to include the study of metazoan or eukaryotic parasites (macroparasites) or organisms (some protists, helminths and arthropods) is hereby proposed. The establishment of the department of microbiology and parasitology in the medical and veterinary schools is strongly recommended at least where the department of microbiology is currently in existence.

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† Gauthier, J. and Richardson, D. (2001) Knowledge and attitudes about zoonotic helminths: a survey of Connecticut pediatricians and veterinarians. Proceedings of the 46th Annual Meeting of the American Association of Veterinary Parasitologists, Boston, MA, USA, held 14–18 July, p. 58.

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References

1 Olsen, O.W. (1967) Parasitism. *Animal Parasites: Their Biology and Life Cycles*, 2nd edn, pp. 1–7, Burgess Publishing Co
2 Marquardt, W.C. *et al.* (2000) *Parasitology and Vector Biology*, Harcourt Academic Press, pp. 1–26
3 Roberts, L.S. and Janovy, J. Jr (2000) Introduction to parasitology. *Foundations of Parasitology*, 6th edn, pp. 1–8, McGraw Hill
4 Despommier, D.D. *et al.* (2000) Preface. *Parasitic Diseases*, 4th edn, pp. viii–ix, Apple Trees Publications
5 Schetters, T. (2001) Parasites on the move. *Trends Parasitol.* 17, 312
6 Couvillion, C.E. *et al.* (1996) Epidemiological study of nematode infections in a grazing beef cow-calf herd in Mississippi. *Vet. Parasitol.* 64, 207–218
7 Acholonu, A.D.W. *et al.* (1999) Gastrointestinal parasites of swine from Southwestern Mississippi. *J. Miss. Acad. Sci.* 44, 103
8 Zajac, A.M. and Gipson, T.A. (2000) Multiple anthelmintic resistance in a goat herd. *Vet. Parasitol.* 87, 163–172
9 Wischnitzer, S. and Wischnitzer, E. (1997) Medical school profiles. *Barrow's Guide to Medical and Dental Schools*, pp. 184–305, Educational Series, Inc
10 Smith, R.L. and Smith, T.M. (2001) Coevolutionary interactions: parasitism and mutualism. *Ecology and Field Biology*, 6th edn, pp. 306–334, Benjamin Cummings
11 Zimmer, C. (2000) Do parasites rule the world? *Discover* 21, 80–85
12 Overgaauw, P.A. and van Knapen, F. (1996) On effects of the educational campaign among family physicians on Toxocara infections in humans. *Ned. Tijdschr. Geneeskd.* 140, 2282–2285
13 Overgaauw, P.A. and Boersema, J.H. (1996) Assessment of an educational campaign by practicing veterinarians in The Netherlands on human and animal Toxocara infections. *Tijdschir. Diergeneeskd.* 121, 615–618
14 Iafaev, R.K. *et al.* (1998) Means for improving the teaching of parasitology in higher medical academic institutions. *Med. Parazitol. (Mosk.)* 1, 47–49
15 Acholonu, A.D.W. (1987) The place of parasitology in medical education in Nigeria. *Parasitosis and Human Health in Nigeria: Present Situation and Future Needs*, pp. 306–334, University of Lagos Press

Arginases in parasitic diseases

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Parasites have elaborated a variety of strategies for invading hosts and escaping immune responses. This article proposes that a common mechanism whereby different parasites escape nitric oxide (NO) toxicity is the activation of arginase. This leads to a depletion of L-arginine (substrate of NO synthase, resulting in lower levels of cytotoxic NO) and increased production of polyamines (necessary for parasite growth and differentiation).

Parasites have elaborated various strategies to escape the immune system and to take advantage of host growth factors. The host immune response produces toxic molecules, but this reaction is limited by regulatory mechanisms. Importantly, it is necessary for the parasites to modulate production of the numerous toxic molecules synthesized by the immune system. Several parasites are highly sensitive to nitric oxide (NO) and its derivatives [1–3]. NO is produced in macrophages by NO synthase (NOS II) from L-arginine, following macrophage activation by microbial products and antigen-specific T-cell-derived cytokines. NO in micromolar concentrations is cytotoxic for microbial organisms and tumor cells. L-arginine is involved in the production of both NO (mediated by NOS II) and L-ornithine (mediated by arginase) (Fig. 1).

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NOS II oxidizes L-arginine in two steps: L-arginine is first hydroxylated to N^{ω}-hydroxy-L-arginine (NOHA), which is further oxidized to L-citrulline and NO. NOHA is also a competitive inhibitor of arginase. Arginase hydrolyzes L-arginine to L-ornithine and urea. L-ornithine favors parasite growth and is a precursor for the synthesis of L-glutamine, L-proline and polyamines via the ornithine decarboxylase (ODC) pathway. Polyamines have multiple roles in stabilizing nucleic acid and membranes, as well as regulating cell growth and differentiation [4].

Two arginase isoforms (arginase I and II) have been identified in hosts. The expression of arginase isoforms in tissues and cells has been reviewed recently [5]. Moreover, arginases, a primordial enzyme family, are highly conserved across kingdoms. Arginase activity from pathogens interferes and competes in host L-arginine pathways. Thus, arginase from *Helicobacter pylori* inhibits NO production by eukaryotic cells [6]. Arginase I and ODC are both located in the cell cytosol, facilitating polyamine synthesis from L-ornithine. Arginase II is a mitochondrial enzyme that could preferentially enhance L-proline or L-glutamate synthesis from L-ornithine because ornithine aminotransferase is also located in the mitochondria. However, it has been shown that L-proline can be converted to L-ornithine, which can be transported from the mitochondria to the cytosol [7]. It has been reported that both arginase I and II regulate polyamine synthesis [8].