Principles and Practice of Clinical Parasitology.
Edited by S. Gillespie & Richard D. Pearson

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Stephen H. Gillespie

Royal Free Hospital and School of Medicine

and

Richard D. Pearson

University of Virginia Health Sciences Center, Charlottesville, Virginia, USA

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Preface

In the 1970s and 1980s, in an attempt to focus world attention on parasitic diseases, the World Health Organization formed the Tropical Diseases Research Group. Their target was six major infections that damaged the health of individuals in developing countries, and five of these six were parasitic diseases. The Rockefeller Foundation also identified parasitic infections as a major target for health improvement for the world community. They formed a research network to develop new drugs and vaccines by understanding the pathogenesis of diseases. Its title 'The Great Neglected Diseases Network' emphasised that, in the post-colonial world, parasitic diseases were no longer identified by governments and pharmaceutical companies as important subjects for medical research. Despite the success of these two ventures in developing our understanding of the immunology, molecular biology and potential for vaccines and drugs, the position of parasitic diseases in the world is, if anything, worse than it was 30 years ago. The territories in which malaria is endemic have expanded and the number of cases with it. Malaria causes more than a million child deaths in Africa every year. The number of individuals suffering from intestinal helminth infections has more than doubled in the last 50 years and the prevalence of schistosomiasis is rising. Urbanisation in Brazil, where more than 80% of the population live in cities, has resulted in large peri-urban epidemics of Chagas' disease and epidemics of visceral leishmaniasis. This general global deterioration has occurred in a context where, for many countries, endemic parasitic diseases are a thing of the past. In epidemiological terms, parasitic infections are over-dispersed or, in more everyday terms, focused in the poorest sector of the world community.

Globalisation has changed the spectrum of parasitic infection in clinical medical practice. Not only has the incidence of disease worldwide risen, but frequency of travel, migration and population dispersal due to war has resulted in individuals presenting with parasitic infections in locations where these diseases have become rare. Patients with malaria and intestinal protozoan and helminth infections are now an everyday occurrence in family practice throughout the world. The diagnosis of parasitic diseases has also become an everyday component of medical laboratory practice worldwide.

The HIV pandemic has also had a potent influence on the spectrum of parasitic infections. A number of organisms that cause disease rarely have become commonplace. The HIV epidemic itself was identified through an apparent epidemic of *Pneumocystis carinii* infection, at that time considered to be a protozoan and now considered to be a fungus. Intractable cryptosporidiosis and isosporiasis, and the recognition of microsporidium infections and cerebral toxoplasmosis, have all been consequences of severe immunocompromise secondary to HIV infection. Visceral leishmaniasis, too, has been recognised as a major opportunistic disease in HIV-infected individuals in Southern France and Italy.

New technologies have increased our ability to investigate parasitic diseases and to understand the biology of the organisms and the hosts' immune response to them. Developments in immunology and molecular biology have enabled diagnostic laboratories to improve the diagnosis of parasitic infections through enzyme-immunoassays and DNA amplification techniques. Genome sequence programmes are under way for parasites, including malaria, *Leishmania* and

amoebas and these may lead to the identification of new virulence determinants, or targets for chemotherapy or vaccine development. Although new treatments and vaccines have progressed more slowly than in other infection disciplines, effective chemotherapy is now available for almost all parasitic infections.

An international panel of authors have drawn together their experience and understanding of parasitic infections. The chapters contain a clinically orientated overview of all the major parasitic infections in medical practice. The editors hope that those who read and use this book will develop their clinical diagnostic and therapeutic skills, and that these skills will be used for the benefit of those who most need them—the people who are often the poorest in the world community.

Stephen H. Gillespie
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1

History of Parasitology

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INTRODUCTION

Many of the larger helminths (e.g. *Ascaris lumbricoides*, *Dracunculus medinensis* and *Taenia* spp.) and ectoparasites must have been visualised in ancient times (Foster, 1965)—in fact, since *Homo sapiens* first became aware of his immediate environment. *D. medinensis* was certainly recognised on the shores of the Red Sea in the pre-Christian era. The first clear documentation of these organisms is to be found in the Papyrus Ebers (c. 1550 BC) and other ancient Egyptian writings (Nunn, 1996); these writers were also aware of *Schistosoma* spp., which remain to this day a major scourge of that country. Aristotle was familiar with helminths involving dogs, fish, and pigs (*Cysticercus cellulosae*) (Foster, 1965); the presence of this latter helminth in the tongues of pigs is alluded to in a comedy (*The Knights*) by Aristophanes. Galen (AD 131–199) recognised three human (macro)parasites: *A. lumbricoides*, *Taenia* spp. and *Enterobius vermicularis*. Aretaeus the Cappodocian (AD 81–138) was apparently familiar with human hydatidosis.

The Arabs seem to have added little (if anything) of importance to existing knowledge of human parasitoses; they, too, were familiar with *D. medinensis*. A twelfth century nun, Hildegardis de Pinguia, recognised the ectoparasite (a mite) causing scabies (Foster, 1965). The first fluke to be well documented was *Fasciola hepatica*; this was accurately described by Anthony Fitzherbert (1470–1538) in *A Newe Treate or Treatyse most Profytable for All Husbandemen* in 1532.

Helminths were in some cases considered to *improve* the health of an infected individual (Foster, 1965); the ancient Chinese, for example, believed that a man should harbour at least three worms to remain in good health, and in eighteenth century Europe many regarded the presence of 'worms' in children as being beneficial to their health. By contrast, there were reports of fanciful or imaginary worms causing all manner of disease(s); parasites were in fact implicated in the seventeenth century in the aetiology of many diseases, including syphilis and plague.

The Doctrine of 'Spontaneous Generation'

From ancient times until the mid-nineteenth century, there was a widespread belief that parasites arose by 'spontaneous generation'—either on or in the human body (Foster, 1965), that was part of a much broader hypothesis which held that *all* living things arose in this manner. In the seventeenth century, William Harvey (1578–1657) cast doubt on this doctrine and Jan Swammerdam (1637–1680) was firmly of the opinion that it did not occur. Antony van Leeuwenhoek (1632–1723) did *not* consider that weevils spontaneously generate in corn

seed, and Francesco Redi (1626–1697) disproved the widely-held contemporary view that flies arise spontaneously from meat. By carrying out careful dissections of *A. lumbricoides*, Edward Tyson (1650–1708) showed there were two sexes and that in fact they multiplied by sexual reproduction; like most contemporaries, however, he believed that the original parasites arose by 'spontaneous generation'. Georges Leclerc, Comte de Button (1717–1788) and Albrecht von Haller (1708–1777) undoubtedly believed in 'spontaneous generation' and, as late as 1839, the anatomist Allen Thompson (Foster, 1965) wrote that this form of generation was 'to be looked upon as no more than an exception to the general law of reproduction . . .'. Two distinguished parasitologists of the later eighteenth century—Marcus Bloch (1723–1799) and Johan Göze (1731–1793) (see below)—both believed that parasites were 'inborn' in their hosts. V. L. Brera (1772–1840), professor of medicine at Pavia, wrote in 1798 that he was opposed to the idea of spontaneous generation; although believing that worms develop from eggs ingested with food, he considered that this occurs only in individuals whose constitution is favourable to the worm, i.e. that a 'host-factor' has a significant role in the parasite–host equation. The 'doctrine of spontaneous generation of parasites' was not finally abandoned until late in the nineteenth century (Foster, 1965).

ORIGINS OF THE SPECIALITY—PARASITOLOGY

The Italian, Redi (see above) has perhaps the best claim to the title, 'father of parasitology': he wrote *Osservazioni intorni agli animali viventi che si trovano negli animali viventi*, and was especially interested in ectoparasites (Foster, 1965), particularly lice, although in his classical text he also described dog and cat tapeworms, and had in 1671 produced an illustration of *Fasciola hepatica*. Another early text was that due to Nicolas André (1658–1742), *De la génération des vers dans le corps de l'homme* (1699); he was the first to illustrate the scolex of a human tapeworm—*Taenia saginata*. He also associated worms with venereal disease(s) but apparently doubted a cause–effect relationship (Foster, 1965). André considered that predisposing factors (to infection) were bad air and bad food (both of which contained 'seeds of worms') and overindulgence in food.

One of the most influential figures in eighteenth century parasitology was Pierre Pallas (1741–1811), whose other major interest was exploration (of the Russian Empire) (Foster, 1965); after graduation at Leyden in 1760, he wrote a thesis, *De infestis viventibus intraviventia*. He also wrote a zoological text, *Miscellanea zoologica*, in which he concentrated on bladder worms—all of which, he considered, belonged to a single species, *Taenia hydatigena*.

Göze (see above), an amateur naturalist, made several important contributions to helminthology; his monumental *Versuch einer Naturgeschichte der Eingeweidewürmer tierischer Körper* was published in 1787. He discovered the scolex of *Echinococcus* spp. in hydatid cysts. Bloch (a doctor of medicine in Berlin) (see above), whose prize-winning essay *Abhandlung von der Erzeugung der Eingeweidewürmer* was published in 1782, was the first to draw attention to the hooklets on the head of the tapeworm.

The Nineteenth Century

This century saw several important texts on helminthology. Brera (see above) (at Pavia, where he had access to Göze's fine collection of helminths) poured scorn on the idea that the presence of worms was either necessary for, or contributed to, health. However, like others before him, he confused the two species of human tapeworm—*Taenia solium* and *T. saginata*. Despite Brera's contributions, Carl Rudolphi (1771–1832), the foremost parasitologist of his day, contributed the most important parasitological work of the early nineteenth century. He utilised the microscope for histological studies, and his scholarly two-volume work *Entozoorum sive vermium intestinalium historia naturalis* (1808), together with *Entozoorum synopsis cui accedunt mantissa duplex et indices locupletissima* (1819), substantially increased the list of known

parasites. Other important texts about this time were due to J. S. Olombel (Foster, 1965) in 1816, and Johann Bremser (1767–1827) in 1819. Another parasitologist of distinction in the early nineteenth century was Félix Dujardin (1801–1860); in 1840 he was appointed to the chair of zoology at Rennes, and was the first worker to appreciate that trematodes and cestodes pass part of their life-cycle in an intermediate host, and that 'bladder worms' are part of the life-cycle of tapeworms; these observations were regrettably not published. He also introduced the term 'proglottis' (a segment of the tapeworm). His major parasitological text was *Histoire naturelle des helminthes ou vers intestinaux* (1845).

Early English Texts on Parasitology

At the outset of the nineteenth century there was virtually nothing written on this subject in English, nearly all work emanating from mainland Europe. Matthew Baillie (1761–1823) had included relevant passages in *Morbid Anatomy of Some of the Most Important Parts of the Human Body* (1793); he noted that tapeworm infections were uncommon in Britain (Foster, 1965). In the 1840s several continental works on helminthology were translated into English, most by George Busk FRS (1807–1886) Surgeon to The Seamen's Hospital Society (Cook, 1997a) and issued by the Ray Society; in 1857, the Sydenham Society published two volumes which contained translations of *Manual of Animal and Vegetable Parasites* (by Gottleib Küchenmeister, 1821–1890), and *Tape and Cystic Worms* (by Carl von Siebold, 1804–1885). However, the Ray Society had already published *On the Alternation of Generations; or, the Propagation and Development of Animals through Alternate Generations* (1845) (Figure 1.1) by the Danish naturalist Johannes Steenstrup (1813–1897); in Chapter 4 of this seminal text he described cercariae (liberated by fresh-water molluscs) which remained encysted for several months and contained the parasitic fluke *Distoma*. Steenstrup had therefore elucidated, and published, the complete life-cycle of one species of liver fluke—thus illustrating his hypothesis of the 'alternation of generations'.

Emergence of Thomas Spencer Cobbold (1828–1886)

Until the 1860s, parasitology was virtually neglected in Britain; during his lifetime, Cobbold became the major British authority on the subject. The son of a Suffolk clergyman (Anonymous, 1886), he served an apprenticeship with a Norwich surgeon, J. G. Crosse; after a few months of postgraduate study in Paris, he returned to the anatomy department of John Goodsir at Edinburgh, where he studied comparative anatomy, and observed many animal parasites, including *Fasciola gigantica* in the giraffe. In 1857, he obtained the post of Lecturer in Botany at St Mary's Hospital, London and in 1861 he was appointed to a lectureship at the Middlesex Hospital; in 1864 he was elected FRS, and in 1873 he obtained the post of professor of botany and helminthology at the Royal Veterinary College, London. In 1864, he published *Entozoa, an Introduction to the Study of Helminthology*; this book and its successor (Figure 1.2) contained a detailed account of all the (known) parasites to affect *Homo sapiens*. Following publication of this text (which had many enthusiastic reviews), Cobbold set up as a physician with a specialist interest in parasitic disease. Due to his, by then, worldwide reputation, he presented, on behalf of Patrick Manson (1844–1922; Figure 1.3) the discovery of the development of 'embryo' filariae (microfilariae) in the body of the mosquito, to the Linnean Society of London on 7 March 1878. In 1879 he published *Parasites: a Treatise on the Entozoa of Man and Animals including Some Account of the Ectozoa.*

Other European Contributions in the Nineteenth Century

A French parasitologist (primarily a general practitioner), who is now largely forgotten, was Casimir Davaine (1812–1882); he wrote extensively on anthrax—before Robert Koch (1843–1910) and

ON THE

ALTERNATION OF GENERATIONS;

OR,

THE PROPAGATION AND DEVELOPMENT OF ANIMALS THROUGH ALTERNATE GENERATIONS:

A PECULIAR FORM OF FOSTERING THE YOUNG IN THE LOWER CLASSES OF ANIMALS.

BY

JOH. JAPETUS SM. STEENSTRUP,

LECTURER IN THE ACADEMY OF SÖRO.

TRANSLATED FROM

THE GERMAN VERSION OF C. H. LORENZEN,

BY

GEORGE BUSK.

LONDON:

PRINTED FOR THE RAY SOCIETY.

MDCCCXLV.

Fig. 1.1 Title page of Steenstrup's text, published in 1845. This, for the first time, linked the adult parasite with its intermediate (cystic) form

ENTOZOA

BEING A

SUPPLEMENT

TO THE

INTRODUCTION TO THE STUDY OF

HELMINTHOLOGY

BY

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LONDON

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MDCCCLXIX.

Fig. 1.2 Title page of Cobbold's text. Published in 1869, this formed a supplement to his major text of 1864

Fig. 1.3 Patrick Manson (1844–1922), who discovered the man–mosquito component of lymphatic filariasis, and founded (with the Rt. Hon. Joseph Chamberlain) the formal discipline of tropical medicine

Louis Pasteur (1822–1895), as well as on many other aspects of science, including fungus diseases of plants, the development of the oyster, the science of teratology, the movement of leucocytes, and investigations involving: rotifers, nematodes and infusoria. His work, in fact, gives a very full account of the state of parasitology in the mid-nineteenth century. He described *Pentatrichomonas hominis* and *Inermicapsifer madagascariensis*, and first advocated the widespread diagnosis of intestinal helminthiases by examination of faecal samples (1857). He also demonstrated that the eggs of *A. lumbricoides* remain infective for long periods of time in a damp environment. However, his major contribution to parasitology was *Traité des entozoaires et des maladies vermineuses de l'homme et des animaux domestiques* (1860); although records of the various species are brief, this text contains excellent illustrated descriptions.

DEVELOPMENT OF HELMINTHOLOGY

Dracunculus Medinensis

The first description of this helminthic infection has been attributed to Moses in the Book of Numbers (Foster, 1965); the Israelites were at

that time living in the Gulf of Akaba. The Papyrus Ebers (Nunn, 1996) also describes probable dracontiasis; there were also several convincing reports during the Middle Ages. However, the first scientific descriptions were by British Army medical officers serving in India during the early years of the nineteenth century (Foster, 1965), suggesting that the infection was acquired from contaminated drinking water, which was at this time aired but not proved! Williams Scott (Foster, 1965), Surgeon to the First Battalion Madras Artillery, confirmed the observation that the female worm emerges when the affected limb is immersed in water. In England, George Busk (see above) documented the anatomy of the parasite on the *Dreadnought* Hospital-ship at Greenwich, but he was not able to enlarge upon its life-cycle. Cobbold (see above) in his *Entozoa* (1864), summarised what was then known of this helminth. The role of *Cyclops* in transmission to man was suggested by Karl Leuckart (1822–1898) and later confirmed by Aleksei Fedschenko (1844–1873) in Turkestan in 1869. These observations were later corroborated by Manson (see above) in 1894, using larvae from a patient with this infection who was under his care at the Albert Dock Hospital, London. Richard Charles (1858–1934), working at Lahore, was probably the first to visualise the *male* worm. Details of the life-cycle were elucidated by Robert Leiper (1881–1969) and Manson in the early twentieth century, but the actual site of copulation and the fate of the male worm apparently remain a mystery to this day (Foster, 1965).

The Hookworms

An early description of hookworm disease is to be found in the Papyrus Ebers (Foster, 1965); the ancient Chinese were also familiar with this infection. Lucretius (dates unknown) during the first century BC pointed to skin pallor, which was common in miners. The first modern reports which date back approximately 200 years, refer to the disease in Negro slaves to the West Indies; however, confusion with the anaemia associated with *Plasmodium* sp. infection had arisen. The discovery of *Ancylostoma duodenale* was made in 1838 and was recorded by the Milanese physician Angelo Dubini (1813–1902) in 1843. This helminth was next recorded in Egypt by Franz Pruner-Bey (1808–1882) in *Die Krankheiten des Orients vom Standpunkte der vergleichenden Nosologie betrachtet* (1847). *Severe* anaemia was first attributed to *A. duodenale* infection by Wilhelm Greisinger (1817–1868) and Bilharz (see below) in 1853. This work was confirmed by Otto Wucherer (1820–1873) in 1866; he had attended a Negro slave in Bahia who died, probably as a result of anaemia, and at post mortem his duodenum contained numerous *A. duodenale*. He then carried out similar investigations on a further 20 patients at the General Infirmary, Bahia. His results were corroborated by several helminthologists, including Cobbold (see above). Battista Grassi (1854–1925) demonstrated, in 1878, that infection could be diagnosed by examination of a faecal sample. In 1880, during construction of the St Gotthard tunnel, this infection was often diagnosed by Edoardo Perroncito (1847–1936), Professor of pathology at Turin; this finding was also made at several other mines throughout Europe, including the Cornish tin-mines, as shown by J. S. Haldane (1860–1936) and A. E. Boycott (1877–1938). As a result of a preventive campaign, the infection in German mines diminished from 13% to 0.17% between 1903 and 1914. Arthur Looss (1861–1923) of Leipzig, around the turn of the century, showed that human infection occurred via intact skin (not orally, as had been previously supposed); he accidentally contaminated his hand with a culture of *A. duodenale* larvae and this was followed by excretion of eggs in his own faeces. Following confirmation of the finding, he published a monograph on the subject. In 1902, Charles Bentley (1873–1949), working in an Assam tea plantation, confirmed these results, describing 'ground itch' for the first time.

Knowledge of the life history of *A. duodenale* pointed the way to prevention of the disease and initiated the Rockefeller Foundation's initiative on prevention of infection by this helminth in Puerto Rico: this project subsequently involved all of the southern states of the USA and had international ramifications. The original anthelmintic was of only limited value; thymol was used by Perroncito (see above) and Camillo Bozzolo (1845–1920) about 1880; this agent was

soon followed by oil of chenopodium (1915), carbon tetrachloride, tetrachlorethylene and hexylresorcinol.

There is only limited work, historically, on *Necator americanus*, the other form of human hookworm infection.

Trichinosis

Friedrick Tiedemann (1781–1861) was probably the first investigator in recent times (1822) to record *Trichinella* (nematode) larvae in *human* muscle. On 2 February 1835, James Paget (1814–1899) (a 21 year-old medical student) noted small 'specks' in the muscles of a post-mortem subject; he reported these observations at a meeting of the Abernethian Society on 6 February. On 24 February, Richard Owen (1804–1892) claimed priority for this discovery at the Zoological Society of London; he first used the name *Trichina* (later changed to *Trichinella*) *spiralis*. Disease ('acute rheumatism') caused by this parasitic nematode was first recorded by Henry Wood of Bristol in 1835 (Foster, 1965). The next major advance was by Arthur Farre (1811–1887), who showed in the same year that the parasite had a complex internal arrangement, including a digestive tract; these observations were subsequently expanded by Hubert von Luschka (1820–1875) of Tübingen in 1850, and Ernst Herbst of Göttingen (1803–1893) in 1851. That the infection is caused by ingestion of raw or undercooked pork ['measly' pork had been identified by Aristotle (384–322 BC)] was documented by Leuckart (see above), Rudolph Virchow (1821–1902) and Friedrich Zenker (1825–1898); this gave rise to the widespread view that other febrile illnesses might be a result of (micro)parasitic infections. Several outbreaks of disease in the European mainland were traced to contaminated pork, but the disease has fortunately remained rare in Britain (Cook, 2001).

Lymphatic Filariasis (Including Elephantiasis)

A seminal discovery by Manson (later to become the 'father of modern tropical medicine'), which delineated the man–mosquito component of the life-cycle of *Wuchereria bancrofti* (the major causative agent of lymphatic filariasis), had a profound impact on the development of clinical parasitology and hence tropical medicine (Cook, 1993a). This observation was superimposed upon an expanding interest at the time in natural history, evolution and bacteriology. Also, the resultant disease, elephantiasis, which affects a minority of those affected, is clinically (and in the eyes of the layman) one of the most spectacular of human (tropical) diseases; *W. bancrofti* has a geographical distribution which involves tropical Africa, middle and southern America, the Indian subcontinent, and much of south-east Asia; however, a related species, *Brugia malayi*, is also important in southern India and south-east Asia. Fortuitously, these nematode helminths are common in that part of China (Amoy and Formosa) in which Manson served with the Imperial Maritime Customs in the latter half of the nineteenth century (Cook, 1993a).

Demonstration of minute thread-like 'worms' or 'embryos' (microfilariae) in chylous fluid was initially due to Jean Demarquay (1814–1875) in 1863 (a Frenchman working in Paris, he demonstrated these 'embryos' in hydrocele fluid derived from a patient who originally came from Havana, Cuba). In 1866, Wucherer (see above) (of German ancestry but born in Portugal), working at Bahia, Brazil, and totally unaware of this discovery, recorded these worms in a urine sample (Cook, 1993a). Demarquay and Wucherer's observations were confirmed by, amongst others, Timothy Lewis (1841–1886) in 1870 (Grove, 1990). In 1872, the same investigator (in a more important communication)—who was incidentally to die of pneumonia at the early age of 44—described 'embryos' of *Filaria sanguinis hominis* in the peripheral blood of a patient at the Medical College Hospital in Calcutta. Joseph Bancroft (1836–1894), working in Queensland, then proceeded, in 1876, to demonstrate *adult* forms (*Filaria bancrofti*) of this helminth in lymphatic vessels. This observation was communicated to *The Lancet* by Cobbold, by then undoubtedly the foremost British helminthologist of his day (see above), in 1877; the work was later confirmed independently by Lewis (see above), in India (Foster, 1965; Cook, 1993a).

Between 1876 and 1897, Manson made a series of observations, the most important of which was the demonstration of the man–mosquito component of the life-cycle of this helminth (see above). After ascertaining that his gardener, Hin-Lo, was heavily infected with 'embryos' of *Filaria sanguinis hominis*, he undertook an experiment (on 10 August 1877) in which he attracted *Culex* mosquitoes by means of candles into a hut in which the gardener was sleeping; when there were many, he closed the door. The following morning, dissection of the mosquitoes revealed plentiful 'embryos' of the parasite; this work was published in China, in 1877 (Cook, 1993a). In 1880, Manson demonstrated the diurnal periodicity of the 'embryos', i.e. they appeared in the peripheral blood solely at night. By means of a series of painstaking dissections, he demonstrated (in 1884) the development of the 'embryos' in *Culex* spp. The fact that they migrate to the lungs during the course of the day was not established until 1897, again by Manson, when resident in London; a post mortem examination on an infected patient who had died suicidally as a result of prussic acid poisoning, showed numerous 'embryos' in pulmonary tissue.

Manson, like most others at this time, felt reasonably certain that man contracted lymphatic filariasis by ingesting water that had been contaminated by infected mosquitoes. In this, Manson was probably led astray by a book he had consulted on natural history, which stated that, once their eggs were laid, mosquitoes rapidly die in water; in fact, they live for several weeks after this event! This belief survived for 20 years after Manson's original discovery implicating the mosquito as the intermediate host. The demonstration of the mosquito–man component of the life-cycle was due to George Carmichael Low (1872–1952) (Cook, 1993b). Manson had sent Low, who had recently joined the staff of the London School of Tropical Medicine (LSTM) to Vienna and Heidelberg to learn a new technique for sectioning mosquitoes in celloidin; previously used methods had been unsatisfactory. When Low returned to London in 1900, Manson had recently received a batch of mosquitoes preserved in glycerine from Thomas Bancroft (1860–1933) (son of Joseph Bancroft) of Brisbane. On sectioning these Low was able to demonstrate microfilariae in the entire proboscis sheath (pushing forward between the labium and hypopharynx) of the mosquito (Cook, 1993a). Shortly afterwards, this work was confirmed by Sydney Price James (1872–1946), working at Travancore, India. In 1900, Grassi (see above) demonstrated transmission of embryos of *Filaria immitis* (a dog parasite) by anopheline mosquitoes (Foster, 1965). The complete cycle of this helminthic parasite had also been completely elucidated.

Thus, for the first time, the complete life-cycle of a vector-borne parasitosis affecting *Homo sapiens* had been delineated. This series of observations paved the way for the subsequent demonstration of vector transmission of *Plasmodium* spp. and many other 'tropical' infections (not all parasitic in nature).

The Tapeworms (*Cestodes*)

Although the two forms—adult and cystic (larval)—of these common human cestodes, *Taenia solium* and *T. saginata*, had been recognised for many centuries, it was not until the mid-nineteenth century that they were shown to represent different stages of individual life-cycles. Until then, therefore, these two stages had been considered separately.

That tapeworms were in fact animals was accepted by Hippocrates (c. 470–c. 400 BC), Aristotle and Galen. Edward Tyson (see above) was the first to make a detailed study of adult tapeworms (he demonstrated that the head end was more narrow); his observations were published in the *Philosophical Transactions of the Royal Society* for 1683. That there were two distinct species to affect man was not suspected until the late eighteenth century, by Göze (see above). The difference between their scolices had been recognised by Küchenmeister (see above), in 1853. Rudolphi (see above), showed that *T. solium* was the most common in Berlin, while Bremser (see above) maintained that in Vienna, *T. saginata* predominated. Only in the late eighteenth century was it appreciated that the segmented contents contained large ovaries, as stated by Bloch. R. Leuckart, in about 1860, made further advances concerning the adult

worms; he described the generative apparatus in detail in *Parasites of Man* (1862).

The history of the cystic (bladder or larval) forms must be traced separately prior to the mid-nineteenth century. This 'stage' was apparent to the ancients; Aristotle, for example, compared the cysts in pigs to hailstones; Aristophanes, Hippocrates, Galen and Aretaeus were also familiar with these 'bladder' forms. Any cystic swelling was in fact called a 'hydatid cyst' throughout these years, although their nature was totally unknown. Towards the end of the seventeenth century, the animal nature of the cysts was first recorded; this fact was first published by Redi (see above) in 1684 although this did not become widely accepted until the early eighteenth century. The finding, together with those of at least two other investigators, remained generally unknown and was rediscovered by Tyson (see above) in 1691. The Swiss physician, Johann Wepfer (1620–1695) described, also in the seventeenth century, *Cysticercus fasciolaris* of the mouse and cysticerci in the brain of sheep. Pallas (see above), in 1760, considered that all cystic worms from different animals belonged to a single species, '*T. hydatigena*'.

Göze in his *Versuch einer Naturgeschichte der Eingeweidewürmer tierischer Körper* (1782), discovered the relation of the *Echinococcus* cyst to its tapeworm; however, it was not until Steenstrup's publication (see above) that the truth became readily apparent. The German helminthologist von Siebold (see above) held that the cystic worms were 'undeveloped and larvae-form tapeworms'.

But how did man become infected with tapeworms? Küchenmeister (see above) performed in 1854 an experiment on a murderer who was condemned to death; he fed him numerous cysticerci 3 days prior to execution, and at post mortem 10 young tapeworms (4.8 mm in length) were apparent in the lumen of his small intestine. He performed a similar experiment a few years later, but this time the prisoner was executed after 4 months; by this time 19 well-developed adult tapeworms were present at post mortem in the small intestine. Further work by Küchenmeister involved *T. coenuris*. The development of cysticerci from eggs was first observed by Stein (1818–1885) at Prague (Foster, 1965). Towards the end of 1853, Pierre van Beneden (1809–1894) showed that after oral administration of *T. solium* proglottids to the pig, *Cysticercus cellulosae* developed.

From a public health viewpoint, J. L. W. Thudicum (1829–1901), appointed by the Privy Council in 1864, carried out extensive inspections for 'measly' meat at London's meat markets. Tapeworm infection was a major problem in British troops in nineteenth-century India, up to one-third of whom harboured *T. saginata*.

Recorded deaths from hydatid disease in England and Wales between 1837 and 1880 were always < 60 annually; sheep were, however, commonly affected. In the mid- and late nineteenth century, hydatid disease was common in Iceland and Australia (especially Victoria).

Diphyllobothrium latum was originally described by two Swiss physicians, Thadeus Dunus (Foster, 1965) and Felix Plater (1536–1614) of Basle, Switzerland.

The Liver Fluke (*Fasciola Hepatica*)

This trematode has been known to infect sheep from medieval times; it was in fact mentioned in a fourteenth century French text (Foster, 1965). The first illustration was by Redi (see above) in 1668. Van Leeuwenhoek (see below) was of the opinion that sheep swallowed the flukes in water, and that they then migrated into the biliary tract. Carl Linnaeus (1707–1778) named the parasite *Fasciola hepatica* but regarded it as a fresh-water leech that had been swallowed accidentally; not until 1808 did Rudolphi (see above) separate the flukes from the leeches, thus creating the class of trematodes (flat worms with ventral suckers), classification of which was based on the number of suckers—monostomes, distomes, etc. In the late eighteenth century, cercariae were clearly recognised, and in 1831, Karl Mehlis (Foster, 1965) visualised the hatching of a trematode with liberation of the ciliated miracidium; shortly afterwards (in 1837) Friedrich Creplin (Foster, 1965) visualised the ciliated miracidium of *F. hepatica*. Following Steenstrup's text of 1842 (see above) it seemed probable that a mollusc formed the intermediate host of this fluke; this was shown to be *Limnea truncatula* by David

Weinland (Foster, 1965) in 1874; although correct, this view was not immediately accepted. A. P. Thomas (Foster, 1965) at Oxford finally confirmed this fact, and published his results in the *Journal of the Royal Agricultural Society* for 1881. Simultaneously, Leuckart (see above), also in 1881, published observations that also showed this to be the case; in fact, his publication appeared 10 days before that of Thomas. Thus, the entire life-cycle of *F. hepatica* outside its definitive host had been worked out. In 1892, Adolpho Lutz (1855–1940), a pupil of Leuckart, demonstrated that herbivorous animals become infected by eating encysted worms and, to complete the story, in 1914 the Russian parasitologist Dimtry Sinitsin (1871–1937) demonstrated the path taken by the larval fluke from gut to liver—invading the peritoneal cavity in so doing (Foster, 1965).

The Schistosomata

In Egypt, disease caused by *Schistosoma* spp. was known from ancient times (see above, Cook, 1993a; Nunn, 1996). Endemic haematuria is mentioned several times in the medical papyri, and calcified eggs have been identified in Egyptian mummies dating from 1200 BC. The first Europeans known to be affected (suffering from haematuria) were soldiers of Napoleon's stranded army in 1799–1801.

Theodore Bilharz (1825–1862), a German parasitologist, discovered the parasite, *Distomum* spp. responsible for Egyptian haematuria on 1 May 1851; some 30–40% of the local population was infected, more commonly men than women. Meanwhile, Cobbold (see above) had described an identical worm (subsequently named *Schistosoma haematobium*) in an ape dying in the gardens of the Zoological Society, London. John Harley (who lacked tropical experience) gave an account of his findings of a supposed new parasite, *Distomum capensis*, in a patient from South Africa, to the Royal Medical and Chirurgical Society, London, in January 1864.

In 1870, Cobbold obtained a supply of *Schistosoma* spp. eggs from a girl in Natal; he observed the hatching of the eggs (by no means the first person to do so), subsequently shown to be *S. haematobium* (see below), and noted that they preferred fresh, brackish or salt water, and *not* urine, for this transformation. He was, however, unable to determine the intermediate host.

Prospero Sonsini (1835–1901), an Italian graduate of the University of Pisa working in Egypt during 1884–1885, again attempted to elucidate the life-cycle of *S. haematobium*; although he did *not* find a mollusc to support his observations, he claimed to have achieved success in Tunis in 1892; these results (in which he considered that human infection took place orally) were published in 1893. In 1894, G. S. Brock (Foster, 1965), working in the Transvaal and citing circumstantial evidence, suggested that human infection probably occurred not orally, but via intact skin whilst exposed to infected water. Meanwhile, Looss, working in Egypt, concluded that, in the absence of convincing evidence of an intermediate host, transmission must take place from man to man.

Work on other *Schistosoma* species then came to the fore. In April 1904, Fujiro Katsurada (1867–1946) of the Pathological Institute of Okayama recognised eggs of what came to be known as *S. japonicum* in a faecal sample. He also found similar eggs in the portal system of two cats from the province of Yamanashi. Confirmation came from John Catto (1878–1908), of the London School of Tropical Medicine, in a Chinese man who had died at Singapore.

Manson (see above) first drew attention to the fact that the rectal and vesical forms of the disease (previously thought to be caused by a single species) were in fact distinct; he was convinced by observations on an Englishman who came from the West Indies (and had never visited Africa) who passed *only* eggs with lateral spines (*S. mansoni*) in his faeces. That these were two separate species, *S. haematobium* and *S. mansoni*, was taken up by Louis Sambon (1866–1931) in 1907, only to be challenged by an acrimonious correspondence from Looss (who still considered that *S. haematobium* and *S. mansoni* represented the same species and that infection occurred directly from man to man).

The complete life-cycle of *Schistosoma* spp. was elucidated in mice, using *S. japonicum*, by Akira Fujinami (1870–1934) and Hachitaro

Nakamura (Foster, 1965) in 1910. Shortly afterwards, Keinosuke Miyairi (1865–1946) and Masatsugu Suzuki (Foster, 1965) infected fresh water snails with miracidia, whilst Ogata (Foster, 1965) described the cercarial stage of the parasite. This work was both confirmed and extended by Leiper (see above) and Edward Atkinson (1882–1929); the former also elucidated the life-cycle of *S. haematobium* in Egypt in 1915: *Bulinus* (*S. haematobium*) and *Biomphalaria* (*S. mansoni*) were shown to be the intermediate hosts.

DEVELOPMENT OF PROTOZOOLOGY

The development of this discipline was totally dependent on the introduction of satisfactory microscopes (Cole, 1926). Although Gesner was probably the first to visualise a protozoan parasite in 1565, it was a century later that Robert Hooke (1635–1703) produced a diagram in his *Micrographia*. The birth of protozoology as a science was, however, due to van Leeuwenhoek (Dobell, 1932) (Figure 1.4) who, in 1674, visualised free-living ciliates in fresh water; he later described cysts of *Eimeria stediae* in rabbit bile. In 1680, the same worker observed motile 'animalcules' in the gut of a horse-fly, and in 1681 in his own stool; these were almost certainly *Giardia lamblia*.

Antony van Leeuwenhoek was born in the small Dutch town of Delft. Lacking scientific training, he became a respected local tradesman (he ran a small haberdashery business) but had sufficient leisure time to devote to scientific pursuits. He made his own lenses and microscopes, through which he originally observed 'animalcules' in marshy water. Most of his results were communicated to the Royal Society in London, to which he was duly elected. van Leeuwenhoek wrote a great deal, and his last letter was written in 1723, his 91st year. He was without doubt the 'father of protozoology'.

More than 100 years were to pass before further parasitic protozoa were recorded, although many free-living forms were described during this time. The term 'Protozoa' was probably introduced about 1820; shortly after this C. G. Ehrenberg (1795–1876) and Felix Dujardin (1801–1860) published important texts on the subject. Various protozoa of insects and fish received a great deal of attention at this time. In 1836, Alfred Donné (1801–1878) discovered *Trichomonas vaginalis* and in 1858 a probable case of coccidiosis, accompanied by a post-mortem report, was published. Around the mid-nineteenth century, a number of human intestinal flagellates were documented, and in 1856 Pehr Malmsten (1811–1883) of Stockholm, described what was probably *Balantidium coli*. The first major pathogenic protozoan of *Homo sapiens* to be described was *Entamoeba histolytica*, which was described by Lösch (see below) in 1873.

Entamoeba histolytica

James Annesley (1780–1847) of the East India Company, was aware of two forms of dysentery. In his classic two-volume work, *Researches into the Causes, Nature and Treatment of the More Prevalent Diseases of India*... (1828) he clearly differentiated between what were to become known as amoebic colitis and shigellosis; he associated the former with hepatic problems (including 'abscess of the liver'). Lösch recorded his observations in *Virchow's Archiv* for 1875, but did not recognise that some *E. histolytica* were pathogenic whereas others were not (as later suggested by Emile Brumpt [1877–1951]), and furthermore he considered that this organism was not the *cause* of dysentery but acted as an 'irritant', thus preventing the colonic ulcers (caused by another agent) from healing. Following this observation, Robert Koch (1843–1910), who was carrying out his researches in Egypt into cholera in 1883, noted *E. histolytica* in both the colon and liver abscess; he was meanwhile too interested in cholera to pursue this organism, but his observation acted as a catalyst for Staphanos Kartulis (1852–1920), who was working in Alexandria, and in 1887 demonstrated the organism in necrotic tissue of a liver 'abscess'; in 1904, he published an account of *E. histolytica* in a cerebral 'abscess'. The results of Kartulis's studies were published in *Virchow's Archiv* and attracted the attention of William Osler (1849–1919), at that time working in Baltimore (Cook, 1995). Heinrich Quincke (1842–1922) and Ernst Roos (1866–?) meanwhile described the *cystic* form of

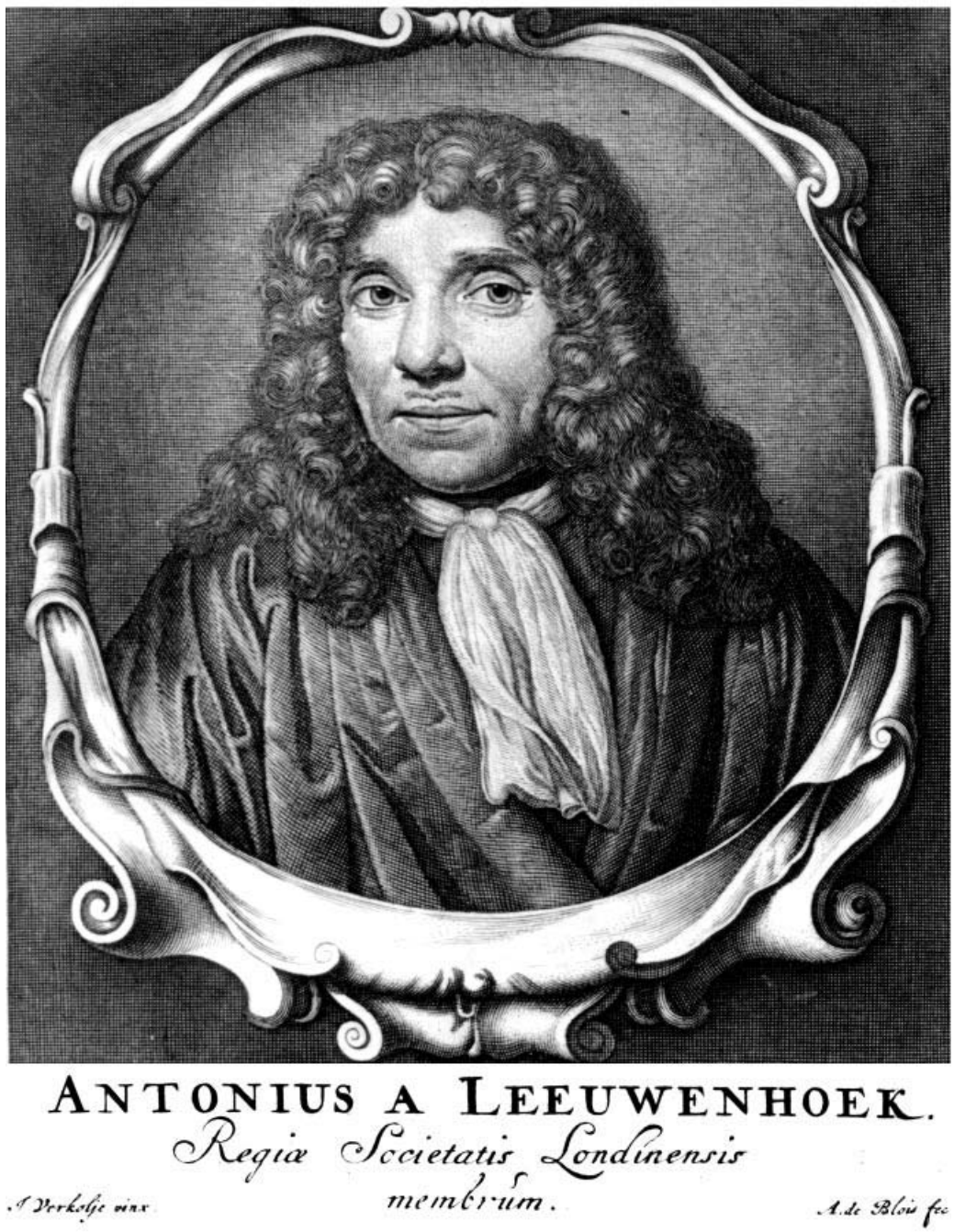

Fig. 1.4 Antony van Leeuwenhoek (1632–1723), the founder of protozoology, who probably visualised *Giardia lamblia* in his own faecal sample. Reproduced by courtesy of the Wellcome Institute Library, London

this protozoan parasite, which they showed was infective to cats when given by mouth. At the commencement of the twentieth century, the role of *E. histolytica* in dysentery was far from clear; however, in 1903 Leonard Rogers (1868–1962) published a paper from Calcutta, in which he described how the organism(s) spread from gut to liver via the portal veins. As late as 1909, however, Manson was not totally convinced that *E. histolytica* was the *cause* of 'tropical dysentery'.

Ernest Walker (1870–1952) working in Manila, The Philippines, between 1910 and 1913 again suggested that there were two forms of *E. histolytica*, one pathogenic and the other not. During the First World War (1914–1918), C. M. Wenyon (1878–1948), working in Alexandria, emphasised the importance of the 'carrier state'. Clifford Dobell (1886–1949) published his classic monograph, *The Amoebae Living in Man*, in 1919.

Babesia spp.

Elucidation of the life-cycle of *Babesia* spp. the cause of Texas Fever (in cattle) is of interest (Foster, 1965), although this organism is not of great practical importance. Theobold Smith (1859–1934) a pupil of Daniel Salmon (1850–1914) (of *Salmonella* fame) together with Frederick Kilborne (1858–1936), published *Investigations into the Nature, Causation and Prevention of Texas or Southern Cattle Fever* (1893). The disease seemed to be caused by an intra-erythrocytic protozoan parasite, a finding that did not fit into any of the then known classifications. Furthermore, transmission seemed to be associated with a tick (*Ixodes bovis*); details of the development of the parasite (in the tick) were not finally worked out until some 40 years after Smith's work. In 1888, V. Babes (who in fact gave his name to babesiosis) had previously visualised an intra-erythrocytic protozoan in affected cattle in Romania.

Plasmodium spp. and 'the Great Malaria Problem' (Cook, 1997b)

In the latter years of the nineteenth century, the cause of malaria (and its treatment) had not progressed since the introduction of cinchona bark, a specific for the 'intermittent fevers'. The fact that malaria is transmitted by the bite of mosquitoes had been suspected for many centuries (Cook and Webb, 2000). Mosquito nets were in fact used in ancient Rome to prevent 'the fever'. Furthermore, there are suggestions in writings over several centuries that the mosquito was indeed involved; for example, in 1717 Giovanni Lancisi (1654–1720), physician to the Pope and a professor at the Sapienzia in Rome, suggested this form of transmission, whilst at the same time accepting the miasmatic theory for transmission of disease. In 1716, Lancisi had demonstrated 'grey-black pigment' in malaria tissue. In 1882, Dr Albert Freeman Africanus King (1841–1914) read a paper to the Philosophical Society of Washington, suggesting (on epidemiological grounds) that *Plasmodium* was transmitted by the bite of the mosquito. It was not until 1880 that Alphonse Laveran (1845–1922), recipient of the Nobel prize for 'medicine or physiology' in 1907 working in Algeria, demonstrated *Plasmodium* in the human erythrocyte (Bruce-Chwatt, 1988; Cook, 1993a); on 6 November of that year he visualised several long flagella being extruded from a hyaline body in a 24 year-old artilleryman. In 1885, Camillo Golgi (1843–1926) was able to show that in malaria, 'fevers' correlated with the liberation of merozoites into peripheral blood; he showed furthermore, that tertian and quartan fevers were caused by different parasites. Ettore Marchiafava (1847–1935) and Amico Bignami (1862–1929) were the first to distinguish *P. falciparum* from the 'benign' malarias. In 1893, Bignami and Giuseppe Bastianelli (1862–1959) showed, by inoculating volunteers with blood known to contain *Plasmodium* spp., that 'fever' was always caused by the 'young' parasite, and never the 'crescent' (the sexual form, or gametocyte). By 1890 it was widely accepted that Laveran's parasites were the cause of malaria (Cook, 1995).

In three classical Goulstonian Lectures delivered to the Royal College of Physicians of London in 1896, Manson (in the light of his filaria researches; see above) spelled out his mosquito–malaria hypothesis (which he had first formulated in 1894) in great depth (Cook, 1993a). This, without doubt, formed the stimulus

Fig. 1.5 Ronald Ross (1857–1932) who established the role of the mosquito in transmission of *Plasmodium* spp. and elucidated the complete life-cycle of avian malaria (*Proteosoma* spp.) in Secunderabad and Calcutta, India, respectively

for the subsequent researches of Ronald Ross (1857–1932) (Bynum and Overy, 1998).

Ross (Figure 1.5) had been born in India. His father, of Scottish descent, was a general in the Indian Army. Ross first became interested in malaria in 1889. After discussions with Manson, who subsequently became his mentor (Bynum and Overy, 1998), he worked on human malaria in India; however, he failed to produce infection in volunteers by the bites of *Culex* or *Aëdes* mosquitoes, but demonstrated malaria pigment in a mosquito at Secunderbad on 20 August 1897 ('mosquito day'). He was then posted to a region where he was not able to study human disease, and therefore turned his attention to avian malaria (*Proteosoma* spp., which is transmitted by the bite of *Culex*). By a series of careful experiments begun in 1897, he demonstrated the

bird–mosquito–bird cycle of this protozoan parasite in 1898; the culmination of this work came on 4 July of that year (Bynum and Overy, 1998). These observations were communicated by Manson to the British Medical Association's meeting, held in Edinburgh on 28 July 1898. Also in 1898 (November–December), Amico Bignami, Guiseppe Bastianelli and Battista Grassi (see above) were able to demonstrate the man–mosquito–man cycle in a series of experiments carried out in Italy; this work was confirmed by Ross in Sierra Leone in 1899. However, because malaria was endemic in both Italy and Sierra Leone, neither study could possibly be definitive, because a *new* infection might easily have been introduced. In 1900, Manson initiated two experiments in order to clinch the man–mosquito–man component of the cycle. A team consisting of Low (see above), Louis Sambon (1865–1931), Signor Terzi (an artist) and a servant slept in a mosquito-proof hut in the Roman Campagna, approximately 8 km from Rome, for a period of 3 months (19 July–19 October 1900); they lived normal outside lives during the course of the day, but did *not* become infected with malaria. In the second experiment, it was arranged (with the collaboration of Bastianelli) to send mosquitoes infected with *P. vivax* from Rome to London in a mosquito box (as late as the 1920s and 1930s *P. vivax* infection was common in the Roman Campagna). On arrival in London, the surviving specimens were allowed to feed on P. T. Manson (1878–1902) (Manson's elder son) and a laboratory technician (George Warren). In both cases, clinical malaria developed; the former subsequently experienced two relapses following quinine chemotherapy. The two experiments were published, like so many early major discoveries in clinical parasitology, in the *British Medical Journal*—for 1900.

Despite his successes, Ross was an extremely difficult individual with whom to work; evidence has been summarised by Eli Chernin (Cook, 1993a). For example, Manson was requested to write a testimonial for a Dr Prout who had applied for Ross's post in Liverpool, which had become vacant in 1912 after his removal to London. He made two comments to which Ross took great exception: 'I sincerely hope that his appointment may be successful, for it would, if I may use the expression, make good a defect in your system of teaching . . .' and, furthermore, 'A teacher of Tropical Medicine, to be considered efficient, should be not only a scientific man, but one having had extensive experience in tropical practice'. Manson was, either consciously or subconsciously, highlighting the fact that Ross was not a great clinician, even though his scientific work was satisfactory. As a result, Ross sought legal advice, the matter being narrowly resolved without a court case. It seems exceedingly ungrateful of Ross to have pursued this libel action against his mentor who was, in effect, largely responsible for an FRS and Nobel Prize (Cook, 1993a); however, this merely reflects the eccentric nature of Ross, who has variously been described as '. . . capable of magnifying a petty affair out of all proportions', 'chronically maladjusted', or 'a tortured man' (Cook, 1993a).

It was not until the early 1940s that Neil Hamilton Fairley (1891–1966) clearly demonstrated the non-haematogenous phase in the life cycle of *Plasmodium* spp. (Cook, 1993a). He observed that a parasitaemia was present in peripheral blood immediately after infection, but that this disappeared during the incubation period of the disease. In 1948, Henry Shortt (1887–1987) and Percy Garnham (1901–1993) were able to demonstrate the 'hypnozoite' phase of *P. vivax* within the hepatocyte, thus putting a seal on the life-cycles of all human (and monkey) *Plasmodium* spp. infections recognised at that time.

The first attempt(s) at malaria prophylaxis by prevention of anopheles mosquito bites was made by Angelo Celli (1857–1914) in 1899.

Therefore, by the end of 1900, the life-cycles of two vector-borne parasitoses, one helminthic and the other protozoan—lymphatic filariasis and *Plasmodium* spp. infection—had been clearly delineated (see above, Cook, 1993a). In the same year, mosquito transmission of the viral infection yellow fever (see above), was also clearly demonstrated, this time by American workers. The major figures in this breakthrough were Carlos Finlay (1833–1915) and Walter Reed (1851–1902) (Cook, 1993a). However, it seems most unlikely that this discovery could have taken place in the absence of the foregoing British work.

Trypanosomiasis: Slow Elucidation of the Cause

African Trypanosomiasis

David Livingstone (1813–1873) had been convinced in the mid-nineteenth century that the tsetse fly was responsible for transmission of 'nagana', a disease which affected cattle in Central Africa. This is clearly recorded in his classic *Missionary Travels*, first published in 1857; there is, in this work, an accurate drawing of the tsetse fly. It seems probable that he had in fact associated the bite of *Glossina palpalis* with 'nagana' as early as 1847. It was not until 1894, however, that the causative role of *Trypanosoma* (later designated *T. brucei*) was delineated in nagana and this resulted from David Bruce's (Figure 1.6) brilliant work in Zululand, where he had been posted from military duty in Natal (Cook, 1994). Shortly before this, animal trypanosomes had been visualised, and in 1878 Timothy Lewis (see above) had first indicated that trypanosomes could cause infection in mammals.

A febrile illness associated with cervical lymphadenopathy and lethargy had been clearly recorded in Sierra Leone by T. M. Winterbottom (1765–1859) in 1803. In 1902, Joseph Dutton

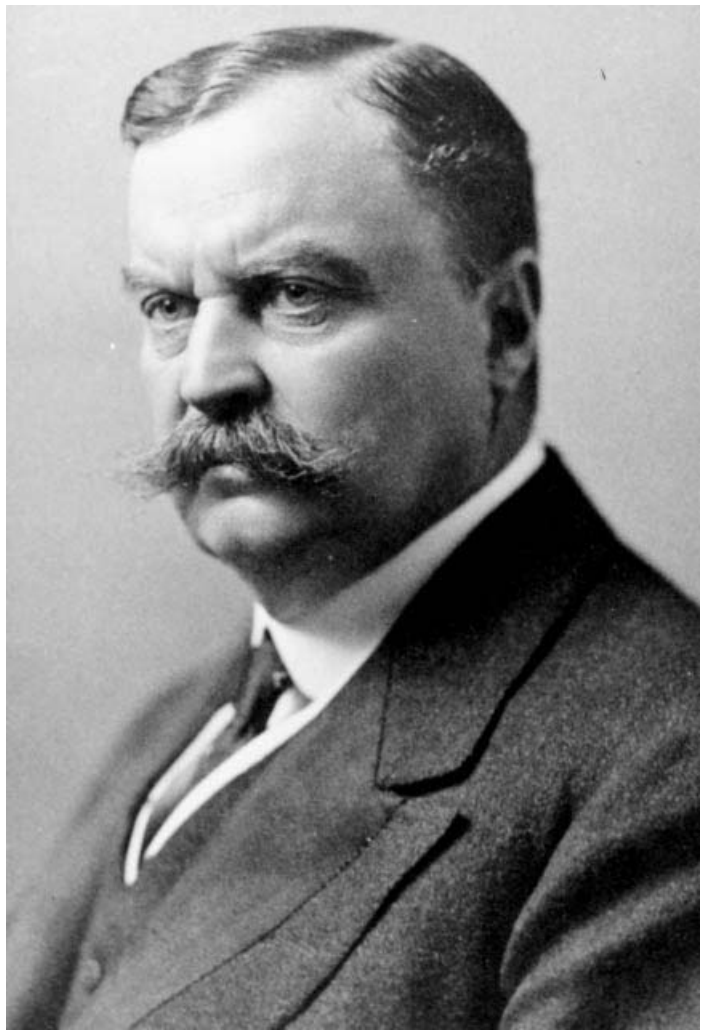

Fig. 1.6 David Bruce (1855–1931), who established the causes of *nagana* (in Zululand) and the 'negro lethargy' (in Uganda)

(1874–1905) (Braybrooke and Cook, 1997) and John Todd (1876–1949) demonstrated that *Trypanosoma* spp. were responsible for this condition, then named 'trypanosome fever' in West Africa; their observations were made on an Englishman who had been infected in the Gambia. Studies were carried out in both the Gambia and Liverpool. This work was published in 1902 with a full clinical description, accompanied by temperature charts.

Early in the twentieth century an outbreak that was described at the time as 'negro lethargy' swept Central Africa; this involved the northern shores of Lake Victoria Nyanza (Cook, 1993b). No-one, it seems equated the disease with 'trypanosome fever'. In 1902, the Royal Society sent a Sleeping Sickness Expedition, consisting of Low (see above), Aldo Castellani (1877–1971) and Cuthbert Christy (1864–1932) in an attempt to determine the aetiological agent responsible for this disease. Manson was of the opinion that *Filaria perstans* was responsible; he had visualised this parasite in three cases of sleeping sickness investigated in London, at the London and Charing Cross Hospitals. After a great deal of painstaking work, Castellani concluded that the disease was caused by a streptococcus. He reported his finding to the Royal Society's Malaria Committee, chaired by Joseph Lister (1827–1912), but they were far from enthusiastic. In the meantime, Castellani had visualised *Trypanosoma* spp. in the cerebrospinal fluid of a single case of 'negro lethargy'; however, he disregarded this organism, and favoured the streptococcal theory. The Royal Society proceeded to send a second team to Uganda in 1903, consisting of Bruce (Figure 1.6) (Cook, 1994) and David Nabarro (1874–1958). They demonstrated *Trypanosoma* spp. in numerous cases of sleeping sickness (in both cerebrospinal fluid and blood) and furthermore, were able to transmit *T. gambiense* to monkeys via the bite of infected *Glossina palpalis* (the local species of tsetse fly); this work clinched the aetiological agent responsible for this disease.

Castellani remained convinced, however, that he should be given credit for discovering the cause of sleeping sickness, now correctly attributed to Bruce and Nabarro. Acrimonious correspondence emerged, some being recorded in *The Times* for 1908 (Cook, 1993b). In retrospect, it seems likely that Castellani was unduly influenced by a report from some Portuguese workers which concluded that a diplostreptococcus was responsible for the disease; Castellani, a trained bacteriologist, was clearly far more impressed with this organism than with *Trypanosoma* spp.!

Several years were to pass before the animal reservoirs of African trypanosomiasis were delineated. Was the causative organism of nagana identical with that which caused African trypanosomiasis? It was not until 1910 that J. W. W. Stephens (1865–1946) and H. B. Fantham (1875–1937) discovered *T. rhodesiense* in Nyasaland (now Malawi) and Northern Rhodesia (now Zambia). In 1911, Allan Kinghorn (?–1955) and Warrington Yorke (1883–1943) demonstrated the transmission of *T. rhodesiense* to man by *Glossina morsitans*.

South American Trypanosomiasis

Human South American trypanosomiasis was first recorded in 1910. Carlos Chagas (1879–1934), working in a remote part of Brazil, became aware that a high proportion of houses were infected with the reduviid bug (the 'kissing bug'), which bit at night. The bug harboured an organism (which developed in the gut and migrated to the proboscis for subsequent inoculation) which was infective to monkeys and guinea-pigs. Chagas showed, furthermore, that an acute febrile illness in children (characterised by oedema, especially of the eyelids, anaemia and lymphadenopathy) was caused by this organism. In 1917 Torres described the cardiac lesions of Chagas' disease. Recognition of the 'mega' syndromes followed. That faecal material from the bug caused infection had been suggested by Chagas, but demonstrated conclusively by Dias (Foster, 1965) in the early 1930s.

Visceral Leishmaniasis (Kala Azar): a Disease with a Potential Influence on the 'Jewel in the Crown'—India

The protozoan parasite responsible for kala azar (or 'dum-dum' fever) has a patchy distribution