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Origins of Coccidiosis Research in the Fowl—The First Fifty Years

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SUMMARY. In 1910, H. B. Fantham described the life cycle of a coccidian parasite in birds. Fantham was a parasitologist at Cambridge University in the United Kingdom working for an enquiry into diseases affecting the red grouse. Despite the growing importance of the poultry industry and the realization that coccidiosis was an important disease of the fowl, little further work was carried out in the United Kingdom until coccidiosis research was initiated at the Veterinary Laboratory, Weybridge almost 30 yr later. Further progress depended upon research carried out at academic and agricultural institutions in the United States. E. E. Tyzzer at Harvard University provided the solid foundation upon which our present knowledge of coccidiosis, and the species of *Eimeria* involved in the disease, is based. Agricultural experiment stations (AESs) throughout the nation played an important role in communicating advances to the agricultural community. W. T. Johnson at Western Washington and, subsequently, Oregon AES made significant contributions to our understanding of the disease, as did C. A. Herrick and coworkers at Wisconsin AES, J. P. Delaplane and coworkers at Rhode Island AES, and P. P. Levine at Cornell University.

Key words: *Eimeria,* coccidiosis, poultry, history, avian disease, agricultural experiment station

Abbreviation: AES = agricultural experiment station

Coccidiosis research in the fowl originated in the United States and United Kingdom during the first half of the 20th century. This review is concerned with the vital role that institutions in both countries (predominantly in the United States), and researchers trained in parasitology, pathology, and veterinary science, played in this research. The review covers a period of 50 yr, from 1899, when the earliest textbook concerned with poultry diseases, which included a section on coccidiosis, was published (146), to 1949, when the first coccidiosis conference was organized by the New York Academy of Sciences (12).

Much early work was undertaken by agricultural experiment stations (AESs) in the United States and has not previously been cited in the scientific literature. Although it is now considered important to publish original research in peer reviewed journals, in the past fewer specialist journals were available, and it was considered important to communicate to the agricultural community by means of bulletins, annual reports, circulars, and the proceedings of professional societies. This creates a problem for those interested in literature of the period because these articles are often difficult to obtain and usually are not indexed either by subject or by author.

Coccidiosis has long been known as important in poultry, and even today, control requires significant financial expenditure. It is difficult to imagine the problem farmers must have faced with a disease that was seemingly present in every flock and impossible to eradicate. During the latter half of the 19th century, the U.S. government came under considerable pressure to solve problems of the agricultural community. This led to the creation of AESs throughout the nation, with a role to conduct research into diseases of livestock and to disseminate findings rapidly to the public. In contrast to the United States, apart from some early work carried out at Cambridge University, there was

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very little coccidiosis research in the United Kingdom during the period. An editorial in 1933 from the *Veterinary Record,* quoted by Payne, states, "It is safe to say that many members of our profession have not yet realized the magnitude of the poultry industry in this country, or the remarkable and steady expansion it has made in the past decade" (134).

Hawkins divides the history of coccidiosis research into three phases (74). The first phase precedes 1929, before the "monumental work of Tyzzer," and the second from 1929 to 1936 when Herrick and Holmes reported the activity of sulphur against *Eimeria tenella.* This ushered in the third stage when most research was concerned with chemotherapy. Previous historical reviews are principally concerned with the "blackhead story" as it relates to coccidiosis (116) and control of the disease (141). Becker (24,25) and Morgan and Hawkins (130) reviewed some of the early literature. Annotated bibliographies by Merck and Co. have been consulted for references from the 1930s and are a valuable source of information regarding chemotherapy (13,14).

EARLY RESEARCH

The grouse enquiry in the United Kingdom. The first detailed investigation of the life cycle of a coccidian parasite in birds was carried out by Harold Benjamin Fantham (1876–1937), a distinguished zoologist and parasitologist who during his career studied many different microbial organisms including trypanosomes, herpetomonads, amoebae, microsporidia, and myxosporidia (references in 169). Fantham was at one time an assistant to the Quick Professor of Biology at Cambridge University and was employed as a protozoologist to the Grouse Disease Enquiry that was established in the United Kingdom to investigate heavy mortality occurring in grouse chicks reared on Scottish moors. He believed only one species of coccidia occurs in birds and gave this the name *Eimeria avium* after the recommendation of Doflein (45). By administering oocysts from feces of diseased grouse to chickens and pigeons, Fantham thought he could produce coccidiosis in these hosts (55).

Fantham was aware of pioneering studies of protozoan parasites carried out in Italy, France, and Germany during the last decades of the 19th century. In Italy, Rivolta and Silvestrini were the first to recognize a coccidian in the fowl and provide an account of sporulation of the oocyst (144). Rivolta described *Gregarina avium intestinalis* (143), a parasite that Tyzzer was subsequently able to identify as the cause of acute cecal coccidiosis in chickens (159). The French workers Raillet and Lucet measured oocysts from ceca of chickens and described a new species, *Coccidium tenellum,* a name later changed by Railliet to *E. tenella* (139,140). In Germany, details of the life cycle were gradually elucidated. Pfeiffer had proposed a cycle involving alternation of parasite generations with a multiplicative phase in cells of the gut epithelium and a reproductive phase leading to formation of oocysts (135). Subsequently, Schaudinn described the complete life cycle of *Eimeria schubergi* from the centipede (147). Fantham notes that in this "celebrated memoir" three essential phases of the life cycle, involving multiplication, reproduction, and spore formation, are reported with a "wealth of morphological and cytological detail."

Fantham described, in intricate detail, the entire life cycle of an eimerian parasite from an avian host (55). He recorded sporozoite liberation from sporocysts (with the aid of pancreatic juices), cell penetration by sporozoites, formation of nuclei within schizonts, merozoite formation, several generations of schizogony, formation of macrogametes with wall forming bodies, and microgametes with flagella, fertilization, oocyst wall formation, and sporogony. The life cycle of *E. avium* as drawn by Fantham is reproduced in Fig. 1.

Information was also obtained on the pathologic effects of infection upon the host. Lesions caused by the parasite were thought to admit bacteria to the circulation, thus providing a possible explanation for various theories from American sources of causes of "white diarrhea" in chickens. Oocysts had been reported in eggs (137), but Fantham was unable to observe oocysts in "genitalia of adult grouse" and thought that their presence could be explained by contamination of eggs as they pass through the cloaca.

The development of *E. avium* was restricted to the intestinal tract; "examination of kidneys, spleen, liver, and gall bladder of infected grouse has yielded negative results" (56). Unfortunately, in later articles Fantham did not restrict

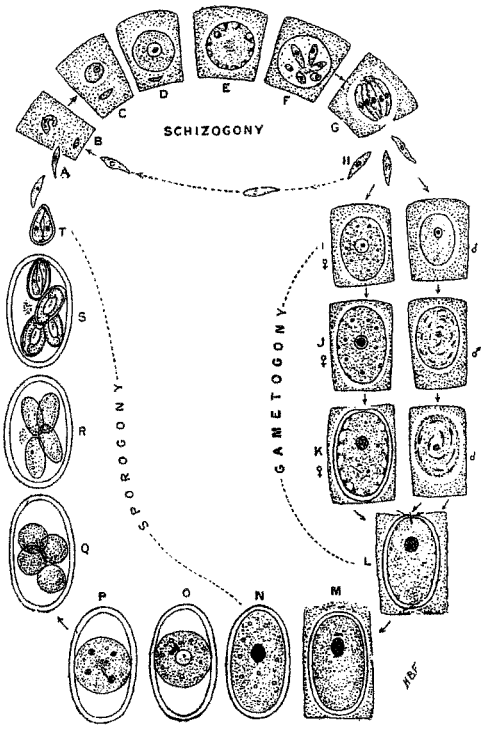

Fig. 1. The life cycle of *E. avium* as drawn by H. B. Fantham (55). Reproduced with permission of the Zoological Society of London.

comments to his own findings but repeated recurrent themes that *E. avium* occurs in many avian hosts and is responsible for blackhead disease in turkeys (57,58).

The Bureau of Animal Industry. Whereas in the United Kingdom coccidiosis research originated in an academic setting, and was sponsored by sporting interests, in the United States research involved those in animal agriculture. In 1884, Congress established a Bureau of Animal Industry with a remit to investigate the condition of domestic animals, causes of disease among them, and means for prevention and cure and to collect information that could be valuable to agricultural and commercial interests of the country.

A veterinarian, D. E. Salmon, was appointed chief of the Bureau and served in this capacity for the first 20 yr. Although Salmon was principally concerned with devastating plagues affecting cattle (Texas fever and pleuropneumonia), he also wrote the earliest textbook concerned with poultry diseases, which included a section on coccidiosis (146). He mentioned two species, *C. tenellum,* a parasite of ceca causing whitish patches, denuded surfaces, and ulcers (resulting in inflammation, diarrhea, whitish excrement, loss of appetite, weakness, and death), and *Eimeria dubia* (perhaps appropriately named), thought to cause lesions resembling those of tuberculosis. *Eimeria dubia* also developed in the intestine but could spread to the liver and lungs. Despite lack of basic knowledge, Salmon gave advice on prevention and treatment. Sanitation was emphasized (disinfection of feeding troughs and drinkers, changing ground followed by ploughing, and restocking with incubator reared chicks from healthy flocks). Treatments recommended included hyposulfite of soda, quinine, subnitrate of bismuth, and a mixture of fennel, anis, coriander, gentian, ginger, and aloes in the feed.

Salmon recruited a graduate of Cornell University, pathologist Theobald Smith, and set him to work on the problem of Texas fever. In 1893, Smith and his colleague Kilborne produced the classic monograph on the causative agent, *Babesia bigemina,* and the mode of transmission via the cattle tick (153). Research at the Bureau was primarily concerned with cattle and swine, but in 1893, Smith received organs of an adult turkey from Rhode Island AES and found that the ceca and liver were "extensively destroyed" by a "peculiar" disease. The next year, Smith spent 3 wk at the station and examined livers and ceca of 50 turkeys, of which 18 were affected by a protozoan parasite that he named *Amoeba meleagridis.* This research led to a detailed description of infectious enterohepatitis or blackhead (151). Parasites in the ceca of two turkeys were identical with *C. tenellum,* but Smith thought it improbable they were related to the true parasites causing the disease.

In a bureau circular, G. B. Morse reported that *C. tenellum* occurs in various domestic and wild birds, but commented, with some foresight, that use of the name *C. tenellum* was tentative and without prejudice to any other "variety" that might be recognized (131). Confusion over the cause of various pathologic conditions in poultry was evident because the parasite, in addition to causing "white diarrhea," was found in cases of "limberneck," "leg weakness," and "going light." In 1910, the Bureau acquired a farm near Beltsville, MD (later known as Beltsville Research Center), and lim-

ited poultry work began in 1914. Early work was greatly handicapped by the reappearance of coccidiosis. "This has rendered it impossible to rear satisfactory young stock, those escaping death being stunted and entirely unfit to save for breeding purposes" (128).

AESs. In 1887, Congress passed the Hatch Act that created a system of state AESs with a remit to conduct original research on subjects bearing directly upon the agricultural industry. The stations were placed on campuses of land grant institutions, thus creating a strong link between agriculture and the research and education mission of the latter organizations. One of the earliest bulletins concerned with parasitic diseases, from North Carolina AES, refers to the "cholera germ—*Gregarina avium intestinalis,*" a parasite of the bowels, liver, and lungs (127). In a bulletin from Delaware AES, Frederick Chester wrote, "there are no free popular publications at hand to inform the farmer or the farmer's wife how these troubles (diseases of fowls) are to be controlled or treated" (35). He noted that the best books on the subject were written in German or French and that Salmon's book had not generally been circulated.

Chester was aware of Theobald Smith's work regarding blackhead but thought he could produce typical enterohepatitis by feeding liver tissue containing coccidia to fowls, "therefore there can be no doubt as to their causative relation to the disease" (35). Thirteen years after Smith's work, Cole and Hadley stated that blackhead is a form of coccidiosis and that Smith's organism is a stage in the coccidian life cycle (36). This must have been galling for Smith because Cole and Hadley's work was carried out at Rhode Island AES where he had conducted his earlier studies. In a subsequent bulletin, "cysts" of coccidia were reported from many birds such as guinea fowl, ducks, pheasants, quail, grouse, pigeons, sparrows, and turkeys (37). Everett Lund (116) noted that Smith, by then Professor of Comparative Pathology at Harvard University, wrote a scathing denunciation of Cole and Hadley for confusing the two diseases (152). Undeterred, Hadley continued his investigations and some years later identified two types of parasite in cases of blackhead, *E. avium* and an unidentified flagellate protozoan (70). During the 1920s, circulars continued to report that the liver is occasionally involved in cases of coccidiosis (32,67). Final resolution of the blackhead controversy awaited work of another professor from Harvard, E. E. Tyzzer.

Although G. B. Morse believed that "white diarrhea" was caused by *C. tenellum,* L. F. Rettger at Yale University, in collaboration with F. H. Stoneburn at the Storrs AES, Connecticut, demonstrated that a bacterium, designated *Bacterium pullorum,* was responsible for this condition (142). A circular from California AES noted that the term "white diarrhea" causes confusion "since any disorder of very young chicks is liable to be manifested by a disturbance of the digestive system and consequent diarrhea" (17). Bacillary white diarrhea caused by *B. pullorum* was distinguished from enteritis caused by *C. tenellum,* although lesions due to the latter were thought to occasionally occur in the liver, lung, and other organs, as well as in the intestine. B. F. Kaupp, a distinguished pathologist from the North Carolina AES, subsequently reported three separate causes of diarrhea in chicks, *B. pullorum, C. tenellum,* and a flagellate named *Trichomonas pullorum* (100,101).

Coccidiosis was recognized by most AESs as a common and widespread disease of poultry. Roy L. Mayhew at the Louisiana AES estimated that in natural outbreaks losses could exceed 50%, with survivors in "a poor and unthrifty condition for months afterward," and that the loss in profit could amount to 10%–40% due to slower rate of growth (122). The Michigan AES reported that *E. avium* was present in at least 90% of all poultry yards (33), and data from Massachusetts AES indicated that coccidiosis was the most frequent disease diagnosed in flocks reared under intensive management (106). In California, coccidiosis was so widespread that "practically all established poultry farms are infected" (19). In Nebraska, however, coccidiosis was "only rarely encountered in material examined but may have been overlooked" (53). The disease was considered not common enough to deserve a great deal of attention. At New Jersey AES, coccidiosis was the most important disease reported in chickens, and at New Hampshire AES, coccidiosis was the second most frequently diagnosed condition and was considered the most important disease confronting poultry raisers (22,64). An extensive survey of the incidence of poultry diseases was undertaken at New Jersey from July 1923 to

June 1930 (23). A total of 9952 specimens from 3719 farms were examined and coccidiosis was diagnosed in 14%, a number exceeded only by cases of pullorum. Mortality did not give an accurate picture of disease frequency because some conditions were so common that specimens were not sent in for diagnosis.

A concern of poultry growers was a condition known as fowl or range paralysis, and a circular from the California Extension Service showed a picture of a recumbent bird, with legs splayed out horizontally, with a legend "four month old pullet with chronic coccidiosis" (21). Eighty percent of birds with paralysis at Florida AES showed "inflammation of the duodenum and the duodenal type of coccidia in the intestinal tract" (149). At Michigan, H. J. Stafseth thought that "so-called cases of range paralysis are nothing more or less than duodenal coccidiosis" and that other symptoms seen included inflammation of the iris, blindness, incoordination of movement, drooping wings, and emaciation (154). Rickets was also considered a secondary manifestation of coccidiosis and a consequence of interference with digestion of nutrients (155). A circular from the Wyoming Extension Service reported that chronic coccidiosis was the most common cause of fowl paralysis (105), and a survey conducted by Storrs AES (Connecticut), revealed that eight of 49 stations (California, Colorado, Illinois, Massachusetts, Michigan, New Hampshire, South Dakota, and Texas) believed that coccidiosis was associated with or the cause of fowl paralysis (133). Histologic observations of birds with paralysis, however, failed to reveal a correlation with coccidiosis (133), and W. T. Johnson noted that fowl experimentally infected with coccidia showed no paralysis even when kept for several months (92).

Researchers continued to look for chemical remedies. A report from the Pennsylvania State Sanitary Board optimistically concluded that calomel and methylene blue might have value in controlling coccidiosis (129). An arsenical compound, neoarsphenamine, had been successful in treating protozoan diseases in humans, but at Missouri AES, this drug was found to be ineffective against coccidiosis (51). Ward and Gallagher (166) considered that catechu (recommended by Fantham) was more effective than other preparations, but Beach and Corl tested various chemicals, including catechu, and found none effective (18). A circular from Utah AES advised that administration of drugs is of questionable value, "poultrymen should beware of various patented powders and liquids sold on the market as cures for coccidiosis" (117). Colorful language was often employed to promote these remedies. For example, coccidiosis was considered "a tramp that follows the spring rains and warm sunshine and leaves a trail of dismantled poultry farms due to dead chicks" (52).

Walter T. Johnson (1892–1937). W. T. Johnson was a graduate of Washington State College and worked for 6 yr at Western Washington AES. In 1925, he moved to Oregon to take up a position as poultry pathologist and spent the next 13 yr at the State College AES, attaining the rank of Professor of Veterinary Medicine. During this period, he made many important contributions to our understanding of coccidiosis. He demonstrated that coccidia from sparrows are morphologically different from those of chickens and not infective for poultry. He was unable to infect turkeys with coccidia from chickens, thus indicating the host specificity of *Eimeria* (88). He examined turkeys showing typical lesions of blackhead and found no coccidial parasites in the ceca, but he did find many motile flagellates and concluded that it is unlikely the coccidium has a direct relationship to blackhead disease. His findings concerning morphologic variability were significant. "Distinctly noticeable variations are seen as to size, shape, and structure of similar stages of apparently the same species of coccidium. The differences are often so marked as to suggest very strongly the probability of more than one species of coccidia being found in the chicken" (89). Initially, he was uncertain if there was more than one species, ". . . present information indicates that the same coccidium may be so variable that one can be readily misled to the belief that more than one species is being observed even when this is not true. . . . only one species—*E. avium*—is here recognized" (89). The publications committee of the American Association of Instructors and Investigators in Poultry Husbandry requested that Johnson prepare a series of photomicrographs for readers of *Poultry Science* to "provide a clear picture of what happens when a chicken becomes infected with coccidiosis." Some of the micrographs are reproduced in Fig. 2, and, on

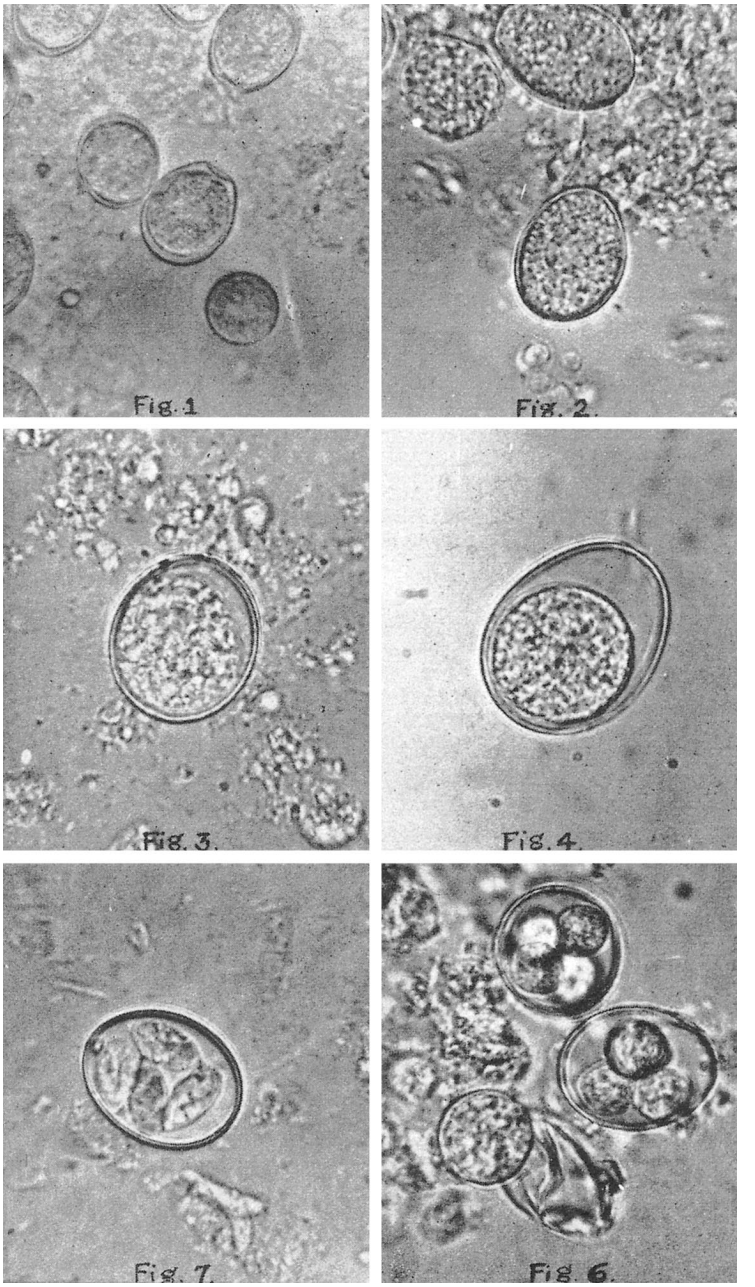

Fig. 2. Illustration of oocysts of *Eimeria* (875× magnification) by W. T. Johnson (89). Oocysts were obtained from smears of intestinal scrapings from the duodenum (fig. 1), and cecum (figs. 2, 3, 6, 7). Origin of the oocyst depicted in fig. 4 was not given. Reproduced with permission of *Poultry Science.*

the basis of the size of the oocysts it seems that at least three species were illustrated (89). These *Eimeria* species were subsequently identified by Tyzzer (159) as *E. acervulina* (89: Fig. 1), *E. tenella* (89: Figs. 2, 6, 7), and *E. maxima* (89: Fig. 4).

In an AES bulletin published in December 1928, Johnson stated that four kinds of coccid-

ia were present in Oregon and illustrated this with photomicrographs of small and large oocysts from the small intestine and midsized oocysts from ceca (92). In March that year, Johnson had corresponded with Tyzzer, who told him he had isolated four similar species of *Eimeria.* Two years earlier, at the December (1926) meeting of the American Society of Parasitologists, Tyzzer had reported that *E. tenella* was different from species that develop in the small intestine (158). Tyzzer had also confirmed Johnson's suggestion that a species of *Eimeria* from turkeys was different from *E. avium* and named this *Eimeria meleagridis.* In the biennial report of the Oregon AES for 1928–30, Johnson recognized six species of *Eimeria* in the chicken and provided a brief description of two new species, *Eimeria praecox* and *Eimeria necatrix* (8). The description included average dimensions of 50 *E. praecox* oocysts (20.6 × 23.8 μm), but the size of *E. necatrix* oocysts was not given. Nine schizonts of *E. necatrix* were measured, "the largest of any species" (average of 49.2 × 23.8 μm). Oocysts of *E. praecox* appear on the fourth day after inoculation, a few hours earlier than for *E. acervulina. Eimeria praecox* "attacks the small intestine beginning near the gizzard." *Eimeria necatrix* also attacks the small intestine and, in severe infections, produces marked hemorrhage. It was not possible to demonstrate cross-immunization between *E. praecox* and species that had been described by Tyzzer (*E. acervulina, E. maxima,* and *E. mitis*).

Johnson was the first to relate the number of sporulated oocysts ingested to severity of infection (91). He showed that the life cycle is self-limiting, "infected fowls rid themselves of coccidial forms in a comparatively short time" (91). He used potassium dichromate to prevent "putrefaction" in cultures of sporulating oocysts, an idea that suggested itself following information provided by Hadley, formerly from Rhode Island AES (91).

Johnson carried out pioneering studies concerned with immunity. He noted that immunity could be produced by experimental inoculation, that there are many observations that older fowls are less affected by coccidiosis than younger birds, but age is not necessarily the determining factor (90). He found that chickens given oocysts obtained from the small intestine do not develop resistance to subsequent challenge with oocysts obtained from ceca. He was interested in producing immunity by controlled inoculation (92,94) and showed it is possible to immunize chickens by including low doses of oocysts of five species each day in the feed (93). Chandler was skeptical, "the possibility of immunizing a flock of chicks against severe infections by feeding chicks a few oocysts seems to be remote" (33), but Jungherr was of the opinion that "the search should be continued for a universally applicable method of early immunization against all types of coccidia" (98).

After Johnson's death in 1937, Oregon AES claimed, "more information on the parasitic disease coccidiosis has been discovered at the Oregon station than at almost any other place. The Oregon station is probably the only institution in the world where six known species of coccidia of the chicken are available in pure culture" (10). Losses in Oregon due to coccidiosis were estimated as $250,000 annually for an industry valued at $8,000,000. Mrs. Johnson wrote an article, "from rough manuscript notes and tables prepared by her husband over a period of research that occupied the later years of his life" (95). M. C. Hall of the Bureau of Animal Industry was acknowledged for suggesting the names *E. necatrix* and *E. praecox,* the former signifying murderess because of extreme pathogenicity, and the latter signifying precocity because of early oocyst development. In addition to detailed information on pathogenicity and life cycles, photomicrographs were presented illustrating three types of oocysts and intestinal lesions.

Johnson's views on control were ahead of his time. "With the chicken susceptible to at least six species of coccidia . . . infection occurring at irregular times . . . it seems inconceivable that a treatment can be considered an important means of control unless it is highly effective, practical, and economical to apply for indefinite periods" (95). ". . . actual inoculation of young stock on poultry farms, as a control measure, is becoming more valid as the facts regarding coccidiosis are ascertained. The recommendation to purposely infect by actually feeding oocysts involves a rather complicated procedure . . . must first be approached experimentally. The multiplicity of coccidial species certainly complicates the solution" (95).

Edward E. Tyzzer (1875–1965). Elery Becker wrote, in the preface of the first book devoted to coccidiosis, "take away the monu-

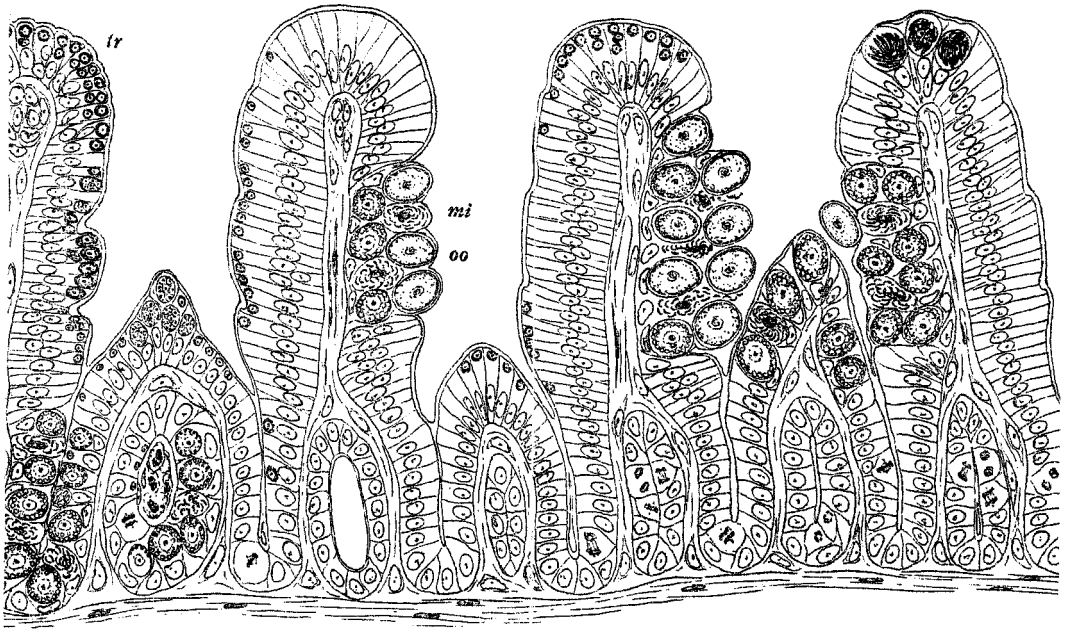

Fig. 3. Life cycle stages of *E. acervulina* as drawn by E. E. Tyzzer (159). Key: mi = microgametocyte; oo = oocyst; tr = trophozoite. Reproduced with permission of Oxford University Press.

mental researches of Tyzzer and of Perard and how different would our conception of host–parasite relationships in the coccidia be today" (24). Tyzzer, Doctor of Medicine at the Department of Comparative Pathology in the medical school at Harvard University, like Fantham and Smith, had studied many different parasitic protozoa (references in 169). His early achievements include a description of *Cryptosporidium parvum* from mice and resolution of earlier blackhead controversies by naming *Histomonas* as the flagellate responsible for this disease.

Tyzzer's papers in the *American Journal of Hygiene* are recognized as the most significant contributions to our knowledge of coccidiosis in poultry (159,163). The work published in 1929 (159) "was undertaken primarily for the purpose of reconciling apparently contradictory observations relative to the pathogenicity of *Eimeria avium* for chickens." In addition to providing a detailed description of *E. tenella,* he described three new *Eimeria* species from the chicken (*E. mitis, E. maxima,* and *E. acervulina*) and new species from the pheasant, quail, and turkey (*E. dispersa, E. meleagrimitis,* and *E. meleagridis*). He presented exquisitely detailed drawings of life cycle stages of *Eimeria* in sections of intestine; examples of the drawings of *E. acervulina, E. mitis, E. maxima,* and *E. tenella* are reproduced in Figs. 3–6. Tyzzer described nuclear division in schizogony and gave new information on host and site specificity and immunity. Concerning site specificity, "the characteristic habitat of each species is not determined by the part reached by the infective form, but rather by the suitability of the tissue for the further development of the parasite." Because he had developed methods for working with single rather than mixed species, he was able to describe characteristic lesions of species, such as obvious hemorrhage in the ceca caused by *E. tenella,* superficial grayish spots in the upper small intestine caused by *E. acervulina,* and a pinkish tinged exudate in the middle intestine caused by *E. maxima.* In combination with oocyst dimensions, he prepared the first meaningful chart for differential species diagnosis. He noted that more pronounced pathologic changes are associated with stages that penetrate deeply into the mucosa and attain large size. Thus, with *E. tenella,* "the most serious damage is wrought by the large schizonts, while with *E. maxima* nearly all the injury results from growth of the sexually differentiated forms."

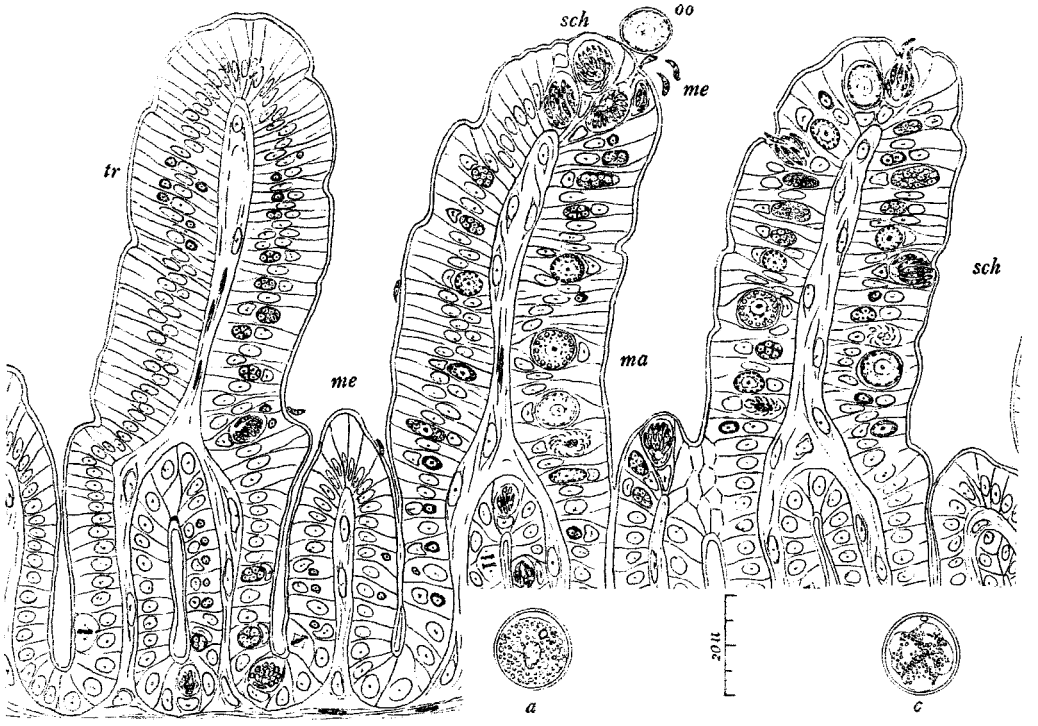

Fig. 4. Life cycle stages of *E. mitis* as drawn by E. E. Tyzzer (159). Key: ma = macrogametocyte; me = merozoite; oo = oocyst; sch = schizont; tr = trophozoite. Reproduced with permission of Oxford University Press.

In the 1932 paper, Tyzzer provided detailed descriptions of *E. necatrix* and *E. praecox* and generously credited these species to Johnson, "notwithstanding the brevity of his descriptions, it appears reasonably certain that the two species which we have independently discovered are *E. praecox* and *E. necatrix* of Johnson" (163). Tyzzer addressed many topics such as protective immunity, sources of infection, and use of chemicals, "up to the present time none of the chemicals advocated serve either to prevent coccidial infection in the chicken or eradicate it after it is established." His views on control were similar to those of Johnson, "attempts to rear chickens in the absence of all coccidial infection are in general ill advised and the gradual building up of immunity through repeated light infections appears to furnish more promise."

At the 35th meeting of the United States Livestock Sanitary Association (160) and in an article for *Science* (161), Tyzzer described the criteria and methods used in his investigations. He pointed out that coccidian infections are ubiquitous, "failure to take account of adventitious infection has led to much confusion of species" and that the host response "has no basis in humoral reactions but in a cellular one." Histologic studies establish that "the organisms are destroyed in the sporozoite stage. Large numbers of the sporozoites penetrate the cells in the immune bird but the cells, instead of enlarging and taking on a development that is favorable to the growth of the organisms, react unfavorably. The nucleus shrivels up, the cell dies and the organism is thus unable to develop." W. L. Chandler had proposed a contrary explanation for host resistance to reinfection. "While it is quite probable that coccidial infections may result in the production of specific antibodies or in phagocytosis, immunity probably results principally because of slight changes in the physiology of the organ invaded" (34).

At the 2nd International Congress for Microbiology held in London, it was evident that Tyzzer was concerned with regulation of infection (162). He recognized self-limiting infections that run a brief course and are not ter-

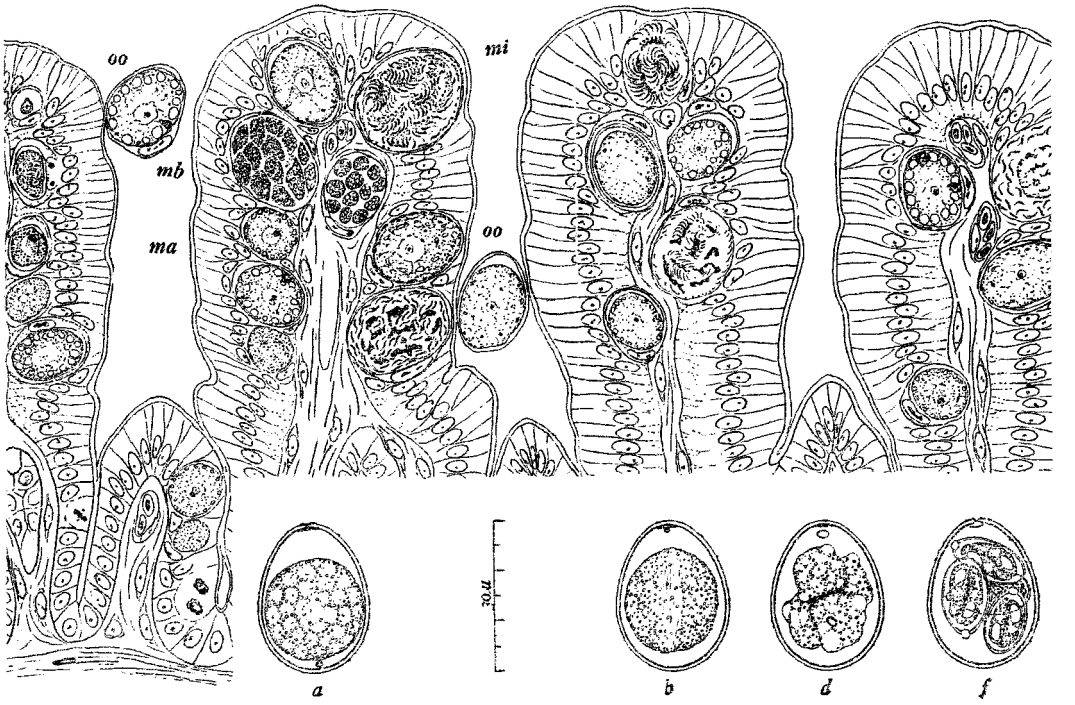

Fig. 5. Life cycle stages of *E. maxima* as drawn by E. E. Tyzzer (159). Key: ma = macrogametocyte; mi = microgametocyte; oo = oocyst. Reproduced with permission of Oxford University Press.

minated by any protective reaction and chronic infections in which organisms persist in the host indefinitely. He believed that the difference was related to the population of asexual forms in successive generations and "a very delicate balance in regard to reproduction."

In March 1949, the New York Academy of Sciences organized a conference exclusively devoted to coccidiosis, and Tyzzer, then 74 yr old, was invited to be honorary chairman (12). Although not present in person, his introductory comments indicated a continued interest in chronic infections: "I became much interested, at one time, in the occurrence in certain individuals of infections in which the course was indefinitely prolonged. . . . Such observations suggest that there may occur a condition diametrically opposed to immunity for which, at present, we only have the rather inadequate term lowered resistance."

RESEARCH AFTER TYZZER

AESs. AESs played an important role in transmitting new information to the poultry industry. For example, publications from Arizona (136), Connecticut (97), Illinois (66), Missouri (47), Nebraska (54), New Jersey (86), and Oregon (43) AESs provided descriptions of the newly identified species. Old ideas, such as supposed lack of host specificity, and links with blackhead, paralysis, and other unrelated conditions, were abandoned. Remedies available were generally recognized of questionable value, and the Bureau of Animal Industry advised that more attention should be given to improving sanitation and hygiene (31). A circular from the Extension Service of the University of Arkansas reported excellent results in treating coccidiosis by including formalin in the drinking water (27), one of the few publications concerned with poultry diseases from a state that would become one of the principal broiler producers in the United States (62,63). Georgia would also become a major broiler producer, but apart from a brief mention in a bulletin from the University of Georgia AES (61), and some work on sulphonamides (16), little coccidiosis research was carried out during the period reviewed.

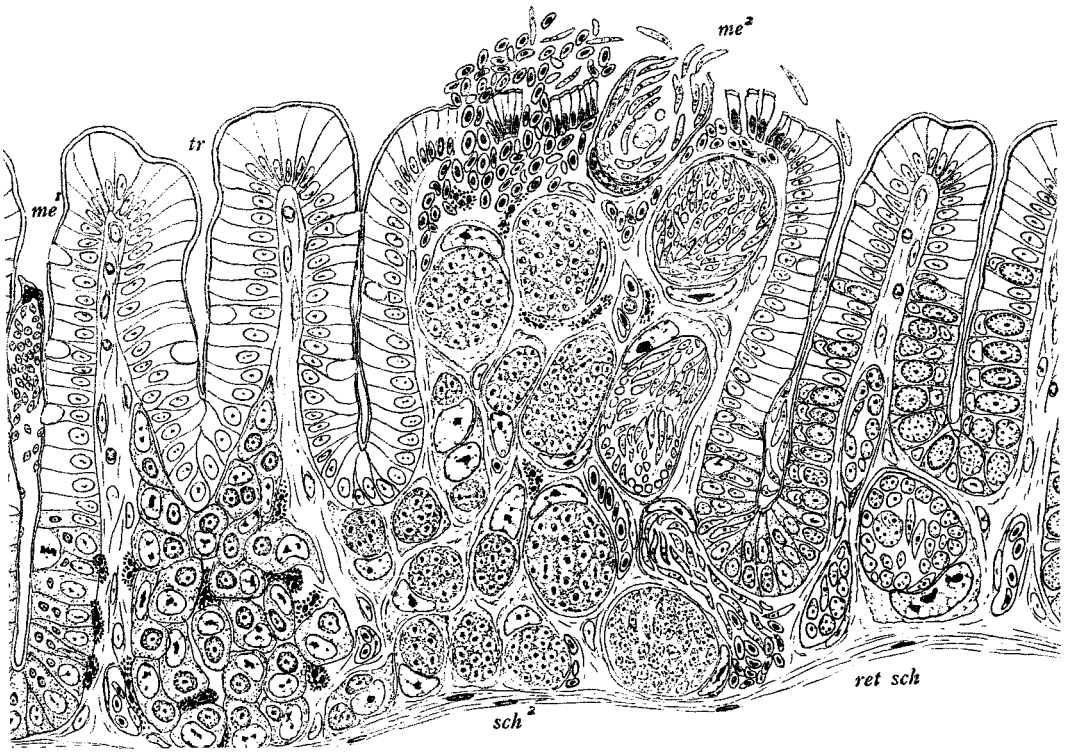

Fig. 6. Life cycle stages of *E. tenella* as drawn by E. E. Tyzzer (159). Key: me² = generation 2 merozoite; ret sch = retained schizont; sch² = generation 2 schizont; tr = trophozoite. Reproduced with permission of Oxford University Press.

Studies on the pathogenicity of *E. tenella* were carried out at Louisiana AES, and in addition to effects on weight gain and mortality, infection in hens was shown to result in fewer eggs and delayed egg production (123,124,125). The Michigan AES found that coccidiosis causes reduced egg production (41). Other investigators were interested in whether modifications of diet could affect the severity of coccidiosis. During the 1920s, there had been widespread use of milk products because it was thought that fermentation of milk produces an acid environment in the digestive tract that is unfavorable to parasite development (20). Tyzzer had been unable to show any protection against coccidiosis by including skimmed milk in the diet and concluded that the chief virtue of milk was its nutritional quality (159). Mayhew was unable to demonstrate any advantage of using buttermilk (126), and Becker and Waters found that dried skimmed milk increased severity of infection (26). Despite these observations, milk treatment continued to be advocated for the control of coccidiosis. A press bulletin from Florida indicated that "beneficial results should be noted almost immediately" (50), and in Missouri, milk products were "recommended unhesitatingly for the control of the disease—until some other more successful treatment has been devised" (48). An interesting theory by W. L. Chandler for the purported benefits was that lactose in milk favored multiplication of *Lactobacillus acidophilus* and *Bacillus megatherium* and that these suppressed various organisms responsible for secondary bacterial infections that accompany coccidiosis (34). At the Bureau of Animal Industry, diets high in protein were shown to be of value (1), but Tyzzer's coworker, Elizabeth E. Jones, could not confirm this (96). Vitamin A provided some protection against *Eimeria* infection (1), and vitamin K was able to reduce severity of hemorrhage caused by *E. tenella* (15).

Chester A. Herrick and others carried out extensive studies at the University of Wisconsin AES. Specificity of *E. tenella* was investigated

by surgically reconnecting the cecum with other sections of the intestinal tract (76). Changes in blood sugar of infected birds were measured (138,167), and glycogen (later shown to be amylopectin) was demonstrated in macrogametocytes (49). Respiration of oocysts was measured with a Warburg apparatus (150). Researchers at Wisconsin also carried out pathologic and immunologic experiments. Colon bacilli were isolated from the liver and spleen of chickens after infection with *E. tenella,* indicating that bacterial invasion occurs after damage to the cecum (132). Lactobacilli and enterococci in the ceca of chickens decreased in number during infection with *E. tenella* but anaerobic organisms resembling *Clostridium perfringens* increased (87). Attempts were made to immunize chickens by administration of oocysts treated by X-rays (168). Evidence was obtained that susceptibility of chickens to cecal coccidiosis is inherited (145). After one generation of selection, a difference in resistance of progeny was evident between two lines of chickens. Perhaps the most significant finding from Wisconsin was that sulphur prevented cecal coccidiosis (77). This finding was later supported by reports from Oregon and Louisiana AESs (44,65).

Considerable attention was given to destruction of oocysts and chemical means of disinfection. Sporulation was retarded if oocysts were suspended in broth cultures of *Escherichia coli* containing fecal material, and the ever-controversial W. L. Chandler believed that bacterial decomposition of organic matter resulted in products that were toxic to oocysts (34). Oocysts were killed if suspended in solutions of some disinfectants (60), but none was effective in the presence of organic material (130). An effective disinfectant must penetrate the oocyst wall, and at Michigan AES, colloidal iodine was shown to possess this characteristic (6). Colloidal iodine was sold for decontamination of hatching eggs prior to placement in incubators (Iodine Suspensoid Merck) because oocysts on the eggshell were believed to be a source of infection for chicks. Experiments at Texas AES showed that *E. tenella* infection could be prevented by fumigation of soil with methyl bromide (28).

An interesting observation from Wyoming AES concerned an outbreak of coccidiosis in sage grouse on ranches where chickens were not confined (78). Oocysts from the grouse were not infective if given to chickens, a result of interest in view of Fantham's earlier observations (55).

P. Philip Levine (1907–79). P. P. Levine made several important contributions to knowledge of coccidiosis. Levine worked in the Department of Pathology and Bacteriology, New York State Veterinary College, Cornell University. He described two new *Eimeria* species, *E. hagani* and *E. brunetti,* on the basis of oocyst size and cross immunity studies (107, 114). The description of *E. hagani* was brief and insufficient to justify consideration as a new species, but *E. brunetti* has stood the test of time and, unlike *E. hagani,* has been isolated independently by others. *Eimeria brunetti* was named after Dr. E. L. Brunett, who had produced several extension bulletins concerned with coccidiosis (29,30).

Levine was able to infect chickens by inoculating merozoites into the intestine and used this method to separate *E. tenella* from *E. necatrix* (109). He showed that ligation of pancreatic ducts prevents establishment of these species, indicating the importance of pancreatic secretions for excystation, and that trypsin is necessary for liberation of sporozoites (113). Levine found six species (*E. acervulina, E. mitis, E. praecox, E. maxima, E. tenella,* and *E. necatrix*) in poultry flocks near Ithaca, NY, thus indicating the ubiquitous nature of coccidian infections (110).

Most significant, from a practical point of view, was the study of sulphanilamide (108). Lund described this as a "landmark contribution" that determined "the direction of research efforts for decades to come" (116). At a meeting of the American Veterinary Medical Association in Chicago, Levine explained that sulphanilamide and sulphur are toxic and cannot be included permanently in feed (115). He believed that use of drugs should be an adjunct to management, "medication can never take the place of proper husbandry." In the panel discussion, his views on chemotherapy were clear: "if domestic animals, including poultry, have to be medicated continually in order to keep them healthy or alive, there is something fundamentally wrong."

Beltsville Research Center. From 1900 to 1950, poultry keeping in the United States grew from a small scale in which many farmers maintained small flocks of less than 100 chick-

ens to large holdings of several thousands of birds in farms where rearing of poultry was the predominant occupation. Growth of the industry necessitated development of organizations, such as the Research Center at Beltsville, with resources and facilities necessary to conduct disease research. Nutritional studies (already mentioned) were carried out in the 1930s by Ena Allen, and brief reports were provided on the pathogenicity of *E. mitis,* the value of vinegar for treatment of *E. tenella* infection, and a case of prolonged cecal coccidiosis (2,3,4). During the next decade, research was concerned with chemotherapy, and a series of papers were produced on the action of sulphonamides (see below).

Research in the United Kingdom. Very little coccidiosis research was conducted in the United Kingdom after Fantham's pioneering studies. D. C. Matheson, Professor of Pathology at the Royal (Dick) Veterinary College, Edinburgh, presented a report on coccidiosis at the 4th World's Poultry Congress (119). He believed that a reduction in incidence might be achieved by strict attention to sanitation and hygiene and by establishing a register of coccidiosis-free flocks. Some years later, Matheson produced guide notes for the veterinary profession for the diagnosis of coccidiosis (120). At a meeting in Belfast, Northern Ireland, research developments in the United States provided the basis for a stimulating discussion of practical issues relating to coccidiosis control (104). The eminent helminthologist E. L. Taylor advised the Lancashire Utility Poultry Society that chicks "be exposed to slight infection to prevent serious trouble later" (157).

A station "for practical experiments in the breeding of poultry for the table" at the southeastern Agricultural College, Wye, in Kent, reported that type of ration had a major influence on mortality due to coccidiosis (9). The composition of diets, however, was not indicated. The premier institution concerned with poultry husbandry in the United Kingdom was Harper Adams Agricultural College at Newport, Shropshire, and experiments were carried out on the value of disinfectants and possible inclusion of iodine in milk as a remedy for coccidiosis (102). An experiment at the Biological Research Laboratory in the Wirral, Lancashire, indicated that cecal coccidiosis was more severe in chicks given diets with a high fiber content (118). It was suggested that this was due to bacterial proliferation, but no evidence to support this contention was provided. In the United States, it had been suggested that an acid environment in the digestive tract is unfavorable to parasite development and that administration of acids might be beneficial (20). Research at the ministry of agriculture for Northern Ireland, however, indicated that treatment with hydrochloric acid had no effect upon intestinal or cecal pH (103).

In a letter to the editor of the *Veterinary Record,* G. Mayall raised the issue of host specificity and referred to experiments in which coccidia from rabbits were transmitted to chicks (121). The chicks showed no illness and passed only a few oocysts, but if these were recovered, sporulated, and fed to new chicks, the new chicks apparently fell ill with typical coccidiosis. J. S. Steward, veterinarian at Imperial Chemical Industries laboratory in Cheshire, investigated host specificity of the turkey species *E. meleagridis.* Tyzzer (159) had been unable to infect chickens, quail, or pheasants with this species, but Steward inoculated chickens with large numbers of *E. meleagridis* and obtained limited development in the foreign host (156).

Discussions concerning need for a poultry research institute in the United Kingdom had been ongoing since 1908, and in 1917, the Board of Agriculture and Fisheries established a veterinary laboratory at Weybridge, Surrey, to conduct research into poultry diseases (39,40). A poultry section was created in 1920, but coccidiosis work did not commence until the 1940s (134). Research was concerned with methods for disinfecting poultry houses. Tyzzer had dismissed use of the fire-gun, but the blowlamp was tested and found impractical as a means to destroy oocysts (83). Gaseous ammonia was an effective fumigant, but it was necessary to cover buildings to prevent leakage of gas (85). In 1948, the Veterinary Educational Trust (a private body later known as the Animal Health Trust) established a research station for study of poultry diseases at Houghton, Huntingdonshire. Horton-Smith transferred to Houghton and, as at Beltsville and Weybridge, a research program principally concerned with sulphonamides was initiated (81).

ADVENT OF CHEMOTHERAPY

The report that sulphur could prevent cecal coccidiosis was the first indication that control

might be achieved by medication (77). The use of sulphur was encouraged during the 1940s as a contribution to the national war effort, enabling the poultryman to produce more and better poultry (7). Sulphur was effective against *E. tenella* and *E. necatrix* but ineffective against other species (111). Furthermore, sulphur had serious side effects including rickets, dermatitis, and poor feathering. Sulphanilamide was first synthesized in 1908, but its therapeutic value against bacterial infections was not demonstrated until 1935 (46). The contributions of Philip Levine have already been noted. Sulphanilamide was effective against intestinal species that develop "superficially" in epithelial cells of villi but ineffective against *E. tenella* and *E. necatrix* that develop more deeply in the "glandular epithelium" (108). Levine also investigated sulphaguanidine, a less toxic drug than sulphanilamide, which at high concentrations is effective against *E. tenella* and *E. necatrix* in addition to intestinal species of *Eimeria* (112). Sulphaguanidine was used quite extensively for prevention but was ineffective for treatment of established infections. Many laboratories investigated the new drugs and some of these studies are mentioned here. Researchers at Weybridge and Beltsville confirmed Levine's findings (5,59,79). Studies at Weybridge showed that sulphamezathine and sulphadiazine could be used to treat established infections, but these drugs were toxic and could not be given for more than 3–5 days (84). Reports from Michigan AES confirmed the efficacy of sulphamezathine but concluded the drug was too toxic for continuous use in poultry (73,75). The effects of sulphonamides could be neutralized by paraaminobenzoic acid, thus providing a clue to the mode of action of these drugs (82,164). Studies at Rhode Island AES showed that sulphaquinoxaline was effective against *E. tenella* and did not interfere with immunity development (42). Sulphaquinoxaline was lethal to sporozoites and schizonts, but development of these stages was not completely inhibited (38), thus explaining the lack of interference with immunity. Sulphaquinoxaline was also effective against *E. necatrix* when given in an interrupted schedule of medication (68). The latter study was funded by a grant from Merck and Co., a forerunner of the role pharmaceutical companies would play in funding research in the academic sector.

Sulphonamide treatment was often followed by recurring outbreaks of coccidiosis and, therefore, an intermittent schedule of medication involving treatment every fifth day, beginning with the appearance of clinical signs, was widely adopted. Intermittent treatment combined with intentional exposure to infection by placing birds on known infected ground was proposed as a method of immunizing birds against coccidiosis (148). At the meeting of the 8th World's Poultry Congress in Copenhagen, Horton-Smith expressed the opinion that the aim of chemotherapy should be to permit the acquisition of immunity (80). He thought that intentional exposure to infection had great possibilities providing "we do not promote sulphonamide fast strains." Interestingly, at this meeting, a speaker from Belgium stated that "the mixing of small quantities of sulphonamide with the meal had produced strains of coccidiosis resistant to sulphonamides," but no data were presented (11).

A major advance was the demonstration by J. P. Delaplane and colleagues that sulphaquinoxaline could be administered at low concentrations continuously in the feed, thus demonstrating the feasibility of prophylaxis (42,69). Field trials at Storrs AES indicated that continuous medication with sulphaquinoxaline in mash rations "provides an effective, efficient, and economical control for cecal and intestinal coccidiosis" (99). Medication on a continuous basis gave better control than strict sanitation (71). At the annual meeting of the American Veterinary Medical Association in July 1949, Philip Hawkins said, "In sulfaquinoxaline, we now have the most satisfactory sulfonamide for the prevention of coccidiosis in poultry. Whether we like the idea of medicated feed or not, we have no choice in the matter; it is here to stay. Although we may object to the adulteration of feedstuffs with medicine, we must remember that our unnatural methods of livestock and poultry production have forced us to this extreme" (74).

The 1949 conference organized by the New York Academy of Sciences brought together leading researchers from government, universities, and industry. In addition to papers concerned with chemotherapy, information was presented on economic losses due to coccidiosis, regional differences in the incidence of some species of *Eimeria,* and factors involved in eti-

ology of the disease (reviewed by Reid [141]). Attention was also given to coccidiosis in game birds, turkeys, and rabbits. The significance of chemotherapy is evident because 11 of the 22 poultry presentations were concerned with drugs. New compounds effective against *E. tenella* (nitrophenide and nitrofurazone) were discussed (72,165). Several of the contributions were from pharmaceutical companies, indicating an important role the commercial sector would play in drug discovery (a process requiring considerable resources and intellectual effort) and control of the disease.

CONCLUSION

The foundation of our knowledge of host–parasite relationships in *Eimeria* of the fowl was established by pioneering studies undertaken during the first half of the 20th century. In retrospect, it is remarkable how much knowledge regarding coccidiosis was obtained. During this period, animal facilities at most institutions were limited, and although the chicken is inexpensive and relatively easy to maintain, the prevalence of *Eimeria* and the difficulty of raising birds in the absence of infection has proved a major constraint on research. Many AESs and laboratories that contributed to our early understanding of coccidiosis no longer conduct research in this field. During the latter half of the 20th century, coccidiosis research was undertaken at those institutions (government, university, and private) with resources and specialized facilities necessary for producing and maintaining coccidia-free birds. Examples in the public sector include the Parasite Research Laboratory at Beltsville in the United States, the Central Veterinary Laboratory at Weybridge, and Houghton Poultry Research Station in the United Kingdom. The ability to raise chickens in the absence of infection has also been important for mass screening of chemicals for anticoccidial activity, and many pharmaceutical companies have been involved in this process. Control of coccidiosis has been achieved by the joint efforts of the academic community, government organizations, and private industry.

Success in controlling coccidiosis was built upon solid foundations established by Johnson, Tyzzer, and others during the first half of the 20th century. It is fitting to end this review with Tyzzer's final words to those attending the meeting at the New York Academy of Sciences. "When I started my investigations on avian infections somewhat over thirty years ago, there was little reliable information in regard to avian pathology, the literature being pretty well packed with misinformation. One can not but be impressed by the progress that has been made during the ensuing years and at present one expects as critical work in this field as in any other" (12).

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ADDENDUM

In addition to research at Wisconsin AES (145), studies at Hawaii AES, initiated in 1845, indicated that susceptibility to cecal coccidiosis in chickens is inherited. (Palafox, A., J. E. Alicara, and L. Kartman. Breeding chickens for resistance to cecal coccidiosis. World's Poult. Sci. J. 5:84–87. 1949.)