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ERNEST EDWARD TYZZER

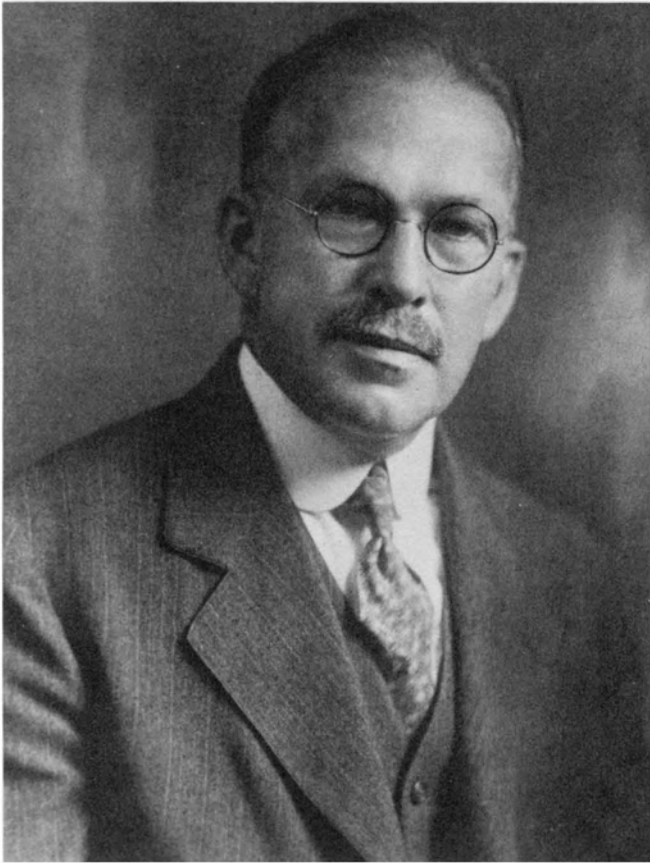
1875—1965

A Biographical Memoir by
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Biographical Memoir

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WASHINGTON D.C.



E. E. Tyzzer.

ERNEST EDWARD TYZZER

August 30, 1875—January 23, 1965

BY THOMAS H. WELLER

ERNEST EDWARD TYZZER was born and lived close to nature in Wakefield, Massachusetts, a northern suburb of Boston. As a boy on a small farm, with many chores and few playmates, he prepared with parental encouragement collections of beetles, dragonflies, and arrowheads. Throughout his years in college and medical school, he trapped muskrat, fox, mink, skunk, and weasel to provide funds for educational expenses. This activity also provided a focus for a maturing intellectual curiosity that was to determine his future career. In 1899, he spent the spring recess of his second year at Harvard Medical School trapping. Tyzzer found interesting parasites in the carcass of a fox, brought the carcass to class, and thus came to the attention of Dr. W. T. Councilman, the Professor of Pathology.

With Councilman's support and direction, Tyzzer then began a program of research that was to characterize his life and would eventually establish him among the leading parasitologists in the world. His subject material was broad, ever reflecting his interest in natural history as he studied a spectrum of infectious agents found in indigenous small rodents, surveyed the parasites of ruffed grouse in New England, or recovered the virus of equine encephalitis from pheasants. Tyzzer's research would also reflect his sympathy with the problems of the farmer; his studies on blackhead disease of turkeys and the elucidation

of practical procedures for its control would later bring him citations for preserving the turkey-raising industry from threatened extinction.

Colleagues briefly characterized Tyzzer in a memorial minute: "His background also contributed to his total personality. He was a large, kindly man, who spoke slowly, softly, simply and succinctly. He was modest to a fault. His prose was lucid and to the point. He loved all living things and was noted for his gentleness in handling animals."* It is appropriate to add that an element of shyness in Tyzzer's personality made him seem brusque in contacts with students and left an impression of unapproachability. Thus the contacts of this writer, as a second-year medical student at Harvard in 1937, with Tyzzer the teacher provided little understanding of Tyzzer the scientist and warm human being. This element of Tyzzer's personality may account for the fact that most of his papers were authored alone or with senior associates. Few young scientists were attracted to his laboratory. Not until this writer had been in Tyzzer's department for two years, under the congenial sponsorship of Drs. D. L. Augustine and A. W. Sellards, did Tyzzer become approachable at noontime sandwich sessions. Only then did the facade of brusqueness disappear, and the image emerge of a warmhearted individual who, as conversation roamed widely, would draw on a vast knowledge of nature, farming, and archeology. However, rarely would there be a casual reference to his own work, as reticence and modesty prevailed. The autobiographical material prepared by Tyzzer for the National Academy of Sciences contains a pertinent statement: "I was of course taught that God created all things but then the question arose in my mind as to

* Donald Augustine, C. Sidney Burwell, Lemuel R. Cleveland, John F. Enders, George C. Shattuck, Thomas H. Weller, and Arthur T. Hertig (Chairman), "Memorial Minute on the Life and Work of Ernest Edward Tyzzer, M.D., George Fabyan Professor of Comparative Pathology, Emeritus, and Professor of Tropical Medicine, Emeritus," *Harvard University Gazette* 61(1966):204-5.

who made God. Yet, there was the fact of the visible world about me to consider. Thus I was reduced to a state of wonder, bordering even on amazement, an attitude that has lasted up to the present day."

His parents, George Roberts Tyzzer and Matilda Jane Edwards Tyzzer, were of Cornish extraction from families who had come to the United States in the mid-1840s. When Ernest, the youngest of five children, was two years old, his father purchased a small farm that yielded an annual income of \$800 or less. Tyzzer attended the Wakefield public schools and encountered some difficulty in high school, for homework was done in a common room occupied by other members of the family. As a consequence, while he graduated with his class, he entered Brown University in the fall of 1893 with a condition in Latin. His capital resources were fifty dollars earned from trapping. The first year was one of extreme financial difficulty, but thereafter a job in the college refectory and scholarship support eased the way. Tyzzer credits Professors Bumpus, Meade, Gorham, and Tower of the faculty of biological sciences for awakening his interest in science. He characterized Bumpus, who taught comparative anatomy, as the most inspiring teacher he had encountered. Tyzzer's academic performance improved rapidly at Brown; and, in his senior year in 1897, he was elected to Phi Beta Kappa. He postponed entering medical school for one year and acquired a masters degree for studies on the central nervous system of the flounder, performed in part at Woods Hole Oceanographic Institution.

Tyzzer enrolled at Harvard Medical School in the fall of 1898. He had anticipated much of the academic work in prior courses at Brown and thus found ample time to run his trap lines. As a second-year student, his encounter with Professor Councilman over the carcass of a fox brought a sudden change; Councilman thereafter assigned him to a series of projects that took precedence over course work and trapping. He was sent to

Woods Hole for the summer of 1900 to study the possible relationship between parasites and tumors in fish. No fish with tumors were found, but Tyzzer demonstrated that white spots observed in the musculature of young menhaden were produced by an undescribed species of *Myxosporidia*. This observation became the subject of his first scientific paper. During Tyzzer's junior year, he was assigned projects on coccidial infections and leucocytogenesis in rabbits.

When Tyzzer was a senior medical student, an outbreak of smallpox in Boston in 1901 stimulated a series of papers on variola and was directly responsible for his classic contribution on the histopathology of varicella. Councilman first had Tyzzer study the lesions produced by vaccinia and variola virus in the scarified rabbit's cornea. With Walter R. Brinckerhoff, Assistant in Pathology, Tyzzer was sent to the quarantine station on Gal-lup's Island in Boston Harbor to collect material from fatal cases of smallpox. As a consequence, he missed the course in dermatology and failed the examination in that subject; nonetheless, he graduated with his class in 1902. He spent the year after graduation as a Bullard Fellow in Dr. Charles Sedgewick Minot's Department of Histology and Embryology at Harvard applying new staining techniques to embryologic material. Then Councilman again prevailed, and Tyzzer began an investigation of vaccinia in calves. The vaccine lymph obtained from a commercial source was contaminated with foot-and-mouth virus. The latter disease killed not only Tyzzer's calves, but also initiated a focal outbreak that was contained only by slaughter of livestock in the area. An investigation by federal authorities showed that the contaminated vaccine lymph was the source of the outbreak. The commercial producer, however, was erroneously given a clean bill of health; it was concluded that the contamination had occurred at Harvard. Tyzzer later wrote that "having produced an outbreak of foot-and-mouth disease, with all of the embargoes involved, I was not at this time a popular

young man." Vindication came much later, when two additional outbreaks of foot-and-mouth disease were traced to contaminated vaccinia virus from the same commercial source.

Councilman was interested in the susceptibility of monkeys to smallpox and vaccinia; therefore, in 1904, Tyzzer and Brinckerhoff were sent to the Philippines, where monkeys and smallpox coexisted. At this period, under the influence of Councilman, the intracellular inclusions seen in smallpox and vaccinia lesions were regarded as morphological stages of some sort of protozoan parasite; the term "Cytoryctes" was applied. Tyzzer used Councilman's nomenclature in reporting the smallpox-vaccinia studies. Yet, when an outbreak of varicella (chickenpox) occurred in inmates of Bilibid Prison, Manila, his studies on this entity, published in 1906, demonstrated an independence of thought. At the time, in some quarters, the view still prevailed that variola and varicella were manifestations of a single disease. Tyzzer studied thirty-eight individuals with varicella. The evolution of the cutaneous lesions was followed by histopathological examination of serial biopsies. Attempts at experimental transfer of the disease were made by inoculation of the scarified rabbit's cornea and by cutaneous and intranasal inoculation of monkeys. No specific lesions were obtained in the animals. The histopathological studies resulted in the first description of the intranuclear inclusions characteristically induced by varicella virus. The presence of inclusion bodies in the endothelium of blood vessels in the corium led Tyzzer to postulate that the epidermal lesion was preceded by a viremic phase. He stated that no evidence was obtained to support the view that the inclusions were of a parasitic nature. Three practical techniques, each still useful, for differentiating varicella from smallpox were succinctly outlined. Microscopic examination of fluid from a varicella vesicle will reveal multinucleated giant cells; he stated that "this test seems quite reliable and may be applied at the bedside." Histologic examination of a biopsy of a lesion will permit

differential diagnosis depending on the presence or absence of multinucleated giant cells. In contrast to results obtained with materials from variola-vaccinia lesions, varicella-vesicle fluid will not produce lesions on inoculation of the cornea of a rabbit.

The classical study of Tyzzer on varicella illustrates lifelong attributes that characterized his research. The histologic sections personally prepared in 1904 are technically superb and retain brilliance of staining to this day. His drawings in color of varicella-infected cells as observed microscopically under high magnification are meticulously accurate, delicately detailed, and aesthetically pleasing. His records were meticulously maintained. Each slide prepared received a sequential serial number; descriptions and drawings were recorded on numbered cards filed sequentially. Tyzzer designed a compact cabinet for storage of slides in a vertical position that he described in a paper published in 1907. In 1957, he wrote: "The main accession series (i.e., slides) represents work from the time I was a second year medical student to my retirement in 1942. The records . . . to be found on the card collection numbered from 1 to 9800± are quite complete and cross catalogued to some extent by subject." (Representative slides, record cards, and drawings prepared by Tyzzer in the course of his study of varicella have been deposited in the Registry of the Armed Forces Institute of Pathology and in the historical archives of the Countway Library at Harvard.)

On return to Boston in 1905, Tyzzer was assigned work on cancer and later became Director of Research for the Harvard Cancer Commission. For the next eleven years, research on cancer was interdigitated with that on other interests. Investigations were carried out on the occurrence of spontaneous tumors in mice, on the host response of mice to transplantable tumors, and alone and in collaboration with Dr. Clarence Cook Little on the inheritance of susceptibility to transplantable tumors. It was experimentally demonstrated that manual manipulation or massage of an implanted tumor would produce metastasis. Pro-

phetic of current concepts are Tyzzer's statements in 1916 that "malignant tumors are parasitic in nature especially since they develop at the expense of other tissues of the body" and "immunity to transplanted tumor is based on foreignness or incompatibility to tumor and host . . . it appears probable that an immune body is formed which, in the presence of antigen—or living tumor . . . excites an inflammatory reaction in the tissues around the tumor so that the latter is isolated and eventually destroyed." Tyzzer's contributions to research on cancer were recognized by his election to the presidency of the American Association for Cancer Research in 1913 and by receipt of the Bronze Medal of the American Cancer Society in 1952. An interesting sidelight of his association with Little is that the DBA inbred strain of mice now commonly used in medical research derived from a trio of mice supplied by Tyzzer.

Other scientific problems were pursued concurrently. The pathogenesis of dermatitis produced on contact with caterpillars of the browntailed moth was elucidated. Specialized nettling hairs of the caterpillar were incriminated, and simple but elegant experiments demonstrated for the first time that the hairs released an irritating substance that could be detected by changes induced in the morphology of red blood cells. The mouse colony provided material for continued study. A new genus (*Cryptosporidium*) was established for new species of extracellular coccidia discovered in mice, and the morphological stages were described; one species was found on epithelium of the gastric glands, and a second on intestinal epithelium. An undescribed disease of Japanese waltzing mice was encountered, and the etiologic agent was shown to be a new intracellular-dwelling, spore-forming bacillus that was named *B. piliformis*.

In 1913, under the leadership of Dr. Richard P. Strong, Tyzzer participated in an expedition to Peru and other South American countries. Several tropical diseases were investigated. *Leishmania* spp. were shown to be the cause of uta, a disease

characterized by extensive cutaneous ulcers, most often about the face. However, Oroya fever and verruga peruviana received major attention. The intracellular organisms previously seen by others in red cells in Oroya fever were found in large numbers in the reticuloendothelial cells of the spleen, liver, and lymph nodes; later Tyzzer wrote that "this discovery resulted from my personal observations." Other conclusions in the collaborative report were not as sound. The name *Bartonella bacilliformis* was established for the parasite of Oroya fever, which was mistakenly considered a protozoan. It was incorrectly concluded that verruga peruviana was distinct from Oroya fever.

In 1916, Tyzzer succeeded Theobald Smith as Fabyan Professor and head of the Department of Comparative Pathology at Harvard, a chair he held until retirement in 1942. When the economic stringencies of the 1930s led to a merger of two departments, Tyzzer acquired the additional title of Professor of Tropical Medicine. From 1916 until retirement, however, his research material derived from the domestic scene; the period of foreign travel was over. Studies on the pathogenesis of diseases of man were supplanted by investigations on diseases of domestic fowl and of indigenous animals.

In the years between 1919 and 1936, infectious enterohepatitis of turkeys, commonly known as blackhead, was a subject of continued investigation. The causal agent had been described by Theobald Smith in 1895 and then classified as an amoeba. In 1920, Tyzzer demonstrated that the responsible organism was in fact a flagellate, which he renamed *Histomonas meleagridis*. The scientific interaction between Smith and Tyzzer continued. In 1920, Smith noted an association between infection with the cecal worm (*Heterakis vesicularis*) and blackhead in turkeys. Smith and H. W. Graybill, by feeding eggs of *Heterakis* to turkeys, produced blackhead and suggested that the nematode in some way enhanced the invasive potential of a preexistent proto-

zoan. Tyzzer, however, in collaboration with Marshall Fabyan, experimentally demonstrated that the protozoan could be harbored within the egg of the nematode and that blackhead followed ingestion of contaminated eggs. It was shown that *Heterakis* was not essential for the transmission of blackhead, because the direct contact of young turkeys with cecal discharges from infected worm-free turkeys—or from chickens that were demonstrated to be an important reservoir of asymptomatic infection—was followed by a fatal infection.

With this information in hand, Tyzzer established an experimental turkey farm. Application of simple principles involving the selection of uncontaminated land, the establishment of a clean breeding stock through use of incubator-hatched eggs, and the elimination of contact with latently infected fowls—especially chickens—yielded healthy turkeys. The essential technology was outlined for farmers in pamphlets written under the aegis of the Massachusetts Department of Agriculture. In 1942, Tyzzer received a citation from Governor Leverett Saltonstall for saving the turkey industry of Massachusetts. During this period, other studies on *Histomonas* yielded techniques for cultivation of the organism *in vitro*, information on immunity and use of attenuated vaccines, and data on chemotherapeutic agents.

While blackhead was the dominant theme of research for many years, investigations on coccidiosis in gallinaceous birds provided a continuing minor theme. Whereas it had been generally assumed that one species of coccidium was widely distributed in many birds, Tyzzer marshalled evidence indicating that multiple species of coccidia could occur in a single host, each producing a specific pathology. Five species, of which three were new, were differentiated in chickens and two each in turkeys and pheasants. The life histories of four species were elucidated and summarized in monographic form in 1929; the monograph contained minutely detailed diagrams drawn by

Tyzzer with the aid of a magnifying glass. A second publication in 1932, written with Hans Theiler and E. E. Jones, dealt with two additional species of *Eimeria* from chickens.

In the final phase of a long innovative scientific career, Tyzzer carried out pioneering studies that resulted in a series of papers on the blood parasites of indigenous rodents. A new parasite, *Cytoecytes microti*, in the white blood cells of voles was described and its mammalian host range defined. The vole also yielded a new bartonella-like organism that could be cultured. In contrast to *Bartonella*, which Tyzzer twenty-six years earlier demonstrated could multiply in fixed tissue cells, the form found in the vole replicated only in red cells. Therefore, a new genus, *Haemobartonella*, was defined. *Grahamella* sp. was definitely established as a parasite, and isolates were obtained in culture from several species of small rodents. A natural interference phenomenon in rodents simultaneously infected with eperythrozoa and bartonella was investigated. These and additional observations on the blood infections of the field vole were summarized in a final major paper that appeared in 1942.

In the final decade of his illustrious career, Tyzzer also carried out significant studies on two additional disparate subjects, each again illustrating his reliance on natural events. The recovery of the virus of equine encephalitis from the brain tissues of pheasants found dying in the wild led Tyzzer to suggest that birds, rather than horses, were the primary reservoir of human infection. Tyzzer himself provided the material for the other study. Investigation of an episode of rectal bleeding, later traced to a polyp, revealed a heavy infection with *Endamoeba coli*. In contrast to textbook statements, the trophozoites of this non-pathogenic amoeba contained phagocytosed red cells. In the published report the patient was not identified. Tyzzer's sense of humor is reflected in the passage "owing to the non-cooperative attitude of the patient no continuous systematic study of the

condition could be arranged until the January of the following year."

Tyzzer's scientific stature was recognized by election to the National Academy of Sciences in 1942, as well as to the American Academy of Arts and Sciences and to the American Philosophical Society. Brown University conferred an honorary Doctor of Science degree on him in 1935. His colleagues elected him President of the American Society of Parasitologists in 1954. His presidential address to that society conveyed the philosophy of a scientist whose training and forte were as a skilled microscopist and histopathologist. With mixed humor and irony, he commented on those who believe that "the biological sciences do not make the grade, so to speak, unless they are placed on a mathematical basis." He emphasized that biological observations or events furnish data in many respects as exact as may be found in any other field. He continued:

It would appear for some reason or other, the satisfaction derived from the mathematical method tends to supplant any curiosity as to underlying causes. In fact, it seems there is much in common between liquor and mathematics. While there are certain hard headed individuals who are apparently able to carry considerable amounts of one or the other, it may be well for the biologist to consider the effects of the adoption of mathematics as a technique very carefully before embarking on its habitual use.

It is not surprising that in Tyzzer's numerous publications the statistical approach is conspicuously absent. Nor has the significance of his observations been challenged.

Prior to retirement in 1942, Tyzzer pursued the study of Indian artifacts as an avocation. He fabricated arrows fitted with bone points and compared the fractures produced when his arrows were shot at a hard object with similar fractures typical of bone points found in shell heaps. His final scientific paper in 1958 described the experimental manufacture of bone points, using as tools stone materials found in shell heaps.

When Ernest Tyzzer passed away in his nintieth year, on January 23, 1965, he was survived by his wife, Helen Bartlett Tyzzer (since deceased), and two sons, Gerald E. of Falmouth, Maine, and Franklyn G. of Geneva, Illinois.

THE PREPARATION of this memoir was expedited by the availability of autobiographical material desposited by Dr. Tyzzer with the National Academy of Sciences. Dr. Tyzzer's publications are preserved in bound volumes at the Department of Tropical Public Health at Harvard.

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KEY TO ABBREVIATIONS

- Am. Antiq. = American Antiquity
 Am. J. Hyg. = American Journal of Hygiene
 J. Am. Med. Assoc. = Journal of the American Medical Association
 J. Cancer Res. = Journal of Cancer Research
 J. Exp. Med. = Journal of Experimental Medicine
 J. Infect. Dis. = Journal of Infectious Diseases
 J. Med. Res. = Journal of Medical Research
 J. Parasitol. = Journal of Parasitology
 Philipp. J. Sci. = Philippine Journal of Science
 Proc. Am. Acad. Arts Sci. = Proceedings of the American Academy of Arts and Sciences
 Proc. Am. Philos. Soc. = Proceedings of the American Philosophical Society
 Proc. Soc. Exp. Biol. Med. = Proceedings of the Society for Experimental Biology and Medicine

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