John McFadyean and the Centenary of the First Isolation of *Campylobacter* Species

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Campylobacter **species recently emerged as a leading cause of acute diarrhea in humans, but it is not generally known that these species were first cultured from samples from aborting ewes as far back as 1906. This took place in the United Kingdom during a study that spanned several years of epizootic abortion in cattle and sheep. The chief investigator in this major undertaking was John McFadyean, a little-known yet remarkable man who founded veterinary pathology in Britain and who made immense contributions to public health. A brief portrayal illustrates his uncompromising dedication to scientific accuracy and to his profession, often in the face of opposition.**

> Smears made from the uterine mucus and stained with Loeffler's blue showed large numbers of a peculiar organism, which was apparently present in pure culture. Most of the elements were comma shaped, but long spirillar forms, apparently consisting of several commas joined end to end, were also present. In hanging drops these organisms were actively motile. . . . The broth tubes showed an abundant and pure culture of the vibrio after about four days' incubation. . . . [1, Appendix, p. 3]

So wrote John McFadyean and his associate Stewart Stockman in their description of the first isolation of what we now know as *Campylobacter* species. The date was 2 February 1906, and the sample was from the uterine mucus of a pregnant sheep from a flock of 150 Devon longwoolled ewes that were experiencing an abortion rate of 33% (figure 1). As described below, this flock was one of many these men investigated during the course of a government inquiry started in 1905 into epizootic abortion in cattle and sheep. A few years later, an apparently identical organism was isolated from aborting cattle by Theobald Smith and Marian Taylor in the United States and was named *Vibrio fetus* [2]. It was renamed *Campylobacter fetus* in 1973, after French workers showed that these microaerophilic "vibrios" constituted a distinct bacterial group [3]. The disease, which became known as "vibrionic abortion," subsequently proved to be an affliction of major economic importance.

At this point, medical readers might well be surprised—first by the fact that *Campylobacter* species were cultured so long ago, and second for wondering why there is no mention of diarrhea, because *Campylobacter* species are a leading cause of acute bacterial diarrhea in humans [4]. The fact that their role as enteric pathogens remained undiscovered until the 1970s may seem extraordinary, but a prime reason was the technical difficulty of isolating these exacting bacteria from feces, owing to the overgrowth of more vigorous fecal flora [5, 6]. In fact, this had been achieved in calves with diarrhea in 1931 by Jones et al. [7], who painstakingly washed and prepared specimens of jejunal mucosa, and by Doyle [8], who isolated the organisms from pigs with swine dysentery. However, neither work was further pursued.

Another reason for the failure to recognize enteropathogenicity in these organisms, even by veterinarians, was that McFadyean's organism was almost certainly *C. fetus* subspecies *fetus,* whereas the dominant species to cause diarrhea are *Campylobacter jejuni* and *Campylobacter coli,* although these species can also cause ovine abortion. *C. fetus* subspecies *fetus* is an uncommon human pathogen that causes systemic infection in subjects with immunodeficiency or, rarely, septic abortion in otherwise healthy women [9]; the first recorded isolation from a human involved such an abortion [10]. Then, in the late 1950s, Elizabeth King [11] described a link between bacteria that fit the description of Jones and colleagues' organism (her "related vibrios") and human diarrhea; her 4 isolates were all recovered from blood samples.

Earlier recognition of the importance of *Campylobacter* species in human disease might well have been different had other medical microbiologists been more active in the field of comparative pathology. Indeed, the breakthrough—namely, the isolation of *Campylobacter* species from fecal specimens—occurred in Belgium through the foresight of Butzler et al. [5], who sought the help of a veterinary colleague, having isolated a *Campylobacter* species from the blood specimen of a young nurse with acute diarrhea. Success lay in the application of

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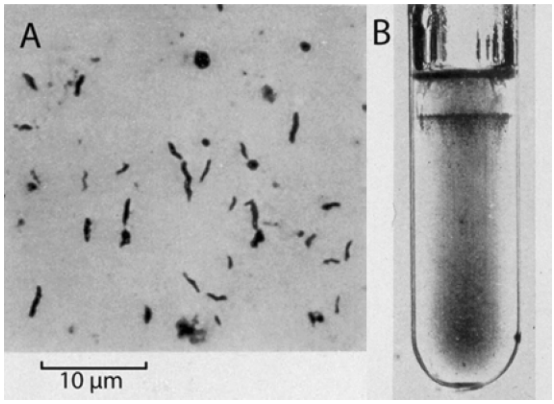


Figure 1. John McFadyean and Stewart Stockman's photographs of the *"Vibrio"* species in smears of uterine exudate from an infected ewe *(A)* and a culture of the *"Vibrio"* species in agar *(B),* which had been inoculated and mixed while liquid and then solidified [1]. The characteristic subsurface band of growth, where there is reduced oxygen tension, resembles that of *Brucella abortus.*

methods used to isolate *Campylobacter* species from ovine and bovine genital tracts.

In view of this dual importance of *Campylobacter* species, it is appropriate to commemorate the centenary of their first isolation and, in so doing, to pay homage to the very remarkable man who achieved it, John McFadyean, who is regrettably almost unknown outside British veterinary circles (figure 2). At the time of the study, McFadyean was Principal of the Royal Veterinary College in London.

The inquiry into epizootic abortion. In 1905, the Board of Agriculture and Fisheries of the British government appointed a committee to inquire into epizootic abortion; McFadyean was the chairman, and the main investigators were McFadyean himself and Stewart Stockman, who had recently been appointed Chief Veterinary Officer to the Board. Stockman was junior to McFadyean by 16 years, but the 2 men had shared a long and fruitful association dating from an earlier time when they were in Edinburgh together.

The task before these men was immense. The studies lasted >5 years and were presented in 3 parts. Parts I and II dealt with the diagnosis, epidemiology, and control of contagious bovine abortion caused by *Brucella abortus* (or Bang's bacillus, as it was then called). Part III of the report dealt with epizootic abortion in sheep, and details of the investigation and experimental work were described in an appendix (figure 3).

Little was known about ovine abortion at the time, other than that serious outbreaks were known to occur and that ewes could be experimentally infected with Bang's bacillus. To determine the size of the problem, McFadyean and Stockman sent out questionnaires to several hundred farmers throughout the United Kingdom and got replies from no less than 476 sheep owners, who represented >250,000 breeding ewes. From these, McFadyean and Stockman found that the background abortion rate was 1%–3% and that 70 (14.7%) of the 476 farms had experienced outbreaks of abortion, which affected ⩾10% of the flock at least once in the preceding 5 years. Outbreaks did not seem to occur year by year on any one farm.

Notification of abortion outbreaks was then requested from the Board's Agricultural Correspondents and Inspectors. This yielded reports of 15 outbreaks, which arose mostly in southern England but extended up as far as Lincolnshire (~200 km north of London). The abortion rate in these outbreaks ranged from 5% to 50%, with an average rate of 23.2%. Samples were taken from 12 flocks that had abortion rates >10%; mainly smear specimens from cotyledons were obtained from aborting ewes and aborted lambs, but in some cases, gravid uteri were obtained from slaughtered ewes suspected of being infected. The gravid uteri were delivered to the laboratory and examined on the day of collection by performing autopsies on farms in the early morning and conveying the uteri by passenger train. "*Vibrio* species" were isolated from 9 of the 12 flocks.

It proved fortuitous that the conditions suitable for the culture of *Brucella abortus* are similar to those required by *Campylobacter* species: both are microaerophilic and form a band of growth 2–4 mm beneath the surface of an agar-containing broth, which is inoculated while fluid and then solidified (figure 1*B*). McFadyean's initial reaction was that they had grown the agent that caused cattle abortion, but microscopic evaluation revealed a new spiral motile organism, which he initially thought was a spirochete but later classed as a *Vibrio* species. The initial isolation medium was the "agar-gelatin-serum" medium used for Bang's bacillus, but subsequently, "plain agar," gelatin, and peptone broth were used, with the latter supplemented with small blocks of potato. Most of the cultures were in solid media inoculated while still liquid, a method that assisted both identification and purification. Growth appeared after 1–4 days at an incubation temperature of 35°C–37°C or after 10 days at room temperature. McFadyean emphasized that growth on the surface of agar was absent or very poor, but it was favored by a rarefied atmosphere; there was no anaerobic growth. He described the appearance of coccal "granular" forms both in cultures and in pathological material, a well-recognized feature of *Campylobacter* species. He also observed that the vibrios survived heating for 5 min at 56.5°C–57°C but not for 10 min.

McFadyean and Stockman's detailed epidemiological observations showed that these infections were essentially enzootic in character, and the pair correctly deduced that infection was most likely to be acquired by mouth rather than via the genital tract. McFadyean and Stockman also performed numerous experiments to show that infection can be transmitted to pregnant ewes and cows by the inoculation of pure cultures. Experiments with a diagnostic serum agglutination test and immunization by subcutaneous inoculation of live cultures did not get far, owing

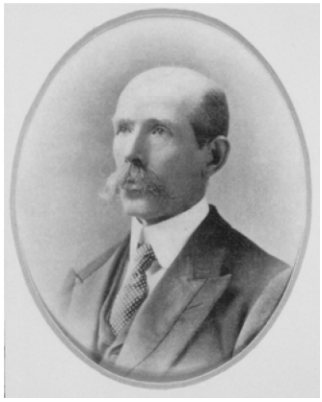


Figure 2. Photograph of Sir John McFadyean (courtesy of the Royal Veterinary College, London, UK).

to the difficulty of growing a sufficient bulk of organisms. Towards the end of the study, 2 naturally occurring outbreaks of "vibrionic" abortion in cows were detected, thus anticipating the work of Smith and Taylor in the USA mentioned earlier [2].

The thoroughness and success of the study is all the more remarkable in light of particular problems linked with this infection. First, unlike cattle breeding which goes on all the year round, sheep breeding is seasonal, which means that there was a period of only ~6 weeks in January and February during which material could be collected for study. Second, the infected fetus usually dies and becomes infected with putrefying bacteria before it is aborted, thus rendering it useless for microbiological examination. Third, the detection of ewes at an earlier stage of infection was difficult, as they rarely showed any signs. This meant that ewes had to be killed at random in the hopes of finding some with infected fetuses before putrefaction set in. Fourth, the "*Vibrio*" organisms were difficult to maintain in the laboratory, and they lost virulence under conditions of in vitro cultivation. Virulent organisms could not be maintained in pregnant ewes beyond July, because ewes refuse to take rams later than February.

It is a tribute to these men that, during the 100 years since they did their work, little has been added to our knowledge about the pathogenicity and epidemiology of *Campylobacter*-associated abortion in sheep. One of the reasons for their success arose from McFadyean's philosophy of providing a direct and free consultancy service to farmers and practicing veterinary surgeons—he regarded them as an extension of the college. This admirable attitude undoubtedly stemmed from the years he spent as a young man working on his father's farm in Scotland, as we shall now see.

John McFadyean, the Man. In a short article, one can do no more than pick out a few items that give an insight into the character of John McFadyean. A full account of his life is given in the brilliantly written biography by the late Iain Pattison [12], on which I have drawn freely.

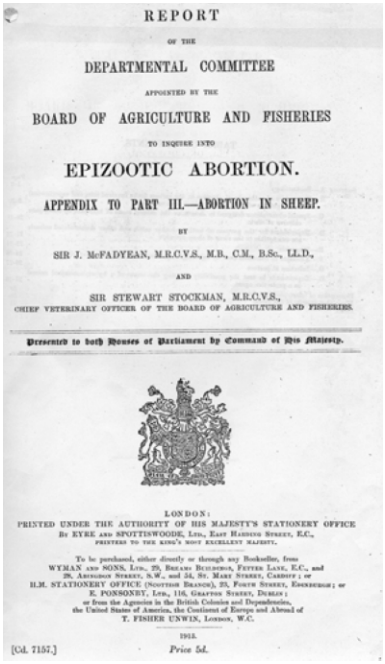
John McFadyean was born in 1853, the son of a tenant farmer in a remote part of the Scottish lowlands near Wigtown in Galloway. After an exceptionally enlightened tuition in a local school, he turned down an offer of an apprenticeship with a solicitor in favor of working on his father's farm. This he did for 5 years. Pattison describes it thus:

> He worked with the hired men, receiving no favours as a son of the house. In a year or two he had mastered every farming skill—milking, ploughing, sowing, scything, stacking, threshing. He could buy and sell, and bargain, and sniff rain in a stiffening wind [12, p. 23].

This farm apprenticeship had a strong influence on McFadyean's future work. It not only gave him a sharp understanding of the purpose of his profession, but it enabled him to treat farmers as part of an investigation team. The veterinary surgeon who attended his father's farm was the catalyst that prompted McFadyean to go to veterinary school. At the age of 21 years, he went to study at the Dick Veterinary College in Edinburgh. In those days, the number of students was very small, and the course was just 2 years long, but McFadyean qualified in 18 months with several medals. He had particularly excelled in anatomy, and he accepted the offer of lecturer in anatomy at the school.

Then, in 1877, came Koch's momentous discovery that anthrax was caused by infection with a specific microorganism. McFadyean was full of admiration for Koch's work employing the skills he most admired: methodical experimentation, acute observation, and logical deduction. But there was a problem: in those days, pathology in the veterinary field was so undeveloped that the detailed histopathologic characteristics of not one major disease of animals was known. The only way that McFadyean could learn pathology was to study medicine. So, in the autumn of 1877, he enrolled as a medical and science student at the University of Edinburgh, and he graduated in 1882.

Throughout his life, McFadyean had a passionate loyalty to the veterinary profession and an unforgiving attitude to anything that was likely to compromise standards of scientific discipline. This was soon to bring him into conflict with the establishment of the day. Later in the year of his medical graduation, he was invited to give the inaugural address at the start of the 60th winter session of the Dick Veterinary College. In his address, he criticized the veterinary profession for complacency and lack of initiative, veterinary teachers for a poor educational system, and the government for lack of financial support and a failure to recognize the veterinary contribution to public health. He went on to attack the Royal College of Veterinary Surgeons for attempting to take credit for the education of veterinary surgeons, when in reality, their responsibility was only to examine them. He said their "monstrous" claim was designed only to obtain a grant to erect in London "a building in which the Council of 30 members might be luxuriously



REPORT

OF THE

DEPARTMENTAL COMMITTEE

APPOINTED BY THE

BOARD OF AGRICULTURE AND FISHERIES

TO INQUIRE INTO

EPIZOOTIC ABORTION.

APPENDIX TO PART III.—ABORTION IN SHEEP.

BY

SIR J. McFADYEAN, M.R.C.V.S., M.B., C.M., B.Sc., LL.D.,

AND

SIR STEWART STOCKMAN, M.R.C.V.S.,
CHIEF VETERINARY OFFICER OF THE BOARD OF AGRICULTURE AND FISHERIES.

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Figure 3. Title page of the appendix to the third part of John McFadyean and Stewart Stockman's report on epizootic abortion [1].

accommodated on the four or five occasions on which they must meet each year" [13, 14]. His address was published in full. George Fleming, President of the Royal College of Veterinary Surgeons and the most powerful man in the profession, was furious and reacted in a vitriolic and not entirely accurate public letter. Most thought that the young McFadyean was finished, but many recognized that there was truth in what McFadyean had said and that his integrity was beyond reproach.

During his 11 years at the Dick College, McFadyean was able to collaborate with Sims Woodhead in the Edinburgh Royal Infirmary pathology laboratory. He studied animals with anthrax, glanders, swine fever, louping ill, and (especially) tuberculosis. He also published 2 highly acclaimed books: one on the anatomy of the horse, and the other on the comparative anatomy of domestic animals. But a far bigger undertaking was the launch of a new journal, *The Journal of Comparative Pathology & Therapeutics,* in 1888. This was a huge and risky private venture for McFadyean, who was the journal's sole editor. His friends and colleagues kept their fingers crossed that he would not bankrupt or kill himself. The themes of the journal were humility in ignorance, observation before speculation, patience in experimentation, and logic in conclusion. A section of each issue was devoted to abstracts and reports, many of which were summaries of McFadyean's translations of articles in French and German. He was to remain editor for 50 years, and the journal flourishes to this day under the shorter title *The Journal of Comparative Pathology.*

A major change came in 1892, when McFadyean was appointed Dean and Professor of Pathology and Bacteriology at the Royal Veterinary College in London (not to be confused with the Royal College of Veterinary Surgeons mentioned above). This was the first such chair to be made in a veterinary school in Britain. Two years later, he was appointed Principal, a post in which he was to remain until his retirement 33 years later in 1927.

McFadyean's achievements during this time were prodigious. Pattison describes how McFadyean's annual reports to the Royal Agricultural Society (the main financiers of the College) grew into an agriculturalist's textbook of veterinary endeavor and achievement. In reality, the work of the college's research laboratory was done part-time by McFadyean, with assistance from 1 man and a boy in grossly inadequate premises, and was chronically short of money. The Research Institute in Animal Pathology was a 5-room cottage with a single open fire and antiquated equipment. The electric centrifuge so frequently shocked its handlers that they operated in pairs, so that if one was shocked, the other could pull him clear. Yet, tiers of shelves around the walls held some 2000 preserved specimens from which pieces were cut for dispatch to laboratories all over the world. They represented the first comprehensive collection of animal tumors in Britain.

McFadyean's extensive work on tuberculosis brought him to the unenviable position of having to disagree in public with Robert Koch at the British Tuberculosis congress of 1901, a major international event with 2500 delegates. At the first plenary session, Koch astounded the Congress by stating that he did not think that the flesh or dairy products of tubercular cattle posed a risk to human health. In 2 days' time, McFadyean was due to address the same audience on the danger to man of tubercle bacilli in cows' milk. In his opening, he said, "I am overwhelmed at finding myself in a position which compels me to offer some criticism on the pronouncement of one the latchet of whose shoes I am not worthy to unloose" [15, p. 49]. He then proceeded, with compelling logic, to dissect Koch's lecture and to present evidence refuting Koch's conclusion. He went on, "The almost entire absence of any law [in Britain] dealing with tuberculous udder disease in cows is a scandal and reproach to civilisation. No penalty attaches to this crime of deliberately or carelessly placing on the market a food material charged with the germs of a dangerous disease" (p. 49). As Pattison puts it, although McFadyean might have considered himself unworthy to untie Koch's shoelaces, he felt no obligation to agree with his views on milk from tubercular cattle! The upshot from this was the immediate appointment of a Royal Commission to address the question of the public health significance of bovine tuberculosis.

In 1905 came recognition of McFadyean's work in the form of knighthood. The conferring of a knighthood on a veterinary surgeon with no senior position in government was unprece-

dented. What made it so rewarding for McFadyean—and, indeed, for the entire veterinary profession—was that it was an official recognition of his work purely as a veterinary surgeon.

McFadyean was not primarily a family man, but his marriage to Mara Eleanor Walley was a highly successful one. She was the daughter of Thomas Walley, Principal of the Dick Veterinary College in Edinburgh and McFadyean's highly valued teacher and mentor. Mara Eleanor gave her husband immense support and even made bacteriological media in her kitchen (her "jellies"). Pressure of work did not allow McFadyean to give much time to his 5 surviving children, but it gave him intense pleasure to give his eldest daughter, Ethel, in marriage to Stewart Stockman in 1908. Stockman, in turn, was knighted in 1913. His premature death in 1926 at the age of 57 years was a devastating blow to McFadyean, and it marked the end of an era and a long partnership. However, McFadyean remained active for many years after his retirement, serving on the Council of the Royal College of Veterinary Surgeons until 1939, and he received many national and international honors. He died on 1 February 1941.

Conclusions. In summary, John McFadyean stands as the founder of veterinary pathology and research in Britain, with all the implications these hold for public health. A renewed awareness of the need for cooperation between human and animal health systems, as exemplified by McFadyean [16], is long overdue. If an example is needed, avian influenza serves well to give credence to the discipline of comparative pathology and Schwabe's concept of "one medicine" [17].

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