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Salmonella Typhi — historical perspective of discovery and forgotten contribution of Polish anatomopathology

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Abstract: Outbreaks of typhoid fever for centuries decimated armies, cities and large hosts of people. Discovery of an agent causing such a grave disease became one of the most important achievements of bacteriology — science, which had experienced rapid development in the last quarter of the 19th century and changed the course of our civilization.
The article deals with the discovery of Tadeusz Browicz, Polish anatomopathologist, who in 1874 reported about rod-shaped "parasites" in viscera of typhoid fever victim. His achievement became shaded by the later discoveries of Eberth, Klebs and Gaffky, but as authors stated below, Browicz should be recognized with mentioned scientists as a co-discoverer of the typhoid fever bacillus.

Keywords: *Salmonella Typhi*, typhoid fever, bacteriology, Eberth, Browicz, Gaffky.

Introduction

Salmonella enterica subspecies serovar Typhi (*Salmonella Typhi*) is a pathogen causing typhoid fever in humans, and the disease is restricted to human hosts, as well as humans are its chronic carriers [1–2]. High fever, malaise, then prostration, abdominal discomfort and headache are the most obvious, however non-specific symptoms of *Salmonella Typhi* caused infection. In more than 25% registered cases high-grade fever is the only clinical symptom of disease, while patients with more severe illness, are suffering from anorexia, hepatomegaly and vomiting [3]. During the second week of illness the rose spots can appear on the chest and abdomen in 10–50% of sick individuals [4]. Before antibiotic treatment was introduced, an average time of the

disease course could be estimated on several weeks, with case-fatality rate of approximately 10%–20% [5]. The Gram-negative Typhoid bacilli are shed in stool of asymptomatic carriers, or in stool and urine of people with active disease. The infection is usually transmitted by ingestion of food or water contaminated with feces, however transmission by direct contact is also possible [6]. That's why typhoid fever was nightmare to any larger groups of people when sanitary conditions rapidly deteriorated, e.g. during army marches, wars, in refugee or a prisoner-of-war camps (POW camps).

Materials and Methods

The paper uses original works and studies devoted to the history of detecting and discovery of the pathogenic agent causing typhoid fever. Comparative analyze is conducted in accordance with historical methodology.

Historical analyses

In 1873 William Budd's *Typhoid Fever: Its Nature, Mode of Spreading and Prevention* became available bringing a clear description of the contagious nature of the disease. Budd was convinced that fecally contaminated water is to be blamed for spread of infections, however he could not point on the causative agent of typhoid fever. It was in late 1879 when German bacteriologist and physician Karl Joseph Eberth, then a full professor of pathological anatomy at the University of Zurich, discovered the bacillus, as was then named, in the abdominal lymph nodes and spleen [7]. Eberth was not the first to search for causative agent but was convinced that if the subject would be researched systematically on macro- and micropathological levels simultaneously, then it can end with success. He mentions Fredrich von Recklinghausen's observation of micrococcal masses in purulent lesions associated with typhoid fever, which was communicated in summer of 1871, as one of earliest in that subject and then Klein's findings of micrococci in lymph and blood vessels published in 1874 and Sokoloff's report coming from 1876 on the presence of micrococci in the spleen of 3 from 12 typhoid fever victims [7]. Finally Eberth recognizes results of Fichsel's investigation on the pathological changes of the internal organs of diseased confirming that in 15 from 29 autopsied cases the micrococci settlements were present in spleen, and even more often found in the lymph nodes [7]. Eberth, in sterile conditions, made a deep investigation into the typhoid fever cases observing then a short, rode-shaped bacteria in Payer's patches and mesenteric lymph nodes in 18 of 40 postmortem examined typhoid fever victims. Concentrating his attention mainly on mesenteric lymph nodes and spleen sections, he distinguished a rod-shaped microorganism from the ordinary putrefactive bacilli, using the analine stains and clearing by means of acetic acid.

When Eberth checked material coming from autopsies of sick, who died from other illnesses, he never found short, rode-shaped bacteria present. He also mentioned, that the rods at times were possessing spores. Eberth's report was published in July 1880.

However, in April 1880 a German bacteriologist and former assistant to Rudollf Virchow, Edwin Klebs came out with his own paper describing findings in 24 fatal cases of typhoid fever. He was giving evidence on the presence of the rode-shaped microorganism in different tissues, including mesenteric lymph nodes, spleen, blood vessels, Peyer's patches, kidneys, lungs and meninges. Even more, Klebs made a connection between rode-shaped bacteria with inflammation process and subsequent degeneration of tissues. Nevertheless he had observed also, in some cases, presence of, as described, unbranching, bacterial filaments. Klebs speculated, that it could be a second stage in the development of the rod-like form [8]. Next year Eberth and Klebs both brought their communications [9, 10]. Eberth was presenting the examination of 17 fatal cases of typhoid fever. In 6 cases, he found again the previously described bacterial organism present in spleen tissue and lymph nodes. At the same time he investigated material from 11 autopsies of individuals who suffered and died from other conditions like pneumonia, pleuritis or lobular hepatization, not finding a single trace of rod-like bacteria. In the pursuit of checking special conditions favorable to infections, Eberth selected 13 cases of tuberculosis with erosion of the intestinal wall, but again with the negative result for bacillus typhi presence. Although still lacking experimental evidence, Eberth became convinced that he discovered the pathogen responsible for typhoid fever. He also twice made remarks to the Klebs research results [9].

Klebs in his second communication described a method of inoculation liquid gelatin media with contagious material from mesenteric lymph nodes of a typhoid fever case with subsequent finding of rods present in the culture medium, which however was not in pure state. When he inoculated rabbits with the turbid culture it provoked hemorrhages but no ulcers in the caecum were detected. He also discussed Eberth's results [10]. It was again 1881 when Robert Koch, who was then a rising star of modern bacteriology, published his work devoted to studying methods of different pathogenic organisms responsible for the infectious diseases, including typhoid fever [11]. Having already perfected staining techniques and sophisticated methods of microphotography Koch was able to obtain good quality pictures of pathogens. From 19 plates included to the text, plate 14 (Tafel XIV), with five microphotographs (nr 49–53), was illustrating typhoid fever bacteria. Koch having investigated the problem of typhoid fever claimed that the presence of micrococci, reported earlier by Eberth, was rather a rare, however short, rode-shaped bacteria (*kurzen Bazillen* in Koch's original expression) were observed by him in half of the examined cases. Koch also denied that Klebs unbranching, bacterial filaments are specific for typhoid fever.

Finally, he credited observations of Eberth and Klebs concerning rod-like bacteria as a specific pathogen, which was in fact detected by both researches independently [11].

Polish researcher Zdana Brandówna has pointed on the Meyer's doctoral thesis published in 1881 as an important work, which should be included in the discussion [12]. Young German physician analyzed pathological lesions from 24 human cadavers, all victims of the typhoid fever. He concentrated his research on fragments of intestinal mucosa, extracting from it a liquid suspension, which then drayed and stained with gentian violet was observed under a microscope. Meyer was able to see clearly the bacterial forms matching descriptions left by Eberth and Klebs. He was also convinced, that they should be concerned as the causative agent for the typhoid fever infection [13].

Although works of Eberth, Klebs, Koch and Meyer were based on the firm research data the experimental proof based on the pure bacterial colonies was still needed. It was Georg Theodor Gaffky, an army surgeon and later, an assistant to Robert Koch, who was to resolve this problem. He dedicated continuous efforts to improve culture methods, so to isolate the bacillus successfully. Working intensively from 1881 till 1883, in 1884 he published final results of his research, confirming that the rod-like bacillus was the agent of typhoid fever, and named it as *Eberthella typhi* [14]. Gaffky examined 28 cases of typhoid fever and in 26 he could find microorganisms described by Eberth, Klebs, Koch and Meyer. He deliberately was not giving much attention to the results obtained from intestinal wall examination arguing that natural presence of many non-specific to typhoid fever microorganisms would only obscure the research. So Gaffky focused on the spleen, kidneys, liver and lymph nodes sections of patients with typhoid fever. Extracting a piece of spleen he took stripes of it directly onto gelatin base. After 48 hours the pure colony was ready to be stained and microscopically investigated. Then, using different media, boiled potatoes and blood serum among them, Gaffky was able to investigate deeper into the structure and nature of bacteria. Pathogen was arranged in irregular groups, could move independently, was prone to aniline dyes and did not dissolve gelatin media. Gaffky discredited Klebs thread-like forms as a part of pathomechanism concerned with typhoid fever and failed to produce lesions in animals with his pure cultures similar to those that had been previously described by Klebs [14, 15].

Discussion

However, it was a Polish anatomo-pathologist Tadeusz Browicz, who first detected and observed *Salmonella typhi*. Browicz reported his discovery in the separate paper entitled *Pasorzyty roślinne w durze jelitowym* (*Vegetable parasites in typhoid fever*) which was published in 1874 in Polish, six years earlier that the first edition of Eberth's treatise and 10 years prior to Gaffky's publication of his results [16]. Regretfully, he

published his observations in Polish (in a journal of Academy of Sciences in Krakow), which hindered non-Polish-speaking scientists from learning about the Browicz's discovery. First known summary of Browicz's observations on *Salmonella typhi* given in foreign language was a short note published one year later in a German medical journal [17]. Soon after it was recognized by a German pathologist Felix Victor Birch-Hirschfeld, who mentioned in his manual of pathological anatomy, that Browicz had found the rod-shaped bacteria (Stäbchenbakterie, so bacilli in Birch-Hirschfeld expression) in kidneys, spleen and intestines of typhoid fever victim [18]. Rapid development of research on *Salmonella typhi* obscured Browicz's achievement. His name is often omitted and when the problem is discussed the obvious heroes are Eberth, Klebs, Koch and Gaffky. In Frederick P. Gay classic monography on typhoid fever there is not a single note on Browicz given [15]. The same can be observed in the majority of texts concerned with the historical background of *Salmonella Typhi* discovery [19–22].

Precedence of the Browicz's discovery was not totally forgotten. In the last quarter of the 19th century it was mentioned in the number of works, mainly written by military doctors struggling with typhoid fever in army camps. In the United Kingdom they were sir William Watson Cheyne and Alexander Wynter Blyth [23–24]. The Polish scientist was also mentioned by the famous British toxicologist sir Thomas Stevenson in his treaty on public health [25]. In the United States Browicz's achievement was recognized by US Army pioneer bacteriologists like George Miller Sternberg [26–29] and Victor C. Vaughan [30–32]. The latter one became an expert on typhoid fever, being a member of a Walter Reed's commission, which investigated causes of typhoid fever epidemy in the US Army during the Spanish-American War in 1898. Vaughan's biographist Richard Adler also presented short information about Browicz's work, expressing opinion that honor of identification of rod-shaped organism in the intestinal tissue of typhoid fever victims should be given to Browicz [33]. The very same is repeated in Richard Adler's and Elise Mara's book *Typhoid Fever: A History* [34]. In the 19th century Browicz was also mentioned in a few American works concerning public health or practical medicine [35–36]. French scientists gave credit to the Browicz's precedence, too [37–38].

Discoveries of Eberth, Klebs, Koch and Gaffky slowly shaded knowledge of the Browicz discovery. He was sometimes mentioned in non-Polish catalogues of scientific papers but the fame of his finding lasted only in Poland [39]. It was until centenary of Browicz's discovery, when Symcha Wajs wrought an English-language article bringing back this achievement to the wider masses of readers [40].

In 1874 then young physician and anatomical pathologist working as an assistant in Departament of Pathological Anatomy in Jagiellonian University examined a single case of young female patient which died in St. Lazarus Hospital [41]. Clinical report, then confirmed by careful autopsy examination conducted by Browicz, pointed unequivocally at typhoid fever as a cause of death. He thoroughly described patholo-

gical changes present in various internal organs; including spleen, kidneys, liver, heart, lungs and intestines. All observed by him then lesions were typical result of the typhoid fever. In Browicz's own words: "Situated above several Peyer's patches and isolated glands, there is a thin, yellowish necrotizing layer, which can be separated only at some places. The mesenteric glands are the size of a hazelnut, congested and juicy" [41]. Then he added "Infiltration and surface necrosis of the mesenteric glands, characteristic to typhoid fever, justify the above diagnosis". When heart and kidneys were microscopically investigated, then immobile, "short rod-like" structures became clearly visible. Browicz remarks that those structures were less numerous in kidneys, however were still present in spleen and intestinal content, and occured in greater numbers in faeces of the ill people.

The preparations of rod-like structures were then kept in the moist chamber. As Browicz reported they could reproduce and on the third day "thread formations, long, not branching, composed of rosary grouped oval bodies" were visible. Browicz was cautious in making final statements. He openly admitted that one, although carefully investigated case, was not enough to prejudge about detected microorganism as a causative agent of typhoid fever. Nonetheless Browicz admited that discovered by him structures were not found in any lesions of other examined diseases. He predicted that further research should resolve this problem [41].

Conclusions

It is almost certain that Browicz's rod-like structures should be considered as the same ones observed few years later by Eberth and Klebs, however it must be admitted that Browicz's report from 1874 lacks illustrations, while in Eberth's paper dating 1880 has separate table included, an in Kleb's communication from 1881 there is clear drawing present. Nevertheless descriptions given in discussed texts coincide with each other. Browicz assumption that observed by him rod-like structures were in fact living entities able to reproduce themselves, was positively checked in culturing process. The same conclusions were present in the works of Eberth and Klebs. Browicz supported by clinical and autopsy records became convinced that rod-like structures could be the specific pathogen for typhoid fever, although clearly understood that further research was needed to confirm his hypothesis. His report was built upon examination of single typhoid victim case, while in 1880 Eberth published results of 40 and Klebs of 24 autopsies performed on the cadavers of those who died from typhoid fever. It is then obvious that German researchers were bringing much more data for comparative evaluation and could investigate deeper, then Browicz was in his work, which then can be considered as preliminary communication. Browicz's, contrary to Klebs, did not implemented any experimental proceedings.

In summary we can say that that subsequent investigations of Eberth, Klebs and Koch were in fact, although unknowingly, following the path marked already by Browicz, which finally was completed by Gaffky. Neither Ebert, Klebs, Koch or Gaffky mentioned Browicz's communication, most certainly not being aware of its existence. Nonetheless Michał Hanecki's proposal that because of historic reasons the pathogen should be named Browicz-Eberth-Gaffky bacillus, to commemorate achievements of those three researchers, who were pioneering investigation in the field, is justified [42].

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