Medical Discoveries in the Ghettos: The Anti-Typhus Battle

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Mortality in the Nazi ghettos increased parallel to the duration of the incarceration. Death was the result of hunger-induced depleted body resistance, the appalling sanitary conditions and the lack of medications. All attempts by ingenious physicians to improve nutrition (by artificially produced food and vitamins) could not overcome the starvation. The physicians could not control infectious diseases (tuberculosis, gastroenteritis) without rudimentary sanitary conditions, medications (clandestinely imported or manufactured), or vaccines. Neither could they prevent the infestation of lice with its resultant high morbidity, nor mortality from typhus exanthematicus (spotted fever, ‘fleck fieber’) in those not yet designated for extermination. This brief review article pays tribute to the heroic physicians who battled typhus in the ghettos.

Epidemics of typhus during wartime are fatal, a fact well documented. A mass grave incidentally discovered in 2001 in the surroundings of Vilna immediately raised the suspicion of yet another atrocity of the Nazis. However, the intact skulls (no fractures and no penetration) and the presence of French uniforms indicated that the grave was that of the Napoleonic Grand Army. DNA testing proved the presence of typhus, suggesting it as the cause of death [1]. This corresponded to historical descriptions of the demise of a large part of the Emperor’s Army – not by the Arctic conditions, but by a feverish illness that caused severe weakness, extreme thirst, exanthema on the skin, hemorrhagic pneumonitis and encephalitis-induced delirium.

The history of “trench fever” described typhus in the fighting armies of the First World War and epidemics in the armies of both the Reich and the Allies in 1942 [2]. The Eastern Front countries (Poland, Baltics, Ukraine) were also endemic plague by this disease. Therefore, it is of no surprise that a major part of anti-typhus medicine was developed in Poland. Many of the researchers were Jewish, as were many of the victims.

The louse was identified as the vector in 1908 by Nicolle; the first vaccine was developed in 1915 at Mt. Sinai Hospital by H. Plotz, a 25 year old New Yorker [3]. The pathogen was named by the Brazilian discoverer Rocha-Lima after H.T. Rickett (USA) and Stanislaw Prowazek (Poland), the two co-researchers who succumbed to the disease – hence *Rickettsia prowazeki*. A mild form of the European strain in the United States was described by Nathan Brill (a recent refugee from Europe) and Hans Zissner, both at Mt. Sinai Hospital in New York – hence the term Bliss-Zissner disease [4]. A more effective vaccine, albeit difficult and costly to produce, was developed by Weigl in Lwow in 1921. The laboratory typhus identification by cross-agglutination with Proteus X19 was made by Bronislawa Fejgin (who perished in the Warsaw ghetto). [5] The serology was studied by Ludwik Hirszfeld (who escaped from the ghetto and survived on the Aryan side of Warsaw). Kidney failure in typhus was described by Jacob Penson, also in the Warsaw ghetto (he escaped and was hidden in a village). Ludwik Fleck, in the Lwow ghetto, developed the urine antigen diagnosis and prepared a vaccine (he survived Auschwitz and Buchenwald). The final vaccine was prepared at the Pasteur Institute in 1948 [6], while Fleck’s test was replicated in Australia in 1949 [7]. The legacy of Drs. Penson and Fleck in the 21st century is indeed heroic and warrants narrating.

Dr. Penson and Dr. Fleck were remarkable physicians who, working in extraordinary circumstances, made outstanding medical contributions whose benefits are enjoyed today.

**Dr. Penson and Kidney Failure**

Jakub Penson was born in 1899 in Plock, Poland and obtained his medical degree in 1927. He worked in the Czyste Jewish Hospital in Warsaw from 1939, and in 1942 was moved into the ghetto. Typhus exanthematicus was one of several epidemics flourishing in the crowded population of the ghetto. Together with tuberculosis, it was the major cause of death from infectious diseases.

Although continuously present, two major epidemics were recorded in the five years of the ghetto’s existence: a “small epidemic” of some 10,000 patients between January and June 1940 and 1941, and a “great epidemic” that began in May 1942 and ended in January 1943 with about 12,000 cases. The death rate from typhus was especially high in the early months of the ghetto’s existence, when the population was at its peak (approximately 150,000) and the sanitary conditions were at their worst. The death rate then declined as the population decreased and the sanitary conditions improved.

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1940, with 5000 deaths, and a "great epidemic" between May 1941 and April 1942, with 100,000 people infected and 10,000 recorded deaths [8,9]. The clinical observations were conducted by a team of six researchers headed by Dr. Jakub Penson. The results of 6500 observed patients were presented at the monthly clinical meeting in the Czyste Hospital, the main “academic” institution in the Warsaw ghetto. The description of kidney failure in typhus was presented at the hospital in March/April 1941.

In March 1941, the British Medical Journal published a report on the extra-renal cause of renal parenchymal failure observed in crush syndrome victims of the London bombardments [10]. The Warsaw ghetto medical authorities, completely cut off from any scientific communication, could not have had this information. The typhus-induced parenchymal renal failure identified in the ghetto should be considered a parallel, but original, discovery of renal failure from extra-renal disease. Based on histological studies, Dr. Penson coined the term "destructive thrombo-vasculitis" of the renal parenchyma.

Dr. Penson studied laboratory and pathology reports, daily temperature charts, urine analysis (specific gravity, volume, and urea and chloride excretion) and recorded serum urea levels. He described three stages in typhus kidney failure: oliguria, with reduced urine output; 1–2 days of anuria; and a recovery stage of polyuria, with gradual return to normality.

The discovery was described in detail in a monograph written by Penson’s followers in Gdansk [8]. A complete explanation of this organ failure, with metabolic values, appeared in the nephrological literature much later [11].

Dr. Penson managed to escape from the ghetto and was hidden by friends on the Aryan side of Warsaw and later in a country village. After the war he worked in Lodz, Warsaw and eventually in Gdansk. He was the author of 84 publications and 3 textbooks and was honoured with various awards. He also became a Member of the Academy of Sciences and organized the opening of one of the first nephrological units in Poland. He died at age 71. His legacy, apart from a score of graduates who he educated, is in the management of kidney failure in typhus. He proved that apart from encephalitis, kidney disease is also an end stage in typhus infection. This condition should rightly be called “Penson syndrome.”

Clandestinely they also expressed resistance to the Nazis. While in Buchenwald, Dr. Fleck falsified the anti-typhus vaccine prepared for the German Army and, undetected, produced pure water

**DR. FLECK’S FIGHT AGAINST FLECK TYPHUS**

Ludwik Fleck was born in Lwow in 1896 and graduated from the Lwow University Medical School. His weighty contribution to medical science started with an interest in infectious diseases, and he was renowned already before World War II. In his pre-ghetto period Fleck contributed to the literature on various diseases, he developed a skin test for typhus and conducted various other immunological studies.

During the period 1941–43, Dr. Fleck lived in a walled-in ghetto with his family. In collaboration with other inmate doctors, Drs. Olga Elster, Bernard Unschweif, Anhalt and Kurzov (all of whom perished), Fleck worked in a laboratory and in two hospitals, one general and one for infectious diseases. The conditions in the ghetto were catastrophic, both nutritionally and hygienically. Typhus usually ravaged in 70–100% of the population, with a mortality rate of 30% [12].

![Figure 1](image-url). Diagram illustrating the typical course of azotemia in a typhus patient (reproduced with Dr. Rutkowski’s permission)
diagnostic and therapeutic articles on bacteriology, serology and immunology, as well as his thoughts on the Philosophy of Science. Among these publications were his reconstructed Lwow ghetto laboratory documents, published in the Polish Medical Journal in 1946 and followed by the English version in the United States in 1947. Fleck was the first to apply the urine antigen test in clinical practice, and the first to obtain a partially protective anti-typhus vaccine [16]. Dr. Fleck lived his last 4 years in Israel and continued to conduct research and write. While being treated for lymphoma, he suffered his second and fatal coronary event in 1961.

Since ghetto documents were lost, the veracity of the Lwow experiments was open to question [17]. Apart from an anecdotal narration given by Adolph Folkmann, an escapee from the Lwow ghetto to Sweden who stated that "A Jewish doctor named Fleck had just succeeded in producing a new and more effective serum against spotted fever" [18], no official publication on Fleck's discovery existed. Fleck's scientific data were confirmed in later publications by his son, Richard (Arie), who was 18 when he was in the ghetto.

These subjective statements were subsequently confirmed by objective documents. The testimony of Prof. Hirszfeld is of particular importance. On 29 September 1942, Hirszfeld had presented a preliminary announcement on "Serological-bacteriological identification of spotted fever" at a clinical meeting in Stawski Hospital, Warsaw [19]. His manuscript was handed to Prof. Przesmycki for preservation and publication in the event that he did not survive. His collaborator, Dr. T. Epstein, indeed did not survive. Dr. Hirszfeld was fortunate not only to survive but also to retrieve his manuscript. On 18 March 1946 Hirszfeld finally published the 1942 version of his presentation. He testified that "independently from us and in a different way, on the 27.5.1942, in the daily Jewish Gazette in Lwow, Dr Fleck presented the discovery of a precipitate in the urine of sick people with spotted fever."

After an extensive search in Polish libraries, a copy of the Jewish Gazette was only recently found in the Jagellonian University of Krakow (by Dr. A. Grzybowski and librarian M. Kucz). The text, translated by Dr. Grzybowski reads as follows:

"Important experiments in the fight against typhus in the bacteriology laboratory of the Jewish Hospital in Lwow

The bacteriology Laboratory in the Jewish Hospital in Lwow (at Kuszewica Street 5) with the Dept. of Infectious
Diseases (at Zamarstynowska Street 132) is involved actively in the fight against typhus. It was detected that typhus patients excrete large amounts of antigen in their urine. The head of the laboratory Dr. Fleck found the typhus antigen in the first days of fever. It might be used for early and specific diagnosis of typhus (tested with serum of immunized rabbit or serum of patients with specifically prepared urine), and for easy and inexpensive preparation of protective vaccine from the patients’ urine. The already conducted tests gave encouraging results.”

Objective confirmations also appeared in the literature: Some four months after Fleck’s publication in the ghetto, a report appeared in a medical journal in Mexico, authored by Dr. Alberto Leon [20]. This almost parallel discovery was recognized by Fleck in his 1947 American paper. Leon’s description appeared in September 1942, with a slightly different technique. He reports that he detected antigens in the urine of a typhus patient only on the seventh day of the disease, in contrast to Fleck’s diagnosis on day 2 and 3 of the illness.

Early in the post-war period, the first confirmation of Fleck’s hypothesis came from the Australian researchers O’Connor and McDonald, who in 1949 identified urinary antigens in scrub typhus, another rickettsial strain [7]. The second post-war validation appeared in 1960, when Dr. Fleck managed to reproduce his own pre-war diagnostic experiments with a third strain of *Rickettsia*, namely, the murine type. He reported a “precipitation ring” in urine, obtained when activated with the serum of patients with established typhus disease from two Israeli hospitals (Kaplan and Tel Hashomer) [21]. We propose that the development of the identification and clinical applications of the urine typhus antigen could at best be shared. The discovery of the *Pneumococcus* urine antigen by Avery in 1917 was followed by cross-agglutination tests in typhus by Feigin in 1926 and was first clinically implemented in 1942 by Fleck. Fleck expected that the future would bring forth “the possibility of making a specific diagnosis from urine that could also be utilised in other infectious diseases” [22].

Today, in 2011, typhus disease is generally contained, but not eradicated. Prophylactic, hygienic and anti-parasitic measures, various inoculations and antibiotics have localized the disease to occasional endemic events. Although vaccine preparation has been superseded, the principle of the urine diagnostic test is now widely applied. Several infectious diseases lend themselves to the urinary antigen identification; indeed today they are performed globally in millions of patients.

Below are some examples of Fleck’s contributions to health care. Urine antigen diagnosis was applied in bacterial infections: *Pneumococcus, Streptococcus*, typhoid fever, typhus, *Pertussis*, and *Chlamydia melioidosis*, *Mycobacterium*, legionellosis and borreliosis. The technique is performed in parasitic infestations such as cysticercosis, bilharzias (Schistosoma), leptospirosis, leishmaniasis, filariasis and trypanosoma. It is also used in the diagnosis of mycotic (fungal) infections: blastomycosis, paracoccidiomycosis, cryptococcosis, penicilliosis, *Candida*, histoplasmosis; and in viral hepatitis B and Andes (hanta virus) cardiopulmonary syndrome.

The urinary antigen detection used in academic centers today is a molecular test performed with biochemical, electrophoretic and immunological techniques. All these elective diagnostic techniques require academic centers for their application [22]. Practitioners today are most likely unaware of the origin of this diagnostic test. Its significance is even more evident in the diagnosis of acute cases. The success of this test relies on the rapidity and simplicity of a bedside, ‘urine-drop’ test, also feasible in underdeveloped settings. Other laboratory measures to diagnose the agent are slow to yield results; empirically initiated antibiotic treatment might be non-specific. Therefore, any simple test that can be performed by the nursing staff and is available at any time of the day or night is essential. Indeed, it is important that a simple urine test can be performed within 15 minutes in any distant community hospital, with no blood collection and no spinal fluid tapping. Such a test is feasible even in underdeveloped countries.

Examples of such clinical application came from widespread medical practice, all with high sensitivity and specificity. In the 21st century, rapid diagnoses were reported from Spain, from Boston’s Children Hospital, from Japan, from Russia regarding community-acquired pneumonia; and from the USA in immune-suppressed patients. Finally, Gottlieb and Weatherall [23] from Australia reported that the rapid test was employed in an emergency department of a community hospital, and was performed by clinical staff rather than sent to a laboratory.

**CONCLUSION**

The heroism of Jewish doctors in the ghettos and camps was remarkable, and despite the risks their dedication was absolute. The exact number of Jewish physicians lost in the Holocaust is unknown, but it is realistically assumed to have been in the

"And You, Jewish physicians, you deserve some words of recognition"

Dr. Israel Milejkowski, Chief Medical Officer, Warsaw Ghetto, 1942

![Urine antigen test kit (Binax Lab, California, USA)](image)
thousands. Indeed, some 2500 names were enumerated in Poland and 800 were recorded in the Warsaw ghetto [24,25]. In Theresienstadt, a camp of total 243 medical practitioners were interned and 41 survived. A similar situation existed in the Shargorod camp in Transnitria, where 27 Jewish doctors from Romania were interned, 23 were infected with typhus and 12 of them succumbed to it.

Although the above examples refer mostly to pneumococcal or Legionella disease, the clinical application of the urine antigen test remains Fleck’s legacy.

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Capsule

A multistage tuberculosis vaccine that confers efficient protection before and after exposure

All tuberculosis vaccines currently in clinical trials are designed as prophylactic vaccines based on early expressed antigens. Aagaard et al. have developed a multistage vaccination strategy in which the early antigens Ag85B and 6 kDa early secretory antigenic target (ESAT-6) are combined with the latency-associated protein Rv2660c (H56 vaccine). The authors show in CB6F1 mice that Rv2660c is stably expressed in late stages of infection despite an overall reduced transcription. The H56 vaccine promotes a T cell response against all protein components that is characterized by a high proportion of polyfunctional CD4+ T cells. In three different pre-exposure mouse models, H56 conferred protective immunity characterized by a more efficient containment of late-stage infection than the Ag85B-ESAT6 vaccine (H1) and BCG (bacille Calmette-Guerin). In two mouse models of latent tuberculosis, the authors show that H56 vaccination after exposure is able to control reactivation and significantly lower the bacterial load compared to adjuvant control mice.

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“A sculptor is a person who is interested in the shape of things, a poet in words, a musician by sounds”

Henry Moore (1898-1986), English sculptor and artist best known for his abstract monumental bronze sculptures that are located around the world as public works of art. His forms are usually abstractions of the human figure, typically depicting mother-and-child or reclining figures.