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.

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

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, exanthemata 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 endemically plagued 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 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, 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.

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

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."

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. Diagram illustrating the typical course of azotemia in a typhus patient (reproduced with Dr. Rutkowski's permission)

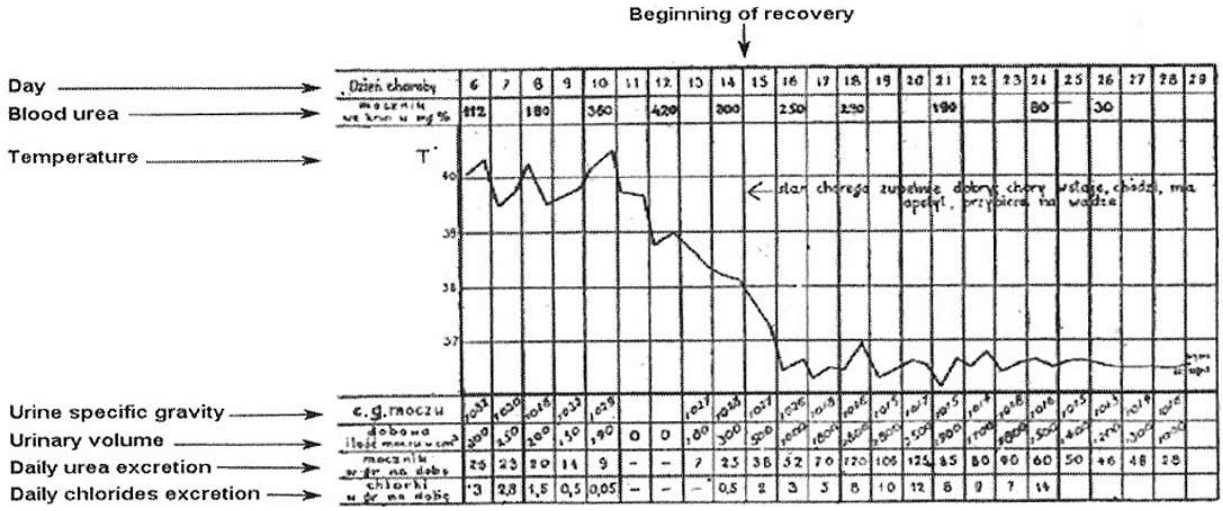
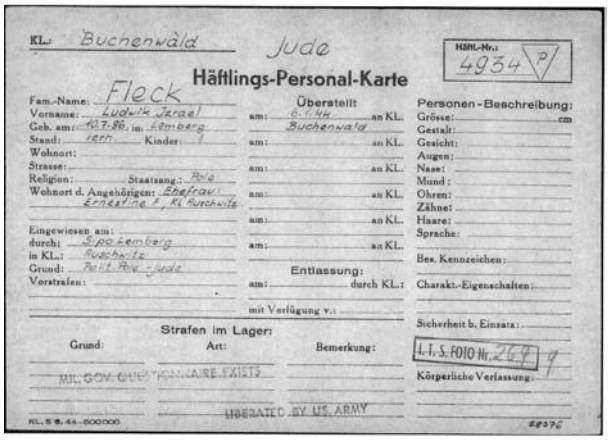


Figure 2. Dr. Fleck's identity card in Buchenwald concentration camp (courtesy of Yad Vashem)


KL.: Buchenwald Jude

HBNL-No.: 4934 P

Häftlings-Personal-Karte

Fam.-Name: Fleck
Vorname: Ludwik Israel
Geb. am: 10.7.96 in: Lemberg
Stand: verh. Kinder: 1
Wohnort:
Strasse:
Religion: Staatsang.: Pole
Wohnort d. Angehörigen: Ehefrau: Ernestine F. Kl Buchwald

Eingewiesen am:
durch: Sipo Lemberg
in KL.: Buchenwald
Grund: Pol. Pole - Jude
Vorstrafen:

Überstellt
am: 6.1.44 an KL. Buchenwald
am: an KL.
am: an KL.
am: an KL.
am: an KL.
am: an KL.

Entlassung:
am: durch KL.:
mit Verfügung v.:

Strafen im Lager:
Grund: Art: Bemerkung:

MIL. GOV. QUESTIONNAIRE EXISTS

LIBERATED BY US. ARMY

Personen-Beschreibung:
Grösse: cm
Gestalt:
Gesicht:
Augen:
Nase:
Mund:
Ohren:
Zähne:
Haare:
Sprache:

Bes. Kennzeichen:
Charakt.-Eigenschaften:

Sicherheit b. Einsatz:

I. T. S. FOTO Nr. 267

Körperliche Verfassung:

KL. S 8. 44 - 500000

The medical and pharmaceutical supplies in the ghetto eventually ran out. The Weigl vaccine that had initially protected the population was not re-supplied. Fleck and his colleagues undertook to find an alternative vaccine that they could manufacture locally since the Weigl technique was not practical. Fleck thought of searching for antigens to provoke the immune system into producing antibodies. This would be named the "Fleck hypothesis" [13].

Inspired by Avery's discovery of pneumococcal antigens in urine in 1917, Fleck looked for an antigen in the urine of sick people [14]. He found that the typhus antigen was excreted on the second or third day of fever, when no other signs of the disease were clinically evident. The antigen, used first for diagnosis, was also prepared as an active vaccine and its effect was studied in guinea pigs. It proved to be protective against typhus, and once in a sterile solution it was tested in humans. Fleck first inoculated himself, his wife and his son, and then the voluntary medical team of some 30 individuals. Eventually, it was injected into some 500 inmates. Dr. Fleck reported the results at a staff meeting in the ghetto hospital in May 1942. They were subsequently published in the local *Jewish Gazette*. The information was disseminated, sent to Professor Franciszek Groër in Lwow and to Professor Ludwik Hirszfeld in Warsaw.

Dr. Fleck was soon arrested by the Nazis and transferred first to a local pharmaceutical factory, the "Laokoon." In 1943 Fleck became Haftling (prisoner) # 100967 in Auschwitz. After an initial period of exhausting manual work he was transferred to a laboratory where he worked on an anti-typhus vaccine [15]. In 1944 he was transferred to Buchenwald as Haftling # 4934, where he was also forced to work on anti-typhus serology.

Dr. Fleck was liberated by the American Army and was interned first in Buchenwald and then in Bunzlau (Boleslawiec) Hospital. Upon discharge, he returned to Lwow and was soon involved in research and writing. He published more than 170 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

Figure 3. Article on the front page of the *Jewish Gazette* 27 May 1942


GAZETA ŻYDOWSKA

ROK III Nr 62

Kraków, środa dn. 27-go maja 1942 r.

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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.

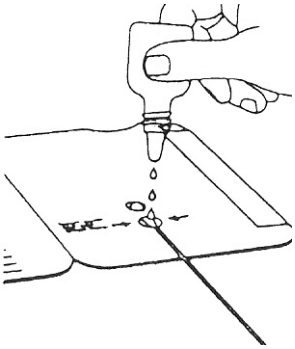
Early in the post-war period, the first confirmation of Fleck's hypothesis came from the Australian researchers O'Connor and McDonald, who in 1949 identified urinary antigens in scrub typhus, another rickettsial strain [7]. The second post-war validation appeared in 1960, when Dr. Fleck managed to reproduce 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 Fejgin 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].

"*And You, Jewish physicians, you deserve some words of recognition*"
Dr. Israel Milejkowski,
Chief Medical Officer, Warsaw Ghetto, 1942

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, paraccocidiomycosis, cryptococcosis, penicilliosis, *Candida*, histoplasmosis; and in viral hepatitis B and Andes (hanta virus) cardiopulmonary syndrome.

Figure 4. Urine antigen test kit (Binax Lab, California, USA)



The urinary antigen detection used in academic centers today is a molecular test performed with biochemical, electrophoretic, mass spectrographic 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; an empirically initiated antibiotic treatment might be nonspecific. 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

thousands. Indeed, some 2500 names were enumerated in Poland and 800 were recorded in the Warsaw ghetto [24,25]. In Theresienstandt camp, a total of 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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