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Workers Died of Dyes: The Discovery of Occupational Bladder Cancers

Behnam Nabavizadeh, Gregory M. Amend, and Benjamin N. Breyer

Bladder cancer has been linked with well-known carcinogens. It is estimated that nearly 27% of global bladder cancer deaths are attributed to smoking.[1] High arsenic levels in drinking water, some medications, and Schistosoma haematobium infection are examples of other environmental risk factors.[2] Well-known occupational carcinogens include aromatic amines (eg, benzidine, α-Naphthylamine, ß-Naphthylamine, etc.).[3] The history of the discovery of these occupational carcinogens is paradoxically not well-acknowledged in contemporary urology literature. Here we chronicle the physicians and their discoveries which led to this pivotal public health breakthrough, particularly the animal experiments by a German pathologist, Dr. Wilhelm Hueper, which formed the basis of our current understanding of occupational carcinogens in bladder cancer.

It was in the mid 19th century when the commercial production of synthetic dyes began. In 1856, Sir William Henry Perkin (1838–1907) was an 18-year-old British chemistry student working on the production of synthetic quinine from coal tar for the treatment of malaria. During the Easter holidays, he performed an experiment in his laboratory at home which was unsuccessful and resulted in the accidental production of a dark mass. That substance was the product of a chemical reaction of aniline available in coal tar.[4]

Instead of throwing it away, he studied it and serendipitously—like many other great scientific discoveries—produced a mixture of compounds with an intense bright mauve color which he found could dye silk. Soon after, Perkin patented that substance, called it "mauveine," and established a factory in Essex, England to commercialize the first synthetic dye. Subsequently, aniline dye industries spread rapidly throughout the Europe most notably in Germany, Switzerland, and France.

It was not until the mid 1890s that a German surgeon reported the first cases of bladder cancer in dye workers. Ludwig Wilhelm Carl Rehn (1849–1930), born in Allendorf was the fifth child of a German physician. He received his medical degree from University of Marburg in 1874 and started as a general practitioner near Frankfurt, which was a major center of German chemical industries. Rehn was a pioneer surgeon who performed the first thyroidectomy and the first successful repair of a cardiac stab wound in an era when heart injuries were considered fatal.[5]

Rehn observed a disproportionately high number of bladder cancer cases among dye workers who presented with hematuria. In April 1895, during the 24th Congress of the German Association of Surgeons, he presented his findings entitled "Urinary Bladder Tumors Among Fuchsine Workers." Rehn had used the cystoscope invented by Maximilian Nitze to diagnose bladder cancer in three of the 45 workers. He hypothesized that inhalation of aniline fumes during fuchsine production resulted in noxious metabolites excreted into the urine by the kidneys, and that long-term stagnation of urine in the ureters, their origin in the base of the bladder, and the trigone ultimately led to formation of tumors.[6]

Dr. Grandhomme, the surgeon directly employed by the dye factory in Germany immediately disputed Rehn's discoveries. Those refuting Rehn's claims argued that although a large number of workers presented with urinary symptoms, few of them were eventually diagnosed with bladder cancers.[7] Nevertheless, additional cases of bladder cancer in patients working or living near dye industries continued to appear. Rehn identified 38 cases of bladder cancer by 1906. Though he was not eventually able to identify a precise chemical culprit nor demonstrate a causal effect between the dye and bladder cancer, his outstanding observations paved the road for future research in the field of occupational cancers.

After World War I, dye patents were seized from Germany and the industry spread to other countries including the United States (U.S.). Several large chemical manufacturers began producing synthetic dyes including E. I. du Pont de Nemours and Company in Deepwater, New Jersey. In the meantime, the body of evidence supporting the association of bladder cancer with dyestuffs continued to grow. In 1920, R. Oppenheimer from Germany suggested people living in the vicinity of dye plants may develop bladder cancer as well and recommended regular microscopic examination of urine for detection of red blood

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cells as a tool for early diagnosis of bladder cancer in those exposed to industrial carcinogens.[8] By that time, available evidences were all in the format of case reports/series, which was insufficient to establish a causal relationship. Additionally, the means of determining precise exposure of the patients and controlling for nonoccupational factors were limited at that time.[9] There were also conflicting results from experimental animal studies. Bierich (1922), Kennaway (1924), Berenblum and Bonser (1937) were unable to induce bladder cancer in rabbits and mice using multiple aromatic amines.[10,11] Simultaneously, Wilmington physicians nearby the DuPont factory diagnosed three dye workers with bladder cancer in early 1930s—nearly 15 years after manufacture of dyestuff had begun in that area. More cases quickly accumulated and a symposium —"Symposium on Aniline Tumors of the Bladder"—was held in 1933 to further scrutinize the emerging cases. Different aspects of "aniline tumors" were discussed in that symposium including the etiology, incidence, pathology, and treatment.[12] The medical director of DuPont, Dr. George H. Gehrmann, reported 25 positive cases in a group of 532 cystoscopically-examined workers.[13] They suspected α-Naphthylamine, ß-Naphthylamine, and benzidine as the causative agents given no cases were found in aniline workers.

It is reported that the bladder cancer outbreak was not a surprise to DuPont management because a German-trained pathologist working in Philadelphia had warned them around 1930 that dye workers in Germany with similar exposures had an increased incidence of bladder cancer.[9] That pathologist was Wilhelm Carl Heinrich Hueper (1894–1978) (Fig. 1). He was born in Schwerin, Mecklenburg, Germany. He earned his medical degree from Rostock University in 1920 and then emigrated to the U.S. in 1923 and started his career as a pathologist for Mercy Hospital in Chicago. At the same time, he was appointed as a faculty member at Loyola University. In 1930, he moved to Philadelphia to join the Cancer Research Laboratory at the University of Pennsylvania.

During an interview, Hueper remarked:

> *"In 1932, I had written to Mr. E. I. duPont [the president of DuPont company], whom I knew personally at that time, that from my observations after visiting the dye works, I had come to the conclusion that their workers would have the same cancer hazards to the bladder as similar workers in European plants, especially Germany, Switzerland, and England and that an investigation would show that these men have an increased incidence of bladder cancer. I didn't get any personal answers to this. My boss at the cancer research laboratories at the University of Pennsylvania told me several months later that they had come to the conclusion that they had no cancer among their workers. "Well," I said, "that may be, but they would get them." Then about four months later, suddenly Gehrmann and the research director of the [DuPont] research station came to us in Philadelphia and said, "We have some now." I said, "How many?" And he said, "We now have 26." I said, "You will have more. This is a going concern now". At that time, I had already figured out that it would take about fifteen years. I told them that men who are getting cancer now are those who your company employed in 1917 when they created the dye work operation."*[7,14]

Figure 1. Dr. Wilhelm Hueper (1894–1978). (Courtesy of the Office of NIH History and Stetten Museum).

After observing an increasing number of bladder cancer cases in the workers, DuPont management decided to scrutinize the etiology by performing animal experiments. In 1934, Dr. Hueper joined their newly established Haskell Laboratory of Industrial Toxicology. Unlike animal studies by his precedents, Hueper chose female mongrel dogs as test subjects because he hypothesized canines metabolize aromatic amines similarly to humans. He focused his work on ß-naphthylamine among several aromatic amines known at that time.

He assigned 16 dogs to the experimental group receiving ß-naphthylamine by subcutaneous injection and oral administration for two to three years, and another four dogs to the control group. The dogs were subsequently monitored with blood and urine tests as well as cystoscopic examination. Ultimately, 13 dogs in the experimental group developed bladder tumors.[15] As a result, Hueper and his team became the first to successfully induce bladder tumors by a carcinogen in an animal model.

As a DuPont scientist, Hueper requested to visit the DuPont dye plant. He was shocked to observe that dyestuffs were spread throughout the plant in a disorderly manner. He provided a report of the conditions to

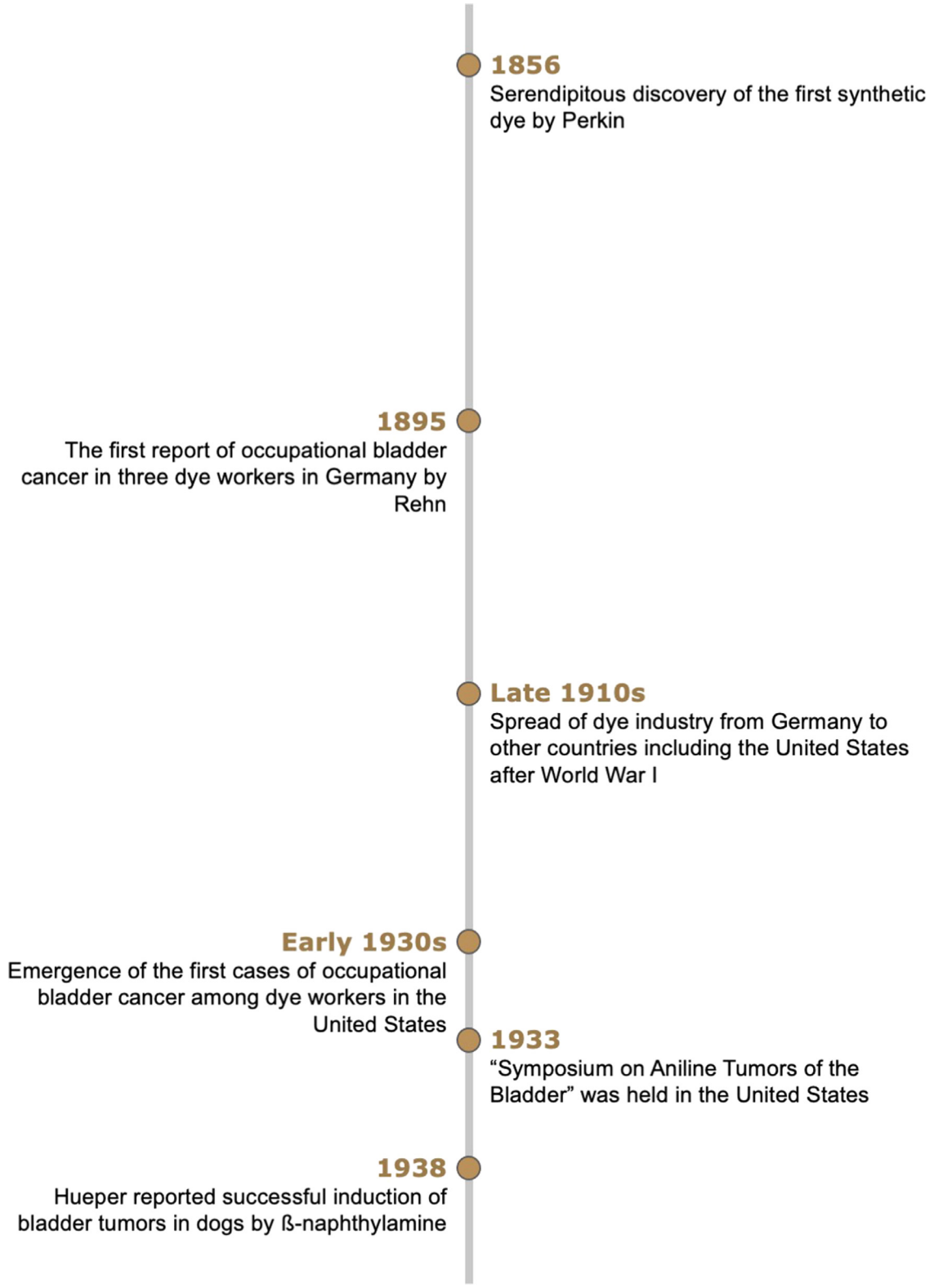

Figure 2. A timeline showing the key events in the discovery of occupational bladder cancers. Color version available online." at the end of the legend of all web color figures. (Color version available online.)

executives of the company who were unappreciative of his information, restricting his access to the plant for further inspection. Furthermore, DuPont obstructed his ability to disseminate and publish the significant results of his animal experiments with aromatic amines.[7] Hueper was eventually dismissed from DuPont in late 1937. Nevertheless, the full report of his work was published in 1938, as he concluded that ß-Naphthylamine is at least one of the

carcinogens leading to bladder cancer in dye workers.[15] He subsequently joined the Warner pharmaceutical laboratories in New York. During these next few years, he wrote his comprehensive book "Occupational Tumors and Allied Diseases," which documented the pathogenesis of different types of cancer as a result of industrial exposure.[16] In 1948, his notable contributions to the field of occupational cancers led to his appointment as chief of the U.S. National Cancer Institute's newly established Environmental Cancer Section where he remained in this position until his retirement in 1964. He received many awards in recognition of his research. Dr. Wilhelm Hueper, 84, died of cardiac arrest on December 28, 1978, at the Wisconsin Avenue Nursing Home.[17]

Many work-related cases of bladder cancer among U. S. dye workers developed after Rehn's initial report in 1895. Although DuPont initially facilitated research to recognize the outbreak amongst its workers, it was not until 1955 when they terminated the manufacturing and use of one of the noxious substances, ß-Naphthylamine. In 1976, DuPont declared that 339 of 2000 workers who were exposed to ß-Naphthylamine during the years 1919 to 1955 were eventually diagnosed with bladder cancer.[14] In 1975, the DuPont manager declared that they paid compensation for workers with bladder cancer. By that time, 130 of cases died.[18] In fact, this number is even underestimated as workers who left the company during those years were not followed. It shows that industry was slow to acknowledge the findings of scientific reports and implement them in practice. Today, it is well recognized that benzidine, α-naphthylamine, ß-Naphthylamine, 4-aminobiphenyl, ortho-toluidine, and chloroaniline are associated with bladder cancer.[3] Although aniline has been refuted as a causative agent, "aniline tumors" is sometimes used to describe bladder cancers secondary to aromatic amines. This exemplary discovery clearly accentuates the importance of epidemiologic and translational research in real life which leads to elimination of noxious substances. Continued efforts in the field of occupational medicine will lead to identification of more environmental carcinogens in future. Figure 2 highlights the key events mentioned in this article.

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