Bladder tumors and aromatic amines – Historical milestones from Ludwig Rehn to Wilhelm Hueper

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1. ABSTRACT

We know today that environmental factors must be regarded as a significant cause of the urinary bladder carcinoma. In Germany, the urinary bladder carcinoma is the second most common urological tumor among men and the most common among women and more than 100 occupational bladder cases are recognized and compensated per year. Scientific studies of this problem reach back to the 18th century. However it was only in 1895 that the surgeon Ludwig Rehn firstly described 3 cases of occupational bladder tumors in at most 45 fuchsine workers in Frankfurt / M. This extremely significant discovery was followed by a description of a large number of cases of urinary bladder tumors among workers in the paint industry. Nevertheless, it was impossible to induce bladder cancer in animals by aromatic amines for many years. In the 1930s, the pathologist Wilhelm C. Hueper was the first to induce bladder cancer in animal experiments, applying ß-naphthylamine to dogs. Based on these experiments and corroborated by epidemiologic studies, ß-naphthylamine was banned in Germany and many countries from the 1950s on. This review will highlight work and life of these two pioneering medical researchers.

2. INTRODUCTION

Work on the etiology of urinary bladder tumors and research on the causal interconnections between chemical carcinogen exposure and the increased occurrence of such carcinoma has a history that is over a hundred years old.

To this day, the etiology of around 80% of occurring urinary bladder tumors is still not understood in detail. So far, only 4-aminodiphenyle, ß-naphthylamine, benzidine and 4-chloro-o-toluidine have been officially recognized as industrial carcinogens worldwide. This fact alone highlights the importance of underlying research in occupational medicine in this field, both for oncology in general and specifically for its sub-section of urology.

At the turn of the 20th century, such a line of research already had a brief tradition. It would be far too extensive for this article to mention all the pioneering work in this field. In 1775, P. Pott (1713-1788) described an increased occurrence of scrotal carcinoma after lengthy exposure to ash (“chimney sweep’s cancer”). When the first synthetic dye (Mauvein) was developed, W.H. Perkin
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Figure 1. Ludwig Rehn (1849-1930).

(1838-1907) reported between 1856 and 1869 on the phenomenon of urinary bladder tumors among workers in the paint industry. In 1875, R. v. Volkman (1830-1889) described an increase in scrotal tumors among men who produced paraffin from brown coal. A large number of bronchial carcinoma were discovered among miners in the Ore Mountains (Schneeberg). The influence of radium was quickly revealed to be the cause.

However it was a German surgeon who created decisive momentum with his scientifically based statements on the etiology of urinary bladder tumors, resulting in broad-based research into the causes of occupational diseases in the following decades. To this day, the study of the etiology of urinary bladder tumors is in flux and remains a fixed element of every major regional or international urology congress.

In the overall context of this publication, two important protagonists in the field of occupational cancer research are especially commended in this short text.

3. MEDICAL RESEARCHERS WHO WERE DECISIVE PIONEERS IN STUDYING THE ETIOLOGY OF URINARY BLADDER TUMORS

3.1. The surgeon Ludwig Rehn

Ludwig Rehn was born in Allendorf an der Werra on April 13, 1849, the fourth child of a doctor (Figure 1). After finishing secondary school, he followed in his father’s footsteps and studied medicine in Marburg between 1869 and 1874. His teachers, who had a sustained effect on his later career, included above all N. Lieberkühn (1821-1887), W. Roser (1817-1888) and E.W. Mannkopf (born 1836). After passing his state examination, Rehn initially went to Frankfurt/Main to work as an assistant to G. Passavant (1815-1893) at the Bürgerhospital. In 1875, he became a doctor of medicine in Marburg after writing his thesis entitled ‘Entwicklung eines großen Collateral-Kreislaufes zwischen der obern und untern Hohlvene durch Struma sternalis’ (‘Development of a large collateral circulation between the upper and lower cavae through struma sternalis’).

The same year, he set up his own practice in Griesheim am Main. “The well-known major chemical factory with its numerous workers provided a good field to extend my medical knowledge with respect to tissue disease...” (6). Seven years later, he moved to Rödelheim, because “a small hospital was made available to me...” (6). During that period, Rehn also made a lengthy study trip to Göttingen, Berlin and Halle / S., which should not be overlooked. It brought him together with men who later played an outstanding role in medical history and included F. König (1832-1910), B. v. Langenbeck (1810-1887), R. Virchow (1821-1902), M. Schede (1844-1902) and Volkman. In 1884, Rehn took his first steps onto the broader public scientific stage: He described patients with Graves’ disease (syn.: Basedow’s disease) that could be healed by means of a subtotal struma-resection. From 1886 onwards, he worked as a surgeon at the Frankfurt/Main City Hospital, during which time he worked intensely on the surgical clinics gradual expansion. However he was only appointed director of that clinic twenty years later. In 1896, Rehn became the first person ever to carry out stitching on the human heart (1). The 22-year-old patient he successfully operated on had been injured by knife wounds in the ribcage area. In April 1897, Rehn presented the healed patient to the surgeons congress in Berlin and concluded with the words: “... I am truly hopeful that this case will not remain a curiosity and instead provide encouragement to continue to work in the field of heart surgery...” (15). The same year, he carried out operations to the thoracic section of the esophagus by accessing it from the rear mediastinum.

In 1914, without having to present a professorial publication – which remains standard practice in Germany even today – the Frankfurt surgeon was appointed professor of surgery at the newly founded Frankfurt University. The appointment was combined with the office of director at the Surgical University Clinic in Frankfurt/Main. He continued to work in that capacity until retiring in 1919. But even afterwards, Rehn remained an active scientist. For instance in 1920, he published the data on the first patient with calcified pericarditis to be successfully operated by him, whereby he carried out pericardial resection followed by fat fascia dermatoplasty to the defect (16). As an honorary Member of the German Association of Surgeons, he continued to play a very active role in the social and scientific development of his field.

Ludwig Rehn, who “had always adapted the latest advances in his field and fought at the forefront everywhere”, died in Frankfurt/Main after a lengthy illness on May 29, 1930 (19).

3.1.1. The milestone finding of Ludwig Rehn in fuchsine production workers

Rehn’s most important contribution specifically to urology and no doubt to medical history in general was his description and communication of the increasing occurrence of urinary bladder tumors among workers in the Frankfurt paint industry (17).

On April 20, 1895, the 4th day of the 24th Congress of the German Association of Surgeons in Berlin,
the surgeon Ludwig Rehn made a speech entitled “Blasengeschwülste bei Fuchsin-Arbeitern” (“Urinary bladder tumors among fuchsine workers”, Figure 2). During the lecture, he reported on the increasing occurrence of urinary bladder tumors among aniline workers at the Hoechst paint works. As a result of his discoveries, he was able to dismiss the possibility of a coincidental increase in the disease. In his diagnoses, Rehn was an early user of the cystoscope introduced by M. Nitze (1848-1906). Using it, he found urinary bladder carcinoma in 3 out of 45 workers (two papillomas and one sarcoma). All the examined workers had initially attracted attention because they had gross hematuria.

At the start of his speech on April 20, 1895, he explained very illustratively the situation of the then gradually emerging field of urology at the end of the 19th century. Rehn stated: “Gentlemen! Our experience of benign and malignant tumors of the urinary bladder has been considerably enhanced in recent years by a number of excellent studies. In addition to the increased safety of surgical operations, we also have the cystoscope to thank for this improvement, since it has had no less than a ground-breaking effect on diagnosis. We may admit that its application causes difficulties here and there, that occasionally diagnostic errors are made, yet this in no way reduces our regard for the invention by Nitze.

Unfortunately, we cannot deny the fact that the instrument is used far too rarely, to the great detriment of our patients. I could name numerous cases where patients with bladder bleeding were deferred for months and finally the first cystoscopic inspection revealed the presence of a tumor. The diagnosis represents very special advances in operative technique. Naturally, there is still work to be done. Currently, most operations fail due to delayed diagnosis…” (14).

The first total cystectomy due to a tumor was carried out by B. Bardenheuer (1839-1913) in Cologne on January 13, 1887. However his patient died on the 14th post-operative day with the clinical symptoms of uraemia. The first successful radical cystectomy was carried out by K. Pawlik (1849-1913/1914) in two stages on August 3 and 27, 1889 at the University Womens Clinic in Prague.

However on April 20, 1895, Rehn’s main focus lay on the etiology of urinary bladder tumors (14). In an obituary, V. Schmieden (1874-1945) stated: “His method of research was very characteristic. With his clear vision, he deliberately overlooked the greater connections and always focused on the most important aspect.” (19).

In his lecture, Rehn extensively described each individual case including the therapy provided and the
historical results. All patients showed symptoms such as cyanosis, dizziness, lethargy and chest pain, as well as the presence of hematuria, dysuria and stranguria. On especially hot days and the accompanying immanence of nitrobenzene and aniline, stranguria was so strong that urine involuntarily flowed into the men’s clothing (14).

By the end of the 19th century, Rehn came to the following conclusions on the basis of his observations: “1. The gases that develop during fuchsine production lead to disruptions in the urinary tract. 2. Long-term work in a fuchsine factory can lead to urinary bladder tumors as a result of permanent inflammation. 3. The damaging effect is mainly due to the inhalation of aniline vapors…” (14).

It is undoubtedly a great achievement for the Frankfurt doctor to be the first to detect the danger facing workers in the paint industry with respect to the occurrence of urinary bladder tumors. He classified these tumors as so-called occupational tumors, thereby initiating modern occupational cancer research in urology with respect to occupational medicine.

In summarizing his research and the insight gained from it, he continued: “It is however without doubt very apparent and not merely due to local conditions that the large majority of all tumors around the ureters, have their origin in the base of the urinary bladder and is seated in the trigone. The findings apparently indicate that the development of such tumors are somehow connected with the urine that flows out of or stagnates in the ureters. For the majority of urinary bladder tumors, it is only possible to imagine that substances are dissolved in the urine ejected by the kidneys, which cause a tumor due to chemical inflammation…” (14). During his lecture in Berlin, Rehn urged collective research to investigate these questions further. As a result, he was invited to join a commission on the research and prevention of aniline cancer that was also requested by the paint works during the 1904 congress. Although Rehn recorded and reported on an increasing number of urinary bladder carcinoma among workers in paint works (94 cases in 1923), he dejectedly wrote about the commission’s work in his autobiography as follows: “The project stalled. I referred to the great significance of the question of aniline, also with respect to the etiology of the cancer. It was in vain…” (6). The statement highlights how the medico-political significance of Rehn’s discoveries was obviously underestimated at the time. Several decades passed before “aniline cancer” was legally recognized in Germany as an occupationally induced cancer disease (17). The disease was only included on the ‘3. Verordnung über Ausdehnung der Unfallversicherung auf Berufskrankheiten’ (“3rd Law on the Extension of Accident Insurance to Cover Occupational Sickness”) on December 16, 1936 (Figure 3). The 1936 law already contained 26 different occupational diseases.
Although Rehn’s conclusion that aniline and fuchsine are the cause of urinary bladder tumors occurrences is now out of date (intermediate substances in the fuchsine production process are carcinogenic to the urinary bladder) and we know today that some toxic symptoms he described are caused by methemoglobin (induced by exposure to aromatic amines, e.g. aniline) that in no way detracts from his pioneering achievement in this field. It includes the first description of a chemical substance that was shown to have a specifically organotropic carcinogenic effect in the urinary bladder after dermal and/or inhalative application (17). In this way he was the first to discover a cancer disease in an organ within the urogenital tract that is caused by external chemical noxae.

Rehn’s work on bladder tumors among aniline workers made a major contribution towards establishing the discipline of urology as a specialist field within clinical medicine. At the same time, Rehn gave cancer research in general and specifically the research of etiological factors decisive momentum that led to scientifically exact work on the problem in the following years.

Another German doctor, who interestingly was lucky enough to experience Rehn’s work at first hand, drove this line of research further forward in the first half of the 20th century and managed significant achievements. Thus his biography and bibliography is discussed in detail here.

3.2. The pathologist Wilhelm Carl Heinrich Hueper

Wilhelm Carl Heinrich Hueper was born in Schwerin/Mecklenburg on November 4, 1894 (Figure 4). After attending primary and secondary school in his hometown, he passed his school-leaving examination in 1913. He then began to study medicine in Marburg, before continuing his studies at the University of Rostock. Between 1914 and 1918, he fought as a volunteer in the First World War. After returning home from French captivity, he continued his medical studies and passed his state examination in Kiel in 1920. He was subsequently a post-graduate assistant at the University Womens Clinic in Kiel.

At the time, the clinic director was W. Stoeckel (1871-1961). Even then, in addition to his lasting achievements in the field of gynecology and obstetrics, Stoeckel was regarded as a humanist man of action. His nature undoubtedly had a lasting influence on Hueper. With the inaugural dissertation ‘Die geburtshilflichen Zerstueckelungsoperationen in der Kieler Universitätsfrauenklinik in den Jahren 1910-1919’ (‘Mutilating obstetric operations at Kiel University Womens Clinic between 1910 and 1919‘), he became doctor of medicine in 1920. From late 1920 to 1921, Hueper worked as assistant doctor at the surgical clinic of the Diocese Hospital in Witten/Ruhr. His main interest however already lay more in pathological anatomy and the scientific opportunities it presented. In 1921, he moved to Berlin to work as an assistant to C. Hart (who died in 1923) at the pathological institute of the Auguste Viktoria Hospital. After his superior’s death, he left the pathological institute and worked for a number of months in the department of medicine of the large Berlin hospital. In the autumn of 1923, Hueper left Germany and went to the United States of America. He initially worked as a general practitioner in the German Evangelical Deaconess Hospital in Chicago. In the spring of 1924, he found a job in the pathological institute of the Mercy Hospital in Chicago, where he worked as a pathologist until 1930. At the same time, he also taught histopathology and macroscopic pathology at Loyola University in his new hometown. In 1926, he became assistant professor and two years later, he was made associate professor for pathology. By then, Hueper was already working intensely on the occurrence of bronchial and cervical carcinoma. His research results found their way into numerous publications and proved to be precursors, as early as the 1920s, of his life-long work in the field of tumor research. In the spring of 1930, Hueper was invited to work at the University of Pennsylvania, which he gratefully accepted. In addition to his office as the head pathologist of the Cancer Research Laboratories, the position also included work as pathologist for the American Oncologic Hospital in Philadelphia.

3.2.1. The application of Hueper for a leading position in Germany in 1933

It is still unknown what motivated Hueper to apply for a leading position in a pathological institute or any new chair vacancies in Germany in September of 1933, since it was apparently without necessity (Figure 5). After all, this was the year the National Socialists came to power and the beginning of the darkest chapter in German history. Certain Social Darwinist thoughts by Hueper cannot however be overlooked when he writes: “…have decided to return to Germany in order, for the sake of myself and my family, and especially my descendants, to avoid the otherwise inescapable fate of being lost as an element of German national and cultural heritage…” (5). His
statements made in 1936 on the medical dangers of mixing races are also more than merely unfortunate and indicate the intended discrimination of individual races and ethnic minorities (7).

But it should also be noted that the National Socialists initiated a cancer prevention program that was clearly respected in Western Europe and overseas. At the time, German cancer research was extremely advanced and played a leading international role. Of course everything was subordinate to the murderous political doctrine of the National Socialists. But it is worth taking a more discriminate look at this chapter of medical history. The scientific situation may have been the reason for Hueper’s desire to return to Germany and collaborate there on modern cancer research. In this respect, Hueper’s career was no doubt problematic and today, like many other cases, we can longer distinguish between opportunism and conviction. The National Socialist minister of culture, B. Rust (1883-1945), ordered the director of the pathological
The pathologist Rössle strictly rejected the 39-year-old Hueper’s application, referring to the different perspectives on the field of pathology in the USA and Germany, and the resulting incompatibility of their scientific research. At the same time, Rössle referred to the large number of German pathologists who should be considered for positions such as prosector or Chair (Figure 6). In November 1933, he wrote to the minister of culture: “Since pathology is not managed in most American universities and hospitals as it is here... it is rather difficult to say whether Dr. Hueper... is suitable. He seems especially unsuitable for a position in view of the fact that he cannot be regarded as a well-established name in our field, and it also seems to me to be unjust if for his sake one of the many deserving assistant professors... are overlooked...” (5).

Overall, Rössle’s opinion is very harsh regardless of the significant national and international achievements during his career. If one assesses Hueper’s overall scientific work, Rössles verdict is certainly unjustified. Up to 1933, Hueper wrote 54 original papers in significant journals of the time. Until then, his work focused on carcinoma in the area of the lung, the uterus, the skin and the scrotum. But the influence of tuberculosis on the occurrence of cancer, as well as the malignant disease of the blood system, were also studied by Hueper. This is an example of the extent to which someone’s own academic career depends on the weal and woe of third parties.

3.2.2. Hueper’s research field of environmental and occupational cancer

From the mid-1930s onwards, Hueper increasingly addressed the question of occupational cancer research. “He was one of the first to study radiation-induced leukemia (1934) and the first to document lung cancer among workers in the chromium industry” (12).

From 1934, he was able to work for DuPont in the newly founded Haskell Laboratory of Industrial Toxicology and was regularly confronted with the problem of the increased occurrence of urinary bladder tumors (11).

However, due to numerous conflicts, he was dismissed from DuPont in late 1937 / early 1938. During the following period, he wrote his extensive, seminal work ‘Occupational tumors and allied diseases’ (9).

From 1948 to his retirement in 1964, he headed the U.S. National Cancer Institutes Environmental Cancer Section (18).
Historical milestones from L. Rehn to W. Hueper

Figure 7. Title page of Hueper’s lecture: Experimental production of bladder tumors in dogs by administration of beta-naphthylamine, 1938.

It should incidentally be noted that during this period, the German research community also supported work on the effect of carcinogenic substances on the human organism. Pioneering work by H. Druckrey (1904-1994) and K. Küpfmüller (1897-1977) published in 1948 and 1949 should be seen in this light. The studies focused on the detailed relationship between the dose and effect with respect to exposure to carcinogenic substances. At the same time, they created the underlying basis of cancer research in the following decades by defining cumulative poisons and the histologic changes in the bladder described by the first mentioned authors were not sufficiently definite in type and character to be generally accepted as benign and malignant neoplastic lesions (Stewart (6), Borenblum and Booser (11)).

The investigations to be reported were undertaken for two reasons: first, to provide, through the experimental production of “alline tumors” in animals, a sound foundation for a future intelligent approach to the study of the various aspects of these occupational neoplasms; second, to obtain by periodic examinations of the blood of the animals used in these experiments, some information in regard to any possible systemic effect of prolonged exposure to one of the suspected carcinogenic aromatic amines (beta-naphthylamine) upon certain constituents of the blood which may have some relation to the development of the tumors in the bladder and which may thereby be of diagnostic significance as premonitory symptoms.

A. Experimental Procedure

Medium sized to large female mongrel dogs weighing from 8 to 20 kg., were selected for the experimental work as the most suitable animals for the following reasons:

1. Dogs eat the same kind of foodstuffs as man, and are, therefore, subjected to similar nutritive influences upon their metabolism.

2. Like man, dogs do not infrequently develop spontaneous tumors of various organs (Sticker (5), Huitler and Wernerich (7)).

3. However rare the spontaneous occurrence of bladder tumors in dogs (Jeeot (8), Hueper (9), H. Muller (10), Sticker (6), Buckingham (11)), shows

3.2.3. The experimental findings on beta-naphthylamine and bladder cancer

From a urological-historical perspective, Hueper’s publications ‘Experimental production of bladder tumors in dogs by administration of beta-naphthylamine’ (Figure 7) and ‘Occupational and Environmental Cancers of the Urinary System’ (Figure 8), and the resulting knowledge with respect to industrial noxae as the cause of urinary bladder tumour occurrence is especially significant (8, 10).

For its animal experiments between 1935 and 1937, Hueper’s team used 20 female mongrel dogs with a weight that varied between 8 kg and 20 kg. The dogs were divided into two groups (16 for the series of experiments and 4 as a control group). Beta-naphthylamine was deliberately chosen from among the three aromatic amines known at the time (aniline, benzidine and beta-naphthylamine), since it had already been shown to cause fibroepithelial lesions in the bladder wall of rabbits among others.

Beta-naphthylamine was injected into the dogs every day in a watery solution (the dose depended on their weight and was doubled according to time slots). Later, parenteral administration was supplemented by oral application (commercially produced amine). The dogs were treated with beta-naphthylamine for a total of almost two years.
The bitches’ general state of health was monitored, including urine analysis (e.g. erythrocytes; pH-value), blood testing and cystoscopic examination (every three months in the first 20 months; every 4-6 weeks after discovering lesions). The article by Hueper et al. described in detail all findings among the laboratory animals, as well as the control group, including histopathological changes. Numerous histologies were also presented in illustrations. The team ultimately found that 13 of the 16 laboratory animals that were subcutaneously or orally treated with β-naphthylamine for 20-26 months developed tumorous changes in the bladder.

As early as 1937/38, his working group postulated from the results of animal experiments that “1. β-naphthylamine can trigger the growth of urinary bladder tumors; 2. The predominant localization of the tumors in the dependent parts of the bladder, as well as the histologic findings, support strongly the urogenous origin of ‘aniline’ tumors and 3. Prolonged administration of relatively large doses of β-naphthylamine produces blood destruction, degenerative changes in the tubular epithelium of the kidneys and in the parenchyma of the liver…” (8).

3.2.4. The legacy of Hueper’s life work

In the foreword to his monograph, which was published in 1969, he practically formulates a résumé of his life’s work: “The existing situation and its developmental trends should stimulate public health agencies, the medical profession, food and drug administrations, industrial safety departments, the affected labor organizations, and legislatures to make use of the already available information on the etiology of cancers of the urinary system in order to establish a broad and well-enforced program of prophylaxis and prevention of hazards. It should include specific worker groups as well as the general population. In addition to serving as a guide for the study of these cancer hazards and for the development of effective preventive control measures, this treatise is offered to the special attention of industrial managements in the hope of enlisting their social and moral support in obviating the human misery and economic distress resulting from ill-controlled and indiscriminate commercial distribution of many of these carcinogens to the population at large…” (10).

Hueper also addressed R. Carson (1907-1964), stating, “…we must pay far greater attention to monitoring the many different carcinogens in the environment. If… preventive measures are not taken, we will increasingly create conditions that will in future cause great harm to the human population…” (2).

Hueper’s work in the second third of the 20th century has undoubtedly contributed to driving forward advanced, socially responsible health reforms. He pushed hard in his commitment to making health authorities aware of the dangers of unventilated uranium mines. Like no other, he worked on researching carcinogenic substances in food (as well as tobacco), the air and water, thereby influencing American and international environmental policy. He is rightly described as the father of American research on cancer risks at work (13). Hueper received numerous honors and awards for his achievements in researching occupational cancer risks and the dangers caused by environmental pollution (12, 20).

Wilhelm C. Hueper died on December 28, 1978 in Bethesda, Maryland following a heart attack.

4. SUMMARY

By now, the urinary bladder carcinoma is one of the worlds most expensive tumor entities and, depending on the population density of a country, leads to costs of up to several billion euros. Underlying scientific research and clinical applied research however seems to be extremely under-represented by comparison.

By excluding exogenous noxae at an early stage, between 25% and 50% of deaths caused by urinary bladder carcinomas could be prevented. Currently existent research funding could clearly be optimized in this respect.

Rehn’s hypothesis that substances dissolved in the urine released by the kidneys cause tumor growth in the region of the deferent urinary tract due to a chemical stimulus has lost none of its validity today.

The expression he invented for this, “aniline carcinoma”, is still used as a synonym for urinary bladder carcinomas caused by aromatic amines.

Mainly based on Hueper’s experimental proof that β-naphthylamine can cause urinary bladder carcinomas, the industrial production and accompanying
handling of ß-naphthylamine has been banned in many countries, e.g. in Germany in 1950s.

The lives and work of Ludwig Rehn and Wilhelm C. Hueper are exemplary for research on harmful chemicals which may release carcinogenic aromatic amines. It has by now been proven that occupational exposure or misuse clearly increases the risk of contracting bladder or lung cancer. Although so-called occupational cancers have become rare due to excellent prevention in strategic combination with identification and elimination, this carcinogenic potential should be proven through constantly renewed scientific experimental methods. Today, that task should be carried out in the field of occupational medicine, whereby urology can provide potent clinical support, as the following articles impressively show.

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