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

Holger Georg Dietrich[1], Klaus Golka[2]

[1]Department of Urology, Hospital Paul Gerhardt Stift, Lutherstadt Wittenberg, [2]Leibniz Research Centre for Working Environment and Human Factors, Dortmund

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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*

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. Volkmann* (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 *Volkmann*. 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 thoracal 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,

XXX.

Blasengeschwülste bei Fuchsin-Arbeitern.

Von

Dr. L. Rehn,

dirig. Arzt zu Frankfurt a. M.[1]).

M. H.! Unsere Erfahrung über die gutartigen und bösartigen Geschwülste der Harnblase ist in den letzten Jahren durch eine Reihe vortrefflicher Arbeiten ausserordentlich gefördert worden. Nächst der erhöhten Sicherheit des chirurgischen Eingriffs verdanken wir diesen Aufschwung dem Cystoscop, welches in diagnostischer Beziehung geradezu bahnbrechend gewirkt hat. Wenn wir auch zugeben, dass sich seiner Anwendung hier und da Schwierigkeiten in den Weg stellen, dass ab und zu diagnostische Irrthümer vorkommen, so kann dies die hohe Anerkennung der Nitze'schen Erfindung keineswegs beeinträchtigen. Leider können wir uns der Thatsache nicht verschliessen, dass zum grossen Schaden unserer Patienten noch viel zu wenig Gebrauch von dem Instrument gemacht wird. Ich könnte verschiedene Fälle anführen, welche monatelang mit Blasenblutungen hingehalten wurden und endlich ergab die erste cystoscopische Untersuchung, dass es sich um einen Tumor handelte.

Mit der Diagnose hat die Operations-Technik ganz besondere Fortschritte aufzuweisen. Freilich sind hier noch manche Aufgaben zu lösen. Unter uns wird wohl kein Zweifel mehr bestehen, dass man Blasentumoren nur durch Sectio alta und bei Beckenhochlagerung entfernen soll. Die Abmeisselung der Symphyse dürfte doch wohl nur ausnahmsweise am Platze sein. Desgl.

[1]) Vorgetragen am 4. Sitzungstage des XXIV. Congresses der Deutschen Gesellschaft für Chirurgie zu Berlin, 20. April 1895.

Figure 2. Title page of Rehn´s lecture on bladder tumors among fuchsine workers 1895.

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

Reichsgesetzblatt 1117

Teil I

1936 | Ausgegeben zu Berlin, den 23. Dezember 1936 | Nr. 122

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Dritte Verordnung über Ausdehnung der Unfallversicherung auf Berufskrankheiten.

Vom 16. Dezember 1936*).

Auf Grund der §§ 547, 922, 1057a der Reichsversicherungsordnung in der Fassung des Dritten Gesetzes über Änderungen in der Unfallversicherung vom 20. Dezember 1928 (Reichsgesetzbl. I S. 405) wird verordnet:

§ 1

Berufskrankheiten im Sinne der Unfallversicherung sind die Krankheiten in Spalte II der Anlage, wenn sie durch berufliche Beschäftigung in einem in Spalte III der Anlage neben der Krankheit bezeichneten Betriebe verursacht sind.

§ 2

Was die Verordnung für Betriebe vorschreibt, gilt entsprechend für Tätigkeiten und Einrichtungen, die unter die Unfallversicherung fallen.

§ 3

(1) Bei Anwendung der Vorschriften über die Unfallversicherung auf Berufskrankheiten steht der Körperverletzung durch Unfall die Erkrankung an einer Berufskrankheit und der Tötung durch Unfall der Tod infolge einer Berufskrankheit gleich.

(2) Als Zeitpunkt des Unfalls gilt der Beginn der Krankheit im Sinne der Krankenversicherung oder, wenn dies für den Versicherten günstiger ist, der Beginn der Erwerbsunfähigkeit im Sinne der Unfallversicherung. Beginnt die Krankheit oder die Erwerbsunfähigkeit während der Beschäftigung des Versicherten in dem der Versicherung unterliegenden Betriebe, so gilt für die Anwendung der §§ 1546, 1547 der Reichsversicherungsordnung das Ende der Beschäftigung als Zeitpunkt des Unfalls.

*) Veröffentlicht im Deutschen Reichsanzeiger und Preußischen Staatsanzeiger Nr. 296 vom 19. Dezember 1936.

(a) Bei Staublungenerkrankungen (Nr. 17 der Anlage) gilt für die Berechnung des Jahresarbeitsverdienstes sowie für die Minderung der Renten (Notverordnung vom 14. Juni 1932, Erster Teil Kapitel II, Artikel 4 § 1 — Reichsgesetzbl. I S. 273, 275 — und Verordnung zur Ergänzung von sozialen Leistungen vom 19. Oktober 1932 Artikel 3 — Reichsgesetzbl. I S. 499, 500) als Zeitpunkt des Unfalls der letzte Tag, an dem der Versicherte in einem der in Spalte III der Anlage aufgeführten Betriebe Arbeiten verrichtet hat, die ihrer Art nach geeignet sind, die Berufskrankheit zu verursachen. Läßt sich der Jahresarbeitsverdienst des Versicherten nicht feststellen, so ist der Berechnung der Verdienst zugrunde zu legen, den ein Versicherter der gleichen Art im Betrieb oder in einem möglichst benachbarten Betrieb gleicher oder ähnlicher Art in dem Jahre vor dem bezeichneten Zeitpunkt bezogen hat. Der durchschnittliche Verdienst dieses Versicherten für den vollen Arbeitstag ist mit der in diesem Jahre betriebsüblich gewesenen Zahl von Arbeitstagen zu vervielfältigen. Die §§ 567 bis 569a, 570 bis 572 der Reichsversicherungsordnung sowie die Vorschriften über die Umrechnung von Renten nach dem Zweiten Gesetz über Änderungen in der Unfallversicherung vom 14. Juli 1925 (Reichsgesetzbl. I S. 97) sind entsprechend anwendbar. Die Vollrente (§ 559a der Reichsversicherungsordnung) beträgt zwei Drittel des hiernach ermittelten Jahresarbeitsverdienstes.

(4) Das Reichsversicherungsamt kann bestimmen, daß die Vorschriften des Absatzes 3 auch auf andere Berufskrankheiten Anwendung finden.

§ 4

Bei Tropenkrankheiten, Fleckfieber und Storbut (Nr. 25 der Anlage) wird den in Betrieben der Seeschiffahrt Versicherten Entschädigung auch dann gewährt, wenn sie sich die Krankheit zugezogen haben, während sie in eigener Sache an Land beurlaubt waren. Das gilt nicht, wenn die Versicherten die Krankheit selbst verschuldet haben.

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Anlage

Lfde. Nr.	Berufskrankheit	Betriebe und Tätigkeiten
I	II	III
1	Erkrankungen durch Blei oder seine Verbindungen	Betriebe, Tätigkeiten und Einrichtungen, die der Unfallversicherung unterliegen
2	Erkrankungen durch Phosphor oder seine Verbindungen	
3	Erkrankungen durch Quecksilber oder seine Verbindungen	
4	Erkrankungen durch Arsen oder seine Verbindungen	
5	Erkrankungen durch Mangan oder seine Verbindungen	
6	Erkrankungen durch Benzol oder seine Homologen	
7	Erkrankungen durch Nitro- und Amidoverbindungen des Benzols oder seiner Homologen und deren Abkömmlinge	
8	Erkrankungen durch Halogen-Kohlenwasserstoffe der Fettreihe	
9	Erkrankungen durch Schwefelkohlenstoff	
10	Erkrankungen durch Schwefelwasserstoff	
11	Erkrankungen durch Kohlenoxyd	
12	Erkrankungen durch Röntgenstrahlen und radioaktive Stoffe	
13	Erkrankungen an Hautkrebs oder zur Krebsbildung neigenden Hautveränderungen durch Ruß, Paraffin, Teer, Anthrazen, Pech und ähnliche Stoffe	
14	Erkrankungen an Krebs oder anderen Neubildungen sowie Schleimhautveränderungen der Harnwege durch aromatische Amine	
15	Schwere oder wiederholt rückfällige berufliche Hauterkrankungen, die zum Wechsel des Berufs oder zur Aufgabe jeder Erwerbsarbeit zwingen	
16	Erkrankungen der Muskeln, Knochen und Gelenke durch Arbeit mit Preßluftwerkzeugen	
17	a) schwere Staublungenerkrankungen (Silikose) b) Staublungenerkrankung (Silikose) in Verbindung mit Lungentuberkulose, wenn die Gesamterkrankung schwer ist und die Staublungenveränderungen einen aktiv-fortschreitenden Verlauf der Tuberkulose wesentlich verursacht haben	
18	Schwere Asbeststaublungenerkrankung (Asbestose)	

Mit Ausnahme von Hauterkrankungen. Diese gelten als Berufskrankheit nur insoweit, als sie Erscheinungen einer durch Aufnahme der schädigenden Stoffe in den Körper bedingten Allgemeinerkrankung sind oder gemäß Nr. 15 entschädigt werden müssen.

Figure 3. Reichsgesetzblatt Nr. 122 Teil I, December 23, 1936. Item 14 states that occupational disease is defined as diseases such as cancer or similar new growth, as well as changes to the mucous membrane in the urinary passage due to aromatic amines.

histological 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.

Figure 4. Wilhelm C. Hueper (1894-1978).

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*

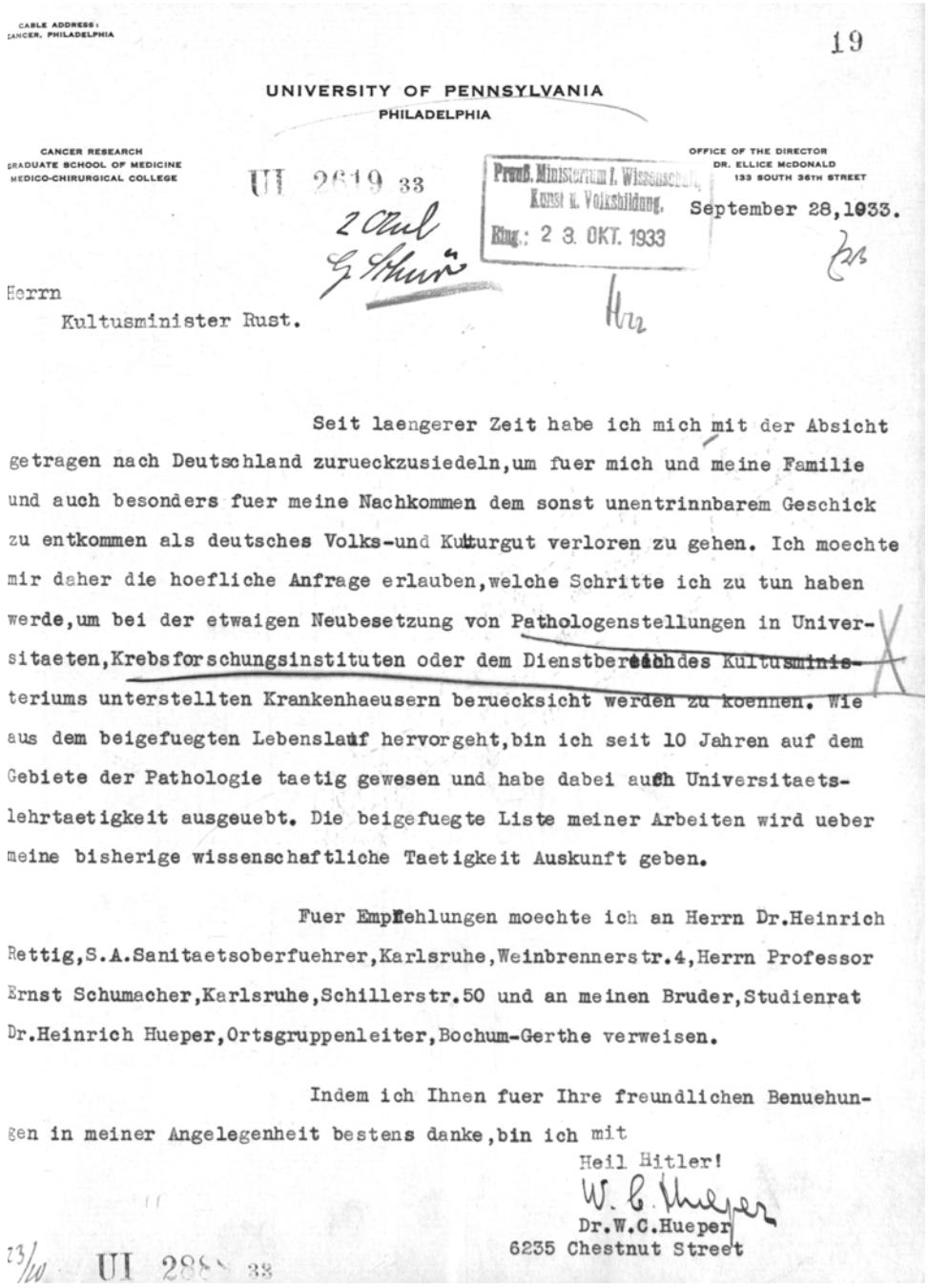
work at first hand, drove this line of research further forward in the first half of the 20th century and managed significant achievements. Thus his biography and bibliography is discussed in detail here.

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



CABLE ADDRESS: CANCER, PHILADELPHIA

19

UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA

CANCER RESEARCH
GRADUATE SCHOOL OF MEDICINE
MEDICO-CHIRURGICAL COLLEGE

OFFICE OF THE DIRECTOR
DR. ELLICE McDONALD
133 SOUTH 36TH STREET

UI 2619 33

Preuß. Ministerium f. Wissenschaft, Kunst u. Volksbildung. Eing.: 2 3. OKT. 1933

September 28, 1933.

Herrn
Kultusminister Rust.

Seit laengerer Zeit habe ich mich mit der Absicht getragen nach Deutschland zurueckzusiedeln, um fuer mich und meine Familie und auch besonders fuer meine Nachkommen dem sonst unentrinnbarem Geschick zu entkommen als deutsches Volks-und Kulturgut verloren zu gehen. Ich moechte mir daher die hoefliche Anfrage erlauben, welche Schritte ich zu tun haben werde, um bei der etwaigen Neubesetzung von Pathologenstellungen in Universitaeten, Krebsforschungsinstituten oder dem Dienstbereiche des Kultusministeriums unterstellten Krankenhaeusern beruecksicht werden zu koennen. Wie aus dem beigefuegten Lebenslauf hervorgeht, bin ich seit 10 Jahren auf dem Gebiete der Pathologie taetig gewesen und habe dabei auch Universitaetslehrtaetigkeit ausgeuebt. Die beigefuegte Liste meiner Arbeiten wird ueber meine bisherige wissenschaftliche Taetigkeit Auskunft geben.

Fuer Empfehlungen moechte ich an Herrn Dr.Heinrich Rettig, S.A.Sanitaetsoberfuehrer, Karlsruhe, Weinbrennerstr.4, Herrn Professor Ernst Schumacher, Karlsruhe, Schillerstr.50 und an meinen Bruder, Studienrat Dr.Heinrich Hueper, Ortsgruppenleiter, Bochum-Gerthe verweisen.

Indem ich Ihnen fuer Ihre freundlichen Benuehungen in meiner Angelegenheit bestens danke, bin ich mit

Heil Hitler!

W. C. Hueper

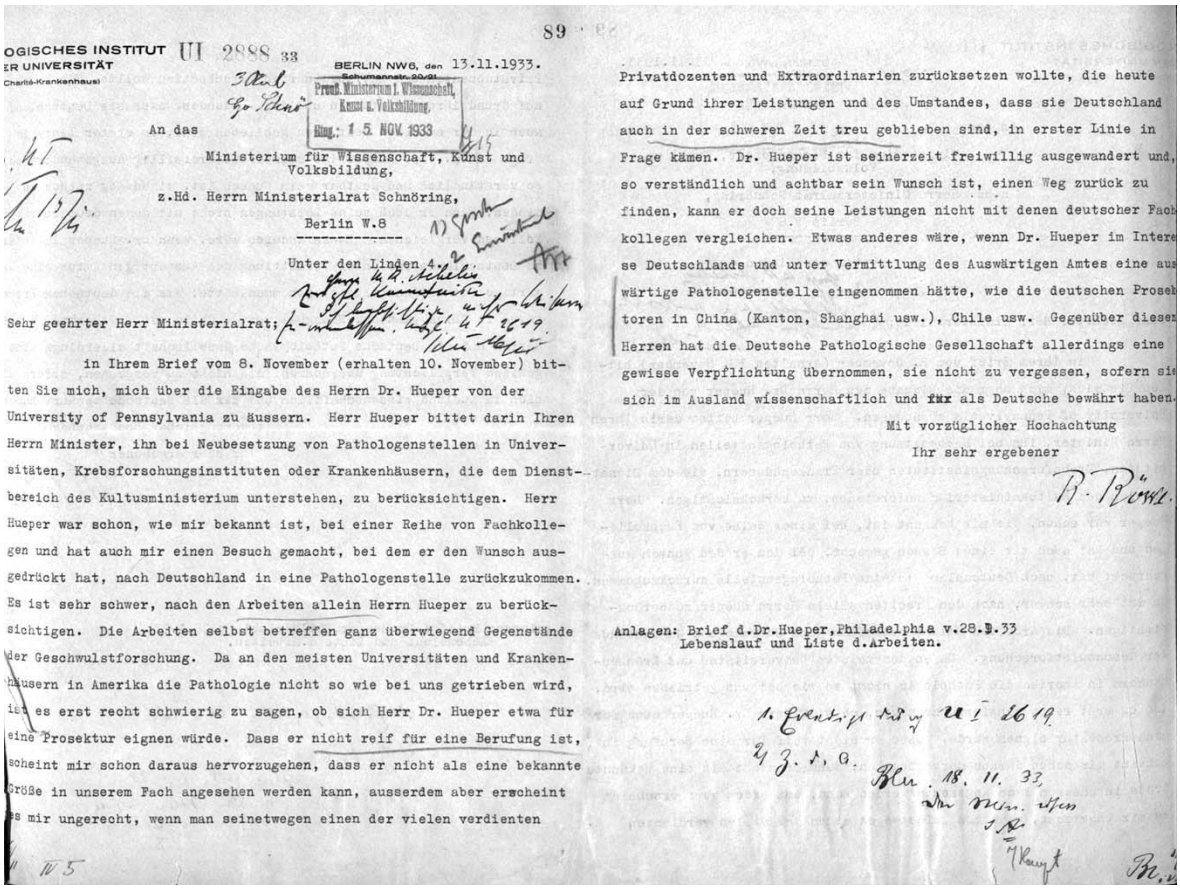
Dr.W.C.Hueper
6235 Chestnut Street

23/10 UI 2885 33

Figure 5. Application by W.C. Hueper to the NS minister of culture B. Rust, dated September 28, 1933.

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



OGISCHES INSTITUT UI 2888 33
ER UNIVERSITÄT
Charité-Krankenhaus)

89

BERLIN NW6, den 13.11.1933.
Schumannstr. 20/21

Preuß. Ministerium f. Wissenschaft, Kunst u. Volksbildung.
Eing.: 15. NOV. 1933

An das
Ministerium für Wissenschaft, Kunst und Volksbildung,
z.Hd. Herrn Ministerialrat Schnöring,
Berlin W.8
Unter den Linden 4

Sehr geehrter Herr Ministerialrat;

in Ihrem Brief vom 8. November (erhalten 10. November) bitten Sie mich, mich über die Eingabe des Herrn Dr. Hueper von der University of Pennsylvania zu äussern. Herr Hueper bittet darin Ihren Herrn Minister, ihn bei Neubesetzung von Pathologenstellen in Universitäten, Krebsforschungsinstituten oder Krankenhäusern, die dem Dienstbereich des Kultusministerium unterstehen, zu berücksichtigen. Herr Hueper war schon, wie mir bekannt ist, bei einer Reihe von Fachkollegen und hat auch mir einen Besuch gemacht, bei dem er den Wunsch ausgedrückt hat, nach Deutschland in eine Pathologenstelle zurückzukommen. Es ist sehr schwer, nach den Arbeiten allein Herrn Hueper zu berücksichtigen. Die Arbeiten selbst betreffen ganz überwiegend Gegenstände der Geschwulstforschung. Da an den meisten Universitäten und Krankenhäusern in Amerika die Pathologie nicht so wie bei uns getrieben wird, ist es erst recht schwierig zu sagen, ob sich Herr Dr. Hueper etwa für eine Prosektur eignen würde. Dass er nicht reif für eine Berufung ist, scheint mir schon daraus hervorzugehen, dass er nicht als eine bekannte Größe in unserem Fach angesehen werden kann, ausserdem aber erscheint es mir ungerecht, wenn man seinetwegen einen der vielen verdienten Privatdozenten und Extraordinarien zurücksetzen wollte, die heute auf Grund ihrer Leistungen und des Umstandes, dass sie Deutschland auch in der schweren Zeit treu geblieben sind, in erster Linie in Frage kämen. Dr. Hueper ist seinerzeit freiwillig ausgewandert und, so verständlich und achtbar sein Wunsch ist, einen Weg zurück zu finden, kann er doch seine Leistungen nicht mit denen deutscher Fachkollegen vergleichen. Etwas anderes wäre, wenn Dr. Hueper im Interesse Deutschlands und unter Vermittlung des Auswärtigen Amtes eine auswärtige Pathologenstelle eingenommen hätte, wie die deutschen Prosektoren in China (Kanton, Shanghai usw.), Chile usw. Gegenüber diesen Herren hat die Deutsche Pathologische Gesellschaft allerdings eine gewisse Verpflichtung übernommen, sie nicht zu vergessen, sofern sie sich im Ausland wissenschaftlich und für als Deutsche bewährt haben.

Mit vorzüglicher Hochachtung
Ihr sehr ergebener

R. Rössle

Anlagen: Brief d.Dr.Hueper, Philadelphia v.28.9.33
Lebenslauf und Liste d.Arbeiten.

Figure 6. Letter by R. Rössle dated November 13, 1933 to the minister for science, art and education.

institute of the Charité, *R. Rössle* (1876-1956), to examine the documents submitted by *Hueper*.

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.

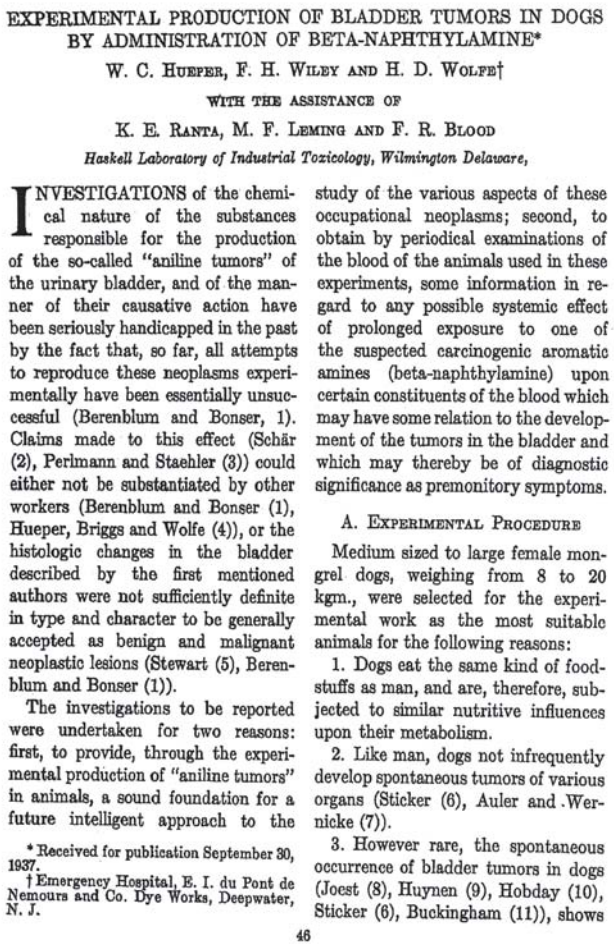
3.2.2. Hueper´s research field of environmental and occupational cancer

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).



EXPERIMENTAL PRODUCTION OF BLADDER TUMORS IN DOGS BY ADMINISTRATION OF BETA-NAPHTHYLAMINE*

W. C. Hueper, F. H. Wilby and H. D. Wolfe†

WITH THE ASSISTANCE OF

K. E. Ranta, M. F. Leming and F. R. Blood

Haskell Laboratory of Industrial Toxicology, Wilmington Delaware,

INVESTIGATIONS of the chemical nature of the substances responsible for the production of the so-called "aniline tumors" of the urinary bladder, and of the manner of their causative action have been seriously handicapped in the past by the fact that, so far, all attempts to reproduce these neoplasms experimentally have been essentially unsuccessful (Berenblum and Bonser, 1). Claims made to this effect (Schär (2), Perlmann and Staehler (3)) could either not be substantiated by other workers (Berenblum and Bonser (1), Hueper, Briggs and Wolfe (4)), or 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 (5), Berenblum and Bonser (1)).

The investigations to be reported were undertaken for two reasons: first, to provide, through the experimental production of "aniline 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 periodical 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 kgm., 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 not infrequently develop spontaneous tumors of various organs (Sticker (6), Auler and Wernicke (7)).

3. However rare, the spontaneous occurrence of bladder tumors in dogs (Joest (8), Huynen (9), Hobday (10), Sticker (6), Buckingham (11)), shows

* Received for publication September 30, 1937.

† Emergency Hospital, E. I. du Pont de Nemours and Co. Dye Works, Deepwater, N. J.

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

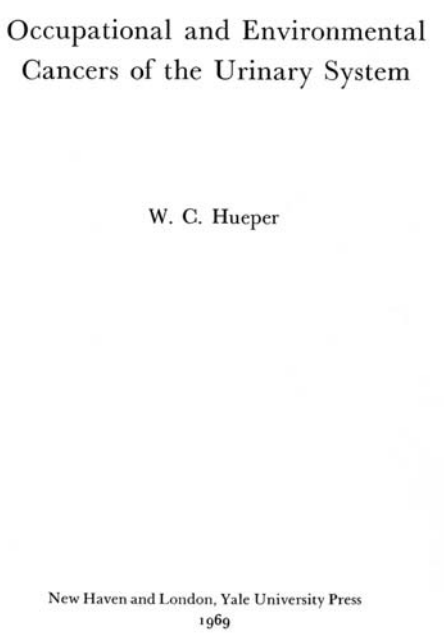
It should incidentally be noted that during this period, the German research community also supported work on the effect of carcinogenic substances on the human organism. Pioneering work by *H. Druckrey* (1904-1994) and *K. Küpfmüller* (1897-1977) published in 1948 and 1949 should be seen in this light. 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 becoming the people to prove the irreversibility of carcinogenic effects (3, 4). However the biographies of the pharmacologist and cancer researcher *Druckrey* and the electro and communications engineer *Küpfmüller* are closely linked with the socio-political events of Nazi Germany. This has been extensively discussed elsewhere (21).

3.2.3. The experimental findings on ß-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 tumors 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 ß-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 ß-naphthylamine for a total of almost two years


Occupational and Environmental
Cancers of the Urinary System

W. C. Hueper

New Haven and London, Yale University Press
1969

Figure 8. Title page of Hueper´s book: Occupational and Environmental Cancers of the Urinary System, 1969.

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 ß-naphthylamine for 20-26 months developed tumorus changes in the bladder.

As early as 1937/38, his working group postulated from the results of animal experiments that "1. ß-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 ß-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 lifes 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 adressed *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 ß-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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Key Words: Bladder cancer, Rehn, Hueper, Occupation, Aromatic Amines, Review

Send correspondence to: Holger G. Dietrich, Head of the Department of Urology, Hospital Paul Gerhardt Stift, Paul-Gerhardt-Strasse 42-45, 06886 Lutherstadt Wittenberg, Germany, Tel: 493491503301, Fax: 493491503280, E-mail: dr.b.dietrich@t-online.de

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