Cancer of the Bladder Among Workers in Aniline Factories.

SUMMARY.


INTRODUCTION.

The problem of tumours among certain classes of workers is undoubtedly one of the most interesting questions of labour pathology.

It had long been known that tumours existed among chimney-sweeps, petrol refiners, workers handling tar, paraffin pitch, and many other occupations. Some years ago attention was also drawn to the frequency of tumours among the miners of Schneeberg, who were exposed to inhalation of dust containing cobalt and arsenic.

It was in 1895 that Rehn reported to the Surgical Congress 3 cases of tumour of the bladder which the medical officers of an aniline factory at Frankfort-on-Main had sent to him for surgical treatment. In a short time observations of a similar character multiplied. The tumours, however, were of different natures, due to different products. It was impossible as yet to determine exactly the industrial origin of the tumours, but the Directors of the factories, disturbed by the frequency and the gravity of the tumours noted, placed at the disposal of the experts and technicians all the material necessary for studying the problem and discovering prophylactic measures.

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The Serological Section of the Höchste Farbwerke took up the question, but the experimental researches carried on for two years did not yield appreciable results. The first cases of tumour were reported among the workers engaged
in the preparation of fuchsine and aniline. Efforts were made
to secure the completest possible protection in this branch, but
the danger was not eliminated.

The Surgical Congress of 1904 again dealt with the question
of tumours of the bladder due to industrial causes and instructed
Rehn to collect material relating to cancer of the bladder
among the workers in aniline factories. The enquiry was
carried on in 18 factories, but the cases observed only concerned
7 factories. The study of the question, the work of
documentation, and the treatment in hospital of the patients,
were entrusted to the Samaritenhaus of Heidelberg; but the
results were not very encouraging.

The reports published, however, had indicated that other
products were capable of engendering tumours of the bladder,
and that among those benzidine and naphthylamine occupied
the most prominent place.

The cases observed were all in the zone of Frankfort, and
the question was raised whether the phenomenon might not
admit of a different explanation. In 1912, however,
Leuenberger published a very interesting study dealing with
18 cases observed among the workers at Basle handling aniline
dyes. From that moment the existence of a very close
connection between the manipulation of aromatic bases (1)
and tumours of the bladder among workers was proved.

The question was again brought before the Congress of
Factory Physicians of the chemical industry (6th May 1920),
which appointed a Commission for the study of the question.

The Commission comprises the representatives of the
Commission of the Association of the Chemical Industry, of
the medical practitioners of Frankfort engaged in the study
of cancer, of the Government, the Province, the manufacturers,
and the workers. The Secretary, Dr. Curschmann, in a recent
pamphlet, has published a questionnaire to be answered, for
the purpose of arriving at the most exact statistics possible.
He points out that the total number of cases of tumours of the
bladder since 1913 cannot be more than 28.

Considering the gravity of the question, especially in the
case of malignant tumours, and considering the fact that the
industry of aromatic bases has undergone a very considerable
development in recent years in countries not perhaps

(1) Organic chemistry is the chemistry of carbon compounds, which
are commonly classified in two groups — compounds of the aliphatic
series, or derivatives of methane, and compounds of the aromatic series,
which have received that name because many of them possess an
agreeable smell. These are also called benzene compounds, because they
are derived from a hydrocarbon C_6 H_6 known as benzene.

Benzene and its homologues, toluene (C_6 H_5 (CH_3)) and xylene
(C_8 H_10 (CH_3)_2), form the starting point of a great number of compounds.

Among the characteristics of the aromatic compounds may be mentioned
the fact that they easily react in combination with azotic acid, in forming
nitrate derivatives, and with concentrated sulphuric acid in producing sul-
phonic acids.
sufficiently informed in regard to the ill effects of these products, a clear presentation of the problem is desirable, especially in view of the fact that the specific action of amino-compounds (1) is only explicable after a long period of contact.

**Frequency.**

A certain number of authors do not admit any direct connection between poisoning by aniline and its derivatives and tumours of the bladder. Grandhomme has repeatedly insisted on the fact that no case was noted from 1883 up to 1896 among 493 workers exposed to aniline poisoning, and that during the same period not a single case was reported among the workers (4,000), at Offenbach or Fechenheim. He concluded that aniline may irritate the mucous membrane of the bladder and produce troubles in passing water, pains, etc., but that it has no connection with the production of tumours.

The observations of Leichtenstern and Schwerin have completely disproved the conclusion of Grandhomme, and the analysis of published works is very conclusive on this subject:

- **1895.** Rehn. Three cases, two of fibropapilloma and one of sarcoma, among workers in contact with fuchsine and aniline.
- **1898.** Bachfeld (of Offenbach) reports 63 cases of poisoning by aniline, toluidine or nitro-benzene, among which 16 exhibited troubles in passing water (strangury).
- **1898.** Leichtenstern: 1 case of sarcoma due to naphthylamine and one case (not clearly characterised from the histological point of view) due to toluidine.
- **1900.** Wendel gives the histological examination of the cases of Eehn and Leichtenstern and reports 3 cases of cancer, of which 2 are due to aniline and one to naphthylamine.
- **1904.** Rehn reports on 20 cases submitted to him for surgical treatment; 8 are cases of carcinoma; 5 of papilloma and 7 without particulars.
- **1904.** Posner studies one case of cancer due to naphthol (or naphthylamine).

(1) By reducing the nitrate derivatives of benzene and its homologues, we obtain the corresponding amines of the aromatic series. These amines form rather feeble bases. They are distinguished as primary, secondary, tertiary, etc. The chemical properties of the amines differ considerably from those of the amides, which may be considered as intermediate products in the transformation of nitriles into acids. The carbonyl group may undergo changes when substitutions by other elements or groups are introduced; thus derivatives of fatty acids are obtained by modification of the carboxyl.
1904. *Strauss.* Publishes one case of cancer due to toluidine and benzidine.

1904. *Bardenheuer.* Two cases, one of cancer and one of papilloma.

1905. *Rehn.* One case of cancer of the bladder, ureter and kidney, due to aniline.

1905. *Schedler.* Two cases due to aniline, one of malignant polypus and one of sarcoma.


In 7 factories out of 18 in which the enquiry was held, 38 cases due to aniline and aromatic bases were observed. They were cases of malignant tumours, of which 18 were fatal; operations were performed in 17 cases; 11 of these were still living, but three had already shown symptoms of relapse.

1907. *Seyberth* reports 5 cases, 3 of papilloma, one of adenocarcinoma and one of cancer due to aniline.

1909. From the reports of the Labour Inspectors one case is known of papilloma due to aniline and toluidine. (This case was reported under the year 1910).

1909. The same source gives one case due to benzidine, without, however, giving the diagnosis.

1911. *Cesabianchi* publishes one case of adenocarcinoma due to fuchsine, and 2 cases of adenocarcinoma of the gall bladder.

1912. *Leuenberger* studies in his thesis 18 cases, 9 of carcinoma, 4 of papilloma, one of sarcoma, one of Sarcocarcinoma, one of cancer of the bladder and kidney, and 2 not specified.

1913. *Schwerin,* who brings into the discussion the fruits of his 21 years practice as a factory physician, collected for the Conference of Medical Officers of Chemical Factories, 117 cases, which he reduced to 100, as 17 were doubtful. During his long practice he had observed 38 cases of tumour of the bladder of industrial origin, as against one which had no such origin; but no case of carcinoma.

1919. *Nassauer* studies in his thesis 32 of the most recent cases of tumours.

1920. *Curschmann* reports on the cases of tumours since 1913, the total of which amounts to 58, of which one is badly described and not counted and 17 have been previously reported. Among the 40 which remain, 11 are not cases of tumours, but only of more or less serious troubles of the bladder, and one is a case of cancer of the kidney. Altogether the cases observed since 1913 are reduced to 28.
According to Curschmann, the total number of cases of tumour reported from the time of the first cases reported by Rehn is 177. The cases of Fehr are doubtful, and those reported by Israel and Casper in Berlin (Urologische Gesellschaft 1913) require closer study before it is possible to decide whether they have an industrial origin. But it seems to us very difficult to accept Curschmann’s conclusion, since it is impossible to obtain precise information on the cases prior to the report of Rehn in 1906, inasmuch as the statistics were based on the figures of the Sickness Insurance Funds, and it might easily have happened that the same cases were counted twice. Thus, of the 38 cases of Rehn, 24 had been previously reported and four are doubtful; so that up to the time of the thesis of Leuenberger the total number of cases would be 41; and as it is impossible to say whether or not the 32 cases of Nassauer include cases previously reported, the total up to 1919 would probably be only 87; that is, 41 plus the 18 cases of Leuenberger and the 28 cases of Curschmann.

The opinion that these tumours were only found in the district of Frankfort-on-Main has been refuted by Leuenberger, who proved the existence of tumours in the district of Basle, among workers handling aniline dyes (dyers). The diagnosis was verified by autopsy in 47 per cent of the cases reported by Leuenberger.

"The examination of the question whether the development of aniline dye factories has been parallel with the occurrence of more numerous cases of tumour of the bladder in the whole of the population of Basle City has not produced exact results. It has, however, been possible to prove that the number of deaths due to tumour of the bladder was 0.007 % of the average population of Basle City for the period 1871-1880 and that it rose to 0.02 % during the period 1901-1910."

"The comparison of the number of deaths recorded among the workers in aniline dye factories due to tumour of the bladder, with the deaths due to the same disease among the rest of the population of Basle has given the following results:

"According to information supplied by the factories in question, the number of workers employed during the period 1901-1910 in the factories producing aniline dyes and aromatic derivatives in Basle City, was 840. In the same period, according to the Office of Statistics, the whole male population of Basle City amounted approximately to 56,500 workers. From 1901 to 1910 six workers employed in aniline dye factories died in Basle City as a result of tumours of the bladder. During the same period, the physicians recorded 12 fatal cases due to the same affection among the rest of the male population of Basle City.

"From these calculations, therefore, it appears that in Basle City during the period 1901-1910, the deaths due to
tumour of the bladder recorded among the workers in factories producing aniline dyes and aromatic substances were 33 times more numerous than the fatal cases recorded for the same number of individuals and for the same disease among the rest of the male population, including old men and children. (Leuenberger).

The data of Leuenberger are in fact even more striking, inasmuch as the statistics taken from the Surgical Clinic of Basle give figures proving the greater morbidity of the aniline workers:

<table>
<thead>
<tr>
<th>Period</th>
<th>Tumours of Patients</th>
<th>Tumours of the Bladder</th>
<th>Aniline Workers</th>
<th>Dyers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before the development</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of the Chemical Industry</td>
<td>1861-1870</td>
<td>2600</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>1871-1880</td>
<td>3450</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>1881-1890</td>
<td>4250</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>1891-1900</td>
<td>5500</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>After the development</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of the Chemical Industry</td>
<td>1901-1910</td>
<td>9650</td>
<td>16</td>
<td>10</td>
</tr>
</tbody>
</table>

Tumours of the bladder among men amounted in the period 1901-1910 in Basle City to 16 out of 570 cases of tumour, thus, 7.8 %. At Vienna, according to Gurtel, out of 16,673 tumours only 66 affected the bladder, or 0.39 %. Other authors give the figure as 0.25 % and 0.76 %. At Frankfort, on the other hand, tumours of the bladder, which appeared in the same percentage among the population generally, amounted to from 25 % to 30 % in a period of 23 years among workers of the class with which we are concerned.

It is certainly not necessary to accept the extreme conclusions of Nassauer, who says that all workers in the factories are exposed to the danger of tumour of the bladder; it is a proposition which may be true in theory, but which fortunately is not so in practice. But the fact remains, although it only affects a minority even among the workers exposed to contact with aniline and similar substances.

A percentage would be difficult to arrive at in default of a census of workers in the past. The percentage would in any case be very remarkable, even if we accept the figure of 177 cases given by Curschmann, out of an average of 80,000 to 10,000 workers.

A classification of the cases reported by different physicians over the period 1895 to 1920 according to types of tumour, age of patients, and period of contact with the poisonous products, would give the following figures:—
### Types of Tumour

<table>
<thead>
<tr>
<th>Types of Tumour</th>
<th>No. of Cases reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papilloma</td>
<td>16</td>
</tr>
<tr>
<td>Fibroma</td>
<td></td>
</tr>
<tr>
<td>Carcinoma</td>
<td>24</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>4</td>
</tr>
<tr>
<td>Sarcocarcinoma</td>
<td>4</td>
</tr>
<tr>
<td>Cancer of the Bladder, Kidney, etc.</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
</tr>
</tbody>
</table>

Reported as Benign Tumours                         | 12                    |
Reported as Malignant Tumours                      | 15                    |
Total                                              | 27                    |
Tumours without specification                      | 10                    |
Grand Total                                        | 88                    |

### Age of Patients

<table>
<thead>
<tr>
<th>Types of Tumour</th>
<th>30-40</th>
<th>41-50</th>
<th>Over 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>4</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Malignant</td>
<td>3</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Not specified</td>
<td>1</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>Grand Total</td>
<td></td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>

Although a tumour which is due to industrial causes generally appears at a precocious period of life (before 40 years: Chimney-Sweeps, Miners etc,) it must be admitted that among workers in contact with aniline, tumours appear especially after the age of 40. But it would be well to remember in this connection that in such cases the action of the poison develops very slowly and after a very long period.

It is more difficult to reply to the question what is the lapse of time necessary for the appearance of the first symptoms of tumour of the bladder. The data are very different and contradictory. Most important of all, the date of the engagement of the workers is not precisely known, and indications given by the workers themselves have to be accepted.

In many cases, especially in the past, the diagnosis was made at a very late stage, as the worker had often had no remarkable symptoms. Thus the following data are given in regard to 52 Cases:—
Types of Tumour.

<table>
<thead>
<tr>
<th>Types of Tumour</th>
<th>First Symptoms of Tumour among Workers after working</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 years</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>2</td>
</tr>
</tbody>
</table>

In six cases it has been impossible to determine the period of latent duration of the tumour.

As regards tumours there is no case which had not at least 10 years’ incubation (in one case even 35 years); but on the other hand there are cases which develop very early, especially among those caused by benzidine (less than 3 years: Schwerin, but other physicians say 8 and 12 years.) The period is also very brief in the case of naphthylamine (5 years). 12 years is indicated in the case of rubine and longer in the case of fuchsine and of work in the acid-bottle department.

Equally interesting in practice is the question of the diagnosis of tumour of the bladder among workers who have left aniline factories. Although the number of such cases is very limited, observations are nevertheless recorded of tumours among workers who had been sent to other department or other factories because they had exhibited vesical phenomena (cystitis). These workers have in most cases come to the doctor for haematuria from two to eight years afterwards, and some have had to be operated on.

In order to secure the most exact information possible in the future, it will be necessary to make use of the following Questionnaire prepared by Curschmann:

**QUESTIONNAIRE**:

1. Christian Name and Surname.
2. Date of Birth.
3. Address.
4. Married or unmarried.
5. Cases of Carcinoma in the family.
6. Former illnesses.
7. Alcoholism.
8. Venereal diseases.
9. Previous poisonings.
11. Date of entry into the Factory.
12. Department and period of employment.
13. With what substances has the patient worked?
14. How many workers (that is, individual workers and not the total number of workers at any one time) have been employed in the Department during the last 10 years?

15. Duration of working day.


17. Examination of Urine, result (Proof of colour).

18. Periodical Medical Examination.

19. Examination of Blood, and with what result.


22. Diagnosis.

23. Treatment.

24. Operation; Operator (Referring to any publications of the Surgeon).


26. Histology of the tumour.

27. Anatomical and Pathological Diagnosis.


29. Has the patient been able to resume his occupation?

30. Where and with what materials has the patient been subsequently employed?

31. Relapse.

32. Has this Relapse been the subject of an operation?

33. Did the Relapse shew any deviations from the original tumour?

34. Have any Metastases been observed?

35. Termination.

36. Remarks on the actual state of the disease and on its subsequent evolution.

Date ...................... Signature ......................

Address ......................

Aetiology.

What are the products capable of engendering the morbid form indicated? The reply is not so simple as one might think. As far as we know, it might be said that almost all the products listed below, or at least the majority of them, may be the cause of tumour of the bladder.

It must be remembered that the worker is not always exposed to the action of a single poisonous compound, even in a single department of the factory, and that unfortunately the details of the cases published do not furnish us with very precise information on this subject.

In effect, the reporters limit themselves to citing the raw material or final product without giving us exact information as to the compounds handled by the worker.
The result is that products well known to be inoffensive, such as naphthol, have been reported as causing malignant diseases, whereas the origin should be attributed to intermediate or accessory products.

The following is a list of the products which, either singly or in association with other products, may cause tumour of the bladder, according to the studies of different observers:

- Nitrobenzene (Rehn), nitrotoluene (Rehn), aniline (Rehn, Wendel, Schedler, Seyberth), aniline and toluidine (anonymous), aniline and naphthol (Rehn), aniline, benzol and toluol (Lewin), aniline dyes (Bardenheure, Bard, Rehn, Seyberth, Leuenberger), fuchsine, rubine (Rehn, Cesabianchi), benzidine (Rehn, anonymous), toluidine (Rehn, Leichtenstern), toluidine and benzidine (Strauss), naphthylamine (Rehn, Wendel, Schedler, Leichtenstern), naphthol (Posner), naphthylamine and diphenylamine (Rehn), phenylnaphthylamine (Rehn), xyidine (Rehn), cumidine (Rehn). Nitro-dyes, triphenylmethane, diphenylnaphthylmethane, acridine, ozazine and thiobenzil have also been indicated.

If the enquiry of Rehn limited itself to the indication of fuchsine and naphthylamine only, Wendel in 1900 definitely established that the suspected products, such as aniline, toluidine, naphthylamine, etc., all belong to the amino-compounds, thus excluding the nitro-compounds.

Poisoning by the latter must be distinguished from poisoning due to amino-compounds, inasmuch as the nitro-compounds are generally more poisonous in proportion as the number of the nitro groups in the nucleus increases.

The researches of Leuenberger among workers handling aniline dyes (Basle City) do not make it possible to give an exact list of the products capable of provoking tumour. It seems however that the following may be the probable cause:—

- Safranine, dianisidine, dehydrothioxüine, Congo red, and benzo-purpurine.

Experience proves that there is no immunity, and that predisposition plays a great part. There are many factors favourable to poisoning — lack of cleanliness, mal-nutrition, alcoholism, excesses of every kind, damp weather, excessive perspiration, etc. Workers new to the trade, and consequently working without precautions, with whom large skin surfaces come in contact with the poisonous products, are special liable. On other hand, workers remaining a long time in the workshops are more exposed to the danger of introducing by deglutition the products floating in the air. Although the permeability of the skin by the products in question is remarkable, it is certain that the older workers, who are accustomed to take great care of their skins, show a smaller number of cases of poisoning.
Technical Survey.

Let us examine more closely the nature and characteristics of the products which have been indicated as the most probable causes of the injuries reported.

Among the products of the illuminating gas industry, tar is undoubtedly of great importance, and a still greater importance has recently been acquired by its derivatives.

By means of distillation, coal forms two great classes of products: light oils and heavy oils. From the light oils proceed the benzols which, treated in columnar apparatus, give the hydrocarbons of the aromatic series (benzene, toluene, xylene, etc.).

Each of these bodies represents, in its turn, the starting point of a series of bodies extensively used as raw materials, especially in the dyeing industry. By nitration and reduction of the above-mentionned carbides the amino-derivatives (aniline, toluidine, xylidine) are obtained.

Benzene is transformed into nitrobenzene in cast-iron apparatus, by the addition of a mixture of sulphuric acid and nitric acid. The introduction of the same mixture in the corresponding aromatic compounds produces nitrotoluene, nitroxyylene, etc.

In order to transform the nitro-compounds into amino-derivatives, the aromatic compound is placed in contact with the hydrogen obtained by the reaction of a small quantity of chlorhydric acid on iron shavings.

The simplest of the aromatic bases, aniline, may be considered as derived either from benzol by substitution of the amino group plus one atom of H (amiobenzene), or from ammoniac by exchange of one atom of H against the phenyl group C₆H₅ (phenylamine). Since 1864, aniline (amidobenzene, phenylamine C₆H₅AzH₂) has been prepared by reduction of nitrobenzene in a columnar apparatus, with cooling, etc., carefully avoiding a too powerful reaction, iron shavings and 5% chlorhydric acid being present. When the reduction is complete, the aniline is distilled under steam, and the reaction being accomplished, the product is alkalinized by means of lime.

Toluidine and xylidine are obtained from nitrotoluene and nitroxyylene by an analogous process.

Among the homologues of aniline must be mentioned the three toluidines C₆H₅(CH3)(AzN₂) obtained by reduction of the three nitrotoluenes: monoamines: toluidines (xylidines, nitranilines, benzylamines, etc.): diamines (phenyldiamine, etc.).

Fuchsine was first prepared industrially in 1859. The dyes of the rosaniline series are derived either from triphenylmethane, or from metolyldiphenylmethane. The first are described as “para compounds” and are prepared by
oxydising a mixture of aniline and paratoluidine, or by heating a mixture of nitrobenzene, aniline and toluidine, with the addition of iron filings and chlorhydric acid. One of the salts of pararosaniline and rosaniline is fuchsine C_{20}H_{20}Az_{3}Cl.

Formerly, the poisoning might have been attributed to arsenic, in view of the method of preparation, for a mixture of aniline and toluidine (Rotöl) was heated with an extremely concentrated solution of arsenic acid. It is now prepared by treating the aniline with formalin.

Naphthaline C_{10}H_{8} is a carbide discovered in 1820, also obtained from coal tar and separated from the fractions of the latter substance which reach a temperature of 180°-200°. The products of substitution of naphthaline may be mono, bi, etc. substituted derivatives. The monosubstituted derivatives always exist in two isomeric forms distinguished by the letters α and β. The α naphthylamine C_{10}H_{8}(AzH_{2}) is obtained by heating α naphthol with ammoniacal chloride of calcium or by reduction of the α nitronaphthaline. Isomeric β C_{10}H_{8}AzH_{2} is produced by heating naphthol β with ammonium sulphide in a current of ammoniac, or in presence of ammoniacal chloride of zinc.

Diphenyl, like benzene, is the fundamental carbide of an important series of derivatives. By reduction of nitrobenzene by means of iron, caustic soda being present, and passing through the intermediate products, azobenzol, etc., benzidine is obtained.

Pathogeny.

The channels by which the poisonous products enter the body are the respiratory organs (volatile products, for example aniline), the alimentary canal (solid products, for example, the paranitraniline), and the skin and mucous membrane which are very permeable, even by the non-volatile aminocompounds. It is no doubt a question of small quantities of the poisonous product, which must moreover apply their action during a number of years and thus constitute in the organism a quantity sufficient (accumulation ?) to engender the tumour.

The local irritant action of these products is proved by the frequent declarations of the workers, who often complain of pains (strangury), and especially by the presence of ulcers on the gland and prepuce. The alterations observed on the skin (tumours) following on contact with the same products must have a pathogeny analogous to that of the tumours of the bladder, since they must be the consequence of the excretion of the products in question through the skin along with the perspiration (Brat Hirt).

It is not possible at present to give the toxic equivalent of these products. Experience has proved that certain
products in small doses under certain conditions give rise to very grave lesions; others, even in strong doses, do not produce any lesion. It has in fact been known for a considerable time that many workers, although exposed to the action of aniline and other products eliminated through the urinary organs, have not shown any signs of vesical lesions. Other substances must therefore be in question.

The toxicity of dyes derived from coal tar is also a very complicated question. It is, in fact, often very difficult to judge of the toxicity of dyes, especially as they are not always pure, while experiments on animals are not decisive and individual reaction is very different.

Pending positive results, it is desirable to establish very exact statistics, which, as has been said, presents serious difficulties. Thus, for example, the hypothesis of Rehn that tumours are more frequent in the preparation of fuchsine and rubine, is not accepted, any more than the hypothesis which indicates aniline as a very frequent cause of tumour of the bladder.

Leuenberger has arrived at the conclusion that the tumours are due more especially to the action of the aromatic amino-compounds with one or more hydroxylated nucleii. It is therefore the intermediate products of the amino-compounds which must be incriminated. During the passage through the organism the amino-compounds must undergo a hydrolysation, an indispensable condition for rendering the products of excretion favourable to the production of tumours in the urinary system.

Kuchenbecher has endeavoured to ascertain whether the suspected products (aniline and its homologues, benzidine and other derivatives of diamidophenol, naphthylamine α and β) really give rise to hydroxylated aromatic amino-compounds. As the result of these researches Kuchenbecher concluded that aniline and its homologues in free para position give rise to hydroxylated aromatic amino-compounds, which may, however, reach the bladder without dangerous action, owing to their being combined with sulphuric acid. In the case of benzidine and naphthylamine (α and β), on the other hand, there is no production of hydroxylated amino-compounds. The hypothesis, therefore, that tumours of the bladder are due to these products is only valid in certain cases.

It is easy to prove that the products with which we are concerned follow a law in their transformations within the organism. This law holds good for the transformation of nitro- into amino-compounds; but it is not yet proved as regards other products. Although experiments in this matter have given excellent results, the question is still open. A fairly considerable part of these amino-compounds, and even aniline itself, do not undergo oxydation in the organism, and are eliminated without modification either through the urine or
through the respiratory organs (aniline). For this reason, in cases of poisoning by aniline and nitrobenzene, analogous final products — that is to say, amidophenols — may be distinguished in the urine. Intermediate products are also partially distinguished. The toxic product is in both cases the same — quinonimine. In the case of nitrobenzene, one must also take into account the action of nitrophenol.

The intermediate products which may be distinguished in the urine have been studied by Kückenbecker, who has also given a practical procedure for diagnosis (see page 18). If he is confirmed, we shall be able to say:

1. What is the toxic substance.
2. What are the alterations produced in the organism.
3. What are the channels of entry into the system.

Researches are still in progress with a view to ascertaining whether, besides the hydrolysed products of excretion, the final and intermediate products of oxidation may also engender tumours. It is certain that this holds good as regards the toxic action, and especially as regards the action exercised on the hemoglobin by the nitro-compounds of the group hydroxylated in the organism before being rendered innocuous by etherification.

It follows that the position of the hydroxyl group is very important in the amino group and in the formation of the bivalent phenols (introduction of the two hydroxylated groups) etc., inasmuch as the possibility of obtaining compounds capable of producing quinones and quinonimines depends upon such position.

What becomes of the aromatic carbides is therefore still a problem full of obscure points. This is the case, for example, with the naphthylamine β. The researches on this point will be carried as far as possible. Very interesting also are the experiments of Curschmann on phenylenediamine, toluididine and paranitraniline, which produce alterations of the vesical mucous membrane which disappear very quickly, without leaving appreciable traces and without giving rise to tumours.

**Pathological Anatomy.**

Only the tumours of the bladder due to aniline, the tumours of the lung among the miners of Schneeberg, and those caused by the X-Rays are properly neoplastic formations.

The other industrial lesions observed among chimney-sweeps and workers handling tar, paraffin, pitch etc.; on the contrary, have no title to the qualification of tumours. They are in fact tegumentary proliferations, which sometimes appear as excrescences in which the cellular elements never lose their normal morphological character or their normal disposition.
There are very few autopsies or histological examinations of cases of aniline tumours which are complete and which make it possible to classify the observations collected. The anatomo-pathological or histological diagnosis is sometimes so uncertain that a precise classification of the tumours is impossible.

Their classification as malignant and benign is too simple. As has been seen, the malignant are very much more frequent than the benign tumours. Out of 88 cases studied, 28 benign tumours have been distinguished, as against 50 malignant and 10 not specified.

The seat of the tumours is very different: on the posterior or anterior segment of the bladder, or in the neck of the bladder, most often on the inferior segment and preferably near the neck, so that the urethra is sometimes obliterated. The tumour rarely has its seat below the meatus of the ureter. Cases have been reported in which the whole of the bladder was occupied by neoplastic masses (Papillomatosis).

The papillomata do not sensibly alter the mucous membrane. They are very liable to relapse, do not produce metastases, and are not always fatal so long as they retain their original character. If they extend, they may prevent the emission of the urine, with all its well-known consequences.

In consequence of the fragility of the vessels and the form of their villosities the tumour readily bleeds, whence the serious and dangerous haemorrhages well-known among aniline workers.

Carcinoma (or adenocarcinoma) generally takes the form of a flattened mass, infiltrating the walls, extending over a greater or lesser segment of the bladder wall, and affecting also the mucous membrane and muscular tissues. Very often the cancer is superimposed on a microscopic or macroscopic papillomatosis of the vesical mucous membrane, and there has been much discussion for and against the metaplasia of the papilloma into a carcinoma.

It is a question, therefore, either of typical epithelial tumours (papillary tumours and adenoma), or of atypical tumours (epithelioma). The papillary form is frequently observed, but it is not always a benign form of local evolution capable of transforming itself into atypical epithelioma.

Proofs of metaplasia are rare, but it cannot be excluded, at least in certain cases. There are numerous cases, however, especially since the introduction of the periodical examination of workers (cystoscopy), of papilloma allowing of early treatment.

(1) Cystoscopy is the examination by the eye of the interior of the bladder which is not normally visible without the assistance of special instruments. The first attempts of Bozzini in 1805 were carried to completion by Nitze (1875), who invented the cystoscope with interior lighting. A tube carried into the bladder through the urethra enables the eye of the physician to
The tumours, especially the epithelial tumours, are accompanied at an early stage by cystitis and nephritis, often causing death before the tumour has had time to reach the neighbouring parts and to become general. In these cases, metastases are found, into the lymphatic vessels, and even into the wall of the abdomen. Only one case is known of metastasis to the liver and lungs (examination, however, proved that the vesical mucous membrane was intact). Cesabianchi reports also two cases of adenocarcinoma of the gall bladder in two workmen in contact with fuchsine (primary tumours?)

It is certain, therefore, that in the whole of the urinary system the constant action over a number of years of hydroxylated aromatic amino-compounds, exercised on the conjunctive tissue or the epithelium, is capable of exciting proliferation developing as infiltration of the urinary passages by an atypical growth of the epithelium of the mucous membrane, with formation of microscopic and macroscopic papilloma, the development of granulated tumours, true carcinoma, adenocarcinoma, sarcoma, etc.

The majority of the tumours have an extraordinary polymorphism, but it may be admitted that all the tumours arise from alterations of pre-cancerous tissue, as is observed in the case of tumours due to X-rays, etc.

Other authors consider that the histogenesis is still obscure, and that the relationship admitted in clinical practice (aniline poisoning = inflammation = tumour of the bladder) is not yet established.

Practice has proved that tumours often appear several years after the cessation of work. The same fact has been observed in the case of tumours and dermatitis caused by X-rays, and it would appear that in such cases the tumours are formed by a processus of inflammation and chronic degenerescence in the sub-epithelial conjunctive tissue (Ribbet).

**Symptoms.**

There is very little information on this subject, but it may be said that the clinical symptoms are the well recognized symptoms of tumour of the bladder.

The cases already known without symptoms necessitate the regular practice of cystoscopy, so as to permit of an early diagnosis, among the workers in the suspected occupations.

In all cases of haematuria, it will be absolutely necessary to subject the worker to a very careful interrogation in order to receive the luminous rays proceeding from the cavity by means of a system of mirrors, lenses or prisms. The interior of the cavity is lighted by special systems of illumination placed in the tube introduced into the cavity and utilising either an exterior or an artificial (electric) source of light. Although the optical systems of cystoscopes with interior lighting are somewhat different, it may, nevertheless, be said that all the apparatus is based on the same principle.
to make sure that he has not been in contact in the past with amino-compounds. This is necessitated by the fact that cases of haematuria among workers who had left the factory two or even five years previously have been subjected to a systematic treatment due to an erroneous diagnosis of stone in the bladder, urogenital tuberculosis, etc.

If the practitioner carefully interrogates the worker he will easily be able to establish whether he has suffered from haematuria in the past.

Generally, the disease shows itself by haematuria, which comes on suddenly without premonitory symptoms. The haematuria is very capricious and may even appear once only. It is accompanied by other symptoms, varying according to the seat of the tumour in the bladder. Pains are rare, more often the patient consults the practitioner for trouble in passing water: dysuria and stranguria. Formerly patients usually called in the practitioner when the tumour was already in a very advanced stage, and treatment was almost impossible.

Before proceeding further, it should be stated that bladder irritation, although it is a characteristic of this form of industrial disease, is not always a premonitory symptom of the tumours. It is prudent and desirable, however, to follow it with attention. Bladder irritation which precedes by a considerable time the more serious alterations due to the action of amino-compounds, may appear, disappear and reappear, and even be cured without leaving noticeable traces.

In other cases, the tumour develops without the slightest symptom, and the attention of the relations or comrades of the patient may only be attracted by the anaemia or cachexy accompanying the tumour in an advanced state of development.

Cystoscopical examination now enables early diagnosis to be made and treatment given, so that it is almost impossible for serious cases to escape detection. It is only in the case of widely extended tumours or metastases that complications may arise, which characterise the final stage of the disease.

Diagnosis.

It is absolutely necessary to use all the means at the disposal of practitioners for making early diagnosis, especially in cases where symptoms are absent. It is necessary also to obtain information on the past of the worker in order to trace a haematuria or the slightest symptoms of cystitis. Many extremely slight irritations of the bladder have been discovered by means of cystoscopical examination.

In the case of workers who have ceased to be in contact with aniline for a long time, it is necessary to be prudent before diagnosing vesical calculus, haematuria or urogenital tuberculosis.
An early diagnosis is facilitated by the periodical examination of the workers (urine, cystoscopy). Cystoscopy should be practised with every worker who shows suspicious symptoms, and even repeated several times a month as long as these symptoms persist. It may be thought that such an examination will produce a bad impression on the workers; experience shows that this fear is without foundation, especially as the test is free and not compulsory, although strongly recommended by the industrial physician to workers already informed of the danger which threatens them.

The examination of urine will be made on the water last passed in the presence of the doctor, and its object will be the microscopic search for the presence of red globules (terminal haematuria). This is not a specific symptom, but it is certain that red globules appear in the urine at a very early period, even when the tumour is not yet capable of diagnosis by the cystoscope.

Schwerin has sought to demonstrate the presence of substances capable of engendering tumours, particularly among workers engaged in handling acid-bottles. The results obtained are truly striking, the more so as the quantity of products introduced into the organism is so small that the urine cannot possibly contain perceptible traces of the products of transformation. Kuchenbecker, following an indirect line, has sought for a substance derived from the amino-aromatic group, the action of which as a colouring agent would make it possible to discover the amino-compound present in the urine. By combining the amino-diazotised compound with a derivative of amino-naphthol-sulphate 2:5-7 (phenyllic acid 2:5-7) he has obtained a colour which tints cotton with the shades characteristic of each incriminated substance. According to the intensity of the shades it is possible to judge the greater or lesser quantity of the substances present in the urine. It is necessary in order to avoid mistakes that the phenyllic acid 2:5-7 should not contain any non-phenylated acids. Benzoyle acid 2:5-7 may also be used. The following is the method:—

50 cubic cms. of urine is cooled in ice and reduced by means of chlorhydric acid until it attains a slight congo red reaction. Four drops of concentrated chlorhydric acid are added and a sufficient quantity of double-normal solution of nitrite (1-10 drops) to show an excess of nitrite by reaction on potassium iodide paper and starch. Diazotization is effected by means of 1 cubic cm. of soda salt of phenyleacid 2:5-7 at 1%, 3 cubic cms. of a solution of soda, 1 part to 10, and a sufficient quantity of water to make up 100 parts. A small piece of cotton cloth is introduced into this solution; the whole is boiled; the cloth is allowed to remain ten minutes in the hot liquid, and then washed in cold water. With a normal urine the liquid retains its colour or becomes slightly red. If the urine contains amino-aromatic compounds it
takes a distinctly pink or even violet colour, which also tints the cotton.

By this method the urine of workers dealing with fuchsine, and particularly those preparing benzidine and naphthylamine, has been periodically examined. Substances capable of diazotation have thus been traced in large quantities among workers exposed to the inhalation of dusts. The efficacy of the means of prevention adopted has been confirmed by such examination, for the quantity of products in the urine has diminished and even disappeared. For the purpose of obtaining exact data as to the value of the quantities traced, a solution of naphthionate is used as standard. Urine very rich in substances capable of diazotation gives a colour the intensity of which is comparable to that of a solution of 1:20,000 of naphthionate; urine with a small quantity, a colour comparable to a solution of 1 : 100,000, and, if it contains only slight traces, to a solution of 1 : 200,000. The reaction of Kuchenbecker is sufficiently perceptible.

The examination of the blood, of the respiratory organs, etc., gives no indications of any value for the purposes of diagnosis.

**Prognosis.**

Prognosis should be very reserved even for benignant tumours (papilloma), having regard to their liability to relapse even after a few months. Relapses after a long period are even more frequent (six to eleven years after treatment).

There are certainly cases of cure, but only after operation. One must also bear in mind the possibility of a metaplasia of papilloma into malignant tumours. It may generally be said that death will supervene in from six months to 1 1/2 years after the first symptoms. The prognosis is infallible in cases of malignant tumours, for they have all a fatal termination even if operated upon (eleven deaths in sixteen cases). Exceptions are known, but they are very rare. Possibly early treatment will improve the statistics.

**Treatment.**

The success of the treatment is naturally in very close relation to the precocity of the diagnosis.

There is legitimate ground for confidence in treatment for malignant tumours, inasmuch as a return to capacity for work and a good state of health is thereby assured, sometimes for a considerable number of years.

If the papillomata are not too greatly developed and especially if they are in a favourable position, the preference is now for endovesical treatment by destroying the tumour by electro-coagulation under the direction of the cystoscope.

The method is a particularly intense diathermic process obtained by a current of high frequency, which is very useful
for the complete destruction, not only of the papillomata but also of their basis, such destruction being carried out much better and with much more certainty by this means than by cystotomic treatment. The diathermic method produces little or no pain; it can be applied in the consulting room; it does not favour the reproduction of the tumour; it obviates surgical treatment and permits of repetition if necessary. This method is also indicated for stopping the repeated and dangerous haematurias produced by the papillomata, and although counter indicated for the treatment of the malignant forms, it is a good palliative in cases of relapse after surgical treatment.

Very recent observations, however, have drawn attention to the necessity for the patient treated with the high frequency current not to leave the hospital immediately, as want of attention is often the cause of serious and sometimes fatal haemorrhages.

The treatment of malignant cases is the province of the surgeon. In general, the results are not very favourable. 66% of the persons operated upon have died, and many of the survivors have speedily suffered relapses.

As a medical treatment in the case of tumours in which direct treatment is impossible, washing of the bladder has been proposed (with solutions of adrenalin, gelatin, antipyrin, or resorcin, 1 to 5%). The last-named is useful in cases of haematuria. Lately collargol in solution of 20% (6-15 cubic cms. to be injected in the bladder under anaesthesia) has also been proposed, one hour later washing with oxicyanide of mercury (1/4-1/2 per 1,000), especially in cases with pains and haematuria.

Prophylaxis.

It must be said at once that the precautions taken in the factories producing amino-compounds, after the researches and reports of the observers, have yielded excellent results. Nitration and reduction particularly are now carried out exclusively by mechanical processes in closed and well-ventilated apparatuses. The transport of the masses is carried out either under compressed air or in a vacuum. The efficacy of these precautions is proved by the following fact: out of the twenty-eight cases reported since 1913, only one took place in the Höchste Farbwerke.

It might have been feared that the development of factories producing aniline dyes, and particularly aromatic bases, would have increased the number of tumours of the bladder.

The last word has not been said on this subject, for the long period of incubation necessary before the appearance of the first symptoms of malignant tumours has been indicated. But it is to be hoped that the application of the precautions summarised below will suppress the serious form of industrial disease in question.
The prophylactic measures are as follows:

Well-ventilated work-rooms with absorption of vitiated air and introduction of fresh and, if necessary, cooled air; rigorous cleanliness of floors and walls; absorption of dust.

Well-closed apparatus, including the apparatus for the mechanical transport of materials; local absorption of dusts and vapours.

Reduced working hours; adoption of shifts, in view of the fact that a very short stay in the incriminated section is sufficient to produce tumours.

Working clothes, always strictly clean, closed at the neck and wrists; gloves and shoes.

Daily bath, careful washing before going to the refectory or leaving the factory.

Medical examination of workers, both on engagement, and periodically; selection of healthy workers; periodical instructions by the medical officer and director of the section. The periodical examination will include examination of urine as previously indicated.

Compulsory notification of haematuria and tumours of the bladder among workers in factories producing amino-compounds.

Distribution of milk; prohibition of smoking and consumption of alcoholic liquors; assistance to the worker in procuring nourishing food.

Legislation.

Regulation of labour in connection with nitro and amino-compounds only exists in Prussia, in which country regulations were introduced by the circular of the Ministry of Commerce and Industry of the 21st October, 1911. England has introduced the regulation of the manufacture of explosives based on nitro and amino-compounds (Regulation 30th December 1908).

Conclusions.

Although it is not possible at present to formulate definite conclusions, inasmuch as the problem still presents too many lacunae and obscure points, it may, nevertheless, be said that:

1. There is a close connection between the manipulation of certain amino-compound products and the existence of tumours of the bladder.

(1) In a recent report (1921) concerning compulsory notification of industrial diseases, it is proposed to add to the list now in force in different countries tumours of the bladder in workers who have 10 years or more previously left work in the explosive and aniline dye industries.
(2) The number of cases of tumour of the bladder proved to have occurred among workers in contact with amino-compounds is certainly small. It must be concluded from this that the individual factor plays a great part in the pathology of the disease, seeing that the patients constitute a small minority.

(3) Action of long duration is necessary to produce tumours of the bladder. There is no relation, however, between their occurrence and the duration of employment.

(4) It is not possible to determine the substance capable of engendering tumours. At present one can go no further than to incriminate the amino-compounds, and particularly benzidine and $n$aphthylamine.

(5) The same substance may produce either simple cystitis, or benignant or malignant tumours.

(6) Hygienic precautions, strictly applied, will assure at the end of a few years the diminution and even the disappearance of the disease.

(7) It is, therefore, absolutely necessary that in factories in which workers are exposed to the dangerous action of aromatic bases, the most rigorous application of hygienic precautions should be required.

(8) Meanwhile, it is desirable that the industries concerned should continue to carry on researches with a view to ascertaining the dangerous substance, and that the statistical particulars in every case should be very precise and should follow the proposed questionnaire.

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ERRATUM

Page 6, line 31: for 10,000, read 100,000.

7, second table, third column, for 5, read 1.

9, line 2: for the total number of workers at any one time, read full-time workers.

11, line 41: for C₅H₄(CH₃)₄N₂, read C₅H₄(CH₃)₄(CH₂)₂.

12, line 5: delete C₂₀H₂₀₂₆Cl₂₆.