INDUSTRIAL TOXICOLOGY

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INDUSTRIAL TOXICOLOGY

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PREFACE TO SECOND EDITION

This new edition of INDUSTRIAL TOXICOLOGY is, of necessity, not only rewritten but also considerably enlarged. During the years which have elapsed since the previous edition, great strides have been made in our knowledge of the long-used industrial poisons, their action on the human body, and the most efficient methods of protection against harm from their use. Such poisons as lead and mercury and arsenic have disappeared from old occupations only to reappear in new ones, often unsuspectedly. Metals such as cadmium and aluminum have been considered afresh, for we know much more about them today. Nearly every page of the book has required rewriting.

While new knowledge of the long-used poisons is now available, the complexity of the problems of industrial toxicology has increased with the enormous expansion in the number of solvents, metals, and radioactive substances encountered in industry. One of the new chapters in the book is devoted to beryllium, a subject with which the junior author has been particularly concerned. There are new chemical agents belonging to the petroleum series and others to the benzene series; there are new industries of which the manufacture of synthetic rubber is the most striking example; and the substitution of autogenous welding for riveting in many industries has made it possible to study on a large scale the nature of the fumes evolved during the process. All this has necessitated the addition of new material throughout the text.

Finally the whole subject of radioactivity, which required but 13 pages in the previous edition, has had to be rewritten in the light of our present knowledge, and the section on occupational cancer has had to be enlarged. A new chapter, "Radiant Energy," takes up ultraviolet and infra-red rays, as well as radioactive substances and the new radioactive isotopes. The relationship of atomic energy to industry is presented.

As before, an attempt has been made to provide the reader with a comprehensive yet practical bibliography. Reflecting progress in the

field there are almost three times as many bibliographic references as before. However, the authors make no claim to an exhaustive treatment of the voluminous records of animal experiments to test the toxicity of the newer chemicals. For these the inquirer is referred to the Industrial Research Laboratory of the National Institute of Health, Bethesda, Maryland.

Industrial skin diseases have been dealt with only casually. For this class of occupational lesions the reader is referred to *The Dermatergoses or Occupational Affections of the Skin* by R. Prosser White, Fourth Edition, H. K. Lewis and Company, London, 1934, and to *Occupational Diseases of the Skin* by Louis Schwartz, Louis Tulipan, and Samuel Peck, Lea and Febiger, Philadelphia, 1947.

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CHAPTER TWENTY-FIVE

Occupational Cancer of the Lung

That there has been a decided increase in the incidence of pulmonary cancer in recent years is asserted by physicians in all industrial countries. This increase affects both sexes, but is distinctly greater in men. Hueper quotes Boycott as saying: "In looking for the cause of the increase of pulmonary malignancy one should look for a change in environmental conditions which took place toward the end of the last century."

As Hueper points out, the tissues of the respiratory tract come in contact with the gases and dusts of industrial work more often and more intimately than do any other body tissues except the skin. It is also true that in our day there is an enormous increase in industrial workers and in the exposure of these workers to harmful dusts and fumes. Therefore the apparent increase in the incidence of cancer of the lungs is probably real. One must not ignore, however, certain non-occupational fumes and dusts, whose prevalence has been greatly increased in our day and whose cancer-producing character is certainly not ruled out. Hueper places under this head: cigarette smoking, paraffin oil spraying of nose and throat, x-ray examination of the chest.

Dorn *(236)* of the Public Health Service presented in 1943 a statistical survey of the incidence and prevalence of cancer of the lung in the United States, based on the mortality records from 1914 to 1940. The very rapid increase in this form of cancer when the death rate from other forms is falling, suggests some cause connected with modern modes of life. The pollution of city air has been suggested as a factor, but Dorn found that the incidence of lung and respiratory cancer in men is less in Pittsburgh, with its great air pollution, than in any of the large cities surveyed, except Denver.

The apparently striking increase in incidence is due certainly in part to improvement in diagnosis and the greater frequency of post-

mortem examinations. Arkin and Wagner stated in 1936 that twenty years earlier, of all lung cancers discovered at autopsy only 5 per cent had been discovered during life, in contrast to 50 per cent in 1936. Peters reported that from 1905 to 1909, 3.8 per cent were clinically diagnosed, whereas for 1927-31 the per cent was 44.2. (See Hueper *[538].*)

In a review of 100 cases of cancer of the lung in Australia, 43 of which were proved by autopsy, 12 by biopsy, Harvey (*473*) notes a distinct increase in recent years, for the cases were collected over a twenty-five-year period but almost half occurred in the last five years. An occupational influence is suggested by the large percentage of victims who were exposed to noxious gases, 38 per cent, or to sunlight, 25 per cent.

Teleky (*1164*) recognizes only two proved causes of occupational lung cancer: (1) chromate dust, and (2) radium-containing dust in the Schneeberg and Joachimsthal mines. (For the latter, see page 481).

Carcinogenic Action of Chromates. For many years the conviction was general among industrial toxicologists that the chromates had no carcinogenic action. Legge stated that chrome ulcers never undergo carcinomatous degeneration and American experience seemed to bear this out.

Lehmann in 1932 wrote an answer to the question "Is there any ground for special uneasiness concerning lung cancer in chromate workers?" Two cases which might be attributed to the action of chromates were referred to him and led him to a careful review of the literature of chromate poisoning up to 1932, which he found to be quite devoid of any mention of lung cancer. That chronic bronchitis, sometimes purulent, was common among chromate workers he had frequently observed and he had been able to produce it in animals made to inhale droplets of chromate solution, but as to pulmonary carcinoma, his conclusion was that the cases so far reported were too few to be significant, that isolated cases occur in all classes of workers, and that the increase of cancer of all kinds is due partly to better diagnostic methods, partly to the increased proportion of the elderly in the population and the successful lowering of other causes of death, especially tuberculosis.

Of late, however, information coming from Germany shows that pulmonary carcinoma has occurred frequently enough in chromate workers to attract the attention of the Government Sickness Insurance Department. We are indebted to L. Teleky for the following information.

In 1936 the law concerning insurance against industrial accidents and diseases was extended to cover pulmonary carcinoma occurring in men who produce chromates from chrome ores and residues and those who use chromates in tanning, plating, and similar procedures. The grounds for this measure were given by Koelsch (Arbeit und Gesundheit, Heft 29, Berlin, 1937). He states that the first cases of carcinoma of the lungs in chromate workers were observed in 1911 and from that date until the end of 1936, some 25 cases were recognized in Germany. The latent period ran from about twenty to forty years, and in some cases the new growth did not appear until several years after the victim had ceased working with chromates. A special idiosyncrasy is evident, since very few of those exposed develop such tumors. Age certainly plays a part.

Teleky notes the fact that no reports of cases of pulmonary carcinoma in chromate workers have come from countries other than Germany and he believes the reason is that in Germany workers are much more likely to stay in the same kind of work, even the same job, all their lives and the time required for such growths to develop is twenty years or more. It is also true that German workers are likely to spend all their lives in one place, so that their records in the Sickness Insurance Office are complete.

In this personal communication Teleky states that he saw a case of pulmonary carcinoma in a chromate worker in 1932 and that Pfeil saw 2 cases (later on, 5 more), but all Pfeil's cases developed some years after exposure had ceased. He also quotes Alwans, Bauke, and Jonas as having reported, in 1936, 6 cases of lung cancer following exposure to chromate dust and 9 additional cases in which the x-ray picture showed the tumor above the diaphragm on the right, also a slight degree of fibrosis and a few honeycomb markings.

Teleky quotes from Baader's book, *Recent Developments in the Field of Cancer,* the chapter on industrial cancers in which Baader says that up to that time 28 cases of "bronchial carcinoma" had been discovered in five chromate factories. In addition he says that in

older chromate workers the x-ray picture often showed a distinct swelling of the lymphatic glands on one side. Whether this was an inflammatory process or, because it was limited to one side, a precancerous process, could not be determined without following up the cases.

Teleky adds what he believes to be the first reported American case. This was in a factory in Baltimore. The man worked from 1939 to 1945 in a plant producing chromates from chromate ores. He spent part of the time in production, part in the shipping department, where probably there was a great deal of dust. He died in 1945 at the age of 31 years and the autopsy revealed bronchiogenic carcinoma with metastases in the liver.

Recently Machle and Gregorins (*756a*) have published the results of the first extensive study so far made to determine the incidence of cancer of the lung in workers exposed to dust in the course of producing chromates, bichromates, and chromic acid. This study was made at the suggestion and with the full cooperation of the five companies in the United States which are now extracting chromates from ore in seven plants employing 1445 men. It was found possible in six of these plants to secure records of 11,019 man-years employment with 156 deaths, among which were 46 from all cancers, and of these 32 were cancers of the respiratory system. The seventh plant, without adequate employment records, yielded 20 deaths from cancer of which 10 were from lung cancer. This means a total of 42 deaths from pulmonary cancer. These figures left no doubt of the influence of occupation on the occurrence of cancer of the lungs.

Since no less than 28.8 per cent of all deaths in the chromate industry were reported as being due to cancer of the respiratory system, the ratio is 16 times the expected ratio of 1.3 per cent. The crude death rate for cancer of the lung averaged 25 times the normal, running from eighteen- to fifty-fold. The rate was higher in the groups 50 years of age and under (20 to 70 times that for a comparable industrial group) than for the age groups over 50 years (10 to 40 times). The rate for cancers other than of the lung was 12.4 per cent, slightly lower than the 15 per cent for a comparable industrial group.

Several other facts of great importance were revealed in the course of this study. The incidence of nasal irritation and perforation does

not run parallel with that of lung cancer, but may occur in plants with no records of lung cancer. In two plants belonging to the same company there was a marked difference in the occurrence of lung cancer although the plant populations were similar with regard to location to race, color, age groups, length of exposure. But in plant D1 17 per cent of all deaths were from lung cancer while in plant D2 there were no deaths from that cause. The difference apparently lay in the nature of the compounds handled. Plant D1 handled chromite, sodium chromate and sodium bichromate. Plant D2 only sodium bichromate, chromic acid, and basic chromic sulphate, a trivalent chromium compound. This suggests that the monochromates may be the compounds responsible for lung cancer.

Association of Lung Cancer with Silicosis and Asbestosis. Klotz *(615)* and also Anderson and Dible *(13)* have demonstrated a possible causal relation between silicosis and lung cancer but in both reports the evidence is presented as tentative only and further study is urged.

Teleky *(1165)*, reviewing the subject in 1939, found that the connection between silicosis and lung cancer is very dubious as shown by statistics. On the other hand, the incidence of cancer of the lungs among asbestos workers is fairly high. Le Coeur *(679)*, discussing lung cancer of occupational origin, says that in a lung with asbestosis it takes some twelve years for a cancer to develop. Islands of cancer cells are deeply embedded in fibrous tissue, which also surrounds the lymph glands, and contain particles of asbestos. The process is a "chronic interstitial indurating pneumonitis with cancerous change." The course is slow, the tendency to metastasis less than in chromate cancer.

Lynch and Smith (See 538) have described 2 cases of pulmonary cancer associated with asbestosis and 1 case of squamous metasplasia of the bronchial epithelium with asbestosis, which they tentatively present as a precancerous condition, since the above-cited cases were of cancer predominantly squamous in type. In their series of 2308 necropsies the rate of primary lung cancer is 0.21 per cent; among 35 cases of asbestosis it was about 6 per cent.

Welz *(1235)* attributes to the irritating action of asbestos 2 cases of lung cancer which were complicated with asbestosis.

Another case of lung cancer in an asbestos worker was reported in 1941 by Linzbach and Wedler (538). The patient had been followed radiologically from 1934 to his death in 1940. By 1938 there was stage III of asbestosis, in 1940, a tumor. Autopsy revealed changes characteristic of asbestosis and a squamous-cell carcinoma.

The Saranac Laboratory group admits the possibility of asbestos dust, which is mechanically irritating, setting up a squamous-cell cancer, but similar changes in the epithelium occur in other chronic inflammations of the lung, notably tuberculosis, and, in their very wide experience, tuberculosis is not attended with an increased incidence of primary cancer of the lung (see Vorwald *[1202]*).

Association of Lung Cancer with Other Irritants. Hueper finds some proof of a connection between pulmonary siderosis and cancer. English statistics show that metal grinders have 2.25 times as many cases of cancer of the lungs as does the general population. He cites some 6 scattered cases, but holds that the connection has not yet been proved. Teleky says that in Germany cancer of the lungs is two and one-half times as frequent among metal grinders as in the general population.

Among the many causes that have been suggested to account for the apparent increase in lung tumors in recent years is the dust from asphalt-paved roads, which is undeniably a feature of modern life and one of constantly increasing importance. Leiter and his colleagues *(700)* produced sarcoma in mice by subcutaneous injection of tar extracted from dust collected in streets of five cities. Kling *et al. (613)* tested the various tars used in road-paving and urge the use of those produced at low temperatures, or those with asphalt base, or bitumens known to be free from carcinogenic elements, to obviate possible danger from street dust.

Hueper is skeptical as to such causes as these. It is true that there are more cases of lung cancer in city populations than in rural, but diagnosis is more accurate in cities and more post-mortem examinations are made.

That exposure to hot, tarry gases may give rise to lung cancer is claimed by Kawahata and Kuroda (*651*) who encountered, during a six-year period, 21 cases of lung cancer among men working in a Japanese steel mill where illuminating gas was generated. The men

were continually exposed to dust, flames, and hot gases containing tar. The ages of the affected men ran from 35 to 65 years, their exposure from nine to seventeen years. The upper lobe of the right lung was most often involved; metastases occurred with relative frequency in the brain and spinal cord.

Lovelock *(744)* describes a complicated and difficult case in a Welsh miner, employed for twenty-two years in coal mines. The patient died, apparently from carcinoma of the liver, but the lungs contained over eight times the normal silica content (a guinea pig injected with substance from the lungs died of generalized tuberculosis), and there was carcinoma of the right lower lobe bronchus.

The theory that severe infectious respiratory disease may predispose to pulmonary cancer is apparently refuted by statistics, for the latter has been on the increase while pulmonary tuberculosis has been decreasing, and the influenza epidemic of 1918 had no demonstrable effect.

English statistics (Kennaway and Kennaway [See 538]) show that there has been an increase not only of lung cancer but of cancer of the larynx. Between 1921 and 1932 these tumors increased 1.4-fold in men and 1.75-fold in women. This may possibly be attributed to cigarette smoking; it would hardly be occupational, or men would be affected more than women.

CHAPTER TWENTY-SIX

Occupational Cancer of the Bladder

An interesting and long unexplained manifestation of slow chronic poisoning by coal-tar derivates is the so-called aniline tumor of the bladder, a papillomatous growth which undergoes carcinomatous degeneration. The German dye industry, since it is the oldest and much the most extensive, was the first to discover that men in contact with certain dye intermediates suffered in abnormal proportion from cancer of the bladder. By 1920 the reported cases numbered 177, and each year new ones were added. It was soon established that whatever was the elimination product in the urine responsible for these tumors, it belonged to the amino group, not the nitro, although in other respects the latter is the more toxic group. Description of an interesting case is to be found in the German factory inspection report for 1929. A man who had worked six years with trinitrotoluene died of cancer of the bladder, and compensation was at first refused on the ground that nitro compounds have never been known to produce such cancers. Further consideration of the case, however, resulted in a reversal of the verdict on the ground that trinitrotoluene is excreted in the urine not as such but as an amino derivative.

Animal experiments have not thrown much light on the question of just which compounds are responsible. Hueper and his colleagues succeeded in producing neoplastic lesions of the bladder in nine of sixteen dogs treated with beta-naphthylamine. Morigami and Nishimura (*845*) had a like success with orthotoluidine and benzidine.

The list of amino compounds which have been incriminated is long. Koelsch (*621*) lists aniline, toluidine, xylidine, cumidine, anisidine, naphthylamines, benzidine, and tolidine, and says it is extremely difficult to pick out one single compound because through the years of employment (usually twenty or more) the victim has come in contact with many different ones. Müller (*857*) thinks benzidine the most important; Wignall *(1246)* in his study of English chemical workers,

found alpha-naphthylamine exposure in the larger number of cases, but he also notes the uncertainty arising from the variety of exposures encountered in these cases. Other apparently cancer-producing chemicals in his experience are meta-phenylendiamine, T.N.T., benzidine, diphenylamine, triphenylmethane dyes, and azo dyes.

In Britain the mortality rate from cancer of the bladder was thirty-eight times as high among chemical workers in general as for the insured male population in 1928-32. The causative agents were held to be aniline, benzidine, alpha- and beta-naphthylamine and their derivatives.

American experience narrows the list down to benzidine, beta-naphthylamine, and alpha-naphthylamine which contains as much as 5 per cent of beta.

In England the first cases of aniline tumor of the bladder appeared much later than in Germany because the dye industry is of more recent origin in the former country (Wignall, Macalpine *[753]*). According to Legge *(686)*, 23 fatal cases were reported in England up to the end of 1931. In the United States the manufacture of coal-tar dyes did not amount to much before the outbreak of the First World War shut off the supply from Germany. Twenty years later, in 1934, the first American publication on aniline tumors of the bladder appeared in the shape of a number of articles by the group of physicians associated with the E. I. du Pont de Nemours Company (Ferguson and associates *[315]*).

This very important collection of papers revealed for the first time the occurrence of so-called aniline tumors of the bladder among American workmen, which had made their appearance in the United States, as they did in England, in less than twenty years after the great expansion of the coal-tar industry. This was to be expected, since it was only a repetition of the German and Swiss experience. Since the foreign literature has been fully reviewed many times, it seems useful to summarize this American contribution rather fully.

Ferguson and Anderson (*315*) both deal with the history of bladder tumors since 1895 when Rehn first demonstrated the causal relationship of aniline to them. For a long time the reports of these tumors were practically confined to Germany, long the leader in the dye and chemical industry and the leader in research for the carcinogenic

agent, since it was soon found that other substances than aniline might give rise to bladder tumors, especially benzidine and the naphthylamines. Experimental studies have been negative with rare exceptions such as the production of carcinoma of the bladder in rabbits by prolonged inhalation of naphthylamines (Schär *[1028]*) or by injection of b-naphthylamine and aniline (Perlman and Staehler *[935]*). Of late, attention has been turned to the changes in the blood caused by coal-tar derivatives and Ferguson hazards the suggestion that the carcinogenic agent may not be in the urine, affecting the mucosa directly, but in the circulating blood, exerting its harmful effect in the terminal capillaries of the mucosa of the bladder.

According to Anderson, a white man employed in the nitrobenzidine department of the dye works in the Wilmington area was found by cystoscopic examination in December 1931 to have a tumor of the bladder. This was the first recognized American case of aniline tumor. Since then 25 have been discovered. Family history seems to have no bearing on the incidence of these tumors. A history of previous attacks of cyanosis was obtained in less than half, 48 per cent, of the subjects and an equal percentage had a history of urinary disturbances, frequency, dysuria, and hematuria, but in 42 per cent there was no such history, which shows that without a cystoscopic examination more than half the cases would not have been discovered.

Gehrmann's contribution to the du Pont symposium *(315)* was one of unusual interest. He was able to report on cystoscopic examinations of 532 men and the discovery of 25 positive cases, or an incidence of 4.5 per cent. Sixteen other cases were found in which there were hemorrhagic areas in the bladder. A second group of 55 cystoscopic examinations yielded 2 positive cases, or about 3.6 per cent. The age of the men affected varied from 30 to 60 years, and the time of exposure from four to eighteen years. Of the twenty-five tumors, fourteen were simple papillomas, eight definitely carcinomas, and three were at the moment doubtful. The men had all been exposed to either b-naphthylamine or benzidine, and only two had not been exposed to the former. The two men in the second group who showed tumors had been exposed to a-naphthylamine. Germans do not connect this last with bladder tumors, but both American and English experience

incriminates it, probably, Gehrman thinks, because in these countries it contains about 5 per cent of beta while in Germany it is beta-free. The three responsible agents, then, in the experience of the du Pont Company seem to be beta-naphthylamine, benzidine, and aniline.

Oppenheimer's *(908)* last report in 1927 deals with 40 German cases, 22 of which have already been discussed in previous papers by the author. The substances to which these subjects were exposed were all amido compounds, aniline being responsible for 16 cases, benzidine for 6, and naphthylamine for 3. The others were exposed to more than one amido compound, but aniline or benzidine were involved in 10 further cases. The duration of employment before development of a tumor ranged from one to seventeen years, with an average of eight years. A striking case was that of a man who left the aniline factory after only two years' employment and developed cancer of the bladder seventeen years later. Oppenheimer finds that irritation of the bladder and cystitis, which are common troubles in chemical workers, do not occur in those who develop tumors of the bladder, and therefore cannot be relied upon to give warning of a precancerous state.

The first report of aniline tumors of the bladder in Russia was published in 1926. Three cases were described, all in users of aniline black. The victims had worked for thirty, thirty-five, and forty-five years, respectively.

Prevention. Preventive measures must be directed toward the three compounds, beta-naphthylamine, benzidine, and aniline, especially by means of a closed system when practicable, supplemented, when not practicable, by exhaust ventilation. Even with these measures the problem of adequate protection for the men making mechanical repairs is a very difficult one. Periodic medical examinations must be kept up throughout employment even if the man is shifted to harmless work, for experience has shown that a tumor may develop as many as thirty-five years following exposure to the inciting agent. If the man is discharged he should be given an examination at least once a year thereafter. No applicant for such work should be accepted who is under 20 or over 45 years of age, and those taken should be physically perfect (carious teeth and diseased tonsils can be attended to), if they are to be put into hazardous work of any kind. If the job

deals with the three agents mentioned, a cyctoscopic examination must be made once a year in every case and immediately if blood appears in the urine. The procedure of shifting victims of bladder tumor to other work has been abandoned, on the advice of the German authorities who maintain that once a man has been exposed removal does not lessen the danger to him and only results in the exposure of a new man. Gehrman speaks of a German dye plant where there is a completely closed method of manufacture and where dust and fumes were entirely eliminated fourteen years ago. No men taken on since have developed tumors but some of the older ones have.

Goldblatt (*392a*) also believes that the victim of "aniline" bladder tumor should be kept on the job, provided he is closely observed and cystoscoped at regular intervals. The earliest warning symptoms are low back pain, suprapubic pain, or even vague hypogastric pain. Hematuria is the first positive sign. These are important if they appear in a man working with beta-naphthylamine or benzidine, perhaps with aniline or alpha-naphthylamine. The prognosis for "aniline" bladder cancer is fairly good, better than that for the nonoccupational kind.

Neither the Germans nor English use cystoscopic examination as a routine measure, being convinced that their workmen would never endure it, and they depend on the detection of blood in the urine. After blood has been found three times the cystoscope is used. Gross, of Elberfeld, and Simon (See Hueper *[538]*) of Ludwigshafen were opposed to biopsy of these tumors holding that it leads to multiple implants and recurrences. They made the diagnosis in doubtful cases after fulguration, claiming that all simple tumors respond favorably to it, malignant do not.

Treatment. The final article by Washburn *(315)* takes up the treatment of bladder tumors, by fulguration and implantation of gold radon seeds, and by open operation.

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