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Pneumoconiosis

BERYLLIUM

BAUXITE FUME

COMPENSATION

LEROY U. GARDNER MEMORIAL VOLUME

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Pneumoconiosis

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Leroy U. Gardner Memorial Volume



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PNEUMOCONIOSIS

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INDUSTRIAL TOXICOLOGY

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CHAPTER FOURTEEN

Aromatic Series
Coal Tar Benzene, or Benzol

Sources of Benzol Poisoning. *Coal tar benzene*, or *benzol* (which is a much more practical name, since benzene and benzine are pronounced exactly the same but are quite different), is much the most interesting of the industrial solvents and, with the exception of tetrachlorethane, the most dangerous. It is so recognized in industry, and its use has been abandoned, often at a good deal of sacrifice, by conscientious employers who refuse to subject their workers to such a risk. But apparently as soon as it is given up in one industry it is adopted in another, and eternal vigilance is needed if chronic benzol poisoning is to be prevented.

Before the First World War the coal tar solvents were not widely used in this country and were not produced at all. What we needed we imported from Germany and American coke ovens were run without any attempt to salvage these valuable vapors. Then the war cut off the German supply and also the supply of important derivatives, dyes and dye intermediates, aniline for rubber compounding, and phenol and toluol for explosives. Coke-by-products plants were built and increasing quantities of benzene and toluene were produced. It was then that benzol poisoning made its appearance in American industry. At first the cases were acute. By 1916, some 14 had been reported, with seven deaths. So little was known about the action of this new solvent that exposures were permitted in those early days which seem shocking to us now: repairing pipes in a benzene still which had to be entered by a manhole just big enough to let a man crawl through, working inside a storage tank or inside a tank car, all of them supposedly emptied of benzene and washed out.

According to Legge (*683*), chronic benzene poisoning was first

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recognized in England in 1918 in two healthy young men employed spreading balloon fabric with rubber dissolved in pure benzene. Formerly petroleum solvent had been used. Both men sickened after some three months exposure, one dying a week later, the other in three weeks. Investigation resulted in the first report of an air analysis to ascertain the amount of benzene in the air. In various parts of the workroom the concentration was from 2.1 to 10.5 parts per 10,000 of air. This is not as bad as the report from an Italian raincoat factory (see Pugliese [*965a*]) where there was one part in 1000 of air. In another Italian factory, where several cases occurred, the concentration was 2 to 3 parts per 10,000. In those days nobody had any idea of what figure represented the danger limit. An American chemist told one of the writers (A.H.) that he did not see how the men in the rubber-spreading department could be poisoned, since there was only 5 per cent of benzol in the air.

Acute Benzol Poisoning. Acute benzene poisoning is of little importance under modern industrial management. The danger is well understood, and no longer are men sent unprotected into tank cars or vats. It is a narcotic poison, which acts with great swiftness producing unconsciousness or helpless confusion. In such cases it is often the rescuer, exerting himself to save the victim, who gets a fatal dose, while the passive victim survives.

Kobert (*616*) put benzene under the heading "Poisons which can kill without causing severe anatomical changes." Schmiedeberg (*1036*) as early as 1881 established the fact that benzene is eliminated partly in the expired air, and partly by the kidneys, being converted to phenol and excreted in the form of conjugated sulphuric or glucuronic acids. This change is, however, fairly slow and, according to Heffter (*481*), the search for phenol bodies fails in cases that are rapidly fatal.

The earliest record of an autopsy on a case of acute benzene poisoning is that of Sury-Bienz (*1144*) in 1888. By 1915 Heffter (*481*) had collected twenty-one reports from German literature. The most characteristic change in man, as in animals, is dark-red blood which is very slow to clot but which does not show hemolysis. Hemorrhages, usually punctate, are found in the lungs and pancreas and in the gas-

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tric and intestinal mucous membranes. The abdominal organs are congested and there are many bright-red spots on the skin.

The record of an autopsy made by Martland in 1931 (personal communication) is interesting because it was performed while the body was still warm. Even then there was no aromatic odor from the lung cavity but chemical analysis showed benzene in the lungs and brain. The other findings were typical of asphyxia.

One does not hear nowadays of sequelae from acute benzene poisoning because acute cases are extremely rare, but some such instances were reported in the earlier days, although they were always exceptional. Kobert described one, in a man who was painting the inside of a reservoir with bitumen dissolved in crude benzol. The victim had an attack similar to that of acute alcohol intoxication, from which he recovered, but later on, without further exposure, he developed pleurisy and apical catarrh of the lungs and was never restored to complete health. One of Lewin's (*716*) patients with relatively light symptoms, had persistent after-effects, a blowing heart murmur, slight jaundice, and nervous exhaustion.

Genhard (*369*) saw a weakly lad of 18 who had acute poisoning after only two days of exposure, extracting pyramidon with hot benzene. This boy had catarrh of the upper air-passages with slight fever, an exanthem over his back, and marked weakness. At the end of twelve days he was still unable to walk.

An unusual history is given in the British Factory Inspection Report for 1918. The victim was a man employed in a benzene distillery, and on a certain night the volume of vapor was greater than the condenser could deal with, consequently some of it escaped and the man was overcome. He was revived with oxygen and the next night returned to work, but although the still was then working well he was again overcome and this time died without regaining consciousness.

Chronic Benzol Poisoning. Chronic benzene poisoning is not only far more frequent but to the industrial physician infinitely more important and difficult to deal with. It was brought to the attention of physicians by Santesson (*1021*), the Swedish toxicologist, who read a paper, now classical, before the International Medical Congress in Moscow in 1897 in which he described 9 cases of purpura hemorrhagica in girls using benzol-rubber cement, 4 of these cases ending in

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death.[1] The next milestone came in 1910, when Selling (*1067*), of Johns Hopkins, reported 3 similar cases in girls using a benzol-rubber seal for tin cans. Selling made extensive animal experiments, and he was the first to assert that the essential characteristic of benzol poisoning is not the purpura hemorrhagica, but an extreme leukopenia caused by aplasia of the bone marrow, affecting especially the granular leucocytes, to a slighter extent the mononuclears, and the lymphadenoid tissues. His work, published in Germany as well as in the United States, attracted widespread attention and led to the advocacy by Koranyi, of Hungary, of the therapeutic use of this leukocytic agent in the treatment of leukemia.

This date marks a sudden increase in interest in benzol and a large number of clinical and experimental observations followed, in which Selling's findings were confirmed and certain important details of the blood changes added. Such are the thrombopenia (Duke [*261*], Hurwitz and Drinker [*549*]), the diminution of defensive substances, precipitins, agglutinins opsonins (Rusk [*1015*], Hektoen [*490*]), and the lowered resistance to infections (Simonds and Jones [*1087*], Smith [*1092*], Winternitz and Hirschfelder [*1267*]), resulting from the loss of these substances, as well as from the disappearance of phagocytic leucocytes. A lack of reaction to mechanical injuries and chemical irritants and to excessive heat was also noted (Camp and Baumgartner [*140*]). Finally a new impetus was given to the study of this interesting poison by the great increase in its industrial use which followed the First World War. A large number of clinical studies of chronic benzol poisoning, always of industrial origin, have appeared since 1922, and we have now a picture of this form of industrial poisoning which is far more varied than in early days and grows more varied all the time (see *1055*).

Duvoir (*263a*) and his colleagues estimate that when benzol vapors enter the body 66–72 per cent are expired and only 28–34 per cent stay in the body and are absorbed in the blood. Of this absorbed benzol 15–30 per cent is oxidized to phenol and diphenols (catechols,

[1] Strangely enough, almost fifty years later in Santesson's own country, mass poisoning from benzene fumes occurred in a raincoat factory where seams were gummed by hand on open tables with a solution of rubber in 90 per cent benzene. The cause of the general ill-health of 184 workers was very slowly recognized. (See *J. Indust. Hyg. & Toxicol. Abstr.* 27: 135, 1945.)

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hydroquinone) and eliminated partly as such but more as esters of sulphuric and glycuronic acids. This is in acute poisoning. In the chronic form 55–60 per cent of the benzol absorbed by the blood is fixed in the bone marrow, fatty tissue, and liver.

Clinical Picture in Benzol Poisoning. In 1923 a committee was appointed by the National Safety Council to determine the prevalence of benzol poisoning in industry, the dangerous concentration of benzol fumes, and the diagnosis of early poisoning. The industries studied were the manufacture of rubber, of artificial leather, of food cans, and of paint and varnish removers. There were also five chemical works and three by-products plants. The investigators collected records of 98 cases of benzene poisoning; 15 of these cases were fatal. Of these, 6 were acute, with four deaths; 92 were chronic, with eleven deaths. The diagnosis of early poisoning was based on changes in the blood, especially in the leukocyte count; a loss of 25 per cent from the normal standard of 7500 white cells was considered suggestive of intoxication. A distinct relation was found between exposure to benzene fumes and signs of early poisoning. Actual findings of benzene concentration in the air of workrooms varied from 28 to 4140 parts per million.

The publication of this report was followed by a great increase of interest in this form of occupational poisoning on the part of industrialists and in many plants routine blood tests were made to detect early cases. Usually an absolute leukocyte count was considered sufficient but might be supplemented by a differential count.

The clinical picture that emerges from the early studies and that dominated the scene for many years is one of progressive weakness, with a sense of malaise and fatigue, then oozing of blood from the gums, throat, and nose followed by rapid decline; petechiae; hemorrhage from the stomach, intestines, uterus, and mouth; sometimes chills, sometimes delirium; and death from anoxemia and heart failure with pulmonary edema, or from toxemia following suppurative lesions in the throat. There is erythropenia, which may reach a very low count, with absence in the circulating blood of any youthful forms of red cells; the index may be low or high; there is a leukopenia which may reach an extraordinarily low level and in which the polynuclears are chiefly involved (with an Arneth swing to the right);

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absence of myelocytes, myeloblasts, and lymphoblasts; decrease of the platelets, sometimes impressive; slow coagulation of the blood, with no retraction of the clot.

For many years Selling's description of the blood picture in benzene poisoning was universally accepted and a picture which did not conform to the standard led to a diagnosis of other diseases, even if the exposure to benzene was clearly proved. The most characteristic and striking sign, according to Selling, is leukopenia; the fall in the red cell count is far less striking; the most important change found postmortem is aplasia of the bone marrow; damage to the lymphadenoid tissues is far less important. Among the leukocytes the polynuclears suffer the most. In the early stage of poisoning stimulation of cell production is seen in the marrow accompanying the destructive process. Regeneration can occur after an advanced degree of aplasia. Benzene also is a direct leukotoxic poison acting on the white cells of the circulating blood.

The general acceptance of this blood picture as characteristic of the action of benzene on the bone marrow led to the establishment of a standard for the guidance of industrial physicians so that they might detect early cases in time. The white cell count was all-important, and a fall below 5,500 was the warning sign of danger (see Winslow [*1265*]). In 1927 Hunter and Hanflig (*548*) were quite justified in asserting, on the basis of published cases of benzene poisoning, that it was not difficult to discover early cases before the stage of marrow aplasia was reached and to remove such individuals from fumes before serious symptoms developed. All that was needed for a diagnosis was an absolute and differential white blood cell count, together with a history of exposure.

But gradually many divergencies from this type of blood picture were discovered. Typically, the leukopenia should be a granulopenia, and in some cases the polynuclears do fall as low as 10 per cent of the leucocytes and even lower counts have been found, but it is not safe to reject the diagnosis of benzol poisoning because of a normal white cell count or even a polynucleosis, for if there is a focus of suppuration present there may still be enough active marrow tissue left to produce a response in the form of increased polynuclears (Paul *et al.*

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[*824*], Meda [*816*]). This has been shown in several clinical cases and in some experiments when the animals developed infection (Weiskotten [*1232*]).

Typically, the red cells should present a perfectly normal picture, but this does not always appear. Some observers have found abnormalities of size, shape, staining properties, stippling, and even nucleated red cells (Hunter and Hanflig, Ronchetti [*1001*], Oettinger [*886*]). The textbooks tell us that one of the diagnostic points between benzol poisoning and pernicious anemia is that the color index is low in the former. Cabot (*136*) says that pernicious anemia is the only blood disease in which there is a high color-index. However, a review of 75 published cases in 1931 showed that while the index was low in 17, in 22 it was high and in 36 it was normal. Apparently the lower the red cell count, the higher the color index, although this rule also has exceptions, for in Selling's famous cases there was profound anemia with a low index.

Hemorrhage is a conspicuous feature of benzol poisoning, traceable, of course, to the thrombopenia, but absence of hemorrhage is not conclusive, for even in patients with a marked loss of platelets, clinical purpura may fail to appear. In women the only evidence of this change in the blood may be an increase of the menstrual flow, or, if pregnant, uterine hemorrhage (Hogan and Schrader [*527*]). In one man, renal hemorrhage was the only abnormal bleeding noted (Oettinger). Animals show dramatically the leucotoxic effect of benzol, but they do not show the fall in red blood cells which in human beings is often even more conspicuous than is the fall in white cells. If the physician depends on a leukopenia for the diagnosis and fails to make a count of the red cells, the patient may be fatally poisoned before the physician discovers that benzol poisoning has caused marrow aplasia. We have the history of a patient with benzol poisoning who had a blood count of 6800 white cells, but only 1.5 million red cells; another with 7000 white cells, but only 1.9 million red. Out of seventy-seven blood counts collected from the literature there were 17 in which the blood picture was such as that seen in benzolized animals (*viz.*, a leucopenia far in excess of the anemia); but there were 22 with the reverse (*viz.*, excessive anemia with a moderate leukopenia), and in

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these cases the white count alone would not have revealed the condition.

Gone are the days when all the industrial physician needed to make certain that his charges were not being harmed by benzol fumes was the determination of leukocyte counts (differential as well as absolute if he was conscientious) at stated intervals. Now he must be alert to note any possible deviation from the normal blood picture.

To illustrate how far we have traveled in recent years one may quote Vaughan's (*1194*) (1944) summary of the blood changes that may be found in benzol poisoning: either an increase or a decrease in the red count; an increase or decrease in the white count; elevated reticulocyte count; eosinophilia; presence of megalocytes; platelet reduction.

The literature has now an impressive number of instances of "atypical" benzene poisoning, so many that it is no longer possible to cling to one typical standard. A few striking instances of deviation from the long-accepted description will be given.

One of Hunter's (*547*) cases illustrates the ease with which a correct diagnosis may be missed. This was in a woman, a telephone operator, whose occupation had nothing to do with benzene and who, though she had a profound anemia (1.3 million red cells; hemoglobin, 22 per cent), had a normal white cell count. Only when biopsy of the sternal marrow revealed marked aplasia was it revealed that she had for the six years prior to the examination used daily a small amount of paint remover to clean her switchboard. The fluid contained about 50 per cent benzol. This patient died two and a half months later and autopsy showed an aplastic marrow.

Another of Hunter's patients had a blood picture characteristic of pernicious anemia and some years ago that diagnosis would have been made without hesitation, especially since gastric analysis showed no free hydrochloric acid. Biopsy of the bone marrow led to the diagnosis of chronic benzene poisoning.

The case described by Heimann (*457*) would have been pronounced in former times one of Vincent's angina, for there was a gangrenous stomatitis which rapidly progressed through the cheek, and the white cell count was 10,000, the temperature 102.2° to

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105° F. Autopsy revealed "a tremendous aplasia of the bone marrow."

Hunter saw an instance of abnormal high red cell count in a young chemist who had worked with benzene only seven weeks, but because the patient liked the odor, he would inhale the fumes deeply. His erythrocytes numbered 7.28 million. He complained of fatigue and loss of appetite, but these disappeared as he quit work for even a couple of days and after one week's absence from the laboratory the erythrocyte count fell to 5.7 million, the leukocyte count from 12,600 to 7,900. In all, in 7 out of Hunter's 57 cases there were increased erythrocyte counts. Hunter calls attention to Smith's similar findings, for among the seventy-one women workers with benzene whom she examined, no less than fourteen had erythrocyte counts over 5 million. This figure is more significant among women factory workers than among men workers.

Recovery may be very slow. Goldwater and Tewksbury (*396*) followed for many months the cases of benzene poisoning in rotogravure printers, studied by Greenburg's group. They examined fifty-six men two months after exposure had ceased, forty-nine at the end of fourteen months and 108 at the end of twenty-four months. Those examined at the end of two months, during which time they were under treatment, showed practically no change, indeed in a number of cases the blood picture was farther from the normal than it was when exposure ceased and treatment began. Those examined at the end of fourteen months showed very decided improvement but not universal recovery. Four were still in the positive class and one border-line case showed regression.

Even after the lapse of two years, four of the 108 men showed distinctly abnormal blood pictures and eight others showed abnormalities of lesser degree.

Helmer (*494*) followed the course of 62 cases of mild, moderate, and severe benzene poisoning in men and women using a rubber-benzene cement in a Swedish raincoat factory. The exposure was excessive, up to 17 mg. per liter of air (5500 ppm). Two of the patients died, 6 took nine to sixteen months to recover, and 12 were still on the sick list after sixteen months.

Two marked features of chronic benzol poisoning are sources of much difficulty in medicolegal cases. One is the great variation in sus-

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ceptibility between individuals, which is shown by the occurrence of a case of severe or fatal poisoning in a factory where only the one worker showed any symptoms of poisoning; the other is the progressive action of the poison after the exposure to it has ceased. It seems that the injury to the marrow, once started, progresses without any further intoxication. This has often been observed in animals as well as in human beings. Four of Santesson's 9 girl patients developed serious symptoms only after they had left the factory, and in a case described by Rohner (*997*), of Iowa University, the victim quit work simply because the fumes irritated his eyes, and it was not until a month later that hemorrhage began and he developed a fatal aplastic anemia.

The number of these cases reported in the literature has increased decidedly in recent years. In 2 of F. T. Hunter's cases, both fatal, there had been no exposure to benzol for sixteen or seventeen months prior to treatment. The British Factory Report for 1931 tells of a man who was exposed to benzol at a distillation plant for thirty years, then for eight years he was in the packing department, with no exposure. Nevertheless he died of what, had not benzol entered the situation, would have been diagnosed as agranulocytic angina. A similar case was found by A. Ross Smith (*413*) among the rotogravure printers who were examined by Greenburg's group. The patient had worked with benzene for three years, using a degreaser with 10 to 35 per cent benzene. He was examined in 1939 and no abnormality was found except for a white cell count of 4900. After that he had no exposure to benzene but in 1943 he died of aplastic anemia. There were ulcers in the mouth.

An even more extraordinary instance of benzene latency is the case described by Meyer and Guisberg (*827*), for here the exposure, though apparently excessive, lasted only one year and was followed by nine or ten years (it is impossible to determine which) of no exposure during which period the patient was employed as watchman and apartment house superintendent. At the time of examination the patient complained of fatigue, of eighteen months' duration, and of weakness, numbness of hands and feet, vertigo, nausea and vomiting, edema of ankles, and precordial pain which was relieved by rest, the latter symptoms being of four weeks' duration. The only striking find-

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ings were in the blood, R.B.C. 1.5 to 2.0 million, hemoglobin 40 per cent (Sahli) W.B.C. 1700 to 3000 with 60 to 80 per cent lymphocytes, platelets were conspicuously absent. No immature or abnormal cells were seen. The patient's course in the hospital was rapidly downward, with hemorrhage, ulceration of the gums, fever of 103° to 105° F. and death after fourteen days. Section of the bone marrow from rib, sternum, and vertebra showed areas of extreme aplasia, but also areas in which hematopoiesis was still active.

Smith hazards the theory that the appearance of symptoms after long periods of freedom from exposure may be explained as caused by infection or disease or even the wear and tear of life, acting on an organism already damaged by benzol, but only to a "subclinical degree," until the added strain causes a failure of the already damaged hemopoietic system.

There is absolutely no ground for the assertion sometimes made that persons exposed to benzene become acclimated to its action. This is refuted by the numerous instances of severe poisoning developing after many years exposure. Of F. T. Hunter's 10 cases, in five exposure had lasted for more than five years, in two of these for twelve years.

Vigliani (932), who has seen many persons with benzene poisoning in Italian rubber-works, divides them into four classes: (1) those with clinically, hematologically, and anatomopathologically typical cases of aplastic anemia; (2) those with clinically typical cases of aplastic anemia but showing an active hemopoiesis especially in the bone marrow, pseudo-aplastic anemia; (3) those with a typical aplastic anemia with myelitic hyperplasia or metaplasia resembling leukemia especially in liver and spleen; (4) those with chronic or acute leukemia, not infrequently appearing as aleukemia. All of these forms have been demonstrated experimentally in animals.

In Mallory's (*766*) 19 cases the picture in the bone marrow (fourteen autopsies and five biopsies) varied from severe hypoplasia to the most extreme hyperplasia and extramedullary hematopoiesis. Contrary to prevailing opinion, hyperplasia proved to be the more common of the two reactions. It was found only in patients with prolonged exposure, whereas hypoplasia may follow either long or short contact.

The spleen was found by Mallory and his colleagues always some-

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what abnormal, the site of remarkable cellular activity, and although splenomegaly was rarely apparent during life it was often discovered post-mortem. Changes in the liver were much less striking and the lymph nodes were occasionally enlarged.

As to the fourth class, evidence is piling up that leukemia, myeloid or lymphatic, may be one of the forms benzene poisoning may take. Vigliani and Penati collected 10 cases, which had been reported in the literature by 1938. An unpublished case of Martland's should be added to the list, a case in which the blood picture was characteristic of myelogenous leukemia (personal communication). Two more cases are described by Mallory and his colleagues. The first was in a man 28 years of age who had worked in an artificial leather factory for four years, using a large amount of benzol solvent. For six years after that his work brought him in contact with benzol fumes only for one hour a day. At the close of his first year of benzol work his blood count was normal, except for the polynuclear cells which were down to 58 per cent; a year later there was a slight fall in erythrocytes also, but no other abnormality. However, six years after all contact with benzene had ceased he had 2.41 million erythrocytes; the hemoglobin was 41 per cent; leukocytes numbered 57,200 with only 10 per cent polynuclear cells, 33 per cent myelocytes, and 47 per cent myeloblasts. The platelets seemed normal. The patient had an ulcer on the side of the neck; his spleen was palpable. The white cell count rose to 147,000 but fell to 33,000 two days before death; the anemia progressed in spite of blood transfusions. Hunter's diagnosis was "acute myeloblastic leukemia."

Mallory's autopsy showed a marrow with the fat entirely obliterated by dense masses of cells, predominantly myelocytes, with some eosinophilic and neutrophilic polymorphonuclear cells, normoblasts, and stem and giant cells.

The second case was in a 12-year-old boy, who spent much time in his father's shop using a paint remover which contained benzol. Severe nosebleed sent him to the hospital where the blood examination showed 900,000 red cells; 25 per cent hemoglobin; 5000 to 12,000 white cells, with only 13 per cent to 16 per cent polynuclear cells. A sternal puncture showed intense cellularity with only a rare fat vacuole, the cells being almost all lymphocytes, few granulocytic elements and

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nucleated red cells and only a moderate degree of mitotic activity. A diagnosis of aleukemic leukemia seemed justified.

The most recent addition to the list is Rachner's (*974*) case which is described as one of "chloroleukemia" and is attributed by him to benzol poisoning during a nineteen-year exposure, in spite of the fact that exposure had ceased two years before the onset of the sickness. Here, together with a profound anemia (1.8 millions R.B.C., hemoglobin 38 per cent), there was leukocytosis of 26,000, 56 per cent of them myelocytes and myeloblasts, only 28 per cent polymorphonuclears, and 14 per cent lymphocytes. Post-mortem examination showed infiltration of sternum, ribs, spinal column, parietal pleura, liver, and kidneys with masses of greenish tissue, consisting of irregular round and oval cells. Lymph glands also were enlarged and green in color. Rachner quotes Schilling's hypothesis, that benzol leukemia is the expression of an overcompensation of the blood-forming tissues following an initial aleukemia.

F. T. Hunter's studies of the blood of eighty-nine persons exposed to benzene fumes led him to lay the greatest stress on anemia as the earliest warning sign of danger, not leucopenia. All of his fatal cases of benzene poisoning, 10 in number, were among those with a low red cell count. As for the leucocytes, a decrease in the polynuclear percentage is a better index of early poisoning than either leukopenia or an absolute polynuclear decrease. The latter is a sign of a more severe form of poisoning and so is a decreased erythrocyte count.

Hunter takes as criteria for a normal blood picture: a red cell count of 4.5 million or over but below 5.2 million per cu. mm.; a white cell count between 6000 and 9900 per cu. mm. (the National Safety Benzol Commission put the lower limit at 5500); a polynuclear percentage between 60 and 80; an absolute number of polynuclears not less than 4500, not more than 7900; an eosinophilic percentage of 3 or less; an absence of young polynuclear leukocytes, myelocytes, myeloblasts, and nucleated red cells. He found eosinophilia often enough to believe that it is one of the signs of early poisoning.

The above papers, which were published in 1939 (*96*) as a Symposium on Benzene (Benzol) Poisoning, added much to our understanding of this many-sided poison. The publication presented the results of two group-studies, made in Boston and in New York. In

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Boston the subjects were workers, men and women, in artificial leather, in the manufacture of crepe rubber soles for shoes, in cementing shoes, making rubber goods, and using paint remover. The examination of the work places and the air analyses were made by Bowditch and Elkins; F. T. Hunter studied the clinical histories of 89 cases of benzol poisoning of various degrees of severity; Mallory, Gall, and Brickly described the post-mortem findings in 14 fatal cases and the biopsy findings in 5 cases.

In New York it was the rotogravure printing industry that furnished the cases. The introduction of benzene into this formerly safe work came with the increased speed of printing which required faster-drying inks, and benzol is the best for that purpose. Greenburg's group from the Division of Industrial Hygiene made the industrial survey and examined 332 pressroom workers. Erf and Rhoades reported the hematologic effects of benzene poisoning as seen in 9 cases.

The tendency of the male to react with hyperplasia, and of the female with aplasia, suggests that the belief that women are more susceptible to benzene than are men may be based on the failure hitherto to recognize the hyperplastic form of benzene poisoning.

A study of the hyperplastic cases reveals what may be called a neoplastic tendency, rapid growth as shown by mitotic figures, the development of cells having no counterpart in normal tissues but common to a variety of malignant tumors.

In a case seen by Johnstone the marrow was full of mitotic figures, and there were occasional giant cells with monstrous nuclei, suggesting a neoplastic tendency. A close similarity between these hyperplastic marrows and those described by Martland (773) in chronic radium poisoning was noted, and in both cases there is a prolonged latency and a tendency for disease to progress for months or years after exposure has ceased.

The influence of benzene on the course of infections in animals has been reviewed. Clinical cases confirm these facts. Thus Rohner and his colleagues noted as an outstanding feature the decided lack of response on the part of their patient to infection. Of F. T. Hunter's first 4 cases, the patients who died had septic temperatures, as did Selling's first patient with benzene poisoning, but the 2 patients who recovered did not. Meda reported a case of prolonged suppurative cysto-

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pyelonephritis; Smith (*1092*) reported one of obstinate suppuration of the axillary lymph nodes, another of abscess in the thigh. Severe lesions of the mouth are the most frequent manifestation of this action of benzene, and Vincent's angina was noted in several cases. Martland saw osteomyelitis of the lower jaw and gangrenous stomatitis. In Loewy's (*734*) patient death was due to gangrenous osteomyelitis of the jaw and gangrene of the lungs.

It is probably true of working people poisoned by benzene, as it was in the early cases of radium poisoning, that a diagnosis of Vincent's angina or osteomeylitis was made in many cases without inquiry into a possible occupational cause.

A recently discovered aid in the diagnosis of early benzene poisoning is the urinary test devised by Schrenk, Yant, and Sayers (*1041*) of the Bureau of Mines. They found uniformly in a series of about 100 animals an early sign of benzene poisoning in the urine, namely, a decrease in the proportion of inorganic sulphates to total sulphates, this decrease being marked in accordance with the severity of the intoxication. The same decrease was found in benzene workers.

Normally the inorganic sulphates make up 85 to 95 per cent, the organic, ethereal or conjugated, 5 to 15 per cent, but in cases of benzene absorption the phenolic products that are formed take up the sulphur, and the result is an increase in the conjugated sulphates which reverses the above proportions. "The most important fact relating to this test is that the decrease occurs rapidly on exposure to benzol and well in advance of leucopenia or anemia or other evidence of damage." Forssman and Frykholm (*338a*) found a marked increase in urinary ethereal sulphate excretion in Swedish rotagravure printers, exposed for long periods to benzene, compared with workers in the same plant not so exposed. They believe that a high excretion of ethereal sulphate is a warning of danger. Fifty-three rotagravure men averaged 27.2 per cent, controls only 7.5 per cent.

In other hands this test has proved of minor value. The studies made by the Boston and New York groups (*96*) showed that it failed in some cases of clinical poisoning and could not be depended on to reveal absorption of benzene. Like conclusions were made by the Public Health Service.

Prevention of Poisoning. Bowditch and Elkins believe that a deter-

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mination of the amount of benzene in the air is the most valuable of the preventive measures, for a dangerous amount in the air can be discovered before any clinical signs have appeared. Their air analyses in artificial-leather and shoe factories showed that a concentration as low as 150 ppm may cause fatal poisoning. In the Boston cases there were eleven deaths (from artificial-leather factories and from rubber and shoe factories) and the benzene concentration in these workplaces ran from 150 to 200 ppm.

Benzene used as a solvent in the stiffening of collars by impregnating the fabric with plastic caused a death from benzene poisoning, as recorded by Heimann and Ford (*487*), and they found early effects in three other persons on the same job. Air analyses showed the following concentrations of benzol in various samples of air: 41—72—111—115—187 parts per million.

Massachusetts has adopted 35 ppm as the maximum permissible concentration for benzol, Oregon and Utah, 75 ppm, and New York adopts 50 ppm "as a guide," not officially. The Public Health Service and the American Standards Association both retain the figure of 100 ppm established twenty years ago (1927) by the National Safety Council, the American Standards Association adding the proviso that this is to be considered a war-time standard.

Schrenk *et al.* compared the effect on dogs of vapors of pure, commercial, and crude benzene. Crude had the least physiologic action, commercial and pure were much the same. Hough and his colleagues (*535*) found in experiments on dogs that pure benzene was more toxic than a mixture of 60 per cent commercial benzene, 30 per cent toluene, and 10 per cent xylene.

It is interesting to note that Lockie and his colleagues (*732a*) succeeded in controlling a case of thrombocytopenia and one of neutropenia by administration of BAL.

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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-

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mortem examinations. Arkin and Wagner stated in 1938 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.

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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

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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 Gregorius (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

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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.

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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

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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.

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