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INDUSTRIAL POISONS IN THE UNITED STATES

BY

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PREFACE

THE sources of our knowledge of industrial poisoning in the United States are neither full nor, for the most part, accurate. We lack the sickness insurance system which obtains in all industrial countries in Europe and which brings to light the incidence of illness of all kinds in all groups of workers. Nothing takes its place in this country. Our private insurance companies sometimes gather important and trustworthy data, but these are never all-inclusive and never can be, they are always restricted to the group of individuals insured in that company. The Census reports are of deaths only, not illness, and the death records lose much of their value because of a poor classification of workers, which puts into the same category men doing work of very different degrees of danger, as for instance paper-hangers and painters. Trades union records are seldom of value, with the exception of those gathered by the typographical unions which were reviewed carefully by Verrill* and found to contain much that was interesting to the statistician.

It has been my task for many years to examine records of hospitals and dispensaries and to interview physicians in many parts of the country in my search for information about a given poisonous trade. Not one hospital in twenty has records which yield the sort of information which the student of industrial toxicology craves and yet this is not elaborate. If the recording interne would only treat the poison from which the man is suffering with as much interest as he gives to the coffee the patient has drunk and the tobacco he has smoked, if he would ask as carefully about the length of time he was exposed to the poison as about the age at which he had measles, the task of the searcher for the truth about industrial poisons would be made so very much easier. I have often had to reject fully one-third of the cases of plumbism which have been treated in a hospital because the interne had no curiosity about the source of the lead, contented himself with the notation, "lead worker," and so made it impossible for me to know from which of the many lead trades the man came.

Physicians in private practice have given me the greatest assistance, yet there are limitations to the value of the information obtained in this way. The diagnosis must be accepted, of course, as the Bureau of the Census accepts the death certificates of all

FACE

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is kind the existence of a prejudice
f some first-class men. Apparently
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y with which they approach those
o the working classes. For a strik-
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n and the evils of trades-unionism.
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ing to give out facts which may seem
the other hand I have often had all
me and been permitted to make what

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ity workers, priests, often let drop
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ho made the blue bed, seemed to me
n handle only clean lead buckles, but
that remnants of old corrosions were
s covered with dusty white lead, and
or the cases.
enormous value for the physiological
the mode of entrance, but it can tell us

nothing about the probable incidence of poisoning in American industry because our methods differ decidedly from the European. Some trades which are dangerous there are quite harmless here. For instance, the making of cheap kitchen ware is one of the bad lead trades of England, here it is not a lead trade. Dyeing cotton and wool and handling them after dyeing, making files, polishing diamonds, these are occupations notoriously fraught with danger of lead poisoning in Europe, but not in the United States. On the other hand we have industries which are much more dangerous than theirs, such as the making of white lead by a dry process instead of a wet one, the use of large quantities of non-fritted white lead in pottery glazing, and the use of lead-laden enamel powder for sanitary iron ware. It is not possible to draw conclusions as to the danger of any occupation in the United States by simply consulting the foreign literature about it.

There has been an enormous increase in the interest of the medical world in industrial toxicology of late years, especially since our entrance into the war in 1917. There are already some studies of poisonous trades in the United States which for thoroughness leave nothing to be desired. Perhaps the study made by Edsall, Wilbur and Drinker * on manganese poisoning stands at the head of these, for they were able to study the incidence in a large group of workmen, the conditions under which poisoning occurred, the mode of entrance, and the clinical manifestations, of early stages of poisoning as well as of the later stages. At the foot would stand the single observation made by a physician in private practice on a case occurring in a plant to which he has no access and the description of which he must take from his patient. He cannot check up his findings, he cannot be certain that this, to him new and unfamiliar poison, is really responsible for the lesions he has observed; all he can do is to present his findings, suggest their possible significance and let it go at that. But he is really performing a valuable service when he does this, for such reports, incomplete as they must be, have often led to the exploration of a new and important field of industrial toxicology.

I have called this a study of industrial poisoning in the United States and have tried so far as possible to present American material, but obviously that is not always practicable and much that we owe to foreign observers has had to be included. It has been my purpose to avoid when I could the earlier writings which have been reviewed in the existing textbooks and to give as much new material as possible. The literature up to January 1, 1924, has been included.

* Edsall, D. L., Wilbur, F. P., and Drinker, C. K. *The Occurrence, Cause and Prevention of Chronic Manganese Poisoning.* *Journ. Indust. Hyg.*, 1919-20, [illegible]

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INDUSTRIAL POISONS IN THE UNITED STATES

tremors of hands and outstretched tongue and a neurasthenic condition.

This long continued neurotic condition is noted by Jaquet (3) in his first case, and by Bing (4) in his first case. Floret (5) describes three cases in one of which there was nausea, double vision, staggering gait, and after five days an attack of frenzy followed by coma and then by delirium with hallucinations, epileptiform attacks and prostration, followed by a prolonged period of mental apathy and languor and apparent muscular weakness.

Löffler and Rütimeyer (6), failing to find any bromin or bromin compounds at autopsy on a case of typical poisoning from methyl bromid, exposed guinea-pigs to the fumes, and found that, if the animal were killed immediately after exposure, the substance could be demonstrated in fluids and organs, but that if it lived for 30 to 70 minutes after removal from the fumes it was almost, if not quite, impossible to detect methyl bromid in the body.

The last cases of industrial poisoning from methyl bromid reported in the literature are Cade and Mazel's (7), from a French chemical factory. In the first case, as in that of Löffler and Rütimeyer, the man was exposed several times to the fumes of methyl bromid and at last succumbed to an exposure rather greater than usual. A leak occurred which he tried to stop with cotton an hour before he left the works. Sixteen hours after the inhalation of fumes he had diplopia with indistinct vision, his fingers and legs became useless, and he was unable to tell his name or to write it. He had violent pains in the legs and marked motor incoördination. In a second case the man, aged 59, had been engaged at times for 32 years in the manufacture of antipyrin and had had four attacks of mild methyl bromid poisoning with complete recovery in the intervals.

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(4) Bing. Quoted by Röhrer (2).
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CHAPTER 33

BENZENE

Benzene, or benzol, as it is usually called, is one of the most important of the industrial poisons, but its use in industry is comparatively recent, and therefore the literature concerning industrial poisoning by coal-tar benzene and its homologues, toluene and xylene, is not very full; indeed most of it has appeared too recently to be incorporated in the text-books. It seems wise, therefore, to handle this subject as completely as possible; for there is every prospect that the use of coal-tar distillates will continue to increase in the near future, and it is of the greatest importance that the dangers attending them should be clearly understood.

Coal-tar benzol is properly called benzene and is represented by the formula C_6H_6. Unfortunately this term is likely to be confused with petroleum benzin, but it is the one insisted upon by the chemists. Toluene (toluol) is methyl-benzene with the formula $C_6H_5CH_3$, and xylene (xylol) is dimethylbenzene, $C_6H_4(CH_3)_2$. These bodies are obtained as by-products in coking coal, and in the production of illuminating gas. They are collected in heavy oils, and distilled off.

Pure benzene distills at 80° to 81° C. It is a very volatile colorless fluid with a pleasant odor which is not locally irritating and which arouses no suspicion of danger. The vapors are three times as heavy as air. Toluene distills at 110° C. and xylene at 137° to 143°.*

Besides pure benzene and toluene and xylene, there are several kinds of commercial benzenes, which contain toluene, xylene, thiophene, and rarely traces of carbon disulphid.

The usual commercial products are:

Pure Benzene—A clear colorless liquid of a characteristic odor. B.P. 79.7° C.

Ninety-per cent Benzene—So called because in the distillation 90 per cent distills over at a temperature of less than 100° C. It is composed of 80 to 85 per cent benzene, 13 to 15 per cent toluene, 2 to 3 per cent xylene, and sometimes contains as impurities traces of olefins, paraffins, sulphuretted hydrogen and other bodies.

Fifty-per cent Benzene—This substance contains 50 per cent of constituents which distill below 100° C., and 90 per cent below 120° C.; it is a very mixed product, with only 40 to 50 per cent. benzene.

* Pierron, C. O. *Chemistry, Inorganic and Organic*, Phila., 1923, p. 537.

SOLVENT NAPHTHA—This material is called solvent naphtha because it is used extensively (especially in England) for dissolving rubber. It is relatively free from benzene, and consists largely of xylene.

In Germany commercial benzene, as used in the rubber trade especially, may contain a large proportion (from 16 to 60 per cent) of carbon disulphid. Thiophene is of no importance toxicologically.

Uses.—Benzene is used on a large scale in solvent extraction work, extracting oil and greases, but this is done in hermetically sealed apparatus, the benzene being removed from the products before they are taken out so that the danger, as in benzene production, is only the risk of some accident to the machinery. In French dry cleaning, benzene was used for a while just after the war, but the increased fire risk has led to its abandonment except in a few cases.

At present, benzene is used in every branch of rubber manufacture, not of course in all departments of every rubber works, but in some department in practically every individual plant. It is a much better solvent for gums, resins, and fats than is any petroleum derivative and it dries faster than high-test gasoline. It is used for cement in shoe factories and in millinery manufacture,* in the making of fabrikoid, artificial leather, and linoleum, in coating leather for upholstery and for automobile tops, and as a constituent of shellacs, varnishes, gilding and bronzing fluids, varnish and paint removers, and quick-drying paints for interior work.† Enormous quantities of benzene rubber mixture are used in the making of so-called sanitary food cans. In the manufacture of pharmaceutical supplies, benzene is used to crystallize out coal-tar drugs. It is the starting point of many important intermediates in dye manufacture, such as anilin, and is also the starting point of synthetic carbolic acid and of the important explosive, picric acid. Copper and zinc are cleaned with benzene in preparation for galvanoplating, and photoengravers use it to dissolve rubber films. It is also used in the manufacture of kodak and moving picture films.

The largest commercial users of benzene at present, aside from the purveyors of motor car gasoline, are manufacturers of the following: rubber cement, rubber tires and shoes; brake linings, particularly for automobile brakes; artificial leather and fabrikoid; lacquers; cement for sanitary food cans; paint and varnish removers. All of these require the use of benzene in more or less open vessels or vessels which have to be opened from time to time.

The National Safety Council undertook to study benzene poisoning in industry during the year 1923 by sending out questionnaires

* The Ohio State Department of Health found in one millinery cement 49.5 per cent by volume, and in another no less than 92 per cent.

† Some of the newer quick-drying "flat coat" paints contain benzene in appreciable quantities. For instance, [illegible] the liquid medium is 10 per cent benzene and the directions call for the addition of benzene if the paint is too thick.

to the producers and users of this compound, obtaining information from 67 firms. Thirty of these firms employed less than five in processes exposing them to benzene; four employed a hundred or over, the largest being a rubber factory where 1080 were so employed. Of the firms employing ten or more people in benzene work, eight were rubber factories, five were chemical works, four were paint and varnish makers, three were gas plants recovering benzene as a by-product, one was making celluloid and artificial leather, one japanned goods, and one was a can factory.

The substitution of benzene for petroleum distillate in motor car fuel leads to a change in the composition of the exhaust gases and undoubtedly adds to the danger from these gases in garage work. Yandell Henderson (1) and his colleagues have compared the amounts of CO found in the blood of dogs dying from exposure to various CO-containing gases and found that death occurred at a lower CO saturation when coal-tar distillate was burned than when gasoline was, and to a slighter degree this is true where illuminating gas is used. When pure CO was used, the blood at death contained 84 per cent CO; after illuminating gas poisoning, only 70 per cent CO was found in the blood; after death from gas from a motor car using gasoline, 83 per cent CO was found in the blood; but after death from gas from a car using coal distillate, only 62 per cent was found. The composition of this distillate was as follows: benzene, 69 per cent; toluene, 15.5 per cent; solvent naphtha, 13.5 per cent; heavy naphtha, 2 per cent.

The symptoms of illuminating gas poisoning differ from those of pure CO poisoning; for there is more respiratory excitement and quicker collapse, and there is nausea and vomiting. Apparently the action of gasoline exhaust gas depends entirely upon the CO that is present, but the exhaust gas from coal distillate causes symptoms resembling illuminating gas poisoning and the difference is attributed to the presence in both of these gases of benzene vapor. Kobert (2) also says that the greater toxicity of illuminating gas as compared with pure CO is to be explained by the presence of benzene in the former, and Staehelin's experiments prove the same. He was using CO on frogs; but, running short of the pure gas, he undertook to substitute illuminating gas, whereupon the frogs developed convulsions, as they had under CO. Staehelin (3) found that benzene vapor in the gas accounted for this difference. (See Haggard's experiments with neuroblasts, p. 396.)

There has been much controversy as to which is most toxic, pure benzene or crude benzene, or the mixtures of benzene and its homologues commonly used in industry. Lewin (4), testing vapor on animals, found impure benzene more toxic than the pure. Chassevent and Garnier (5) say the same. Lehmann (6) tested the pure, the commercial, and the crude, and found them not very

different, the crude being slightly the most toxic; but the individual variations in the susceptibility of animals rendered the conclusions dubious. Lehmann says that the early symptoms come on most quickly with benzene; but narcosis, most quickly with toluene. On the other hand, Kobert (2) says toluene is much less toxic than benzene, but more irritating to the mucous membrane, though with less convulsive effect, for it is changed to hippuric acid in warm-blooded animals. Rambousek (7) found pure benzene the most toxic. Toluene, xylene, and solvent naphtha (which, he says, is a mixture of the higher benzenes, cumene, pseudocumene, and mesitylene cumene) all cause less convulsive effect and slower narcosis. Xylene is less poisonous than toluene. The recovery from toluene poisoning, however, is less rapid than from benzene poisoning. Agasse-Lafont and Heim (8) also insist that pure benzene is more toxic than crude. Hektoen and Brown (9) found far less striking and characteristic changes in chronic toluene poisoning than in chronic benzene poisoning. (See later.) Just recently Pugliese (10), investigating the cause of several deaths from benzene poisoning in a raincoat factory in Milan, tested the comparative toxicity of several varieties of this solvent which were used in the factory, and found that pure C_6H_6 acted most rapidly and intensely on animals, while the impurest and most ill-smelling sample was the least toxic. He found toluene less poisonous than benzene, but the vapors more irritating to mucous membranes, causing watering of the eyes, sneezing, and coughing.*

Effect on Animals.—Benzene has a pronounced action on the central nervous system, narcotizing, and lowering the body temperature. Animal experiments reveal a great difference in susceptibility, not only between different species but between different individuals in the same species. The vapors of benzene are toxic for animals when present in the proportion of 0.015 g. to 0.016 g. per liter of air (Rambousek). At this dilution the animal begins to show jerking of the leg muscles after 50 minutes. This symptom comes on immediately at a concentration of 0.056 g. per liter of air, convulsions develop in eight minutes, unconsciousness in ten. Dogs are more susceptible than rabbits and die after 20 minutes' exposure to 0.042 g. per liter of air. No after-effects are noted in animals surviving the experiment, and in those that die, nothing is found but moderate hyperemia of the brain, lungs, and mesenteric vessels.

Lehmann, experimenting with cats, found a decided variation of susceptibility in individuals, but all of them showed signs of irritation of the mucous membrane, muscular twitchings, and a fall of body temperature. In large doses there were convulsions;

* Cases of industrial poisoning from toluene are rare. British factory inspectors report a death from toluene fumes in a man who entered without a gas mask [illegible] which had held toluene and some ammoniacal [illegible]

narcosis; very deep respirations, first quick then slow; quickened pulse, and death from respiratory paralysis. A narcotic effect begins in cats after two hours' exposure to 0.02 g. per liter of air, and narcosis is complete in six hours. With 0.06 g. the periods are fifteen minutes and one hour, respectively. In man 0.015 g. per liter of air produces listlessness and confusion after half an hour, and exposure to 0.02 to 0.03 gm. (or from 2 to 3 parts per 100,000 parts of air), for a few hours may cause loss of consciousness.

Lehmann found the symptoms in animals very uniform in character, although varying in degree. First comes restlessness and excitement, partly from irritation of the nose and throat, especially with crude benzene, toluene, or xylene. Next, and fairly quickly, come symptoms of central irritation, dizziness, staggering, uncoordinated movements, and twitchings of the muscles lasting from half an hour to many hours and affecting single muscles or groups of muscles or whole limbs. The movements are clonic, sometimes tonic, but there is no tetanus. This condition makes observations on respiration and heart difficult; but apparently the former is first quickened then slowed, and the heart is rapid. At the end of the experiment a decided fall in temperature is always found, and this may be the cause of the twitching. The animals recover completely with no after effects, or else they die suddenly from primary respiratory or heart paralysis. Nothing typical is found at autopsy except that the blood remains fluid for a long time.

Acute Industrial Poisoning.—The earliest cases of acute poisoning were reported from Germany. At the Brussels International Congress of Industrial Hygiene in 1910, Rambousek summarized the histories of 22 cases* which he had gathered from the literature of that time. All these were acute cases and occurred in the following ways. Case 1 was distilling benzene, and forgot to turn on the cool water to condense the vapor. Case 2 was found dead before the building the next morning after he had let 900 liters of benzene overflow from a vat. Cases 3, 4, and 5 were poisoned in a benzene vat in a rubber factory; the two latter entered it to rescue the first. Cases 6 and 7 were exposed to benzene gas in a coke by-products plant. Cases 8, 9, and 10 were exposed to a mixture of benzene, hydrogen sulphid, and cyanogen compounds. Case 11 was cleaning apparatus in a benzene plant. Cases 12, 13, and 14 were reported by Lewin in 1907. They occurred in connection with work in a benzene extraction kettle. The next five were cleaning vats for the transport of benzene. Case 20 occurred in a rubber factory. Of the last two, one was making antipyrin, the other was painting an iron tank with asphalt dissolved in benzene. Eighteen of these cases were fatal.

* I have omitted Santesson's nine cases, which were chronic.

The literature of other European countries and of the United States have added many cases to this list during the thirteen years that have elapsed since then. These are typical histories selected from the mass of available material.

Lewin, in 1907, reported a case of fatal poisoning in a workman who had tried to rescue a man overcome with benzene fumes. A benzene kettle had stood empty for 22 hours, when it was washed out three times with cold water and twice with steam, and was allowed to stand all night filled with cold water. The man who was sent in to make repairs took with him a pipe through which was blowing a strong current of compressed air. Nevertheless, he fainted and fell to the bottom of the kettle. Several men tried to get him out, but all grew dizzy and confused and had to give up, until an engineer, with a diver's helmet succeeded in dragging him out. He was revived, but one of the men who tried to rescue him died ten minutes after climbing out of the kettle.

The German factory inspection report for 1913 contains an account of a similar case. Here, also, the tank was supposedly thoroughly cleaned; for it was boiled out three times, but the workman who went in lost consciousness; and although the two men who had been set to watch him dragged him out promptly he never revived. Beisele's (11) case was that of a man who died after only four minutes' exposure from dipping benzene out of a bowl.

The earliest instances of acute benzene poisoning in American industry were reported from establishments producing and using benzene for the manufacture of anilin and of explosives. By 1916, fourteen acute cases had been reported, seven of them fatal. The first two were in steamfitters employed in repairing pipes inside a benzene still where the manhole through which they entered was just large enough to allow them to crawl through. As usual, the still had been not only emptied but washed out, and it was supposed to be free from dangerous quantities of benzene; but soon after the men went in one of them became excited and irrational, singing and shouting. It was realized that he must be got out as quickly as possible; but this was a difficult thing to do through a narrow manhole, especially since he was irrational enough to resist. It took about ten minutes to get him out, and during much of that time the manhole was completely closed by his body. The second workman, who had been helping to lift him out, was then found to be lying unconscious on the floor of the still. Even more difficulty was encountered in removing him, for he was quite helpless, and when he was at last brought into the open air, which was after about twenty minutes, he was found to be dead.

The third and fourth cases had almost the same history. They, too, were in men who were working inside a still which was supposed to be free from benzene. They began to suffer from the effects

were dragged out in a state of coma, given vigorous treatment by the administration of oxygen and stimulants, but one died, and curiously enough he was the one who had had the shorter exposure. Two other fatal cases were caused by repair work in a benzene still. The fifth death was cause by a leak from a still, and the sixth and seventh were in men working in the sulphonating department of a phenol plant where benzene was sulphonated and where fumes escaped from the supply pump, the sulphonating kettle, and the liming vat.

In many cases it has been impossible to say whether or not death was instantaneous because the victim was not found till some time after. Sury-Bienz's (12) patient died in a very few minutes, as did Beinhauer's (13); but Heffter's (14) lived several hours. He was an assistant manager, and, accompanied by two helpers, he went into a cellar to open a benzene pipe which was stopped up. He started the flow, but could not stop it, and benzene splashed over his clothes. The helpers complained of feeling sick and he went upstairs with them, got two other men and went back to the cellar for half an hour. When he came up he fell in a faint at the top of the stairs, and although oxygen was administered for three hours he never revived.

I have the history of a case of acute benzene poisoning from a Pennsylvania phenol plant in which oxygen was given for more than two hours without saving the man. It is noteworthy that exertion increases the severity of the poisoning, or at least that seems the only way to explain the considerable number of accidents in which it is the rescuer who dies while the original victim, though sometimes exposed longer, survives. Of course individual susceptibility plays a great part. Lehmann (6) believes that this is the underlying cause of sudden death from benzene poisoning in industry. One of the many illustrative instances in the literature is a case described by Lewin. A workman had gone into a benzene extraction kettle and had fainted. His helper climbed part way in to rescue him, felt himself growing dizzy and confused, and backed out at once, but died in ten minutes, while the first man, who lay unconscious in the tank for several minutes before he could be removed, was saved.

That such an anomaly should give rise to controversy in compensation cases is inevitable. In one of the great steel works of Pennsylvania, two workmen were sent into a benzene tank to change the coils after the tank had been thoroughly blown out with steam. One of them was quite unaffected by the benzene vapor, while the other died from its effects. The statement of the company doctor that there was something in the man's constitution which caused his death is true in the same sense in which it is true that something in a man's constitution causes him to succumb to typhoid infection

if he drinks polluted water while another man, drinking the same water, remains quite well.

As a usual thing men recover completely, if they recover at all, from such accidents; but there are a few instances of sequelæ recorded. Kobert described the case of a man who was painting the inside of a reservoir with bitumen and crude benzene and who suffered an attack similar to alcoholic intoxication from which he recovered; but later, without further exposure, developed pleurisy and apical catarrh of the lung, and was never restored to complete health. One of Lewin's cases, with relatively slight symptoms, had persistent after-effects. This man had an acute attack of dizziness, a drunken feeling, pressure in the head, dyspnea, oppression of the heart; and when these passed over, a blowing heart murmur, yellow pallor, and general nervous exhaustion. A rather unusual history is given in the report of the British factory inspectors for 1918. The man was employed on the night shift in a benzene distillery and on a certain night the volume of vapor was greater than the condenser could deal with, some of it escaped, and he was overcome. He was revived with oxygen and the next night returned to work; but although at that time the still was working well he was again overcome and this time he died without regaining consciousness.*

Irritation of the skin, or inflammation with swelling and itching, is noted in some cases of acute benzene poisoning (Simonin (15)).

A strange story, possible only in Czarist Russia, was told by Dworetzky (16) in the spring of 1914. It deals with an epidemic of mysterious illness in the factory population of St. Petersburg, beginning in a large rubber works and extending to chocolate and tobacco factories. It was the cause of widespread excitement, strikes, lockouts, riots, a heated controversy between two schools of doctors, interpellations in the Duma, and ended in the complete suppression of all discussion and inquiry by the chief of police.

* The following regulations have been formulated by the British Factory Inspection Department to govern work in tanks or other receptacles which have contained benzene or toluene: 1. The period of airing the tank must last six days. 2. The tank must be filled with water and then steam introduced till the water boils. The steam pipe must reach to the bottom of the tank and either by stirring or in some other way the sludge must be mixed with water. 3. If a tank has remained empty for some time it must be filled with water and emptied before anyone goes into it. 4. Entering a tank and working inside must be permitted only to men wearing a helmet or mask which is connected by a rubber pipe to fresh air or provided with a breathing apparatus which will allow the man to breathe normal air or a mixture of oxygen and air. 5. Every man who enters a tank must wear a safety belt with a rope attached and the other end of the rope must be held by a man outside. 6. An oxygen flask with face mask and proper connections must always be available.

An excellent precaution is used by the United States Steel Company in their plant at Gary, Indiana. After emptying, washing out, and steaming out the tank, they lower into it a cage of white mice, and if the mice are overcome by the vapors the process of flooding and steaming is repeated until the little animals can be lowered into the tank without showing any effect.

The starting point was the rubber glove department of a great rubber factory where hundreds of women were employed in cementing gloves. The solvent for the cement had recently been changed from an ill-smelling, colored fluid to a colorless one with a pleasanter odor; and following this change an acute illness developed among these women, consisting of headache, dizziness, excitement, in many cases fainting or epileptoid convulsions, and involving, in four days' time, no less than 231 of them. Physicians were divided between those who maintained that there was a toxic substance in the cement, and those who held that it was pure hysteria, the latter group being led by von Bechterew. Color was lent to the hysteria theory by the enormous excitement which the discussion had aroused in the working population who believed there was a conspiracy among the employers to poison them, and by an outbreak of similar symptoms among the women in the tobacco and the chocolate factories. The real nature of the trouble could not be known; for before any investigation could be made, the manufacturers declared a lockout until the workers would promise to be quiet, and the police forbade any inquiry into the nature of the trouble or any discussion of the occurrences, maintaining that it was all the work of agitators and revolutionists.*

Pathology of Acute Benzene Poisoning.—The earliest autopsy record I have found is that published by Sury-Bienz in 1888. He found conspicuous bright red spots on the body; the blood fluid and dark red; small hemorrhages in the pleura and intestinal mucosa; general venous congestion and reddened lining of the air passages which contained blood and mucus. Beinhauer (13), in 1896, described the findings in the body of a man dying of acute poisoning after exposure to fumes in a benzene extraction apparatus. The blood in heart and vessels was fluid, the veins of the abdomen engorged, there was hemorrhage in the gastric mucosa, and bloody foam in the air passages. Beinhauer says that the blood was lake red, weakly acid, and there was evidence of destruction of the red cells; but this is contrary to the great weight of evidence. (See Kobert, on absence of blood destruction in experimental animals, also Lehmann.) There was a curious aromatic odor from the body, but no benzene odor in the blood, and no benzene could be demonstrated chemically.

Heffter, in 1910, reviewed the 21 cases of acute benzene poisoning which had been reported in Germany up to that date. He says that the most characteristic change noted in animals is found also

* While in Moscow in October, 1924, I made inquiries about this occurrence and was told that similar trouble had developed among the women employed in rubber factories in Riga and in Moscow at about the same time as in St. Petersburg. All these factories were using a solvent from Baku which was supposed to be petroleum naphtha. After the excitement had died down, a quiet investigation was permitted and the fact established that the toxic substance was benzene.

in men. The blood remains fluid a long time, dark red; but there is no evidence of destruction of the red corpuscles. Hemorrhages, usually punctate, are found in lungs, pancreas, gastric and intestinal mucous membranes. The abdominal organs show unusual congestion, and there is bloody mucus in the air passages. There are numerous cadaveric bright red spots, there is no odor of benzene and it cannot be detected chemically.

Buchman's (17) case was in a man using benzene as crystallizing material in the production of coal-tar drugs, antipyrin and pyramidon. He was found dead on the floor near a leaking apparatus. There were many wine-red spots on the skin, pronounced hyperemia of the internal organs, and small hemorrhages in the pancreas.

Two of the men who died of benzene poisoning in our munition industry during the war came to autopsy, and I am indebted to Dr. H. S. Martland of New Jersey for the notes of his findings which may be condensed as follows:

Case 1. Cyanosis of the mucous membranes and finger tips: cyanosis of the liver, spleen and kidneys: dilatation of the *right* heart which was *filled* with dark fluid blood: pleural ecchymoses and small areas of acute interstitial emphysema in the lungs.

Case 2. Cyanosis of mouth, of lips, and of finger tips; small amount of frothy fluid escaping from the mouth; cyanosis of brain, heart, liver, and kidneys; petechial hemorrhages in pleura and pericardium; reddened and irritated bronchi. On section of the lungs a decided odor of benzene was given off. There was an abnormal quantity of phenol in the urine, but *no* benzene.

The same statement as to the presence of phenol bodies in the urine is made by Heffter and by Beisele, who failed to find blood or albumin or hematoporphyrin; and by Simonin who found in addition urobilin, diminished urea, and diminished chlorids. The phenol is excreted as conjugated sulphuric or glycuronic acid, but this change is fairly slow and does not occur in rapidly fatal cases (Heffter (14)).

Chronic Benzene Poisoning.—The earliest and probably the most famous cases of chronic benzene poisoning in the literature are Santesson's (18), from a velocipede tire factory in Upsala. These were twelve young women, 15 to 20 years of age, employed in the tire department and recently they had been working overtime. All of them developed more or less severe hemorrhages, nine of them having purpuric spots on the skin, one, epistaxis and hemorrhage from the gums and vomiting of blood, one, uterine hemorrhage, and another, prolonged menstruation. Four of them died after exposure of three weeks to four months. A typical history is that of a girl of 19 who had worked for three to four months and had suffered from dizziness and excitement followed by drowsiness. She lost weight and color and left the factory; but instead of recover-

ing she grew worse, ecchymoses appeared on the skin, the number of red corpuscles fell to 3,764,000 with 80 per cent hemoglobin, there were almost no leucocytes to be seen; she grew gradually weaker, and died after a period of feverishness. Another girl, also 19 years old, who had tuberculosis, worked for eleven to twelve weeks, ten to twelve hours a day, when she was discharged. Three weeks later she had profuse menstrual hemorrhage, purpuric spots appeared over the skin, she had vomiting and dyspnea, and profound anemia. The red cell count fell to 600,000 with hemoglobin 20 per cent just before death.

This same year, 1897, Lenoir and Claude (19) reported a case of purpura hemorrhagica in a man who had been employed for several years in a dye house where he was exposed every day to fumes of benzene. He had bleeding from nose and gums, purpuric spots on the skin, increasing cachexia, and then died suddenly. At autopsy they found bloody effusion into the pleural cavity, hemorrhages into the mucosa of stomach and intestines and under the endocardium, and myocardial infarcts.

It remained for Selling (20) in 1910 to declare that the most characteristic feature of chronic benzene poisoning is not the hemorrhages or the anemia but the profound leucopenia, and that the lesions are essentially those of aplastic anemia with destruction of hemoplastic tissues. Selling's patients, three in number, were employed in the coating room of a tin can works where a sealing mixture was used consisting of pure rubber and resin, dissolved in commercial benzene. Twenty-three persons were employed in this department, 5 men machinists, 4 girl inspectors, and 14 girls at the coating machines. These last were between 14 and 16 years of age, and they suffered most severely. Not only were the cans coated here but they were also dried, and ten gallons of benzene a day evaporated in that room. The windows were open, but it was very hot midsummer weather.

Case 1 entered the hospital in fairly good condition, complaining only of "spots on the body and dizziness." She had worked about four months, and a month before she came to the hospital she had noticed blue spots on arms and legs; then, shortly afterwards, she began to have bleeding from the gums, nose and throat, one nosebleed lasting two days. A few days before admission there was a severe hemorrhage from the throat, controlled only with difficulty by local applications. For a week she had been in bed because of weakness and dizziness. Examination showed only extreme pallor, purpuric spots, bleeding gums, a hemic murmur over the heart. Examination of the fundi showed a number of retinal hemorrhages.

For the first few days the patient was in fair condition, but on the sixth day she suddenly develo[illegible] signs of profound toxemia and fell into a stupor, her pulse small and weak. Transfusion of blood

was followed by decided improvement in symptoms, but not in the blood count, and a relapse occurred two days later from which she did not rally, dying on June 6th, the ninth day after admission. Her temperature ranged from 99.8 to 104.6 F., her pulse from 108 to 165. There was no evidence of hemolysis in the urine nor did jaundice appear.

The blood smear showed the red cells smaller and paler than normal, but no poikilocytosis and no extremely large or small forms. The counts were as follows:

	Reds	Whites	Hemoglobin
June 25th, on entrance.....		1280	28% (Sahli)
July 1st	1,090,000	480	11%
July 3d	800,000	480	
July 4th	640,000	600	8%

Platelets were practically absent; blood clotting was delayed and incomplete. A differential count showed: polymorphonuclears 43 per cent, lymphocytes 41 per cent, large mononuclears 14 per cent, unclassified 2 per cent. Only one myeloblast was seen, but no normoblasts.

Case 2 was also 14 years old, had worked five months, and complained of illness for only one week. Her history, physical examination, and the course of the disease were very similar to those of Case 1. Her blood counts fell from 2,100,000 reds to 1,150,000; from 560 whites to 140; and the hemoglobin fell from 37 per cent to 15 per cent. The lymphocytes constituted 71 per cent of the whites, with 10 per cent large mononuclears and only 16 per cent polymorphonuclears. A platelet count (Pratt's method) yielded only 2,500 per cubic centimeter, and the blood after standing 48 hours in a tube showed no expression of serum.

Case 3, a girl of 14 years, had worked for about three months and had suffered for two months from anorexia, abdominal pain, vomiting and headache, and one or two fainting spells. She had a much lighter purpuric eruption than the others and her blood count was 1,900,000 reds, 4,400 whites, hemoglobin 54 per cent, platelets 104,000. Clotting of blood was incomplete, as in the other cases. She was discharged after six days.

The autopsy of Selling's first case, made by W. G. MacCallum, showed: hemorrhages in skin, viscera and serous surfaces; pallor of the organs; blood pale and watery; muscles a deep red color; some fatty degeneration of heart muscle, slighter in liver; bone marrow of femur fairly consistent, of a dull ochre color, with abundance of blood supply. Smears from the marrow suggested aplasia, showing few cells of any kind, the most numerous being normal red

cells slightly paler, extremely scanty leucocytes, chiefly of lymphocytic or myeloblastic type, with reduced chromatin.

The second autopsy was made by Winternitz who found much the same changes except in the bone marrow which was markedly hyperplastic, but a deeper, darker red than is usual in hyperplasia; and smears showed aplasia, although not of quite so marked a grade as in Case 1.

Selling lays stress on three facts: the cases were in young girls, the course was essentially chronic, although in the end the serious symptoms developed suddenly; and the disease progressed in spite of withdrawal from the poison. These features were also true in Santesson's cases and are noted in many of the subsequent reports.

Following Selling's article came a number of reports of similar poisoning, several of them from the same industry and the same city as his. Thus McClure (21) in 1916 described a case of purpura hemorrhagica in a woman 31 years old who had been working in a Baltimore can factory. She had bleeding from the nose and mouth, and secondary anemia with black and blue spots over the body, and dyspnea. The red blood cell count was 1,460,000, white cells 1,110, hemoglobin 25 per cent, polynuclears 40 per cent, mononuclears 37 per cent, transitionals 15 per cent, no nucleated red blood cells, no myelocytes, and platelets almost absent. This patient was saved by the persistent use of transfusion; splenectomy was also performed. After the 13th transfusion, the red cell count rose to 5,280,000; and some fourteen weeks later the count was still 4,270,000. A year or so later a boy of 17 employed in the same sort of work was treated in the Johns Hopkins Hospital for purpura hemorrhagica and nosebleed. His blood count was as follows: reds, 2,272,000; Hb. 59 per cent; white cells 3200, of which 46 per cent were polynuclears, 34 per cent mononuclears, platelets greatly diminished. He was given five transfusions in the hospital and improved slowly, the improvement being very slow in beginning. He was discharged after two months with a red cell count of 4,030,000 * and white cells 7800, the platelets still reduced and the lymphocytosis still present. In that same year, a woman of 57, also employed in a can factory, died in the Johns Hopkins Hospital with bleeding from the nose, purple spots on the skin, bloody stools, hematuria, hemorrhage into the ear. At autopsy, erythroblastic hyperplasia was found and myeloblastic aplasia. The red cells were 4,784,000 and hemoglobin 100 per cent, while the white cells were 5480. The bleeding time was twenty minutes.

Hogan and Schrader's (22) three cases, with two deaths, are

* In these two cases the blood count was still low, after two months and after 3½ months. It is still a question whether the damage to the bone marrow is permanent. As is shown later, animal experiments point usually to complete [illegible] (See Weichselbaum)

also to be credited to Baltimore can manufacture. These occurred in the spring of 1922 and were reported in detail soon after. I give only the salient features of the cases.

All were employed in the same can factory and all developed within less than four weeks time. They formed part of a force of 58 who worked in the room where the bottoms are fastened to the cans by a rubber cement thinned with benzene. It is in the evaporation of the benzene by steam heat that the benzene vapors are formed, and in the factory in question the removal of these vapors was "lamentably insufficient."

Case 1 was a girl of 17 years who was admitted to the University of Maryland Hospital March 14, 1923, and died five days later. She had worked only six weeks in the "dope room." About March 4th she began to feel weak and lost her appetite, and on the 10th she had a headache and noticed bluish spots on arms and legs. By March 13th her mouth had become very sore so that she could hardly swallow, and the next day she was dizzy and spat blood. At the hospital she was found to be pale, undernourished, weak; and purpuric spots were found on arms and legs. She had shortness of breath, a hemic murmur over the heart, her mouth was sore, and there was bleeding from the vagina. Her blood examination on admission was: red cells, 1,240,000, anisocytosis and poikilocytosis, hemoglobin 39 per cent, white cells 600.

Transfusion of blood was practiced only once, and was followed by improvement, but on the fifth day after it the patient suddenly grew worse and died.

Case 2, a woman of 25 years, was admitted to the Maryland General Hospital March 7th with a diagnosis of placenta praevia and died on the 24th. An attempt was made to deliver her and a macerated fetus was obtained. No history is given, aside from the statement as to her employment in a can factory; but it is evident that there was a hemorrhage from the vagina. The blood count was as follows:

	Red Cells	Hemoglobin	White Cells
March 16th.....			1400
" 17th.....	470,000	19%	538
" 20th.....		22%	434 (following transfusion)
" 24th.....	900,000	12%	104

A differential white cell count on March 24th showed polynuclears 42 per cent, small mononuclears 56 per cent, large 2 per cent.

Case 3, a girl of 15 years, was admitted to St. Joseph's Hospital

April 9th, with a complaint of bleeding from the vagina and weakness. She had worked in the can factory five weeks and after three days she had a nosebleed. At the end of the first week, bleeding began from mucous membranes and she lost her appetite and felt tired after work. By the end of the second week her pallor was commented on by her friends. In another week, bleeding began from the vagina, which she took to be a menstrual flow, but it persisted till she came to the hospital, and for several days after. She vomited twice during the first day of this supposed menstruation, was so weak that she was obliged to give up work, suffered from headache, and her stools were tinged with blood. Physical examination was unimportant except for pallor of skin and mucous membranes, weakness, shortness of breath, and a hemic murmur over the heart.

Repeated blood examinations were made with these results:

Date	W.B.C.	R.B.C.	Hemoglobin	Small Lymphocytes	Large Mononuclears	Polynuclears
4-12-22	950	860,000	16%	52%	8%	38%
4-13-22	1200	930,000	17%	38%	4%	56%
4-14-22	1950	1,544,000	36%	48%	6%	46%
4-15-22	4700	1,985,000	42%	18%	4%	76%
4-18-22	3050	2,184,000	44%	40%	8%	50%

Transfusions were done on April 11th, 13th, and 15th. Her temperature ranged from normal to 102°-103° while in the hospital.

This last case is at once the most rapidly developing instance of chronic benzene poisoning in the literature and the most remarkable instance of recovery. Hogan and Schrader's cases also illustrate the peculiar danger of benzene in youth and in pregnancy.*

In a personal communication the following history came to me of a death from benzene poisoning in an employee of a can factory; but this time on the Pacific Coast. The victim was a woman, 41 years old, described as "always skinny and more or less sallow-complected" and with a goitre about the size of an orange. February 1st, 1922, she was put to work at the discharge of the retort where cans are heated after the ends have been coated with a rubber-benzene cement to drive off the solvent and dry the cement. She removed the warm cans and placed them in boxes. A down-suction draft provided by a fan had been placed here, and just above it was a pipe bringing in fresh air. Nevertheless, about March 16th she began to feel ill, was listless, complained of headache, then of

* One of the industrial insurance companies has sent me a statement concerning a fatal case of chronic benzene poisoning in a pregnant woman, 26 years of age, who also worked in a can factory.

nausea, and later of bleeding from nose and gums. She would feel fairly well in the morning, but as the day wore on (there was an eight-hour day) she would grow drowsy and at night she would suffer from severe headache and nausea. On May 11th a physician was called and found her suffering from nosebleed, bleeding from the gums, unusually profuse menstruation, and over the legs there was a heavy rash †, with here and there purpuric spots. She was taken to a hospital where examination showed hemoglobin 35 per cent, red cells 2,512,000, white cells 2,000. By May 24th the hemoglobin had fallen to 20 per cent, red cells to 1,000,000, and whites to 2,000. No young red cells were found. The rash had disappeared but purpuric spots appeared on the back. Transfusion of blood was practiced only twice, as her condition was considered hopeless. The exact date of her death is not given.

The rubber industry has contributed cases from many lands.

The Austrian factory inspectors' report for 1911 describes two deaths from an unusual illness in rubber workers characterized by purpuric spots on the body and found to be caused by fumes of benzene.

In 1909 the French Ministry of Labor issued a warning to rubber manufacturers against "benzene" fumes which, in a factory using rubber cement to fasten together rubber fabric and leather, had given rise to a number of serious accidents. The symptoms in these cases are described as pains in the liver region and a tendency to bleeding from the nose and mouth.

In 1921 in a French automobile factory the use of benzene rubber cement by six persons, in a hot unventilated room, was the cause of four cases of purpura hemorrhagica which developed in six months' time, and two of the victims died. The history of one of these, a woman, shows that she suffered at first from headache and dizziness. She became strikingly pale, then purpuric spots appeared over the body followed by acute anemia, fever, and death, within two months of the beginning of her exposure. (Flandin and Roberti (23).)

The late Dr. T. F. Harrington (24) of the Massachusetts Board of Labor and Industry published in 1917, the first American cases from rubber works. There were five cases of chronic benzene poisoning, all in men, and three of the men died. All had been using benzene cement in building auto tires, applying it by means of a cloth to the rubber. They would do this about eighteen times during an eight-hour day. Case 1, 33 years old, had worked eleven months. He soon began to suffer from severe headache, then he spat blood from his spongy bleeding gums, and spots like bruises appeared on his legs and arms and body. He had to give up work because of extreme weakness and breathlessness on slight exertion. After two

† Irritation of the skin or inflammation and itching

severe nosebleeds, he came to the hospital with a pulse of 124; his red cells were 2,800,000, hemoglobin 60 per cent, white cells 500. Transfusion of eight ounces of blood was followed by uncontrollable nosebleed which recurred daily. He had headache, vertigo, restlessness, delirium, and loss of power in arms and legs. Coma, convulsions, and death occurred on the eleventh day after he entered the hospital. At this time his hemoglobin had fallen to 35 per cent, red cells 1,616,000, white cells 850, of which 62 per cent were small mononuclears and 14 per cent polynuclears. The second patient had much the same history, and in addition hemorrhage from the bowels. He had worked for six to seven months. The third was more resistant, working for two years before he was severely poisoned. His first symptom was the appearance of red spots on the skin. At death his red cells had fallen to 944,000. After the factory had substituted naphtha for benzene they had no further trouble of this sort. Recently a statement was made to me by an insurance man to the effect that seventy cases of benzene poisoning developed in a rubber works and three of them were fatal.

According to Legge (25), the first known cases of chronic benzene poisoning in Great Britain occurred in rubber work and came to light in January, 1918. Two men, both healthy and young, 29 and 30 years old, were employed in spreading balloon fabric with rubber dissolved in pure crystallizable benzene. Formerly coal-tar naphtha, *i.e.*, a mixture of benzene, toluene, xylene, etc., had been used. Both men sickened after about three months' exposure, one dying a week after, the other in three weeks. Their clinical history was practically identical, beginning with malaise and anemia, followed by hemorrhages under the skin and from the mucous membranes, and later from the nose, gums, and bowels. At autopsy the chief findings were submucous hemorrhages throughout the intestinal tract and hemorrhages under the endothelium of the heart. In one case the characteristic changes of aplastic anemia were found in microscopic examination of the marrow of the long bones. Estimation of the benzene content of the air in the factory showed that it contained at various places in that room from 2.1 to 10.5 parts per 10,000 of air.

Two recent cases in German rubber manufacture are, according to Brücken (26), the first instances of chronic benzene poisoning noted in that country. They were young women using benzene rubber cement to fasten together the two halves of rubber balls, working in a room kept hot and draftless for fear of injury to the product. After working about two and a half years, No. 1, a woman 22 years old, began to feel ill, found it hard to climb stairs, suffered from headache and somnolence. Six months later, when Brücken first saw her, she complained of violent headache,

temperature of 101° F. and a weak, rapid pulse, 100 per minute. A diagnosis of grippe was made, but while the cough and headache subsided, fever and rapid heart action persisted, exhaustion increased, and her pallor was striking. He then elicited a history of excessive menstruation, coming on every three weeks and lasting 8 to 10 days; and the fact that the lightest blow produced big black and blue marks on the skin; while bleeding from the gums was frequent, and occasionally blood came with the stools. A blood examination showed Hb. 26 per cent (Sahli), very striking leucopenia, few platelets, striking anemia, polychromasia and anisocytosis, but no normoblasts. Bleeding time was very prolonged, the drops continuing to flow without any diminution for 16 minutes, when the observation was broken off. Treatment brought about no improvement for some time, temperature persisted at 100-101, bleeding from gums and intestines and two periods of excessive menstrual flow brought great exhaustion, the patient sleeping practically all the time. At the end of four weeks in bed improvement began, and at the end of two months more, convalescence was well established. The blood counts at the beginning and end were as follows:

	Hb.	Color Index	R.B.C.	W.B.C.	Platelets	Bleeding time	Neutrophils	Lymphocytes	Mononuclears	Eosinophils
Feb. 14 ...	32%	1.06	1,515,000	6,832	24,240	16 min.	48%	42%	10%	...
April 22 ...	81%	1.02	3,990,000	2,456	156,610	2 min.	69%	24%	6%	1%

The second case, in a woman 23 years old also employed at this work for three years, was much less severe. The symptoms were similar, malaise, frequent headache, bruised spots on slight injury, menstruation at shortened intervals. Examination showed mottling of the skin of the arm. The blood findings were: Hb. 43 per cent, slight polychromatophilia and anisocytosis; differential count of whites, neutrophils, 47 per cent, lymphocytes 38 per cent, mononuclears 12 per cent, eosinophils 3 per cent.

The city of Milan, which is the center of the rubber industry in Italy, has been the scene of serious benzene poisoning among young women employed in cementing the seams of rubber raincoats. According to Meda (27), in one factory in the winter of 1921 three women died from this form of industrial poisoning and the following March a number of cases developed in another factory and four girls died, with "very severe anemia hemorrhagica of the aplastic type," the rest recovering after a fairly long period. Pugliese (10) says that in the latter factory the air contained one part of benzene per thousand. Meda describes the factory as being modern in construction, operating for only one year and supposedly beyond criticism so far as factory hygiene is concerned. The best commercial benzene was used.

One hundred women, mostly young, were employed in one room cementing seams with a solution of rubber and benzene and wiping off the excess with pure benzene, each having therefore two benzene receptacles on her bench. Many of these women had done the work for several years and no trouble had been experienced but, either because of some change in the composition of the commercial benzene, or perhaps an increase in the density of the vapors (all the Milan cases occurred in winter), poisoning developed. Meda notes that benzene poisoning seems always to appear in sporadic, sudden epidemics, according to the literature. The victims in these factories were probably predisposed to poisoning by something which lowered their resistance and such factors are chlorosis in young girls, tuberculosis and pregnancy. Women are certainly far more susceptible than men.

Of the seven severe cases in 1922, four died and three slowly recovered. The history of one of these latter is given in detail. This was a married woman 25 years old, unusually vigorous and well nourished, who had done similar work for seven years. She was, however, pregnant at this time. In February, 1922, she began to have headache, dizziness, somnolence, nausea, and pain in the epigastrium which she attributed to a change in the cement, for she had noticed that it had a different odor. She grew very pale and thin; she had bleeding from the gums, and finally hemorrhagic spots over the body. She was now in the eighth month of pregnancy, she left the factory, had repeated nosebleeds before delivery, and after her delivery which was normal, she had an outburst of purpuric spots and of hemorrhages, with great weakness. She then came to the hospital with a temperature of 37.6° C., pulse 120, small, soft and regular, respirations 24. The urine contained albumin, indican and a few granular casts and epithelial cells; the red blood cells numbered 1,700,000, whites 1,700, hemoglobin 29 (Fleischl), and there was a marked loss of platelets. The differential count of whites gave polynuclears 54, mononuclears 13, lymphocytes 33; the blood coagulated slowly and without contraction of the clot. Ten days later, the red count was only 600,000 and the hemoglobin down to 15 per cent, but the whites numbered 3,000; there were no platelets and no youthful forms. The patient then developed a pyelonephritis, with a typical temperature curve, the white cell count rose to 7,300 and suppuration was abundant. Meda emphasizes this fact and thinks that the suppurative process was favored by the lowered resistance of the patient but that it also acted as a stimulant to the blood-building tissues.

As the temperature fell, the patient passed into a condition of profound weakness, delirium or stupor, and the white cell count fell to 2,000. Injection of autogenous vaccines cleared up the pyelitis and young blood cells appeared. By the middle of August

recovery had set in, the red cell count was 3,000,000, the white cells 5,500, with a normal leucocytic formula, the hemoglobin was 60 per cent and there were many platelets. Meda considers that the striking facts in this history are the vulnerability to benzene which is caused by the condition of pregnancy, breaking down the resistance of an unusually vigorous woman who had been exposed to it for seven years; the lowered resistance to infection brought about by the benzene poisoning as shown in the infection of the pelvis of the kidneys. He emphasizes the fact that the literature of chronic benzene poisoning consists of single observations on the clinical history and pathological anatomy of individual cases and that there is as yet no comprehensive study of the etiology and prevention of industrial benzene poisoning.

Pugliese (10) studied these same cases in Milan. He says that serious cases of poisoning with loss of consciousness occurred in workers exposed to two or three parts of benzene in ten thousand of air. The symptoms in slight cases were headache, nausea, abdominal pains, dizziness, sensations of chilliness and formication, rapid fatigue, loss of appetite, loss of strength, and breathlessness. Lesions of the skin consist of dryness or an itching erythema or eczema, conjunctivitis, blepharitis, or even keratitis. There may be a polyneuritis, and sometimes a retrobulbar neuritis. In the urine he has found albumin, casts, droplets of fat, hemoglobin and conjugated sulpho bodies. The anemia may continue to increase after the woman is removed from work.

Two cases of fatal purpura hemorrhagica caused by benzene fumes were brought before the New York State Workman's Compensation Commission in 1920. The men had been employed on a machine for coating fabrikoid, which is thus described: the fabric is fed in from the front to an endless traveling apron, which carries it over heated pipes. The coating mixture runs down from a can suspended above a 4-inch (10 cm.) hole in front, and the whole is encased in a wooden box. The temperature inside the machine is sufficient to volatilize all the solvent. The coating mixture consisted at that time of nitrocellulose, pigment, castor oil, grain alcohol, benzene, and ethyl acetate. Fumes escaped from the hole in front, but still more at the back, where the hot, coated fabric left the machine. From evidence given at the hearing, it seems that nosebleed among the men in this department was of fairly frequent occurrence, and that the labor turnover was great. They worked on eight-hour shifts, sometimes, but "not very often," sixteen hours.

Both of the men who died were young and had always been strong and vigorous up to the time of their last illness. The first one worked for about nine months before he began to have bleeding from the gums, and noticed small, red blotches on the skin between the ankles and the knees. Three weeks later, March 21, he had a

severe nosebleed. He was taken to the hospital, March 24, and died April 7, after repeated nosebleeds, bleeding from the mouth, temperature over 101° F. and the appearance of purpuric spots all over the legs up to the waist. The second man worked for less than six months, sickened February 17, and died March 9. He had been feeling ill, complaining of the poor ventilation in the shop and of loss of appetite, and was very pale. Then, on the night shift of February 17, he had what one fellow workman called a chill and another a convulsion, his nose began to bleed, and the blood oozed from his gums. Evidence given by his physician was that from then up to his death he had continual bleeding from the nose and mouth, bruise-like blotches appeared on the legs and body, and the temperature ranged from 102° F. to over 104°. In neither case was any blood examination made, and the medical details are very scanty.

The company had made tests of the air around the coating machines; for it was anxious to prevent the escape of the solvent, which it was desirable to recover for use again. Something less than 5 per cent was reported to be the highest concentration of benzene found in the air, and it is evident that the officials considered this amount too little to cause any anxiety. A personal communication from Canada informed me of a death from benzene poisoning which occurred in a fabrikoid factory, in a man of 50 years.

Newton (28) of Akron, Ohio, and Starr (29) of Columbus, Ohio, have given very valuable data concerning the early stages of slow benzene poisoning. Newton examined three chemists who had been exposed to benzene vapors for about two weeks. Only one complained of ill health, headache, lassitude, anorexia and loss of weight, and then of a sudden attack of pain in the abdomen, nausea and vomiting. Newton found the pulse and temperature normal; but there was a marked leukopenia, 1200 whites, with 39 per cent of them large mononuclears. The erythrocyte count was 5,760,000, but the hemoglobin, only 80 per cent. He then examined the blood of the other two and found white counts of 1250 and 1700, and a low red count, from 3.6 to 4 million. Appropriate treatment resulted in a decided increase in the white cell count, which shows the value of periodic examinations of the blood in workers exposed to benzene.

In this connection it may be noted that Selling (20) examined the other employees in the room from which his cases had come, 5 men and 15 girls, and found purpuric spots on the skin in four, two men and two girls, none of whom complained of illness. Their blood showed a slight grade of anemia and a leucocyte count varying from 3,900 to 5,200 which was somewhat lower than the average (5,200 to 6,000) for those working in other parts of the factory.

An investigation made by the late E. B. Starr (29) of the Ohio State Department of Health brought to light a new source of benzene poisoning in industry, the use of benzene cement in wholesale pil-

linery establishments. Starr had an unusual opportunity to study the early symptoms of benzene poisoning among some 31 girls who were employed in spreading cement on cloth and pasting it on buckram hat crowns. Up to eight years ago such pieces were always sewed together, then cement was introduced, but it was only in the fall of 1921 that any trouble from its use was observed, and then it was found that a change had been made in August in the composition of the cement. Analysis carried out by the Departmnet of Health showed the following constituents in the solvent, the percentages being given by volume:

	Sample A	Sample B
Carbon tetrachlorid	70 per cent	66 per cent
Benzene	30 " "	34 " "
Carbon disulphid	0 " "	0.05 " "

Twenty-seven of the women employed handled cement, and of these twenty-two had definite symptoms, and in addition two out of the four who worked near by were somewhat affected by the fumes. The symptoms consisted in soreness and burning in the throat, sometimes in the eyes; burning in the epigastrium; nausea; vomiting; frequent urination; giddiness; slight air hunger; and a feeling of weakness. It is noteworthy that the symptoms usually increased during the evening after leaving the factory. An itching inflammation over the forearms was sometimes present. Starr was not able to elicit any history of disturbance of menstruation and only one woman had purpuric spots, which disappeared after a month's time. Pulse and heart action seemed normal. A conspicuous symptom was burning in the epigastrium with tenderness on pressure. One of the women in this group had recently died and benzene poisoning was suspected but investigation showed that death was due to a perforating gastric ulcer. Starr, however, calls attention to some experiments of Weiskotten and his colleagues who found in three animals exposed to benzene vapors, hemorrhages into the gastric mucosa and in one of them small ulcers. (See also Chassevent and Garnier (5), page 478.)

A review of all these instances of chronic benzene poisoning in industry fails to throw much light on the danger limits of benzene vapor in the air of a working room. The men in the American fabrikoid factory died after several months' exposure to air containing, according to the company chemist, something under 50 parts per 1,000. Pugliese found only one part per 1,000 in an Italian factory where fatal cases had occurred, and symptoms of poisoning appeared in an atmosphere of 0.2 to 0.3 parts per 1,000. Legge tells us that as little as 0.2 to 1.0 part per 1,000 was present in the English balloon factory where two men contracted fatal ben-

zene poisoning. There is need of a great deal of close observation with analysis of air and probably periodical examinations of the blood of the men and women employed, before this question is definitely settled.

There are certain very puzzling features about benzene poisoning in industry. Some factories use large quantities apparently without any damage, others have deplorable results from much slighter quantities. For instance, I know of one factory employing from 60 to 80 men in an atmosphere heavy with benzene fumes. These men spread a benzene dope over wide surfaces, leaning over the table as they work and using the dope lavishly. They then stand the painted material at one end of the room to dry, and the temperature is kept high to hasten drying. The men have been for two years under the observation of an unusually alert and scientifically trained physician, yet he has never been able to detect one case of poisoning.

In all the epidemics of benzene purpura in the literature there have been some puzzling features. Individual susceptibility of course varies greatly. Lehmann, Weiskotten, Drinker and Hurwitz, and others find that animals show very different degrees of sensitiveness to benzene, from a slight leucopenia to complete disappearance of white cells. Yet this is not enough to explain a sudden outbreak of poisoning in certain individuals of a group which has been exposed a long time to the fumes, without any increase of exposure. It may be that closer study of such occurrences may reveal decided alterations in the composition of commercial benzenes, variations unsuspected by the purchaser. The women in Dworetsky's Russian factory had noticed such a change, as had also those in the Ohio factory investigated by Starr, and the Italian women in Meda's raincoat works.

Benzene has an effect on the skin which probably is traceable to its solvent action on the natural fats of the skin. Painters often suffer from it and, in a recent report from Germany, the men engaged in painting agricultural machinery suffered from a painful itching and burning rash which was traced to the benzene used as a substitute for turpentine and linseed oil. The most widespread trouble of this sort that I have seen was in a factory making leather upholstery and automobile tops by coating leather with a solution of nitrocellulose in benzene, amyl acetate, and butyl acetate. Of the 60 men employed, not one had escaped. Some suffered from severe furunculosis, others from redness and tiny blebs which sometimes became infected, forming small ulcers. Anointing with an animal fat before and after work seemed to be the best preventive.

Pathology of Chronic Benzene Poisoning.—Selling's cases and the animal experiments performed by him in confirmation of his findings led to a long series of experimental studies on the action of benzene, partly because of Koranyis' suggestion that its hematoxic

action might be utilized in the treatment of leukemia, partly because the direct action of benzene on the blood-forming tissues makes it a useful agent for the student of blood pathology and of immunology.

Selling's animal experiments had shown that benzene is a powerful leucotoxin, destroying the white cells of the circulating blood and the parenchymal cells of the blood-forming organs—bone-marrow, spleen, lymphatic glands, and the lymph follicles in the appendix—the myeloid tissue suffering more damage than the lymphadenoid and the polynuclear cells more than the lymphocytes. The erythroblastic tissue of the bone-marrow is destroyed, but the circulating erythrocytes are injured relatively little. The pathology of benzene poisoning is essentially an aplastic anemia. No nucleated reds or abnormal reds are found, platelets are absent or scanty, and there is polymorphonuclear leucopenia. Selling found that while benzene destroys the specific cells of the bone-marrow, causing extreme aplasia, there is at the same time an irritant action, and, for a while, the two actions go on simultaneously. If the injections are stopped at a point when the blood-forming organs are almost wholly aplastic, regenerative changes begin within a few days and are complete in ten days to three weeks, the blood picture also approaching the normal.

Some of the work of Weiskotten (30) and his colleagues has a decided bearing on industrial benzene poisoning, although it was done in connection with the therapeutic use of benzene. His first experiments were carried on with subcutaneous injections of benzene in olive oil. A fall in the leucocyte curve occurred and at this stage the rabbit might die; but if it survived, there was a rise of leucocytes to the normal level, then a secondary fall almost always as low as the first, sometimes lower; and this was followed by a secondary rise if the animal did not die, but the mortality was as great during the secondary fall as during the primary. A single dose of benzene brought about this series of reactions. A return to normal would occur even after a high degree of leucopenia. This had been noted also by Selling who reduced the leucocytes in rabbits almost to the vanishing point, yet saw them return to normal count. Weiskotten (31) has also found that the results of exposure of rabbits to benzene vapor are of the same general nature as those produced by subcutaneous injection of olive oil-benzene mixture. Maximal sublethal dosage causes leucopenia, hemorrhages, and slight anemia. After discontinuance of the exposure, the total leucocyte curve rises to a permanent general level, lower than that existing before exposure. This relative leucopenia is permanent. The percentage and absolute decrease of the small mononuclears is greater than that of the polynuclears, and the small mononuclear curve does not rise to its former level.

Experiments with guinea-pigs made by Fontana (32) showed that a daily injection of 1 c.c. per kilogram for four to ten days resulted in death with almost complete disappearance of the leucocytes, reduction of hemoglobin to abont one-tenth, and a fall in the red cell count to about 3,000,000. He found that the lymphocytes survived longest except in the most rapidly developing cases when this inversion of the leucocytic formula did not occur.

The irritant action of benzene noted by Selling, probably accounts for the findings of several investigators who used very small quantities of benzene. Thus Langlois and Desbouis (33) experimenting with small quantities of benzene administered in vapor form provoked a leucocytosis in guinea-pigs and pigeons, less marked in rabbits and dogs, lacking in cats. There was also a slighter increase of the red cells. This result was due to stimulation of blood formation, not to loss of plasma, and the effect lasted only two days after discontinuance of the exposure. In some cases they observed a slight diminution in the white cells, which they considered accidental.

Eosinophilia, as the only pathological change in the blood, was noted in benzene workers by Agasse-Lafont and Heim (8). They examined workmen who had been exposed to commercial benzene from a few months to six years and found no change in the blood except eosinophilia which was present in 80 per cent and appeared in the early months of exposure, disappearing soon after exposure ceased and bearing no relation to the intensity of the clinical symptoms. The same thing was found by Simonin (15) in a case of acute intoxication with fever, eruption, and bronchial catarrh. There was an enormous eosinophilia, of 25 per cent, on the fifth day, dropping to 2.5 on the thirteenth.

The hemorrhagic features of benzene poisoning were studied by Duke (34) who brought about a rapid rise in the platelet count by injection of benzene in rabbits, followed by a rapid fall. When three doses only were given, the rise was gradual and did not fall subsequently below normal; but in animals receiving five doses the fall was marked, and purpura hemorrhagica and severe anemia, with aplasia of the bone-marrow developed. Fontana (32) noted a marked fall in platelets in about half of his animals (guinea-pigs).

Hurwitz and Drinker (35), following up the work of Selling and of Duke, produced aplasia of the bone-marrow in rabbits by injecting 2 c.c. of pure benzene per kilo daily. Not only were all the formed elements of the blood markedly reduced, but also the factors of blood coagulation, the circulating prothrombin being considerably less than normal.

The fact that Selling's experiments show a selective action of benzene on the tissues and cells that are concerned in the production of antibodies and in defense against infection, led Hektoen (9) to investigate its influence on the course of infection in animals.

He found in rabbits a depression of antibody formation, a reduction of precipitin and lysin, together with grave lesions in the marrow, leucopenia, and reduction in the phagocytic power of the leucocytes. He concludes that "benzene may lower the resistance to infection by reduction (1) of antibody production, (2) of the number of leucocytes, and (3) of leucocytic activity." Two years before, Rusk (36) had found that rabbits, when poisoned with benzene, produced hemolysins and precipitins much less efficiently than normal animals.

Weiskotten (37) made some observations in the course of one of his series of experiments, which go to confirm the findings of Rusk and of Hektoen. During daily subcutaneous injections of olive oil-benzene mixture, in four rabbits, he noticed the development of active acute infection and in at least two of these it seemed that infections present before the injections began were "lighted up" as a result of the injections. In these animals a polymorphonuclear leucopenia did not appear, in fact there was the usual leucocytosis of acute infection and the animals died at the height of their leucocytosis. Weiskotten concludes that the leucocyte count cannot be safely depended upon in connection with the administration of benzene.

As for organic changes, Chassevent and Garnier (5) found in the guinea-pig congestion of the peritoneum and of the abdominal organs, ecchymoses or ulcerations in the gastric mucosa, at the niveau along the artery. Klemperer and Hirschfeld (38) found more or less severe marrow destruction and severe and extensive necrosis of liver and kidneys. Selling found fatty changes in liver and kidneys, and hemorrhage into lungs, pleura, and stomach. Neumann (39) found in rabbits dying within 21 to 33 days after repeated injections of benzene-olive oil, hyperemia and pigmentation of the liver; spleen very hyperemic, aplastic, rich in pigment; marked hypoplasia of the bone-marrow which was also hyperemic and rich in pigment. Like all observers he found a marked variation in the lesions in different animals. Fontana noted diminished volume of the spleen in all animals dying of chronic benzene poisoning.

Two more suggestive observations on benzene deserve mention. Schiff (40), working in Heffter's laboratory in Berlin on the nature of anaphylactic shock, found that small doses of benzene which caused only a slight leucocytosis would increase sensitivity to anaphylaxis toward sheep serum, while large doses, causing leucopenia, would lower sensitivity. Jaffé (41) isolated an N-free acid from the urine of dogs and rabbits after feeding them a long time with benzene, which he identifies with the "Muconsäure" of Rupe and which has the formula $C_6H_6O_4$. The amount found is small, representing only a fraction of the benzene administered, as for instance 0.2 mg. in the urine after 60 gm. of benzene had been administered.

The urine has the characteristics of carbolic acid urine,—dark, almost black in color.

The changes caused by toluene are far less marked and characteristic than those of benzene. Hektoen (9) found that the effect of toluene in repeated doses of about 1 c.c. per kilo lessens antibody output in the earlier stages of antibody production, but under certain conditions causes prolonged persistence of antibody in the blood. The effect produced by benzene on the white blood cells is absent in toluene poisoning, and there is no immediate change as to number, proportion, or phagocytic activity of these cells. Mary W. Brown, in Hektoen's laboratory, found that repeated injections of toluene in rabbits cause a hyperplasia of the myeloid cells of the bone-marrow and a phagocytosis of leucocytes by the giant cells, without a coincident increase in the cells of the circulating blood or changes in liver, spleen or appendix.

To summarize briefly: the effect of chronic benzene poisoning is to cause a loss of red blood corpuscles, resulting in profound anemia; a loss of the elements and substances in the blood which are concerned in blood clotting, resulting in hemorrhage; and a loss of white blood cells and of the substances in the blood serum which are concerned in defending the body against bacterial infection.

A very valuable report has recently been returned by a special committee of the National Safety Council which was appointed in 1923 to study benzene (benzol) poisoning in industry. Their first report has already been mentioned in this chapter, and the manuscript of the 1924 report is now at hand, covering the work done in 1924 with the coöperation of the Hood Rubber Company and the Massachusetts State Department of Labor and Industry. The Committee has collected records of 98 cases of benzene poisoning, 15 of them fatal. Of these, six were of acute poisoning with four deaths, 92 were of chronic poisoning with 11 deaths. In addition two firms reported "several cases of illness."

The Committee studied the methods of use of benzene in industry, of fume removal, and of the actual concentration in the air of the plant and the effect of benzene vapor on the workers as determined by symptoms and physical findings, particularly the findings in the blood. For estimation of the benzene content of the air they utilized activated charcoal prepared according to the standard procedure recommended by the U. S. Bureau of Mines, a method which is claimed to be the most accurate one in use for field work, yielding amounts about 8 to 10 per cent lower than the existing condition.

The benzene-using industries studied fall into two classes. In the first large amounts are used but in a closed apparatus so that except through an accident to the piping system there is no escape of fumes. In this group chronic poisoning will probably not occur, but there is

always danger of acute poisoning which may take place with little warning. Such industries are the production of benzene and motor fuels by distillation of coal and coal tar, and the chemical industries such as oil extraction, dye and dye intermediates, making paints, varnishes and stains and varnish and paint removers. The second group is much more important, for benzene is used as a solvent or vehicle and as a part of the process the benzene must be removed by evaporation, sometimes hastened by heat. In this class come: the rubber industry, making artificial leather, making sanitary cans, dry cleaning, and the use of paints, varnish and stains and paint and varnish removers.

Seventy-eight plants were inspected by field investigators, and in 14 conditions were found satisfactory for an intensive investigation as outlined above. Five were rubber works, three making artificial leather, two making sanitary cans, and one each making paint and varnish remover, insulating electric wires, recovering benzene, and dry cleaning. Twenty-three clinical cases of benzene poisoning had already been recognized in these plants.

Eighty-four workers were examined for signs of early benzene poisoning, the blood count being accepted as the most important early diagnostic sign. They took as a standard a count of 7,500 white cells and a loss of 25 per cent as probably suggestive of poisoning. On this basis 13 suspicious cases were revealed, 12 with a low white count and one whose white count was only slightly lowered but the hemoglobin was far below normal. The tabulation of these cases show hemoglobin running from 23 per cent to 85 per cent, no less than four being as low as 30 per cent; red blood cells, from 800,000 to 5,424,000; white counts from 1,450 to 6,140. Of the latter, one was between 2,000, and 3,000, five between 3,000 and 4,000, four between 4,000 and 5,000, two between 5,000 and 6,000, and one between 6,000 and 6,500. The loss was most marked in the polynucleara.

"It seems to us somewhat significant that out of 84 men employed in processes involving more or less continuous exposure to benzene fumes, 13, or about 15 per cent, should have shown a blood picture strongly suggestive of benzene poisoning. This would appear to confirm the conclusion of our previous report that the benzene hazard in industry is a real, but not a sensational, one. In one dry cleaning plant, however, two out of the three men examined showed this condition, and in an electric insulating plant four out of nine were thus affected." The physical findings and symptoms were very slight, as in Newton's cases, showing that marked changes in the blood cells may occur before subjective symptoms begin to appear. Only four out of nine suffered from dizziness, yet that was the most frequent complaint, one had nosebleed, and six showed pallor. Headache and loss of appetite were complained of in two cases.

The committee found a distinct relation between exposure to benzene fumes and symptoms of early poisoning. Determination of the amount of benzene gave values ranging from 28 to 4,140 parts per million. The variations which occur from time to time in the same plant, especially in summer with the windows open, are very great, but as a general thing where an efficient system of local exhaust ventilation was at work less than 200 parts of benzene vapor per million of air was found, and no abnormal blood counts were observed in workrooms provided with efficient local exhaust ventilation.*

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* The report is signed by C.-E. A. Winslow, Chairman, L. Greenburg, Vice Chairman, J. W. S. Grady, L. E. Weber, W. S. Paine, C. F. Hogan, H. Bradshaw and J. M. Weis.

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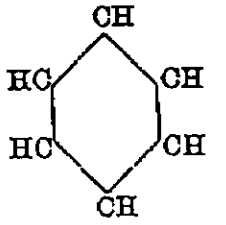
CHAPTER 34

BENZENE DERIVATIVES

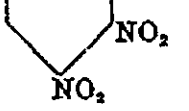
Derivatives of the Coal Tar Series

The chemistry of this group is complicated and yet it is impossible to understand the physiological effects of the different compounds without some knowledge of their chemical structure. I have therefore arranged as simply and briefly as possible the essentials of the organic chemistry of the coal tar series.

Structure of the Benzene Ring and its Principal Derivatives, Isomeric Forms, Etc.—The benzene molecule is for convenience represented by a "ring" or hexagon which, if unmodified, stands for C_6H_6, or

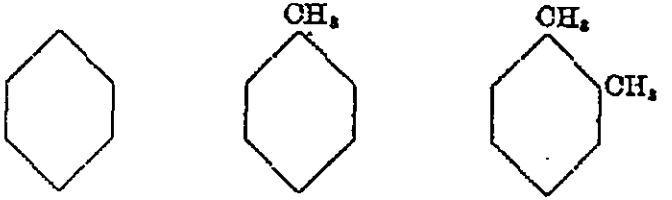


Usually the carbon and hydrogen elements in a graphic formula are not written out, for it is understood that all replacements for the formation of new compounds take place at the expense of the hydrogen atoms and that no matter how complicated a series of such replacements may be, the original 6 carbon atoms of the ring remain unaltered. To illustrate, the formula for picric acid, trinitrophenol, is usually written thus,

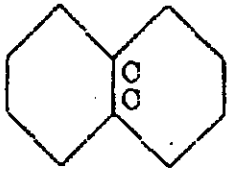


and the unoccupied angles of the hexagon are understood to be taken by the original hydrogen atoms.

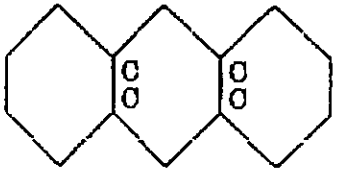
Benzene is C_6H_6. Toluene is methyl-benzene, $C_6H_5CH_3$. Xylene is dimethyl benzene, $C_6H_4(CH_3)_2$. The graphic formulas are these:



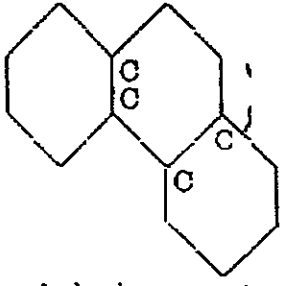
In naphthalene, two benzene rings are joined directly together, at the expense of two hydrogen atoms, which results in the formula $C_{10}H_8$ or



Anthracene is three such rings joined together, or $C_{14}H_{10}$.



Phenanthrene has the same number of atoms as anthracene and its formula is also $C_{14}H_{10}$, but the three rings are differently grouped.

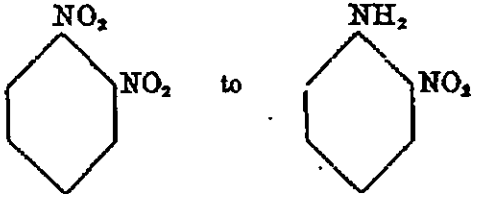


When the hydrogen of the benzene ring is displaced by HO, phenols result:

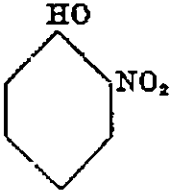
C_6H_5HO, hydroxybenzene, or phenol or carbolic acid.
$C_6H_4(HO)_2$, dihydroxybenzene or resorcin.
$C_6H_3(HO)_3$, trihydroxybenzene or pyrogallic acid.
$C_6H_4CH_3HO$, hydroxytoluene or cresol.

The introduction of the nitro group into the ring produces nitro compounds, such as nitrobenzene, $C_6H_5NO_2$, and dinitrobenzene, $C_6H_4(NO_2)_2$: nitrotoluene, $C_6H_4CH_3NO_2$, and trinitrotoluene, $C_6H_2CH_3(NO_2)_3$; nitronaphthalene, $C_{10}H_7NO_2$, and dinitronaphthol, $C_{10}H_5HO(NO_2)_2$.

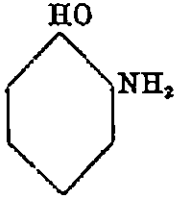
Reduction of a nitro compound changes the NO_2 radical to NH_2 and produces amido compounds. From nitrobenzene comes amidobenzene or anilin, $C_6H_5NH_2$. From nitrotoluene comes amidotoluene or toluidin, $C_6H_4CH_3NH_2$. From nitroxylene comes amidoxylene or xylidin, $C_6H_3(CH_3)_2NH_2$. The reduction may be partial, as when dinitrobenzene is reduced to nitranilin, thus:



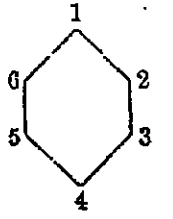
and this may be further hydrolyzed to nitrophenol:



and then reduced to amidophenol:

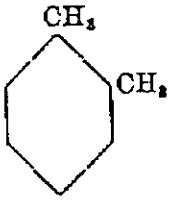


For convenience the angles of the benzene hexagon have been numbered in the order of the figures on the face of the clock.

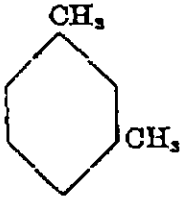


When only one hydrogen atom is replaced by a new atom or radical it is of no importance which of the six is replaced, but

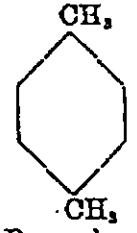
when more than one is substituted, several so-called isomers or isomeric forms are produced, bodies which have the same number of the same atoms, but are differently grouped and differ decidedly from each other in physical properties and in toxicity. For instance there are three xylenes, or dimethylbenzenes, $C_6H_4(CH_3)_2$.



Orthoxylene.

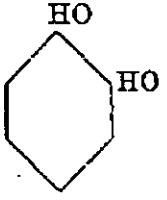


Metaxylene.

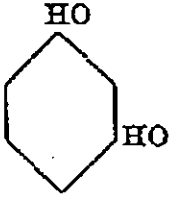


Paraxylene.

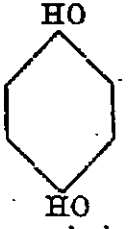
There are three dihydroxybenzenes, $C_6H_4(HO)_2$.



Ortho, or pyrocatechin.

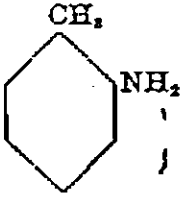


Meta, or resorcin.

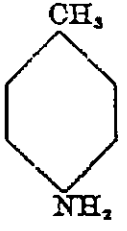


Para, or hydroquinone.

Orthotoluidin,



is an oily liquid at a temperature at which paratoluidin

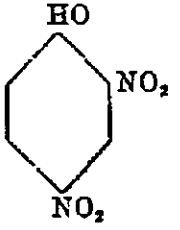


is crystalline.

The prefixes commonly used; ortho, meta, and para, refer, then, to the different forms which result from the displacement of two of

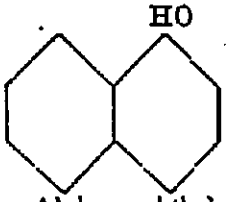
the hydrogen atoms of the ring. When there are more than two substitutions, a much greater number of isomeric forms is possible, and these are designated by the numbers of the angles, 1-2-3, 1-2-4, 1-3-5, etc.

Dinitrophenol 1-2-4 is this:

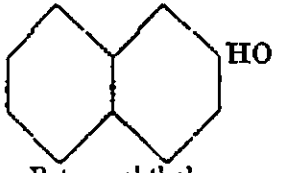


It differs toxicologically from all the other isomers.

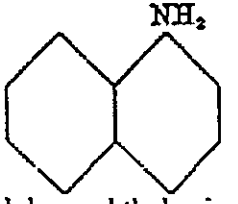
When two or more benzene rings are joined, as in naphthalene, two mono-substitution products are formed, according as the substituting atom or radical is combined with a carbon atom, which is in direct union with one of the common carbon atoms, or not. These two forms, known as alpha and beta, may be illustrated as follows:



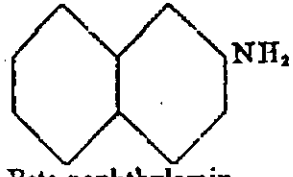
Alpha-naphthol.



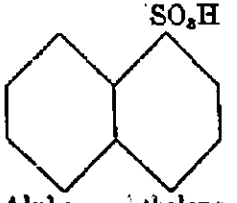
Beta-naphthol.



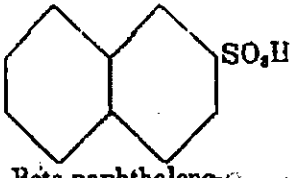
Alpha-naphthylamin.



Beta-naphthylamin.



Alpha-naphthalene-



Beta-naphthalene-

pound is handled. A study of the sickness records in a dye works would show that the compounds responsible for the greatest amount of industrial sickness are not necessarily the most toxic, but are those whose use requires more exposure of the workman to contact or to fumes. For instance, mononitrobenzene does not give rise to nearly so much poisoning as dinitrobenzene, yet it is a fluid, while the latter is a solid, but dinitrobenzene has to be transported much more and handled in the open and therefore it always causes much more poisoning.

Following is a brief statement of what is known as to the relation of chemical constitution to physiological action in the coal-tar or aromatic series (1). The phenols are hydroxy (HO) derivatives; carbolic acid is hydroxy-benzene; cresol is hydroxy-toluene; naphthol is hydroxy-naphthalene. The entrance of this hydroxy nucleus renders the two naphthols, alpha and beta, more irritating in their effect than is naphthalene. An increase in the number of hydroxy groups increases toxicity. Thus, pyrogallol, commonly called pyrogallic acid, trihydroxybenzene, is more toxic than phenol, commonly called carbolic acid, which is monohydroxybenzene. The former is used in at least one plant in the United States to produce gallocyanin, but no case of poisoning has as yet been reported here, although such cases are known to have occurred in Germany. Theoretically, phenol or hydroxybenzene should be more toxic than benzene, but as a matter of fact its use in industry is attended with nothing more serious than burns, except in very rare instances in which an accident has caused an overwhelming exposure.

The entrance of the nitroso group (NO) and the nitro group (NO_2) increase toxicity always, whether they enter the ring or a side chain, but it is not necessarily true that an increasing number of NO_2 groups increases toxicity. For instance, the French experience during the war when they used nitrophenols for explosives, showed that picric acid, trinitrophenol, was not nearly so poisonous as one of the dinitrophenols.

Reduction of the NO_2 group to NH_2, as in changing mononitrobenzene to anilin, mononitrotoluene to toluidin, lessens toxicity, and when these amido compounds are sulphonated they are apparently rendered harmless. The entrance of the sulphonic group (SO_2HO) into any benzene derivative removes its toxicity, as is seen also in the sulphonation of phenol. The entrance of COOH may have the same effect. Nitrobenzoic acid is harmless, although nitrobenzene is very poisonous. The acetyl group ($COCH_3$) makes acetanilin less poisonous than anilin, and the same is true of the introduction of an alkyl group such as methyl (CH_3), for dimethylanilin is less poisonous than anilin.

Chlorin entering an aromatic compound changes it very little, and certainly does not increase its toxicity, for chlorbenzene seems

to be less toxic than benzene. There is no rule as to the toxicity of different isomers, but usually, according to Fraenkel (1), the para position is more toxic than the ortho. Practically, paratoluidin seems to cause more trouble than ortho, and paranitranilin more trouble than meta, but animal experiments made by Lewis (2) showed that for rabbits metanitranilin was more toxic than para. Among the nitrochlorbenzenes, the ortho isomer seems to be the most toxic, next para, and last meta. Usually paraphenylendiamin is regarded as worse than meta, but some dye workers believe the reverse to be true.

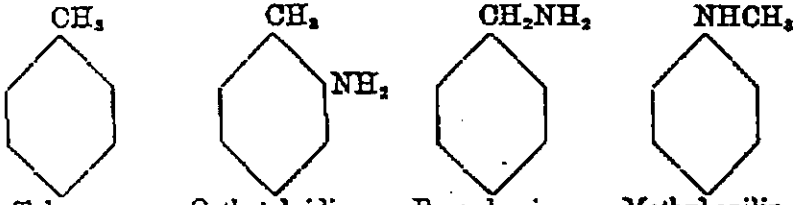
Hydroxy Compounds.—Phenol and the two naphthols, alpha and beta, are the only ones of this group which are of importance industrially. None of them gives rise to much trouble, in spite of their decidedly dangerous nature.* They are readily and easily absorbed from any surface, including the unbroken skin, and within the body they are partly oxidized, partly excreted in the urine in combination with sulphuric and glycuronic acids and also unchanged. The urine of phenol poisoning is dark or "smoky." The symptoms caused by the absorption of phenol through the skin—the only form in which industrial poisoning occurs—come on rapidly. In severe cases there is great muscular weakness, then loss of consciousness and death from respiratory failure, sometimes preceded by muscular twitchings or convulsions. Less severe poisoning causes headache, dizziness, some excitement and mild delirium, pallor, clammy sweat, irregular respirations and a small pulse (3).

A fatal case was reported to me by the late Dr. T. F. Harrington of the Massachusetts State Board of Labor, of a young chemist who stepped into a pool of phenol waste and soaked his leg in it. Soon after he began to complain of ringing in the ears, dyspnea and dizziness. Then he became dazed, excited and almost hysterical. He was allowed to leave the building in this condition, but evidently he soon lost consciousness, for the next morning he was found dead on the road. The leg was then greenish black up to the knee.

Two other fatal cases of industrial phenol poisoning came also from the accidental soaking of the clothing with this liquid. They were reported to me by Dr. F. G. Patterson, formerly Medical Director of the Pennsylvania Department of Labor. The first was that of a workman who was unscrewing a cap on a phenol drum when some of the contents splashed out over him. A fellow workman immediately turned a hose of runing water on him but, according to his statement, the man "became limp almost at once," collapsed, and was dead when the doctor reached him. The second

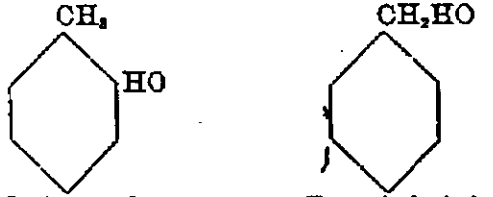
* This is because in the absence of an accident there is no contact with phenol on the part of the workmen. Splashing drops over the skin is a possible risk, and most factories keep a supply of alcohol near at hand so that the phenol may be washed off immediately.

The compounds thus far described are all substitution products formed by replacement of the hydrogen of the ring. They differ in chemical and physical properties and in their effect on human beings from the substitution products which are formed by displacement of hydrogen from a side chain, such as the radical CH_3. Thus, if the hydrogen of the ring in toluene is displaced by NH_2, amidotoluene or toluidin, is formed, while if the replacement takes place in the CH_3 radical, we have benzylamin. A third compound, with the same elementary composition, results when the replacement is in the NH_2 group of amidobenzene, or anilin, and a CH_3 radical enters. This last is methyl anilin. These three compounds are very different in action and in properties.



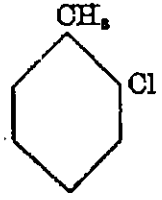
Toluene. Orthotoluidin. Benzylamin. Methyl anilin.

This distinction is very important, for the ring substitutions have in general the physiological action of benzene, while many of the products formed by replacement of hydrogen in the methyl group act like the alcohols. The following are some instances of these two kinds of products: *



Orthocresol. Benzyl alcohol.

Chlortoluene, formed by chlorin gas in toluene with heat, is



* Substitution products of toluene are usually called tolyl or toluyl compounds. Toluylendiamin is $C_6H_3CH_3(NH_2)_2$. Side-chain products are called benzyl. Benzaldehyd is C_6H_5CHO.

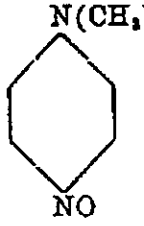
Benzyl chlorid, formed by chlorin gas in toluene with cold, i



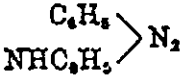
Bodies similar to benzene substitution products may be forme from ammonia, H_3N, by substitution of one of the hydrogen atoms Anilin is $C_6H_5NH_2$. Diphenylamin is $NH(C_6H_5)_2$.

These ammonia substitution products are slightly toxic if at all

An instance of a body which is both a substitution and an addition product is nitrosodimethylanilin



When an amido compound of the benzene ring is acted on b nitrous acid, HNO_2, there results a series of intermediate compound known as diazo compounds, which contain two nuclei bound togeth by—N_2—. Diazoamidobenzene is



Anilin, para- and meta-phenylendiamin, etc., yield these dia compounds and the latter unite with other amido compounds or wi phenols to form azo coloring matters. For instance, the dia compound of benzidin acting on alphanaphthylamin and sulphur acid forms Congo red. The diazo compounds are not poisonous.

For industrial use the most important derivatives of benzene ar toluene are the nitro, amido, diamino, and chlor compounds; f these are the so-called intermediates used in the production of co tar dyes, drugs, and perfumes, and some of them are also used accelerators in the vulcanization of crude rubber. The danger a companying their use in industry depends not only on their chem cal structure, their actual toxicity, but on their physical structur solids being less dangerous to handle than fluids, and those th volatilize readily being attended with much more danger than tho which do not. Another important factor is the way a given co

case was the result of carelessness on the part of a man who had charge of blowing weak phenol into a measuring tank. Without looking to see whether a former charge had been removed from the tank, he blew in another charge. His fellow workman saw the tank overflowing, went up to shut the water off, and got his clothes saturated with 10 per cent phenol. He seemed to be all right, but was sent to the medical department for treatment and when he reached there fell unconscious and died.

The physiological action of the naphthols is similar to that of phenol, and there is also a destructive action on the blood and an injurious effect on the kidney (3). Acute nephritis, even hemorrhagic, has followed the medicinal application of naphthol to the skin. *Alpha-naphthol* is said to be more toxic than beta. The use of *beta-naphthol* in industry seems to be almost without danger, except from irritation to the skin. In plants where beta naphthol is produced the steam is said to be irritating as well as the dust, but in these same departments caustic soda gives more trouble than naphthol.

Nitro and Amido Compounds.—Poisoning from the nitro and amido derivatives produces in general much the same clinical picture, differing in some details and with a few striking exceptions. According to Curschmann (4), there is an important difference between the nitro and amido compounds, in that the latter are simply blood poisons and all of the symptoms produced by them may be referred to their action on the blood, while the nitro compounds have in addition a direct action on the central nervous system. That this is true, with regard to the nitro compounds, is undisputed, but Heubner (5) believes that it is true of the amido derivatives of benzene as well as of the nitro. Heubner succeeded, in his experiments on rabbits, in producing a narcotic effect, with collapse and paralysis, before blood changes had had time to take place, and he believes that not only nitrobenzene, but anilin and phenol, exert a direct action on the lower centers, those of respiration, vasomotor control, and heat regulation.

In a light case of poisoning from one of these aromatic compounds, the face flushes, the man experiences a sense of fullness and throbbing in the head, burning in the throat, tightness in the chest, and then a violent throbbing headache may come on with dizziness, roaring in the ears, and some disturbance of sight. The flushed face now becomes livid, with bluish lips and tongue, and there is a sensation of weakness in the knees, a staggering gait. If prompt treatment is given; that is, if the man is removed from all contact with the poison, which in practice usually means having him strip off his clothes and take a full bath, the attack may last only a few hours, and the man is able to return to work on the following day. Not even in so mild a case as this the bluish color of the lips and

tongue may persist for several days. In severer cases, the color of the face is gray-blue, the lips and tongue are more deeply cyanosed, the muscles tremble, the man staggers and feels as if his knees were caving in. He is nauseated and may vomit and complains of cramps in the abdomen and of extreme weakness. Sometimes, usually a few hours after the onset of the attack, consciousness is lost. The respiration is shallow and quick; the pulse is small, fluttering, irregular, and enormously accelerated; the skin is cold, and the blood pressure is usually low. If coma persists, the respiration and pulse grow slower and slower, there is involuntary defecation and urination, and convulsions usually come on just before death. It is a characteristic feature of all these poisons that the attack seldom takes place while the man is at work, but almost always while he is on his way home, or even some hours later.

Many studies have been made of the blood in poisoning from benzene derivatives, and the changes in acute intoxication seem to occur in the following order. Methemoglobin is formed early in the course of intoxication, and probably coincidentally with it is a destruction of red blood cells. (Curschmann (4), Lehmann (6), Mohr (7).) The blood count and the hemoglobin fall. Microscopic examination shows that the red cells are altered in size, shape, and staining properties. The cells are pale, and there is some fragmentation and polychromatophilia. Early in the attack the blood becomes chocolate colored and thicker than normal, and spectroscopic examination may reveal lines which are said to be those of methemoglobin (Mohr), or rather, lines situated between the methemoglobin and the oxyhemoglobin, and therefore not quite typical (Price-Jones and Boycott (8), Brat (9).) If, however, the spectroscopic test is not made till later in the attack, it is usually impossible to detect these lines. Indeed, Curschmann says that by the time cyanosis is fully developed methemoglobin can no longer be demonstrated.

The evidence of the destruction of red corpuscles is succeeded in a few days, from the second to the fifth, by evidence of active regeneration, and the blood picture then may be very much like that of pernicious anemia, with variations in staining and in size and with the appearance of stippled cells and nucleated cells. The changes in the white cells are not so characteristic, but during an acute attack there is usually a polymorphonuclear leucocytosis. Later, as also in chronic poisoning, there is a lessened number of these cells and a relative increase of lymphocytes (Hudson (10)). In the slower forms of poisoning, the destruction of red cells acts as a stimulus to further cell production on the part of the bone marrow, and an increased red cell count may be found. Malden (11) examined the blood of 13 men employed in an English factory where anilin and nitrobenzene were made. Six of the 13 had a

high red cell count with a low hemoglobin, and many imperfectly developed red cells. Loss of hemoglobin ran from 5 to 50 per cent. The cells showed great variations in size, the large predominating, but more noteworthy was the appearance of stippled cells, which Malden considers quite as characteristic of the early stages of anilin poisoning as it is of lead poisoning. Malden summarizes the changes in the blood caused by small repeated doses of anilin, thus: Red cells increased in number with loss of hemoglobin; low color index; degeneration and imperfect regeneration of red cells; increase of lymphocytes, decrease of polymorphonuclear leucocytes.

Very varying results are reported from the analysis of the urine in cases of acute poisoning. Hay (12) produced in himself symptoms of intoxication with marked cyanosis, but his urine showed no abnormality. Sugar and casts are commonly absent in the urine, although there are occasional instances of reduction of Fehling's solution. Albumin is usually not found, except perhaps a trace, in acute intoxication of moderate degree, even when the urine is a dark brown color. This brown color is very common and is often the first warning the workman has that he is beginning to experience the effects of the poison. A chemist who once had had a severe attack of anilin poisoning from drawing a quantity into his mouth while siphoning, told me that always after that if he came in contact with anilin he would notice this change in the color of his urine, although he might feel no subjective symptoms at all.

In severe poisoning the urine may be a dark brown or the color of port wine, or a smoky red, and in such cases methemoglobin or unchanged hemoglobin or blood pigment, bile pigment, hematoporphyrin may be detected. Albumin can sometimes be demonstrated, but not always, even in severe cases (Mohr). Some observers insist that bile pigment is never found in the urine; others, that bilirubin can be detected in the majority of cases. Mohr found hydrobilirubin frequently after dinitrobenzene and chlorbenzene poisoning.

No thorough study has as yet been made of the reduction of Fehling's solution, although the occurrence of this phenomenon is reported fairly frequently. Six such cases were described in a personal communication by Dr. Kessler, of Marcus Hook, in men who had been working with dinitrobenzene and anilin.* Their urine was dark brown, contained bile pigment, and had reducing properties. A seventh case was one of fairly severe poisoning from mononitrobenzene. Dr. Sutherland, of the Du Pont Company, who has some 1200 men under his care, says that he finds not infrequently urines reducing Fehling's in men who show signs of poisoning from nitro or amido compounds. According to von Jaksch (13), a substance which reduces copper sulphate and is also lævo-rotatory was found in

* See Industrial Poisoning in Making Coal-Tar Dyes and Dye Intermediates. Bull. 280, U. S. Bureau of Labor Statistics. April, 1921.

the urine of a man suffering from nitrobenzene poisoning. This urine smelt strongly of oil of mirbane, and contained a trace of sugar and an increase of ammonia and acetone.

Neubauer (14) says that in severe anilin poisoning, anilin may be found unchanged in the urine, but this is rare. Usually it is changed by oxidation and conjugation to para-amidophenol–sulphuric ester. Nitrobenzene and the nitranilins are also excreted as para-amidophenol, while the reduction product of dinitrophenol, which appears in the urine after poisoning from this substance, is amido-2-nitro-4-phenol.

P. A. Davis (15) of Akron examined over one hundred urines of men in all stages of anilin poisoning, from the early, acute, to the persistent, chronic. He summarizes his findings as follows: specific gravity, 1005 to 1030; reaction usually acid; a large amount of uric acid being present; albumin negative except in extreme anemia; tests for anilin, anilin radicals, phenol, acetone, negative; diacetic acid positive only in severe cases. Nearly all showed traces of hematin if 24 hour specimens were evaporated. Microscopically, there were large quantities of uric acid crystals, urates and oxalates. One specimen had diacetic acid with a trace of sugar, two had involvement of the bladder which improved on change of work and on treatment.

In the early years of the present century the physicians attached to the great color works at Hoechst noticed that workmen in this plant were to an unusual degree victims of tumors of the bladder, sometimes cancerous, sometimes benign. In 1904 they began to ask information from 18 other German dye works concerning the occurrence of bladder tumors and of inflammation of the bladder, cystitis; and the responses to these inquiries brought to light 38 cases, 18 of which were fatal. This report attracted great attention and was followed by others from time to time until, in 1920, the number of known instances of bladder tumor in German dye works reached 177.

At a meeting of industrial physicians in Germany in 1913 Leuenberger (16) spoke on this subject, pointed out the fact that it was undoubtedly an amido, not a nitro body, which must be held responsible for bladder tumor formation, and urged the physicians attached to dye works to tabulate their cases and to discover which were the dangerous departments and what was the compound eliminated in the urine that acted as an irritant to the bladder. The answers to these questions are now appearing in the *Zentralblatt für Gewerbehygiene*.

Industrial poisoning from these compounds, especially from the amido compounds, is rarely fatal. I have records of two cases of fatal poisoning from absorption of nitrobenzene which was spilled on the clothes, and also of two deaths from anilin poisoning, but

of the poisons in question was not understood and prompt measures for thoroughly cleansing the skin were not taken. Death is preceded by coma, increasing paralysis of the heart and respiration, convulsions, and usually by edema of the lungs. Usually there are no characteristic changes in the organs, except in the case of a few compounds, such, for instance, as trinitrotoluene, which during the war caused a number of cases of very characteristic acute yellow atrophy of the liver. The usual findings consist of slight degenerative changes in liver, heart, and kidneys, sometimes of pneumonia or edema of the lungs, or of hemorrhages into the lungs and stomach and intestines.

The benzene derivatives may be inhaled as fumes or fine dust, but the most important mode of entrance into the body is through the skin. Hay (12) experimented on himself, applying to the skin 0.1 gm. of dinitrobenzene in ointment. A few hours afterwards his lips turned a vivid blue, his skin a leaden color; his pulse was 120 with high tension; and there was a sense of fullness and throbbing in his head. Curschmann produced fatal poisoning in cats by rubbing a few grams of paranitranilin on the skin, and the same result was obtained with phenylendiamin. Observations made on an extensive scale in British munition works during the war showed that contact with such substances as trinitrotoluene and tetryl was not only the chief cause of poisoning but was responsible for all the more serious cases (17). This was confirmed by observations made in American munition plants and American dye works (18, 19, 20).

Nevertheless, fumes, especially when mixed with steam, gave rise to unmistakable absorption of TNT, and several instances have been reported to me of undoubted fume poisoning from anilin and other compounds in dye works. For instance, a case of poisoning occurred on the second story of an anilin reduction building from the fumes which passed through the cracks in the wooden floor. The reduction apparatus was very defective and it was often necessary to open up the reducers and to empty them, during which time anilin fumes would escape. In another plant, a man who did not come in contact with anilin at all but worked a machine like a cream separator for separating anilin from water, was taken ill and was under treatment for eight days. The installation of a suction fan to draw away the fumes made it possible for him to go back to his work with no further trouble.

From still another plant came the history of a man who was sent to repair pipes in the ceiling above a reducer where monochloranilin was being made from nitrochlorbenzene. Reduction was over and fumes were rising from the open steaming reducer. After 45 minutes the man was overcome by the fumes and had to be carried down. He was dangerously ill for several days and could not return to work for some weeks. Cases of fume poisoning also occur among

men engaged in centrifuging (called "wringing" or "spinning") mixed toluidins to separate the para crystals from the oily ortho. Even when the centrifuges are out of doors very heavy fumes are given off during the process, and it seems that severe poisoning may occur without any direct contact.

Although the description given above is typical of this group of poisons they differ from one another more or less with regard to the prominence of certain symptoms, the degree of toxicity and in at least one instance (dinitrophenol 1-2-4), there is a decided divergence from the usual type.

The Nitro Compounds.—Mononitrobenzene and meta-dinitrobenzene are very important dye intermediates, and the latter is also one of the most important of the high explosives. *Mononitrobenzene*, known as oil of mirbane, is a yellow, oily fluid smelling like oil of bitter almonds, insoluble in water, but readily soluble in fats. It passes easily through the skin and when spilled or splashed on the skin gives rise to rapid severe intoxication, the blood turning chocolate-colored and the urine dark within a few hours after even a slight accident of this sort. If the clothing is soaked with nitrobenzene, the resulting collapse may be very sudden and severe.

There is the history of a fatal case of nitrobenzene intoxication in the records of the Massachusetts General Hospital for July, 1916. The patient, an elderly man employed in a soap factory, was carrying a five-gallon can of oil of mirbane, some of which he seems to have spilled on his trousers. He suddenly staggered and then collapsed, spilling more of the fluid on himself. It is evident from the record that his mirbane-soaked clothing was not removed but that he was sent to the hospital as he was, practically in a poultice of nitrobenzene. When he reached there he was unconscious, respirations were slow and irregular, his skin was of a dark gray-blue color, his pupils were small, irregular, and did not react to light. The heart, however, was regular with good action until just before death which occurred an hour after he reached the hospital, preceded by increasing respiratory failure. Some blood was withdawn from the vein of the arm before death and it was chocolate-colored. A similar case of profound cyanosis and collapse, but not ending in death, occurred in a man who was using a brass polishing mixture which contained nitrobenzene, and who spilled it on his overalls and went on working till he suddenly collapsed.

Dinitrobenzene (meta) is a solid which volatilizes slightly at room temperature. By general agreement it is pronounced to be the most troublesome compound that is used in coal-tar dye manufacture. This does not mean that it is the most toxic of the intermediates, for it is not, but that the requirements of manufacture are such that men are necessarily brought in contact with it in such a way as to

make it difficult to protect them. A chronic form of dinitrobenzene poisoning has been described by the British and the Germans, both of whom have had ample opportunity to observe it among the workers in roburite, a mixture of dinitrobenzene and ammonium nitrate much used before the war, and in German munition plants where dinitrobenzene was the chief explosive used during the war. Prosser White (21) describes a severe form of anemia in dinitrobenzene workers, with dusky yellow skin, jaundiced sclera, an appearance of partial asphyxia, wasted muscles, dulled sensibility, partial paralysis of the hand, defective vision.

German articles, appearing since the war, emphasize the injurious action of dinitrobenzene on the optic nerve and on the auditory nerve. Cords (22) describes four varieties of optic nerve injury ranging from light temporary disturbances to the most severe progressive disorders. The cases in the third group were most numerous. Here was found a more or less pronounced papillitis, followed by a temporal paling of the optic disk. In all these was an advanced central scotoma with loss of color sense for red and green, and frequently complete loss of color sense. There was often pronounced contraction of the pupils with inactivity toward light and accommodation. (See also Reis (23).)

The reports of the German factory inspectors for the war years show that the principal explosive used was dinitrobenzene and that the susceptibility to poisoning from this compound is practically universal. In Bavaria from 1915 to the end of the war there were fully 1000 cases of DNB poisoning and many of the victims had from two to five attacks. The proportion of cases was greater among women than among men, and the proportion for both sexes increased with the tightening of the food blockade. In 1916 the rate was 66 per cent for women, 56.7 per cent for men; in 1918, 119 per cent for women, 100.1 per cent for men. Apparently there were about 113 deaths from DNB poisoning. The British record for TNT is 96 deaths.

In American dye works DNB is often the only substance that causes real alarm. There is much more exhaustion, depression of the heart, than in poisoning from anilin, and the effects of an acute attack last much longer, dragging on sometimes for days or weeks, while in anilin poisoning a man usually recovers in 48 hours. The anemia of DNB poisoning may be profound and persistent. Severe poisoning from a large dose is always the result of an accident or follows some unusual piece of work, such as tearing out bricks and rafters in an old room once used for the production of DNB. Sixteen men engaged on this work were poisoned, several of them remaining unconscious for six or eight hours, and one having convulsions at intervals for twelve hours.

It is not only in the production of DNB, but in its use as an intermediate, especially for reduction to metaphenylendiamin and to metanitranilin, that the danger occurs. Sometimes molten DNB is run out into open pans, and when it is caked men chop up the cake and shovel the fragments into trucks. In one plant in which this method was used, it was found that no less than 50 per cent of all the sickness was among the DNB men, although they numbered only 24 in a force of 1500. In consequence, this method has been largely abandoned and the hot DNB is now usually run out to meet a stream of cold water which granulates it or pellets it. However, shoveling and dumping the pelleted DNB and conveying it in trucks causes poisoning; for fumes are given off and it is almost impossible to avoid skin contact. A history of 27 cases of DNB poisoning in men engaged in such work showed that the duration of incapacity was from one to 12 days.

The nitrotoluenes, ortho and para mononitrotoluene, are used to produce by reduction the important intermediates, ortho and para toluidin. During the war dinitrotoluene was produced at a stage in the manufacture of TNT, and in the dye industry it is used for the production of toluylendiamin. None of these is so toxic as the corresponding benzene derivatives: they act more slowly, and many men can handle them with seeming impunity. Their pathology and symptoms, however, are the same. The effects of trinitrotoluene were closely studied during the war and it was found to be a poison with slow action to which about one-third of those exposed were susceptible. Its action was chiefly on the bone marrow, causing a great destruction of red blood cells and a resulting hematogenous jaundice. There were 360 notified cases of toxic jaundice from TNT poisoning among the British munition workers, with 96 deaths. Much less common was an aplastic anemia of extreme type without typical degeneration of the liver. Both forms occurred also in American munition works. Trinitrotoluene is not used in dye manufacture,* but the literature with regard to it is of great value because it enables us to picture the action of similar compounds which have not been tested on human beings so thoroughly as has TNT.

The same thing is true of one of the dinitrophenols which is not in itself important since it is used only to a limited extent in dye manufacture, but, like TNT, its physiological action was tested on great numbers of human beings during the war, and it is safe to suppose that the discoveries made with regard to it may prove to apply to other nitro derivatives of benzene. Before the war *dinitrophenol* 1-2-4 was not known to differ in any way from the other

* I have been told that a peace-time use for TNT is in making "Cordu," a fuse for dynamite, and that "TNT oil" is added to some kinds of dynamite. This oil is removed by wringing from the products of the first stage of nitration of toluene and it has the odor of nitrobenzene and produces serious systemic poisoning.

isomeric forms of this compound, but its manufacture on a large scale for the favorite explosive of the French, mélinite, a mixture of picric acid and DNP, revealed a very peculiar and characteristic toxic action on men. Perkins (24) says that acute intoxication comes on suddenly, with a sensation of extreme weariness in the limbs, of painful constriction at the base of the chest, a burning thirst, abundant sweat, and an agitation and anxiety which is quite characteristic. Other very characteristic signs are a dyspnea with especially difficult inspiration, and scanty urine containing a reduction product of dinitrophenol. In severer cases death may take place in a few hours, after a rise of temperature to 104° F. or over, abundant sweats, intense thirst, contraction of the pupils, and sometimes colic and diarrhea. Excitement and terror are followed by coma, convulsions, and death. Temperatures as high as 109.4° F. have been recorded, and in some cases there was a rise of several degrees after death. Autopsy revealed no characteristic lesions.

The French experimenters found that the action of DNP 1-2-4 is highly specific, quite different from the action of the mononitrophenols, except para, which produces similar results, but only in heavy doses and for a transient period. The same thing is true of the 1-3-4 isomer of DNP. The other isomers resemble the nitro compounds in general, causing formation of methemoglobin. The toxic action of DNP 1-2-4 consists in the production of an increased cellular combustion, oxidation, which has no relation to muscular work nor to any action on any special organ nor to a stimulation of nerve centers, for it occurs even in cold-blooded animals. The symptoms are explained as showing an exaggeration of the heat radiation activities caused by the progressive elevation of the temperature, which, in animals, may rise to 113° F. at death.

There were four deaths during the war in the two American factories which manufactured mélinite for the French. Three men who were handling dry DNP died within 24 hours after the first symptoms occurred. From the meager report obtainable it seemed that these cases were like those described by the French. The fourth died after an illness lasting several days, which was apparently the typical toxic jaundice as seen in TNT workers. It is possible that in this factory the DNP handled was not the 1-2-4 isomer. Leymann (25), in 1902, described three cases of sudden and severe poisoning which developed in a dye works from the dinitrophenol used in making sulphur black.

The *nitrochlorbenzenes* are used as intermediates for the production of sulphur dyes, especially sulphur black. They are volatile and very toxic, but it is their irritating action on the skin which attracts the most attention and which probably protects the men from severe general poisoning. *Dinitrochlorbenzene*, used in the manufacture of sulphur blacks, has probably caused more dermati...

than any other compound used in coal-tar dye manufacture. In one Brooklyn plant, every man employed was more or less affected in this way, and during the summer months the place had to close down for lack of labor. One of the men described to me the course of the disease, as follows: it begins with itching behind the knees and at the bend of the elbow and along the inner surface of the thighs, then little red points appear over these areas enlarging and coalescing to form a swollen mass which itches and burns unbearably and which is relieved only by prolonged soaking in alkaline water. Sometimes the face is involved and the eyes swollen shut.

Of the three isomers of nitranilin, two are important—meta and para. Kobert (26) and Rambousek (27) both think that paranitranilin is more toxic than meta. Gibbs and Hare (28) confirmed this and find ortho more toxic than meta, but Lewis (2), experimenting on animals in H. G. Wells' laboratory, found meta more toxic than para. Both, according to Gibbs and Hare, cause formation of methemoglobin and laming of the central nervous system and of the heart.

Paranitranilin is the more important of the two in dye manufacture, being used not only as an intermediate for sulphur dyes and for azo dyes, but also with beta naphthol for the production on the fabric of a bright red dye called para red. The most conspicuous action is on the skin, for it causes a very distressing, burning, itching, eruption, but it is also capable of producing serious and even fatal systemic poisoning. Bachfeld (29) reported nine cases, four of which were serious with scanty and very painful micturition, but with no blood or albumin in the urine. A fatal case was reported from the German dye works at Hoechst in a man who had been working for five hours in paranitranilin dust. Another occurred in an American color works. This was in a white man of 27 years who had been employed for only twelve days in the paranitranilin department. He is said to have been poisoned by dust which resulted from an accident in the drying room, perhaps in tipping over a tray of the powder. The foreman sent him at once to the bath house and he took a bath and remained there for about an hour. Then he went to the works doctor, but after he had been in the waiting room about 20 minutes he lost consciousness and although given stimulants and artificial respiration by means of a lung motor, he died, about two and a half hours after the accident.

Metanitranilin is made from dinitrobenzene by reduction, and poisoning which occurs in such a department may be due to the DNB. I have one instance, however, of a clear case of metanitranilin poisoning in a young workman who was sent to clean out a tub in which metanitranilin had been "processed." Soon afterwards he complained of acute frontal headache, then he vomited, and then

fainted away. He was taken to the hospital and the record reads "vomiting, fainting attacks, headache, rapid heart, very profound cyanosis, with lips and mucous membranes almost black." A similar case is in the records of the New York Department of Labor. The man was sent to clean out a munjer in which metanitranilin had been made. He worked off and on from nine in the evening until midnight, when he went off for half an hour for supper, and when he came back he told the foreman that he felt faint and sick at his stomach, but nevertheless he was told to go back to work. At half past four in the morning he was found lying on the floor unconscious and was taken to the hospital. He was deeply cyanosed, respirations were rapid and shallow, pulse was rapid and of poor quality. Eight ounces of venous blood were removed; the color was dark and coagulated slowly. The man did not regain consciousness till 6:30 in the evening and his convalescence was very slow.*

Amido Compounds.—The symptoms set up by the amido derivatives of the benzene ring are less serious than those caused by bodies which contain the NO or NO_2 group, although the cyanosis is deeper. A case of dinitrobenzene poisoning does not present as alarming an appearance as one of anilin poisoning, but the involvement of the central nervous system, the changes in pulse, respiration, and body temperature, are much more grave; convalescence is also slower. Usually a case of anilin poisoning does not incapacitate a man for more than a day or two, although British physicians hold that he should not be allowed to return to work if his hemoglobin is much below normal. But after dinitrobenzene poisoning, a workman is likely to be ill for a fortnight or more.

The earliest cases of *anilin* poisoning in American literature are, so far as I can discover, two reported by Apfelbach (30) of Chicago in 1913. These men were referred to him by factory inspectors, not because they complained of illness, but because of the lividity of their color. Lips and tongue were a deep blue, but the only discomfort the men experienced was slight headache, dizziness and difficulty in swallowing. The first was a press feeder in a printing shop who had been using a new non-inflammable roller wash to clean the ink off press rollers and this proved to contain anilin. The other was mixing alpha-naphthylamin in an open chaser in a paint and color works. Both had methemoglobin in the blood, as shown by spectroscope.

The next cases were Birge's (31) published in 1914. Two men

* Various nitroso compounds are used as dye intermediates and also used in rubber compounding. They seem always to be irritating to the skin and "nitroso itch" is a common expression in plants making intermediates. The committee appointed by the American Chemical Society to investigate the newer organic accelerators used in rubber compounding reported that para-nitroso-dimethylanilin was [illegible]ive of trade eczema.

were using anilin black paint, applying it with a brush and then washing the surface with hot suds, work which naturally encourages skin absorption. They were seized with nausea and general weakness, palpitation of the heart, then violent headache and vomiting, the skin was very pale, the lips blue and they passed dark-colored urine. In 1915, Hayhurst in the course of a survey of the health hazards of Ohio industry found many cases of anilin poisoning in the large rubber centers, where it had recently been introduced as an accelerator of vulcanization and, after the outbreak of the war shut off the German supply, the production of anilin also had begun. R. V. Luce of Akron and I (32) made a study of anilin poisoning in that rubber city in 1916, and found that the condition was fairly common, the victims being known as "the blue boys," from the color of lips and face. In 1917 Lintz (33) described a case which came under his care at the Brooklyn Jewish Hospital. There was marked cyanosis, great restlessness and pulmonary edema, which subsided under venesection, projectile vomiting, involuntary micturition and expulsion of dark fluid from the rectum. The color of the blood was very dark. The systolic pressure was down to 100, the diastolic was 80. By the fifth day the man was discharged entirely recovered.

Newton (34), in 1920, described four cases of anilin poisoning and one of mixed benzene and anilin, in which, added to the symptoms typical of anilin, there was a benzene leucopenia. The white count fell from 10,600 when the poisoning began, to 1,440 some 16 hours later, and then rose to 6,640 after 72 hours. The four cases of anilin poisoning were in employees of an anilin department. One was working inside an anilin-reducing apparatus, the second washed some clothes with anilin, the third and fourth poured anilin into a receptacle and breathed the fumes. The first case is the most interesting. This man, 49 years old, climbed into a reducer on June 26th to clean it out by flushing with a hose. In a short time he began to feel dizzy and nauseated and he had a "warm, sweet taste" in his mouth. He climbed out at once and went to the hospital where he did not lose consciousness but was overcome by mental confusion and bodily weakness. Newton saw him after an hour, in collapse, intensely cyanosed, complaining of chilliness, although his temperature was 101° F. His pulse was weak, dicrotic, 110; the systolic blood pressure was 110, diastolic, 60, but after a hypodermic injection of camphorated oil it rose to 130 and 85. The blood was chocolate colored and flowed freely, the red cells numbered 3,500,000, whites 10,600, hemoglobin 95 per cent. There was strangury at first and when urine was obtained it was dark, sp. g. 1020, acid, negative for sugar, albumin and bile. On June 30th he was still cyanosed and complaining of headache and the blood count had fallen half a million; the pressure was 115 systolic

and 60 diastolic. The cyanosis was still evident on July 7th but by the 13th it had disappeared and he could be discharged although he still was somewhat nervous and sleepless.

This was a case of moderate severity. More serious poisoning occurred in an Akron man engaged in experiments in connection with rubber compounding, work which involved exposure to contact and fumes (32). One morning he went to work at seven feeling perfectly well in every way, but after about an hour and forty minutes he began to have throbbing in the head and increasing nausea which he attributed to the July weather and to the poorly ventilated room. He next noticed palpitation of the heart, and then a violent headache came on, increasing in intensity and accompanied by vertigo. As he said, "I felt as if I had been standing on my head for a long time and every ounce of blood in my body had rushed to my brain." The dizziness increased, and about 45 minutes after the onset of the first symptoms he lost consciousness. He was hurried to the hospital where oxygen and heart stimulants were administered, but apparently with little effect; for the cyanosis persisted, the heart action was very feeble for more than 16 hours, and he did not regain consciousness till the following morning, a period of about 22 hours. A catheterized specimen of urine obtained on admission showed no abnormality, but a specimen 18 hours later was smoky, with specific gravity 1022, a trace of albumin, no sugar, but hemoglobin was demonstrated by the Heller test and the Schönbein-Almen turpentine-guaiac test. This hemoglobinuria persisted for five days. A blood examination made on entrance gave normal findings in all respects except for a slight eosinophilia, but four days later there were stippled red cells and some irregularity in the size and shape of the red cells. The hemoglobin was 75 per cent (Sahli). The patient suffered from severe headache for five days and complained of weakness and exhaustion some two weeks longer, after which he slowly improved.

Friedländer (35) reported from the Municipal Insane Hospital in Frankfort a case of acute maniacal delirium in a man who had loosed a rubber pipe leading into an anilin receptacle and had received a splash in the face and mouth, swallowing about a mouthful. About four hours later he became delirious and was brought to the hospital in a strait jacket and deeply cyanosed. The next day he was rational but excited, and by the third day the cyanosis had cleared up, but he was still restless and irritable and his heart was still weak and rapid. By the fourth day his mentality was normal. A somewhat similar history was related to me in an American dye works. The man was a pipe fitter making repairs in the ceiling over the anilin reducers. Suddenly he became maniacal and ran amuck over the plant, and it was six hours before he came to himself. The foreman thought this was an instance of fume poisoning but

it seemed to me possible that the steam from the reducers carrying anilin with it had gradually soaked the ceiling and in working there the man's hands had become saturated with anilin.

Chronic anilinism was described by Hirt as characterized by disturbances of sensibility and of the motor nerves, inertia, headache, digestive disorders, skin eruptions, and roaring in the ears. In the early days of rubber compounding with anilin just prior to the war, workmen in Akron who were exposed to anilin were not infrequently treated by their physicians for chronic valvular heart disease with failing compensation, because the cyanosis, the altered pulse, the complaint of palpitation of the heart, breathlessness on exertion, weakness and easy fatigue, and indigestion, all seemed to point to such a diagnosis. A typical case of this sort came to my attention in 1914. The man had worked with anilin for nine months. He complained especially of muscular weakness and fatigue; palpitation of the heart came on when he had any unusual exertion, and almost always at the end of the day's work; and he had frequent headaches while at work, sometimes severe and accompanied by nausea and dizziness. He was never cyanosed, and while examination showed a rapid pulse, 94, there was no abnormality of the heart. His blood examination showed the condition described by Malden (see page 494); namely, a red cell count of 5,400,000, with only 68 per cent hemoglobin.

Davis(15) has seen men in the rubber industry who "seem to acquire a tolerance for anilin, in that they remain cyanotic for years without the development of any apparent serious symptoms. . . . These patients have some blood changes, of course, yet they feel no ill effects except for a slight tired feeling at the end of the day's work. The body attempts to maintain an equilibrium between intake and output of anilin but there is a surplus amount which is absorbed and which causes blood changes that are responsible for the marked cyanotic condition."

It is generally recognized in American anilin plants that long exposure to anilin is likely to make the men irritable, hard to get along with, "grouchy." The foremen say that such men are not really up to a full day's work and if they try to push them it only makes things worse. They are likely to have a poor appetite and complain a good deal of headache. Sometimes eczematous rashes appear, or pustular eruptions, particularly on covered parts of the skin, the scrotum, arm pits, and inguinal regions.

Curschmann (4) lays great stress on a slowly developing form of poisoning, not only from anilin but even more from solid amido compounds. He says that in such cases the earliest sign of chronic poisoning is a loss of hemoglobin, and therefore blood examinations are of great practical importance, because any workman who has lost from 15 to 20 per cent of his hemoglobin is facing the risk

of an acute attack of poisoning and should be temporarily suspended from work. At this stage he may be slightly cyanosed, but typical microscopic changes in the blood are not found till a later stage. He had a case of almost typical neurasthenia and the only thing that pointed to anilin poisoning was the loss of hemoglobin and the rise in blood pressure, which last he considers a valuable diagnostic sign. The average blood pressure (Riva-Rocci) in 100 workmen not exposed to anilin, Curschmann found to be between 110 and 120, but in men intoxicated with anilin it ran from 135 to 165. In cases of pronounced anemia with cyanosis there may be a rise of 40 in pressure, and at the same time the pulse is always slow, down to 48. In these cases the urine is brown and there is slight jaundice.

In the foreign literature there are frequent references to disturbances of vision in the course of anilin poisoning; as, for instance, among the dyers in a Swiss factory as described by Senn (36). This consisted in a loosening of the epithelial covering of the cornea followed by inflammation, cloudiness, and consequent dimness of vision. The men were working over vats of steaming anilin black, containing free anilin, and Senn attributed the trouble to the action of oxidation products of anilin, the quinones, which cause painful smarting of the eyes so that the victim rubs them vigorously and detaches the surface cells, leaving the cornea exposed to further cauterization.

Very few fatalities have occurred from anilin poisoning, and those chiefly in the years before 1917, when its manufacture was still largely experimental in this country. The most recent death of which I have heard took place in a small, poorly managed works in New England. On the afternoon of August 7th, 1922, a workman was overcome by what was said to be anilin poisoning, while making phenyl 1-8 acid. In this process anilin is driven by compressed air from drums to an autoclave, where naphthalene and sulphuric acid are added. The temperature is raised to 160° C. and kept there for some 24 hours, then the mixture is pumped to a still and the remnant of anilin not used in the reaction is distilled off and returned to the drum. The man who suffered from the fumes from this process recovered, but the following night the foreman in charge who was working alone in the room, somehow spilled anilin on his trousers and was found at half past three in the morning in a semi-conscious condition, from which he never recovered.

The *toluidins, ortho* and *para,* are considered by some to be more toxic than anilin, although toluene is much less toxic than benzene. Treitenfeld (37) found that they worked very much as anilin does, with the same effect on the central nervous system, but causing rather less cyanosis. Rambousek says that they act like anilin, but produce more injury to the urinary system, more strangury and he[illegible]ia than does anilin, and this statement is confirmed by

Kessler of the Anilin Products Co. Gibbs and Hare tested the three isomers, para, ortho, and meta toluidin, on animals and found that all destroy red blood cells, lower the body temperature, and lame the spinal cord. The fatal dose per kilogram of body weight is: for para, 0.1 gm.; for meta, 0.125 gm.; and for ortho, 0.208 gm. Metatoluidin is not used in dye manufacture, and experience in American dye works usually shows that para is more toxic than ortho, although it is crystalline, while ortho is an oily liquid. The toluidins are often said to give more trouble than anilin, but this is not necessarily because they are more poisonous, but rather because no process in connection with anilin, except repairing and cleaning apparatus, necessitates so much exposure to fumes and contact as does the centrifuging or "spinning" of the two toluidins. Friedländer (35) and Stark (38) have both reported cases of severe poisoning with coma, maniacal delirium, and great prostration, following the splashing of toluidin on the skin. In both cases there was scanty, bloody urine passed with agonizing pain.

Very little is written of the action of the *xylidins,* but they are undoubtedly much less poisonous than anilin and toluidin. The diamins are well known poisons. Indeed, *toluylendiamin* has long been regarded as a typical blood poison causing extensive destruction of red blood corpuscles, methemoglobin, severe hematogenous jaundice with destruction of liver cells. (Stadelmann (39), Dragendorff (40).) The two *phenylendiamins, meta* and *para,* are very important dye intermediates, and para is also used for dyeing furs under the trade name of Ursol. Formerly, before its dangerous nature was discovered, it was used as a hair dye, and according to Knowles (41) was responsible for not only a dermatitis but severe symptoms of nervous disturbance, sleeplessness, dizziness, weakness of the legs, and even epileptiform convulsions, coma and death.* According to Blaschko (42) and also Olson (43), the irritating effect of hair dyes and fur dyes containing paraphenylendiamin is not caused by this compound but by the presence of a mid-product, quinone dichlordiamin, which is much more irritating to the skin. Very interesting reports have been published lately of the occurrence of attacks of bronchial asthma in furriers using Ursol, attacks which resemble anaphylaxis. (See Olson (43).)

Hanzlik (44), however, rejects the theory that anaphylaxis is

* A report was made by a committee appointed by the Rubber Section of the American Chemical Society to inquire into the toxicity of the organic accelerators of vulcanization (see p. 524), and the one which was pronounced most dangerous was para-phenylendiamin. It was said to produce, when inhaled as dust, symptoms of a common cold with sneezing and extreme depression. A large dose causes death with symptoms of ptomaine poisoning. [illegible] is the only reference to such an effect which I have seen in the literature. The report of the committee may be found in [illegible]

the basis of the asthmatic symptoms which develop in consequence of exposure to phenylendiamin and its oxidation product, quinonediamin. The irritation is the direct result of the inherent chemical properties of these bodies and is independent of precipitation in the tissues. Hanzlik found that all the phenylendiamins are toxic compounds, *dimethylparaphenylendiamin* being the most so, then *diethyl*, then paraphenylendiamin and metaphenylendiamin is probably the least so. The diethyl and dimethyl compounds are absorbed through the skin with extraordinary ease, in fact the dose required for this mode of poisoning is no larger than for poisoning by hypodermic injection, a property due to their marked volatility and lipoid solubility. He estimates that about a teaspoonful of dimethyl-p-phenylendiamin held in the palm of the hand would be enough to kill an adult man. The vapors also may cause death.

The two alkyl compounds are very irritating to the skin, the others are not or are very slightly so in animal experiments. All of them stimulate the circulation and respiration, cause fall of body temperature, tremors, increased reflex excitability, convulsions, coma, death. The hypodermic and gastric administration of paraphenylendiamin produces in rabbits an edema of the face, nose, conjunctiva and neck, while meta-phenylendiamin causes hydrothorax, and therefore it seems probable that the asthma and other respiratory symptoms which have been observed in workers in the fur-dye industry are due to direct irritation and bronchial stimulation and not to anaphylaxis. Paraphenylendiamin is used as an intermediate for sulphur dyes; meta, as an intermediate for Bismarck brown, Manchester brown, and many azo dyes. It is often looked on as more dangerous than para, but this may be because it is made by the reduction of dinitrobenzene, and it is quite possible that this last is responsible for some of the trouble. Paraphenylendiamin, on the other hand, is made by the reduction of para-amidophenol, which is comparatively non-toxic.

Other compounds belonging to this group are the methyl and ethyl derivatives of anilin, which are distinctly less poisonous than anilin. In the early days of American dye manufacture, 1916, two severe cases of poisoning by *dimethylanilin* were reported to the New York State Department of Labor, but such cases are exceptional. One of them was caused by direct contact with dimethylanilin, but the other seems to have been caused by fumes. A man of 22 years had been employed for two weeks on the night shift. One night at half past ten he climbed a ladder to inspect a vat of dye which was said to be crude violet made from dimethylanilin, phenol, and other substances. He lifted the lid, breathed the fumes, and fainted, and the doctor who was summoned thought he had fallen into the violet dye, he was so deeply cyanosed. He did not recover consciousness for eight hours, and then he was taken to the hospital

complaining of impaired vision, roaring in the ears, and intense pain in the abdomen. He was in the hospital for seven days.

Anilin hydrochlorid produces exactly the same symptoms as anilin, and there may be a good deal of poisoning in the course of its production, although the work is usually carried on in an open shed to allow the fumes to escape. A fatal case of anilin poisoning reported by White and Sellers (45) at the Brussels Congress of Industrial Hygiene in 1910 was in a man who splashed anilin over himself while making anilin hydrochlorid and died within 24 hours. Price-Jones and Boycott (8) used this compound in their animal experiments and brought about all the blood changes characteristic of anilin. *Sulfanilic acid* is produced in the same way by the use of sulphuric instead of hydrochloric acid. The same risks attend its production, but there is no proof of its toxicity. A very slightly toxic compound is *anthranilic acid* (ortho-amido-benzoic acid) which is used for lake colors and for the pigment, scarlet B, the dye used for two-cent postage stamps. *Benzaldehyd*, or oil of bitter almonds, is, according to Kobert, quite harmless.

More or less severe trade dermatitis is caused by *para-amidophenol*, an important intermediate, especially for sulphur dyes. It is produced by the reduction of paranitranilin, which is much more poisonous. The excretion of both nitro and amido derivatives of benzene from the body is preceded by their reduction to para-amidophenol, which is found in the urine as an alkaline salt of para-amidophenol-ether-sulphuric acid.

Frequent cases of dermatitis are reported from a German *phenylhydrazin* plant among the men who wrap the product in cloths for the filter. An explosion of a distilling kettle full of this compound resulted in the death some days later of one workman and inflammation of the eyes of a large number of others.

Amidoazotoluene, or scarlet red, is derived from orthotoluidin and is used in alizarin color manufacture. It is known to physicians as a stimulant for tissue growth, useful to hasten healing after severe burns. Two cases are recorded of cyanosis, dizziness, headache, slight fever, rapid pulse, and albuminuria after such an application of scarlet red.

The naphthalene derivatives are far less toxic than benzene or toluene derivatives, as would naturally be expected. The naphthols, which bear the same relation to naphthalene as phenol does to benzene, resemble phenol, but are less soluble and less corrosive. *Alpha-naphthol* is more strongly antiseptic than beta and probably more poisonous. The use of *beta-naphthol* in industry, especially in making para reds, seems to give rise to little if any trouble, except for its effect on the skin, and even the fumes are [illegible] irritating to the skin, but the caustic soda used in producing beta

naphthol is much worse in this respect than the beta-naphthol itself. *Nitroso-beta-naphthol,* formed at one stage in the production of H acid, gives rise to dermatitis, as do all the nitroso compounds; while *dinitro-naphthol,* or Martius yellow or Manchester yellow, has the usual action of a nitro derivative, but is one of the weaker members of the group.

The *naphthylamins, alpha* and *beta,* are capable of producing symptoms characteristic of amido compounds, although, according to the testimony of practical men, alpha never causes severe poisoning. Beta-naphthylamin seems to be distinctly more toxic, and in one large American plant where there is no trouble at all with the alpha compound the men in the crude naphthionic department who come in contact with beta-naphthylamin suffer not only from cyanosis but from frequent micturition, apparently from over-acidity of the urine.

The *pyridins,* used in the making of anthraquinone and in other processes for indanthrene dyes, are said to make the men "dopey," to give them headache, dizziness, dulling of the intelligence. They have also a curious effect on the skin similar to that which has been described in English briquette factories as a result of handling of tarry substances. The skin is raw and sensitive as if from sunburn, and the man suffers most after washing his face and hands and forearms and going out into the open air.

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