PULMONARY IRRITANTS: PHOSGENE, CHLORINE, CHLORPICRIN

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Mr. Chairman, and members of the audience: The pulmonary irritants that I have been asked to discuss before you this afternoon include chlorine, chlorpicrin and phosgene. What one says about phosgene also applies to diphosgene. I will start by telling you a few of the general characteristics of these gases.

General Characteristics

Chlorine, as you pobably all know, is a yellowish-green gas with an irritating effect on the mucous membranes. This gas is approximately two and a half times as heavy as air. Chlorine reacts readily with water to form hydrochloric acid and to liberate oxygen. Its toxicity we will designate as 1.

Chlorpicrin is a light colorless liquid that has a boiling point of 112° Centrigrade. Its vapors are five and a half times as heavy as air and it has a sweetish odor which has been described as resembling that of fresh fly-paper. The gas is quite volatile and it is stable. It does not react readily with acids or alkalis or with water. It has a toxicity of 4 as compared to chlorine.

Phosgene has the odor of moldy hay. It is a musty odor. The boiling point of phosgene is 8° Centrigrade. This gas is three and a half times heavier than air. In a dry atmosphere phosgene is fairly stable. In the presence of moisture it rapidly decomposes to form hydrochloric acid and carbon dioxide. The toxicity of phosgene as compared to that of chlorine is 10. That is to say, it is approximately ten times as toxic, and the lethal dose is one-tenth that of chlorine.

Next we will take up some of the clinical manifestations of acute poisoning by each of these three gases.

Clinical Manifestations

Chlorine: This gas is very irritating to the eyes, nose, mouth and respiratory tract. All moist parts, once they have come in contact with chlorine, itch and burn and smart. The lachrymal, mucosal, and salivary glands all respond to chlorine with increased secretion. Coughing, choking, retching and dyspnoea are all among

the immediate effects following exposure to chlorine. Cyanosis, frothy sputum and pulmonary edema occur within a few hours after contact with a sufficiently high concentration of the gas. The edema is apt to reach a maximum between 10 and 15 hours after exposure to chlorine. In the early stages following exposure to the gas the pulse is full and slow and the blood pressure is well maintained. As pulmonary edema and the anoxia which accompanies it progress the pulse and respiration become more rapid and the blood pressure falls.

Death from pulmonary edema is likely to occur in the first 24 hours. Otherwise, the exudate is absorbed rapidly, so that the chest will be relatively clear within 48 to 72 hours, unless secondary infection occurs.

Bronchial pneumonia is a fairly common complication after chlorine poisoning, more so than for either of the other two gases.

Phosgene: Unlike chlorine, phosgene causes relatively little irritation to the eyes and the mucosa of the mouth and to the upper respiratory tract. Consequently the immediate symptoms may be slight. The retching and paroxysms of coughing observed characteristically after chlorine and chlorpicrin may be almost entirely absent. The patient may merely complain of a sense of tightness in the chest and the symptoms may be so mild that the victim is deceived as to the severity of the injury. There have been several examples of workers exposed to phosgene who felt better in a little while and even wanted to go back to work, but subsequent events indicated that they were in no shape to do so. Dogs that are exposed to phosgene do not lachrymate or show evidence of acute discomfort while in the gassing chamber. Shortly afterwards the majority of the animals will vomit, defecate, urinate and may have diarrhea. Thereafter dyspnoea may be the only gross symptom for some hours.

A. T. Jones reports the case of a man splashed with phosgene when a pipe broke. The patient coughed, became pale and had a nosebleed. Thereafter he felt well and no abnormal physical findings could be demonstrated. He was rested and transported to a hospital as a precautionary measure. Six hours later he complained of feeling ill and presented the typical gray collapse that may occur after phosgene poisoning. His pulse became almost imperceptible, the rate went up to 130 per minute. The heart sounds were essentially inaudible. Fine crepitations were present throughout the chest. The face was pale, with a purple tinge to the tips of his ears; his skin was cold and clammy. There was extreme restlessness, coughing and gasping for breath; respiration was 66 per minute. There was a copious frothy, slightly yellow sputum. Oxygen therapy was continued for five days. On the seventh day diaphragmatic pleurisy developed. There was dyspnea on exertion until the forty-second day.

Vedder reports the case of a chemist who inhaled a breath of phosgene, became pale and coughed slightly. He was removed to a hospital where he remained comfortable and apparently normal for four and a half hours. Afterwards coughing and the expectoration of large quantities of frothy fluid began, his face became gray, and he died five and a half hours after exposure to the gas.

Phosgene cases have been divided into those with blue or with gray cyanosis. The former group is said to have distended veins and may possibly have an increased venous pressure. An increase in venous pressure has not been demonstrated experimentally. The cases with gray cyanosis show signs of a peripheral circulatory collapse. The pulse is rapid and the blood pressure low, the respiration shallow and rapid. These individuals are likely to have received a higher dosage of gas and are generally considered in a terminal state. Patients with blue cyanosis may become gray prior to death.

The pulmonary edema which accompanies the cyanosis is most likely to occur during the first 24 hours after exposure to the gas. The majority of fatalities occur within the first two or three days. The latent period between exposure and the gross manifestations of lung edema is variable, but will depend to some extent upon the amount of gas inhaled.

Dogs gassed with phosgene show beginning lung edema grossly on autopsy two hours after gassing, but physical signs of edema may not be demonstrable before 10 or 12 hours.

Chlorpicrin: Chlorpicrin, as you know, is also called vomiting gas. It has a variety of actions. It resembles chlorine by causing irritation to the mucous membranes and it resembles phosgene in that it also injures the periphery of the lung. In symptomatic characteristics it is intermediate in its position between the two other gases. It causes lachrymation, coughing, nausea, vomiting, colic, diarrhea and all the acute and chronic sequelae which may result from exposure to either of the two gases previously described. These include pulmonary edema, bronchial pneumonia, lung abscesses, atelectasis, chronic bronchitis, bronchiectasis, asthma, and emphysema.

Pathological Physiology

The pulmonary edema which accompanies injury from a sufficient dosage of chlorine is associated with hemoconcentration. The bradycardia observed soon after gassing is replaced by a rapid feeble pulse as the patient becomes worse. Circulatory collapse, anoxia, low blood pressure, and terminal acidosis are all part of the advanced findings following chlorine inhalation.

Typically phosgene causes a preliminary hemodilution which precedes hemoconcentration. This period of hemodilution is called the first stage. There is a question as to whether the hemodilution actually represents an increase of fluid in the blood stream or an accumulation of red blood cells in the lung capillaries. Some authors have failed to find any increase in blood volume during the early stages following phosgene poisoning, whereas others have reported that the volume of blood is increased.

After the preliminary dilution of the blood (apparent dilution) the hematocrit readings will rapidly become higher than they were initially. The hemoconcentration will go to such a point that the cells may represent as much as 80 per cent of the volume of the blood in the experimental animal. This period of hemoconcentration is part of the second stage following phosgene poisoning. The hemoconcentration usually reaches a maximum 12 to 24 hours following exposure to the gas, but less frequently may reach a maximum from 24 to 48 hours following exposure. Experimentally, hemoconcentration does not necessarily precede death. I have seen animals which died in the hemodilution stage. Both demodilution and hemoconcentration are associated with the outpouring of fluid into the lungs, but the edema usually becomes apparent during the stage of hemoconcentration. This fluid is a transudate containing the protein constituents of the blood plasma. Rarely does the pulmonary edema fluid contain many red blood cells.

Following exposure to phosgene, manifestations of vagotonia occur and the heart rate decreases from around 80 or 90 down to 40 or 50 per minute. Retching and defecation are the rule rather than the exception in the gassed dog. These manifestations can be abolished by vagotomy or sufficient atropine. As the pulmonary edema progresses the respiration and rate of the heart are markedly increased. The percentage saturation of the arterial blood with oxygen decreases. Hemoconcentration occurs, cyanosis becomes apparent, the body temperature falls, and the subject becomes restless and apprehensive. There is a terminal acidosis.

Pathology

Chlorine: Chlorine gas injures the oral mucous membranes and upper respiratory tract. There may be a necrosis of the lining of the larynx, trachea, and the bronchi; a fibrinous exudate forms over the injured area and sufficiently injured areas slough. The injury may extend to the smaller radicles of the lung and these may be obstructed with exudate and necrotic epithelium. Leucocytes invade the injured areas. Hyalinization and necrosis may extend to the periphery of the lung. Injury to the alveolar wall results in an edema which fills the air spaces of both the injured and uninjured lung tissue with fluid. Areas of emphysema are interspersed between areas of consolidation. After a few days

the lesions become more local. Bronchial pneumonia and atelectasis may occur. There may be some scarring of the lungs as the foci of secondary infection heal.

Phosgene: Soon after injury of the lungs with this gas a microscopic examination of tissues is very disappointing. One sees little that is abnormal except fluid and capillaries congested with blood. The failure in function far outruns any microscopic manifestations of injury to the lung tissue insofar as its cellular make-up is concerned. A mild hyperemia of the trachea may occur, but is relatively inconsequential. The outpouring of fluid into the alveolar spaces is by far the most outstanding manifestation of pulmonary injury. Patches of emphysema also occur. The fluid fills the periphery of the lung and extends from the periphery toward the main bronchi, limiting the respiratory movement of the lung. The movement of air in and out of the lung churns the transudate into a stable foam, and forms a frothy bubbling fluid which is quite a stable emulsion and which eventually serves as an effective barrier to the free exchange of air. After a few days, necrosis of the bronchcolar epithelium with cellular infiltration occurs. Bronchopneumonia, resulting in some fibrosis of the lung is less likely after phosgene than after chlorine poisoning.

Chlorpicrin: Chlorpicrin causes changes intermediate between those of chlorine and phosgene. There may be superficial necrosis of the upper respiratory tract epithelium and the necrosis may extend to the bronchcolar epithelium. Pulmonary edema and emphysema also occur after chlorpicrin with subsequent focal necrosis.

Treatment

It should be pointed out in the beginning that these pulmonary irritants and injurants react rapidly with the tissues of the body to do irreversible harm. Treatment must be instituted early to be most effective

The object of therapy is to minimize the constitutional reaction to the injury which has occurred, that is, to prevent or minimize the pulmonary edema that so frequently results.

Once an edema develops, a vicious cycle is set up. Exudation leads to impaired lung function and anoxia. Anoxia leads to increased capillary permeability and hence to further exudation. The exudation encroaches on whatever functional lung tissue may remain. Practically all authors agree that rest and moderate warmth are desirable. These conditions reduce the work of the body to a minimum so that the oxygen requirement and the carbon dioxide production may be reduced to a minimum. The subject should not be warm enough to cause perspiration. The room temperature should not be above 75° Fahrenheit nor the relative humidity more than 60 per cent.

The question as to whether or not the gas patient should be considered a stretcher case is perhaps somewhat arbitrary. The aim is to minimize dyspnoea, coughing and spasm and whatever course of behavior will make the symptoms minimal probably is most desirable. Certainly there should be no double-quick, nor any excess of exercise which is likely to increase pulmonary trauma.

Various measures have been recommended by different authors in the treatment of gassed patients. These are not presented in the order of their relative merit.

Venesection: The removal of 500 cc. of blood soon after exposure to phosgene has been recommended. This procedure may be repeated at later intervals if there is evidence of an increased venous pressure. Venesection is contraindicated in individuals who have circulatory collapse which may be indicated by gray cyanosis. Underhill advocated the introduction of small quantities of saline in conjunction with venesection. He would bleed them immediately and then give a little salt solution. It is questionable whether venesection is ever of benefit to the gassed patient.

Oxygen Inhalation: Concentrations of oxygen varying from 50 to 100 per cent have been recommended. The amount of oxygen to be administered must be judged by the findings in the individual case. To minimize dyspnoea, anoxia, restlessness and anxiety and to promote rest, oxygen administration should be instituted as early as possible. Certainly one should not wait until the patient is cyanotic and edematous.

Helium-oxygen Administration: Barach advocates the use of a mixture of 35% oxygen and 65% helium in the treatment of pulmonary edema. He recommends positive pressure respiration as an additional measure to reduce the formation of transudate in the lungs. The positive pressure recommended is in the neighborhood of 6 centimeters of water. A mask or hood is essential for obtaining positive pressure in conjunction with helium and oxygen therapy; however, he states that some benefit can be derived from simply expressing the expired air through a cigarette holder or through pursed lips. There is thought to be a disproportion between the function of the two sides of the heart, the left side not keeping pace. Increasing the intrapulmonary pressure and duration of expiration decreases the amount of blood entering the right heart and hence reduces the pulmonary congestion.

Drugs: Restlessness, anxiety, dyspnoea, coughing and delirium are symptoms one is apt to encounter in a person exposed to these gases. Sedation is frequently necessary to reduce the respiratory effort and to promote rest. Morphine or its derivatives, by injection, are probably the most effective drugs for

the purpose of promoting rest, reducing dyspnoea and making the respiration slow, regular and efficient. These drugs should be given in small doses (1/6 to 1/4 gr.), and no more should be used than is absolutely necessary, for fear of depressing the respiratory center. One should remember that the symptoms of anoxia include restlessness, anxiety and delirium and that these symptoms may respond to increasing the oxygen content of the inspired air.

Solomon suggests that one should avoid if possible the use of morphine in cyanotic patients, but further states that the very restless patient should receive morphine even if deeply cyanosed. It is his opinion that barbiturates may be used in moderate doses. However, they too depress the respiratory center and tend to reduce capillary tone and therefore predispose to shock in the susceptible individual. The cough which so frequently occurs is unproductive in the early stages, only adds trauma to the already injured lungs and disturbs the rest of the individual. Codeine is probably the drug of choice for inhibiting the cough.

Spasm of the bronchial tree and pulmonary vessels may be a factor in the events which follow inhalation of pulmonary irritants. Atropine has been shown capable of relieving the bronchial spasm due to bromine inhalation. Many authors have condemned atropine as being without any value in the treatment of pulmonary edema. There is no unanimity of opinion concerning the importance of spasm as a factor in producing pulmonary edema or upon the most effective method for relieving whatever spasm does occur. Atropine will reduce the manifestations of vagotonia which follow the inhalation of these gases. There is no adequate experimental proof one way or the other as to the value of atropine for other than symptomatic relief. Numerous other drugs that act on the circulatory and respiratory systems have been recommended for treatment of pulmonary edema and its complications. These drugs include coramine, caffeine sodium benzoate, papaverine, and preparations of digitalis. There is no adequate proof of the effectiveness of any of these drugs in pulmonary edema produced by these gases. Postural drainage has been suggested as an aid in draining off the edema fluid formed in the lungs. However, such a posture as would be necessary for drainage of the lungs may have undesirable effects upon the circulation and respiration.

Sulfanilamide and the other sulfa drugs are of value for preventing or minimizing secondary infection following injury to the lungs by these gases. Instrumentation and general anesthetics are not well tolerated by the gassed patient. If some surgical procedure has to be carried out a local anesthetic probably should be used.