Reprinted from ANNALS OF INTERNAL MEDICINE, Vol. 45, No. 3, September, 1956
Printed in U. S. A.

SILAGE GAS POISONING: NITROGEN DIOXIDE PNEUMONIA, A NEW DISEASE IN AGRICULTURAL WORKERS *

By R. R. GRAYSON, M.D., *Perryville, Missouri*

Two cases of acute respiratory disease due to inhalation of silage gas were encountered in August, 1954. One was fatal. A thorough investigation of these two cases and of the silage gas that caused the illness indicates that the disease was caused by the oxides of nitrogen.

A careful review of the literature indicates that, although chemical pneumonia and fatalities due to fumes of the oxides of nitrogen have been described many times in industry, they apparently have not been reported in cases of silage gas poisoning. The following two cases, therefore, are believed to be the first cases reported in the literature of poisoning from silage gas in which it was definitely proved that the noxious agents were the oxides of nitrogen.

CASE REPORTS

Case 1. A 66 year old white male farmer entered an unventilated silo on his farm at noon on August 27, 1954, and was rendered unconscious by a yellowish brown gas present above the silage. He was in the silo approximately five to eight minutes, after which he was rescued by his nephew (the second case), and immediately lowered to the ground, where he was given artificial respiration.

Following this, he recovered consciousness and appeared fairly well but he developed increasing dyspnea and cough and was then seen by his family physician. He was thereupon referred to the Perry County Memorial Hospital and arrived there about nine hours following his exposure to the gas in the silo.

Physical Examination: On admission, examination of the patient revealed an aged, well developed, well nourished white male in severe respiratory distress, cyanotic and semiconscious. The temperature was 97.4° F.; pulse, 140 per minute and regular; respirations, 40 per minute; blood pressure, 104/70 mm. of Hg. The skin was pale, clammy and wet with perspiration. The external jugular veins were distended. The chest was emphysematous and the heart tones could not be heard. Auscultation of the lungs revealed loud, bubbling râles throughout all lung fields, posterior and anterior. Examination of the abdomen was negative. The remainder of the examination was unrevealing.

Past History: According to the family, there was no past history of pulmonary or cardiac disease. No other past history was obtainable.

Laboratory Work: An electrocardiogram taken on admission was normal except for a sinus tachycardia. The hematocrit was 50%. The morning following admission the red blood count was 5,250,000; white blood count, 25,400; hemoglobin 100%; differential: nonsegmented neutrophiles, 18; segmented neutrophiles, 64; lymphocytes, 18. The hematocrit had increased to 54%.

* Received for publication March 21, 1956.
Requests for reprints should be addressed to R. R. Grayson, M.D., Medical Arts Building, Perryville, Missouri.

Treatment and Clinical Course: Oxygen was administered by nasal catheter, and the water bottle on the oxygen tank was filled with half water and half 70% alcohol as a wetting agent. The patient had been coughing up foamy white sputum, and the addition of the alcohol to the water produced temporary relief from the dyspnea. The patient was given Demerol and phenobarbital subcutaneously because of extreme restlessness. Gitaligin, 1.0 mg., was given orally on admission. Strophanthin-K, 0.68 mg., was given intravenously the evening of admission, and then half that dose was repeated one hour later. Within two hours the pulse rate had decreased to 102 and the respirations to 36.

Five hours following admission the above regimen had produced definite improvement. However, by the following morning the patient had gone into shock, was found to be without demonstrable blood pressure and was cyanotic. At this time 200 mg. of Cortef were given intravenously, and Levophed was begun intravenously in 5% glucose and water. Another 100 mg. of Cortef were administered intravenously five hours later.

The patient continued to become worse in spite of this therapy. The pulmonary edema became more severe, the cyanosis deepened, the respirations became more rapid, and the patient died at 5:00 p.m., August 28, 20 hours following admission and 29 hours following exposure to the silage gas.

Postmortem Examination: Autopsy was performed three hours following death. Significant findings at autopsy were limited to the lungs, which were found to be heavy and full of frothy, white fluid, and were completely consolidated in all of the lobes. Gross examination of the heart revealed no abnormality. The coronary arteries were patent and showed little evidence of arteriosclerosis. There were no signs of myocardial infarction or ventricular hypertrophy.

Microscopic Examination (Microscopic examinations were made by John R. Roberts, M.D., of the Hagebusch Clinical Laboratories in St. Louis):

"Sections made of the heart revealed little of interest. There was some atrophy and fragmentation of its fibers. Brownish pigmentation was also present. There was a rather striking capillary engorgement, probably a final circulatory failure.

"The lungs presented a moderate amount of alveolar edema and a very obvious bronchopneumonia. (See figures 1 and 2.)

"The preparations made of the liver showed both passive and active congestion. The former was represented by dilated central veins and pigment deposit in the adjacent liver cords. The latter was seen in the noticeably engorged sinusoids, generally.

"Sections made of the kidney revealed a moderate atherosclerosis of its larger arteries. There was little scarring and degeneration of kidney substance.

"None of the tissues showed anything specific of gas poisoning. The immediate cause of death could well have been the bronchopneumonia with circulatory failure as contributory."

Anatomic Diagnoses: "(1) Acute bronchopneumonia and (2) probable circulatory failure."

Case 2. The nephew, a 31 year old healthy white farmer, was exposed to the same silage gas that caused the previously described fatality. He was exposed, however, for a lesser period of time—approximately two to three minutes, by his own recollection.

The patient entered the silo and, in order to rescue his uncle, descended into a thick yellow layer of gas which had accumulated above the silage. Following this, he left the silo and descended to the ground. He complained at that time that the silage gas was acrid and irritating to his lungs and seemed to have the odor of ammonia.

The patient was admitted for observation to the Perry County Memorial Hos-

pital about 14 hours following exposure because of weakness and vomiting. He did not appear acutely ill at the time of admission. His main complaint was that he "could not take a deep breath."

Past History: Noncontributory. There was no previous history of pulmonary or cardiac disease.

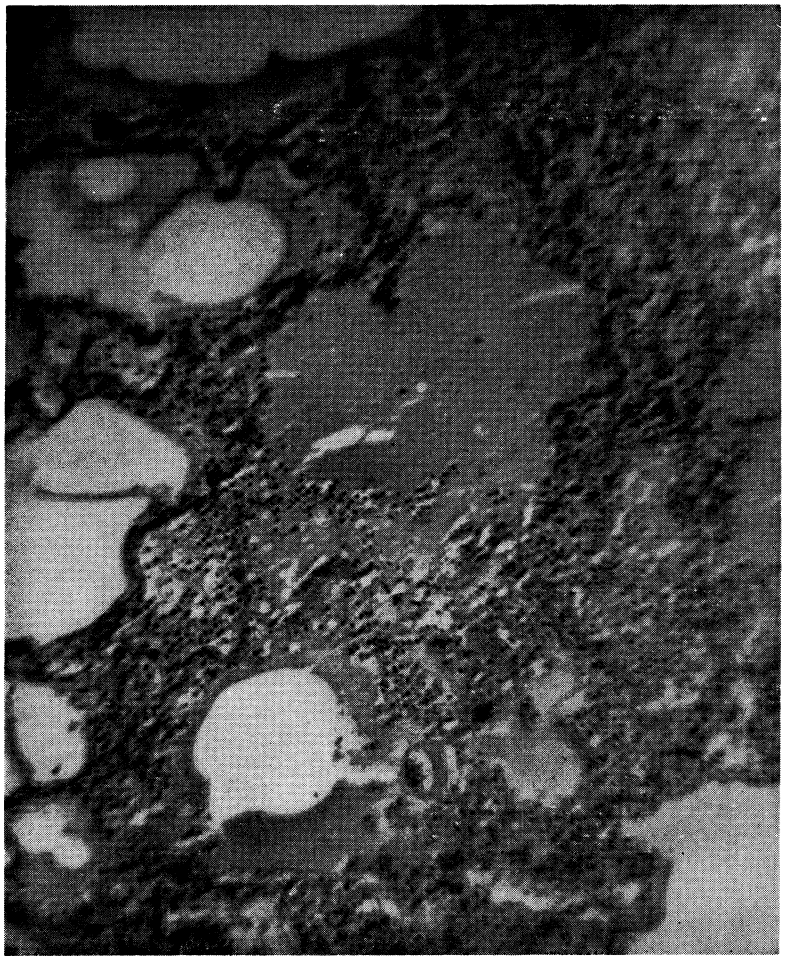

FIG. 1. Section of the lung from case 1 showing edema and areas of bronchopneumonia.

Physical Examination: Physical examination on admission revealed no positive physical findings. The heart and lungs were normal to auscultation and percussion. The blood pressure was 120/80 mm. of Hg; respirations, 18; pulse, 92 and regular.

Clinical Course: Seven hours following admission, reëxamination revealed his respirations to be shallow and rapid. There were a few inspiratory râles over the anterior portions of the chest bilaterally. The patient felt well, was alert and cooperative, and asked to be released to go home.

A chest x-ray taken at this time, however (figure 3), revealed diffuse, patchy and confluent infiltrations throughout the middle two thirds of both lung fields. The

apices and the costophrenic angles were clear. The diaphragms were normal. The cardiac shadow and bony structures were normal. The opinion of the radiologist was that this picture represented a chemical pneumonitis, apparently as a result of the inhalation of the toxic gas.

Laboratory Work: Twenty-four hours following the patient's exposure to the silage gas, the red blood count was 4,600,000; white blood count, 12,800; hemoglobin,

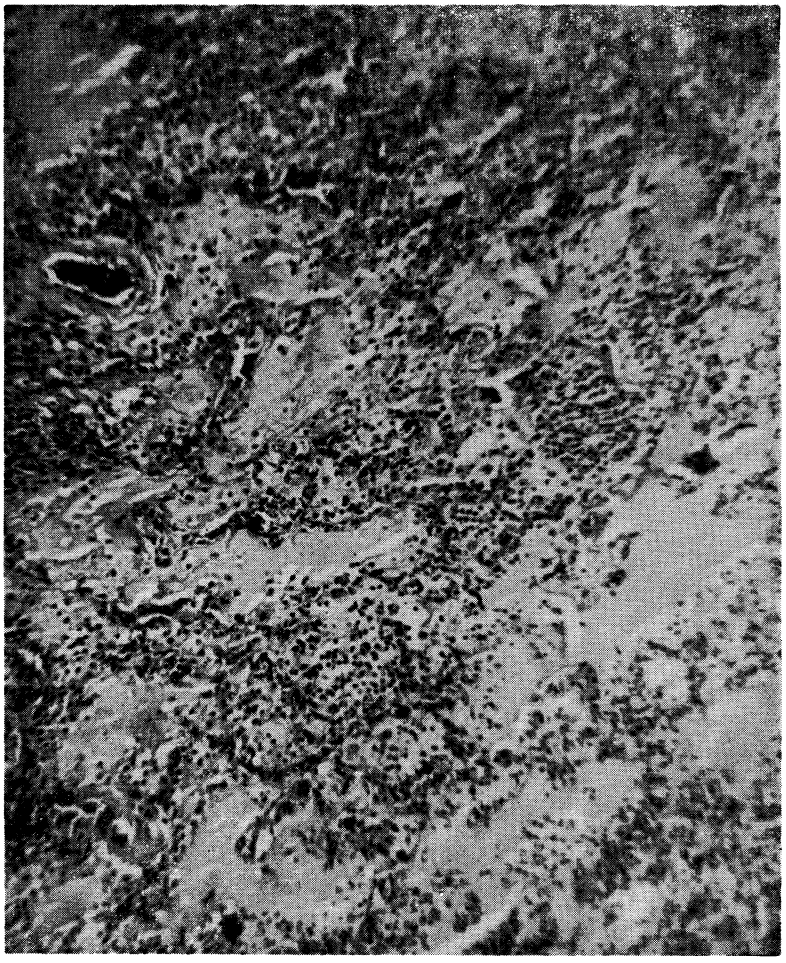

FIG. 2. Section of the lung from case 1 showing edema and bronchopneumonia.

97%; differential: nonsegmented neutrophiles, 10; segmented, 70; lymphocytes, 20. The urinalysis was normal.

Treatment: The patient was given intramuscular penicillin and streptomycin and nasal oxygen. He was transferred to Barnes Hospital, St. Louis, where he was attended by Donald H. Finger, M.D.

Dr. Finger's report on the clinical course of this patient after he reached Barnes Hospital is as follows: "On admission, the respiratory rate was 60, blood pressure 130/80, pulse rate 130 and the temperature 98.6° F.

"On physical examination, his general appearance was that of an acutely ill man. His skin was slightly cyanotic, as were the nail beds. Examination of the eyes revealed only minimal conjunctivitis. Examination of the chest revealed that it was held in full inspiration and the respiratory excursions were limited in depth but were extremely rapid. The percussion note was hyper-resonant. Breath sounds were

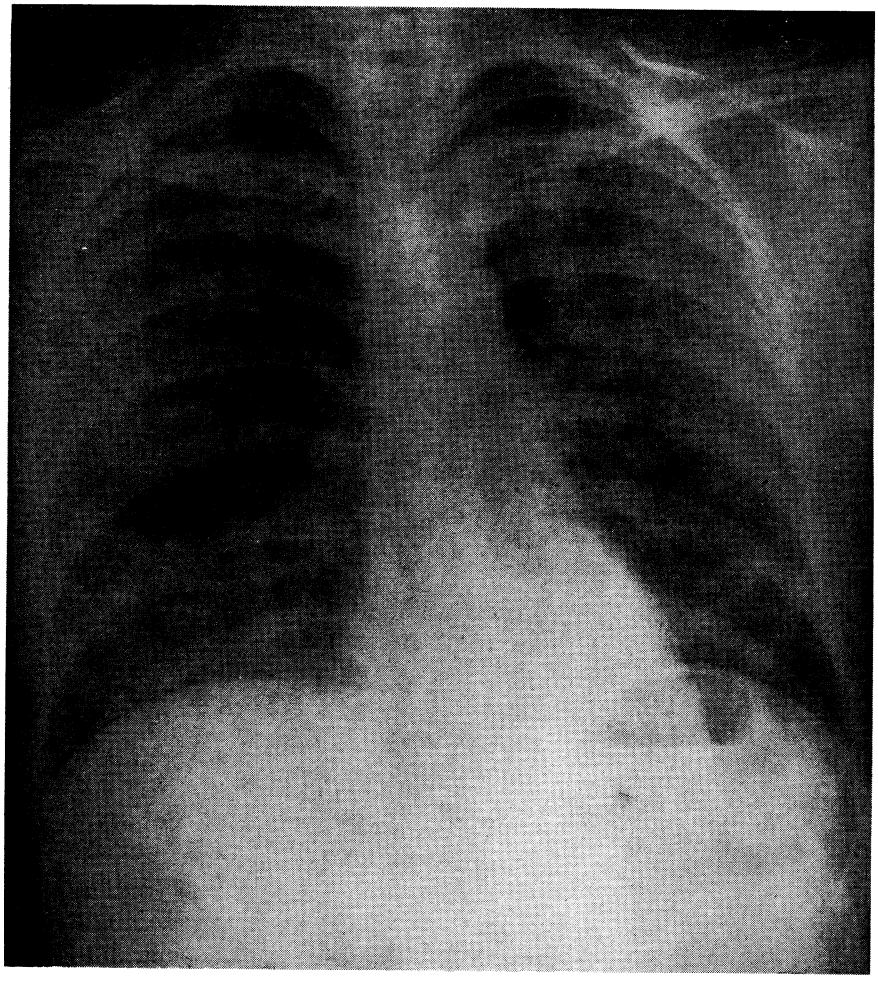

FIG. 3. Roentgenogram of the chest of case 2, showing bilateral diffuse, patchy and confluent infiltrations throughout the middle two-thirds of the lung fields.

extremely distant. There were scattered râles throughout the lungs. The heart was not enlarged to percussion. Sinus tachycardia was present. No murmurs were noted. The remainder of the examination was within normal limits. Chest x-rays taken revealed diffuse pneumonitis involving all lobes of the lungs. An electrocardiogram revealed only a sinus tachycardia. The urinalysis was negative. The blood counts were within normal limits. Electrolyte studies were basically within normal limits.

"His course in the hospital was relatively uneventful in that he responded rather dramatically to oxygen, bronchodilators and antibiotics in the form of large doses of penicillin and streptomycin. He remained afebrile and in 48 hours was clinically much improved other than for persistent râles. On the fifth hospital day, he developed a fever and the antibiotic therapy was changed to Achromycin. He became afebrile within 24 hours and remained so. Progressive chest films were taken and showed rapid clearing of the pneumonitis."

Follow-up Examination: The patient was last examined on May 11, 1955, and at that time had no complaints. There was no cough or sputum. Examination of the chest revealed a resonant percussion note. Breath sounds were within normal limits and there were no râles. The heart was negative. X-ray of the chest showed no infiltration in either lung. The trachea was in the midline. The diaphragm was of normal contour. The heart was of normal size.

Special Toxicologic Studies

Special studies on these two cases were performed by officials at the University of Missouri, and the results of these studies were made available to the author by J. H. Longwell, of the Division of Agricultural Sciences, College of Agriculture, University of Missouri.[1]

Gas was collected from the silo in which the two individuals had been poisoned. Chemical analysis of the actual gas, performed at the University of Missouri, indicated that this gas contained the oxides of nitrogen.[2]

Also, some of the corn from the same silo was brought to the laboratory and placed in a miniature silo for fermentation. The gas produced in this experimental silo was collected and chemically analyzed. This also showed large amounts of the mixed oxides of nitrogen.[3]

It was proved that the gas which came from the corn ensilage was toxic. First of all, it was noticed that around the silo in which the individuals had been stricken a great number and variety of insects had been killed. In addition, the vegetation was killed below the silo drain where the heavy gas would flow.

Albino rats were placed in a miniature silo in the University laboratory and observed under conditions similar to the silage fermentation on the farm where the accident occurred. All the rats allowed to stay in the miniature silo died.

Pfander and Muhrer [4] stated that several cases of forage poisoning in cattle were reported following the feeding of forage grown in 1953, when there was a severe drought in Missouri. The incidence increased in 1954 until it reached a near-epidemic proportion in central Missouri. Dozens of herds were affected, and hundreds of cattle were killed. The University of Missouri performed many tests on the forages consumed by these animals and, in most cases, the feed contained excessive amounts of nitrates. Ensiled corn plants, when high in nitrate, underwent abnormal reactions, and a poisonous yellow gas was often formed. The analysis of this gas showed that it was a mixture of oxides of nitrogen and was highly toxic to animal life.

Nitrates in Corn Ensilage

A series of questions concerning corn and nitrates was put to Dr. Longwell. These questions and résumés of his answers follow: [1]

Q. How do nitrates get into corn stalks?

A. The presence of a low concentration of nitrates in the growing plants such as corn is a normal finding. However, when temperature and moisture conditions interfere with the normal metabolism of nitrates into amino and protein nitrogen, then there is an accumulation of toxic amounts of nitrates in the corn plant. Some of the factors which increase the amount of nitrates to be found in plants are as follows: [5]

(1) High nitrate soils.
(2) Drought, particularly if it occurs when the plants are relatively immature, may leave the vegetation high in nitrates.
(3) Ultra-violet radiation and increasing light intensities or length of photoperiod favor the assimilation of nitrates by plants.

Q. How are nitrates changed into toxic gases in the silo?

A. Potassium nitrate by anaerobic fermentation is changed into potassium nitrite and oxygen. These nitrites combine with organic acids in the ensilage to form nitrous acid, HNO_2. As the temperature of the ensilage rises with fermentation, the nitrous acid decomposes into water and a mixture of nitrogen oxides which include nitrogen trioxide (N_2O_3), nitric oxide (NO), nitrogen dioxide (NO_2), and nitrogen tetroxide (N_2O_4). The nitrogen trioxide is a brown gas, the nitrogen dioxide is a red gas, and the nitrogen tetroxide is a yellow gas. Nitric oxide is colorless.

Q. What are the physical and chemical properties of the gas?

A. Nitric oxide is a very stable gas and is only slightly soluble in water. It is a reducing agent. Nitrogen dioxide readily polymerizes, is water soluble, and has an offensive odor. Nitrogen trioxide dissociates very rapidly into NO and NO_2. Nitrogen tetroxide decomposes to NO_2, is water soluble, and is an oxidizing agent.

Q. How can nitrogen oxide poisoning be prevented in human beings?

A. The prevention of this disease can be attained by education of those individuals that may come in contact with oxides of nitrogen. Rural or industrial people who work around silos or manufacturing plants where this gas may be released should be informed as to its properties and dangers. These people should know that the gas can be trapped in silos, in silo chutes or in buildings at the base of the silo. They should know that the gas is colored from brown through red to yellow and that when inhaled it produces a choking sensation. Rural and industrial safety programs should include information of possible location, detection, and physiological action of this gas.

Previous Cases of Silage Gas Poisoning

The literature has been searched as thoroughly as possible and the following are the cases of silage gas poisoning in humans and animals which have been discovered:

Price et al. in 1937 reported three deaths which had occurred on a farm when a mother and two daughters were overcome by gas above corn ensilage. Analysis of a sample of the gas taken at the surface of the ensilage the day following the accident revealed oxygen, 18.4%, carbon dioxide, 10.2%, and nitrogen, 71.4%. No tests were made for nitrogen dioxide and no mention was made of a brownish color of the gas. The authors felt that the deaths were due to excessive carbon dioxide.[6]

The above authors also reported the following earlier and similar cases:

1. A North Dakota farmer was overcome while attempting to clean the pit of his silo. Four of his children also were suffocated in trying to rescue him. All five died. One other man was overcome but was rescued.
2. Two farmers in Ohio were suffocated when they entered a partially filled silo in the morning to resume the work of filling the silo and tramping the ensilage commenced the day before. The official opinion was that carbon dioxide was the toxic agent.
3. Two men were asphyxiated in a steel bin at a grain company plant in Chicago as the result of entering a bin filled with damp corn.
4. A workman was asphyxiated at a grain-handling plant in Utah when he entered a concrete bin filled to within seven feet of the top with damp barley. Analysis of the air above the barley showed oxygen, 3.48%, carbon dioxide, 12.65%, and nitrogen, 83.87%.
5. Two employees of a grain elevator company in Illinois were asphyxiated in a 12′ by 12′ tile bin about half full of damp oats. Both men died.

A report was discovered about eight chickens and many insects that were killed by yellow gas coming out of a silo in 1949. This report also included that of a man overcome by the same gas. The man was quickly rescued and recovered.[7]

Fostvedt in 1951 reported a case of a 25 year old man who had entered a previously closed silo and became unconscious shortly after entering the silo. He was unconscious for one hour after being retrieved from the silo. The author incriminated carbon dioxide as the toxic gas in this case.[8]

Two heifers were reported in 1952 to have been killed by nitrogen dioxide gas which had come down a silo chute.[9]

The author of a question in the "Queries and Minor Notes Department" of the October, 1953, issue of the *Journal of the American Medical Association*[10] reported the death of a 19 year old man found in a silo that had been filled with new silage 24 hours before. In the answer to the question the consultant said that the toxic gas was carbon dioxide. He did not men-

tion the oxides of nitrogen. He also stated that the absence of oxygen may have accounted for this death.

Poisoning by Oxides of Nitrogen in Industry

The effects of nitrous and nitric gases on 23 men were reported in 1945 by Charleroy.[11] Nine men were seriously affected. The gases were caused by a fire adjacent to a supply of blasting gelatin used for boosters in hand depth charges. The blasting gelatin caught fire and gave off thick, yellowish green fumes. Two of the nine men showed signs of circulatory collapse 15 to 16 hours after exposure to the gas. These two men died. It was noted that there were no symptoms immediately after exposure. The symptoms developed from four to 24 hours later, and all of the cases presented similar prodromal symptoms. The suddenness of the appearance of serious symptoms and complications was a striking feature.

The prodromal symptoms were headache, a sensation of fullness in the head, a sense of tightness in the chest, and a slight cough. The 14 who were least affected by the gas presented no other symptoms.

McAdams and Krop [12] recently reported two cases of serious pulmonary disease due to the fumes of nitric acid. These cases were caused by the fumes of red fuming nitric acid which contains dissolved oxides of nitrogen. These authors state that there are four distinct clinical pictures of acute poisoning by inhalation of nitrous fumes, as have been described by Flury: [13]

1. The *irritant gas* type, in which there is local irritation followed by a latent period of a few hours and then the development of pulmonary edema, with death in one to two days.
2. The *reversible* type, in which there is a rapid succession of dyspnea, cyanosis, vomiting, vertigo and sometimes unconsciousness
3. The *shock* type, in which there is a very rapid onset of signs of suffocation, convulsions and cessation of breathing.
4. A *combined* form, in which there are early cerebral symptoms that subside after removal from the fumes, but after a period of a few hours pulmonary edema develops.

Adley [14] reported acute oxides-of-nitrogen poisoning in a shrinker, followed by death 10 days later from chemical pneumonia.

Rossano [15] reported a case of a man who died 26 hours after exposure to the fumes of nitric acid. The autopsy showed pulmonary edema, acute tracheobronchitis and bronchopneumonia. Feil [16] reported four cases of men exposed to the fumes of nitric acid when a large bottle containing 40 L. of nitric acid was broken and the acid spilled on the ground. The symptoms were characterized by oppression in the chest, respiratory difficulty, pallor, cyanosis and syncope. Three of these patients developed symptoms as above but recovered after a short period of time and returned to work. The author warned that, even though the patient may complain only of a little

throat irritation and cough after exposure to the fumes and may continue working for many hours, he may still develop severe intoxication after a period of several hours. He suggested that the best way to avoid serious sequelae is to have the patient rest not less than 24 hours and to have stimulants. If pulmonary edema ensues, the author suggested oxygen and cardiac stimulants as treatment.

McConnell [17] warned against the exposure to concentrations of nitrous fumes in the manufacture of high explosives and smokeless powder. He wrote: "Following a serious exposure, there may be a latent period of 5 to 24 hours during which the employee may feel well and go about his business or leave the plant at the end of a shift. Some hours later, there may develop a sudden onset of congestion in the lungs which may rapidly lead to shock and death if not vigorously treated." The author stated that exposure to oxides of nitrogen has, in the past, been confined almost entirely to three industries: the smokeless-powder works, the TNT and explosive works, and the chemical works.

Silos and Toxic Ensilage

Fabian [18] stated that every year casualties are reported and that sometimes death results from asphyxiation of workers by carbon dioxide gas arising from fermentation in silos. Numerous studies on ensilage have shown that the green fodder, on being placed in the silo, immediately begins to undergo changes opposite to normal plant metabolism. The oxygen of the surrounding air is consumed and carbon dioxide gas liberated. Because of the high specific gravity of carbon dioxide, it tends to remain at the surface of the ensilage and for a few feet above. Records show that most of the silo accidents occur in the morning, apparently after fermentation has taken place during the night or over Sunday.

The *Farmers' Bulletin* on silos [19] contains a warning concerning the gas danger in silos: "Suffocating gas from fermenting silage, mostly carbon dioxide, forms in all silos shortly after filling begins and continues until the fermentation stops. . . . Many lives have been lost because of carelessness in entering the silo where there may be danger of gas. . . . A victim of silo gas suffers from lack of oxygen and should be moved into fresh air as soon as possible and artificial respiration applied." It is to be noted that this was published in 1948 and that at no point in this publication is the danger from oxides of nitrogen mentioned.

Hogan [20] reported numerous instances in which a brown gas has been noticed above ensilage. The amount of nitrate that is toxic in the ensilage when eaten by cattle is 0.41% of potassium nitrate. Some samples of corn stalks during drought conditions have been found to contain as much as 6.7% of potassium nitrate. There is much more nitrate in the stalk than in the leaves of the corn plant. It has also been definitely shown that when there is a large amount of nitrate in the soil there is a much larger ac-

cumulation of potassium nitrate in the plant. It is emphasized that a severe drought has a marked effect on the accumulation of nitrates in immature plants.

The *Agricultural Gazette* of July, 1939,[21] contained instructions on how to prevent deadly gases from accumulating in silos. It was suggested that the crop should have reached the proper stage of maturity and should not be too dry. Carbon dioxide is incriminated, and oxides of nitrogen are not mentioned. It was stated that, in exceptional cases, the gases given off may be inflammable. Therefore, a candle should not be lowered in a silo to test for carbon dioxide—a guinea pig or a fowl should be used instead.

A consultant to the Queries and Minor Notes Department of the *Journal of the American Medical Association* in 1932 [22] stated that the prime harmful gas associated with the storage of ensilage is carbon dioxide, and that this gas may exist in quantities of up to 75%. The author stated further that there may also be irritants in the gas composed of volatile ingredients such as butyric, propionic and lactic acids. Oxides of nitrogen are not mentioned.

Toxicology of Oxides of Nitrogen

The common oxides of nitrogen [23] are nitrous oxide (N_2O), nitric oxide (NO), and two forms of a dioxide (NO_2 and N_2O_4); in addition, there are the trioxide (N_2O_3) and the pentoxide (N_2O_5). At ordinary temperatures the trioxide and pentoxide decompose and, on contact with air, react in such a way that the principal product is a mixture of NO_2 and N_2O_4.

Nitrous oxide has no irritating action and is used extensively as an anesthetic for surgical operations and dental extractions. Nitric oxide (NO) at ordinary temperatures reacts with oxygen or air to form brown nitrogen dioxide (NO_2).

Nitrogen dioxide (NO_2) and its dimer, nitrogen tetroxide (N_2O_4), are the oxides responsible for the toxicity. At room temperature this is an orange gas, which becomes reddish brown as the temperature rises. This gas is responsible for the yellowish brown color usually associated with the oxides of nitrogen in the air. When nitrogen dioxide is inhaled it is at once changed to that molecular form corresponding to the body temperature. At 40° C., therefore, approximately 30% of the dioxide is in the form of NO_2 and 70% in the form of N_2O_4. N_2O_4 reacts with water in the respiratory tract to produce nitric and nitrous acids. The NO_2 reacts with water and oxygen from the air to produce nitric acid and nitric oxide. These acids react with the alkali salts in the tissues of the respiratory tract forming nitrates and nitrites, and in so doing have an irritative action. The nitrates have no effect, but the nitrites when absorbed exert a systemic action. This phenomenon, however, does not play an important part in poisoning.

Because of the insidious action of the gases of nitrogen oxide, it is necessary that anyone who has inhaled a considerable amount of this gas be

removed at once to a hospital for immediate treatment. After a latent interval the patient develops pulmonary edema. Following this the patient may develop pneumonia, bronchiectasis or emphysema. Methemoglobinemia may also occur.

The permissible concentration of oxides of nitrogen in the atmosphere at work places has been set at 25 parts per million for eight hours per day.

Discussion

It is apparent from the foregoing review that silage gas poisoning due to the oxides of nitrogen is a little-known disease and one that has not been adequately reported in the medical literature.

Under ordinary circumstances, when there is sufficient moisture for the production of normal corn plants, high concentrations of nitrates do not occur in the corn stalks and the abnormal chemical reactions that produce oxides of nitrogen do not take place. Therefore, in normally wet years poisoning by oxides of nitrogen will not be suspected, but rather, if any silage gas poisoning cases do occur, their cause can usually be ascribed to carbon dioxide or to asphyxia from oxygen depletion.

In years of drought, however, in areas where irrigation is not common practice, it may be expected that high concentrations of poisonous nitrates will occur in corn ensilage, which will be poisonous when fed as fodder to cattle and other beasts and will produce noxious gases in unventilated silos.

The disease produced by inhaling the gases from high nitrate ensilage is in every way identical to the disease described in industrial toxicology as that produced by the fumes of nitric acid and from other sources of nitrates, such as gunpowder and other explosives. This disease is essentially an acute chemical pneumonitis which is generalized over the entire pulmonary structure. It is caused by the toxic action of nitrogen dioxide in the respiratory tree, producing a reaction which essentially is due to nitric and nitrous acids. This produces an intense inflammatory response after a latent interval of from one to many hours which then progresses to either minor or severe forms of chemical bronchopneumonia. The longer the exposure to the noxious gases, and the more intense the fumes, the more severe the pneumonia. If the exposure has been severe, there is little that present therapy can offer in preventing fatalities.

The treatment of this disease is nonspecific and primarily supportive until the organism can recover pulmonary function by natural means. Oxygen should be given. Probably oxygen under pressure during the phase of pulmonary edema would be of benefit. Antibiotics must be given to prevent secondary bacterial pneumonitis. The methemoglobinemia caused by nitrites apparently has not been a serious problem in the reported cases. However, studies should be done on this aspect of the problem; and if methemoglobinemia is found to be a significant cause of the disability, treatment should be directed toward alleviating this aspect of the disease. Broncho-

dilators are indicated but are probably of minimal value. Should evidence of cardiac decompensation occur, digitalization should be instituted.

Summary

1. Two cases of silage gas poisoning are presented, one of them fatal. The oxides of nitrogen were definitely found to be the noxious agents.

2. Silage gas poisoning due to oxides of nitrogen is essentially a diffuse chemical bronchopneumonia caused by the irritating action of nitrous and nitric acids on the respiratory tree. The disease may be mild or severe, depending upon the degree of exposure. Nitrogen dioxide pneumonia has been described many times in industrial toxicology but apparently has not previously been described in the medical literature as due to inhalation of gases from ensilage.

3. Special studies done on the corn ensilage and on the actual gas from the silo in which the two patients were poisoned proved that there was a poisonous concentration of the oxides of nitrogen. This condition was due to a combination of drought, high-nitrate soils and an unventilated silo. Other studies demonstrated the toxicity of the actual gas and of experimentally-produced gas from the same ensilage.

4. The literature on silage gas poisoning is reviewed. Heretofore, all silage gas poisoning in man was thought to be due to carbon dioxide inhalation or simple asphyxia.

5. The industrial and agricultural literature on the toxicology of nitrogen oxides and on silos and toxic ensilage is reviewed.

6. Silage gas poisoning due to the oxides of nitrogen with the production of chemical pneumonia is a disease which probably occurs more commonly than is recognized. Physicians in rural areas should be aware of the possibility of this disease during summer periods when corn is being placed in silos, particularly during times of drought.

7. No specific treatment is known for the resulting bronchopneumonia. Research should be directed toward the discovery of a specific therapy.

Addendum

Since this paper was submitted for publication, Lowry and Schuman at the University of Minnesota have informed the author of four additional cases. In the fall of 1955, they encountered four cases of nitrogen dioxide pneumonia among farmers giving a history of entering silos shortly after filling with dry corn, all of whom presented clinical and roentgenographic findings of bronchiolitis fibrosa obliterans. Of these, two died and at autopsy showed the condition in classic form.

The authors describe this as a newly recognized clinical entity caused by the inhalation of oxides of nitrogen produced in recently filled silos. They

have chosen to designate the syndrome as "silo-filler's disease," indicating its limitation to silo workers and also its occurrence predominantly among individuals inhaling fumes from freshly filled silos. Lowry and Schuman suggest that there is a hypothetical spectrum of nitrogen dioxide poisoning in men. They suggest that there are six different degrees of exposure with correspondingly different clinical syndromes resulting from exposure to nitrogen dioxide.

In the most severely exposed (500 parts per million or more of nitrogen dioxide in air) the patients develop acute pulmonary edema with death in less than 48 hours. In patients exposed to concentrations of 300 to 400 parts per million of nitrogen dioxide, pulmonary edema with bronchopneumonia develops with death in 2 to 10 days. Those who are exposed to concentrations of 150 to 200 parts per million develop bronchiolitis fibrosa obliterans which is fatal in three to five weeks. Others who are exposed to 50 to 100 parts per million develop bronchiolitis with focal pneumonitis lasting six to eight weeks with spontaneous recovery. They suggest that individuals exposed to concentrations of nitrogen dioxide in the range of 25 to 75 parts per million develop varying degrees of bronchitis and bronchopneumonia with complete recovery. One of their most interesting hypotheses is the possibility of development of chronic pulmonary fibrosis and emphysema in individuals who have chronic intermittent exposure to concentrations of nitrogen dioxide in the order of 10 to 40 parts per million. This may explain some instances of so-called "farmer's lung."

Delaney, Schmidt and Stroebel of the Mayo Clinic have recently published an article on "Silo-Filler's Disease," [25] the first article in the medical literature to be published about this disease.

The authors report two cases of severe pneumonitis in farmers who had worked inside silos with corn silage. The first patient was a 43 year old farmer who had had three episodes of pneumonia prior to his fatal episode. It was implied that the three nonfatal episodes of pneumonia might have been due to silage gas poisoning. The fatal episode of pneumonitis occurred in October, 1955, following five days of work in cleaning out old silos and filling them with new corn silage. A postmortem examination in this case revealed extensive congestion and edema of all lobes of both lungs.

The second patient was a 59 year old farmer who became acutely ill in August, 1955, after working in a silo in which there was newly chopped corn silage. The patient remembered noticing acidlike fumes in the form of a thin haze in the silo. He developed a chronic pulmonary disease which became acute about one month after he had worked in the silo, at which time he was admitted to a hospital where a roentgenogram of the thorax revealed extensive, bilateral, diffuse miliary mottling. He was treated by bed-rest alone and, three weeks following his admission, was clinically well.

The authors review experimental work done by Peterson and his coworkers at the College of Agriculture, University of Wisconsin, on the pro-

duction of oxides of nitrogen by corn silage, and conclude that their two cases were caused by the inhalation of excessive amounts of nitric oxide and nitrogen dioxide.

The authors speculate about the relationship between the pneumonitis caused by nitrogen dioxide and a syndrome of pulmonary fibrosis among farmers, known as "farmer's lung." They suggest that if pulmonary fibrosis proves to be the troublesome sequel among those patients who survive, consideration should be given to the prescription of cortisone, in addition to the use of antibiotic agents and supportive therapy, as a possible means of retarding such fibrosis.

Summario in Interlingua

Es describite duo casos de acute pneumonitis causate per le inhalation de gas de bioxydo de nitrogeno in un silo. Un patiente moriva de edema pulmonar 29 horas post su exposition, le altere se restabliva.

Solmente sex altere casos de pneumonia a bioxydo de nitrogeno causate per le inhalation de gas de insilage es cognoscite. Illos occurreva in 1955. Sin dubita, il non se tracta hic de un nove morbo, sed illo es un morbo que ha solo recentemente essite recognoscite per le profession medical. Illo es probabilemente plus commun que lo que es indicate per le total de octo casos.

Sub conditiones ordinari—quando le humiditate suffice pro le production de normal plantas de mais—il non occurre alte concentrationes de nitratos in le cannas de mais, e le anormal reactiones chimic que produce oxydos de nitrogeno non ha loco. Ergo, in annos de humiditate normal, invenenamento per oxydos de nitrogeno non es a suspicer. Si nonobstante il occurre casos de invenenamento per gas de insilage, lor causa pote usualmente esser trovate in bioxydo de carbon.

Tamen, in annos de siccitate—in areas ubi irrigation non es un practica commun e ubi fertilisation per nitratos es costumari—on pote expectar le occurrentia de alte concentrationes de nitratos in mais insilate. Isto es toxic quando alimentate al bestial e altere animales e produce un gas pesante que contine grande concentrationes de oxydos de nitrogeno durante le periodo de fermentation.

Le morbo producite per le inhalation de gases ab insilatos ric in nitrato es identic in omne respectos con le morbo describite per toxicologos industrial como effecto de vapores de acido nitric e de vapores ab altere fontes de nitrato, como per exemplo pulvere de cannon. Le morbo pote esser designate accuratemente como "pneumonia a bioxydo de nitrogeno." Illo es un acute pneumonitis chimic que es generalisate in le integre structura pulmonar. Bioxydo de nitrogeno es inhalate e alterate in acidos nitric e nitrose, e istos—post un intervallo latente de inter un e multe horas—produce un intense responsa inflammatori. Isto causa minor o sever formas de broncho-pneumonia chimic. Quanto plus longe le exposition a bioxydo de nitrogeno e quanto plus intense le vapores, tanto plus sever es le pneumonia que resulta. Si le exposition ha essite sever, il ha pauco in nostre currente cognoscentias therapeutic a prevenir un exito letal.

Le tractamento de pneumonia a bioxydo de nitrogeno es nonspecific e primarimente supportative usque le patiente pote restaurar su functiones pulmonar per medios natural. Le administration de oxygeno es desirabile. Oxygeno sub pression durante le phase del edema pulmonar esserea probabilemente benefic. Antibioticos debe esser administrate pro prevenir infectiones bacterial secundari. Le methemoglobinemia causate per nitratos non pare haber essite un grave problema in le casos reportate. Bronchodilatatores es indicate, sed illos es probabilemente de pauc valor. On ha

proponite le uso de cortisona. Si discompensation cardiac deveni evidente, digitalisation es necessari. Recercas deberea esser interprendite pro discoperir un therapia specific pro le morbo.

BIBLIOGRAPHY

1. Personal communication from J. H. Longwell, Director, University of Missouri, Division of Agricultural Sciences, Columbia, Missouri, July 8, 1955.
2. Association of Official Agricultural Chemists: Official methods of analysis of the Association of Official Agricultural Chemists, 7th Ed. 1950, page 204.
3. Saltzman, B. E.: Colorimetric microdetermination of nitrogen dioxide in the atmosphere, Analytical Chemistry **26**: 1949–1955, 1954.
4. Pfander, W. H., and Muhrer, M. E.: Forage poisoning in Missouri due to excessive amounts of nitrate, Missouri Agricultural Experiment Station Bulletin 652, pp. 19–20, April 1, 1955.
5. South Dakota Experiment Station Bulletin 424, Nitrate poisoning, 1952.
6. Price, D. J., Roethe, H. E., and Bradshaw, M. A.: Prevention of silo gas accidents, Agricultural Engineering **18**: 104–106 (Mar.) 1937.
7. Peterson, W. H., Thoma, R. W., and Anderson, R. F.: Yellow gas from corn silage, Hoard's Dairyman, December, 1949, pp. 870–871.
8. Fostvedt, G. A.: Silage gas poisoning, Wisconsin M. J. **50**: 1103–1104 (Nov.) 1951.
9. Yellow silo gas is nitrogen dioxide, University of Wisconsin Bulletin 496, pp. 87–89, 1952.
10. Schroeppel, J. E.: Death in a silo, J. A. M. A. **153**: 893 (Oct. 31) 1953.
11. Charleroy, D. K.: Nitrous and nitric gas casualties, U. S. Nav. M. Bull. **44**: 435–437 (Feb.) 1945.
12. McAdams, A. J., Jr., and Krop, S.: Injury and death from red fuming nitric acid, J. A. M. A. **158**: 1022–1024 (July 23) 1955.
13. Flury, F.: Die Rolle des Stickstoffmonoxyds bei der Vergiftung durch Nitrose Gase, Arch. f. exper. Path. u. Pharmakol. **157**: 104, 1930, quoted by McAdams.[12]
14. Adley, F. E.: Exposures to oxides of nitrogen accompanying shrinking operations, J. Indust. Hyg. and Toxicol. **28**: 17–20, 1946.
15. Rossano, A. T., Jr.: A fatal case of poisoning by oxides of nitrogen, J. Indust. Hyg. and Toxicol. **27**: 207–208, 1945.
16. Feil, A.: Notes de medecine pratique hygiene et medecine du travail, Presse méd. **59**: 1688 (Dec.) 1951.
17. McConnell, W. J., Flinn, R. H., and Brandt, A. D.: Occupational diseases in government-owned ordnance explosive plants, Occup. Med. **1**: 551–618, 1946.
18. Fabian, F. W.: Dangers from poisonous gases in silo filling, Michigan Agricultural Experiment Station Quarterly Bulletin No. 9, page 23, August 23, 1926.
19. Silos: Types and Construction, Farmers' Bulletin No. 1820, U. S. Department of Agriculture: Warning—gas danger in silos, May 1939, Revised September 1948, Cover.
20. Personal communication: Excerpt from letter on nitrate poisoning (University of Missouri), A. G. Hogan, June 8, 1955.
21. Deadly gases sometimes accumulate in silos, Agricultural Gaz. New South Wales **50**: 371 (July 1) 1939.
22. LeRossignol, W. J.: Irritants and gases affecting workers in silo, J. A. M. A. **98**: 2307 (June 25) 1932.
23. Fairhall, L. T.: Nitrogen oxides, *in* Industrial toxicology, 1949, The Williams and Wilkins Co., Baltimore, pp. 116–120.
24. Lowry, T., and Schuman, L. M.: Personal communication, to be published. (U. of Minn. Med. School.)
25. Delaney, L. T., Jr., Schmidt, H. W., and Stroebel, C. F.: Silo-filler's disease, Proc. Staff Meet., Mayo Clin. **31**: 189–198 (Apr. 4) 1956.