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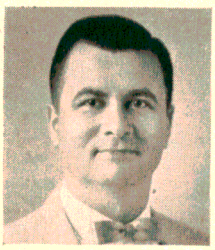
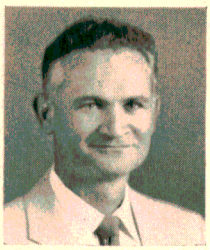
This Month's Authors

Academy Member Leonard Casser, who has written for *GP* as guest editorialist, is the author of "Literacy—The Forgotten Factor in Modern Diagnosis and Therapy." A native of Cresskill, N. J., where he has practiced since 1948, Dr. Casser is a graduate of the University of Pennsylvania School of Medicine. He took his internship at Englewood Hospital, Englewood, N. J., where he is now a staff member, and a residency at the U.S. Naval Hospital, San Diego, Calif. In 1951, Dr. Casser served with the First Cavalry Infantry Division in Korea. In addition to his practice, he is Cresskill's police surgeon, school doctor and a member of the Board of Health. *Page 101*

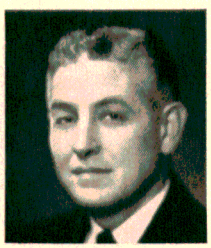


Richard R. Grayson, M.D., for the past five years, has been a family physician in Perryville, Mo. A graduate of the University of Illinois, Dr. Grayson took a two-year rotating internship at Cook County Hospital, Chicago. Author of "Nitrogen Dioxide Pneumonia: A Recently Discovered Malady in Silo-Fillers," he has confined his practice in recent years largely to internal medicine. He is a past president of the Perry County Medical Society, and is a member of the Missouri State Medical Association and the AAGP. Active in civic affairs, Dr. Grayson is vice president of the Perryville Lions Club and is on the Board of Directors of the Senior Chamber of Commerce. *Page 90*

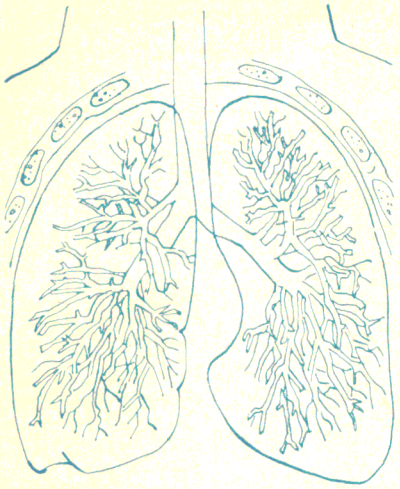


J. J. Kirschenfeld, M.D., who, with H. H. Tew, wrote "Anemia as Seen in a Rural General Practice," is a general practitioner in southern Alabama. A native of New York City, he graduated from New York University Medical College. Academy Member Kirschenfeld served two years as a flight surgeon in the Air Force and later moved to Fort Deposit, Ala. Convinced that modern medicine can be brought to rural areas, he now operates his own clinic-hospital, with chemical laboratory, x-ray, EKG, physiotherapy and BMR. Dr. Kirschenfeld is active in community affairs and, in 1955, was named "Man of the Year" by the local Chamber of Commerce. He lists horse raising and golf as hobbies. *Page 107*

Robert C. McElroy, M.D., assistant professor of clinical obstetrics and gynecology at the University of Pennsylvania School of Medicine, is the author of "Treatment of Leukorrhea." A 1937 graduate of Jefferson Medical College, he took his internship and residency at Philadelphia General Hospital. Dr. McElroy is at present attending obstetrician and gynecologist at several Philadelphia hospitals, including the University of Pennsylvania hospital, Philadelphia General and Pennsylvania hospital. He is certified by the American Board of Obstetrics and Gynecology and is a fellow of the American College of Surgeons and the College of Obstetricians and Gynecologists. *Page 114*



Gordon McHardy, M.D. collaborated with Drs. Robert McHardy and Claude C. Craighead on "Erosive Esophagitis." Dr. Gordon McHardy, associate professor of medicine at Louisiana State University, is a member of the department of medicine at Browne-McHardy Clinic, New Orleans. He serves as president of the American Association of Medical Clinics and the Medical Research Fund and is treasurer and a member of the board of governors of the American Gastroenterological Association. A member of the Central Committee of the World Congress of Gastroenterology, Dr. McHardy is senior gastroenterologist at Touro Infirmary and senior physician at Charity Hospital, both in New Orleans. *Page 74*



Inhalation of the oxides of nitrogen produces a clinical spectrum ranging up to fulminating fatal bronchopneumonia. Nitrogen dioxide pneumonia in farmers who fill silos—"silo-filler's disease"—is the same illness that occurs in industrial and chemical installations, and following fires where nitrate compounds (plastics) have burned. Illnesses in cattle, toxic smog and exploding silos are related to this gas. Therapy is supportive. The characteristic latent period between inhalation and the onset of symptoms may provide time for several effective prophylactic and therapeutic measures.

Nitrogen Dioxide Pneumonia: A Recently Discovered Malady in Silo-Fillers

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THERE IS A FORM OF PNEUMONIA that until recently had no name and that was practically unknown. I reported the first two recognized cases of this disease. These occurred August 27, 1954. I have chosen to call this condition "nitrogen dioxide pneumonia." In the first place, this term describes the pathology and the etiology of the condition. Second, nitrogen dioxide pneumonia is not confined to people who fill silos, but has afflicted others in many occupations and places and no doubt is a factor in other obscure respiratory illnesses. A review of nitrogen dioxide poisoning in 1941 refers to at least 175 documented fatalities due to inhalation of this gas. None of these was in silo-fillers.

Synonyms

The term, "silo-filler's disease," has been used frequently since it was first reported in 1956. This term was coined by Delaney, Schmidt and Stroebel of the Mayo Clinic to describe two cases of severe pneumonitis in farmers who had worked inside silos with corn silage. Four other cases of nitrogen dioxide pneumonia occurred in 1955. These were described by Lowry and Schuman at the University of Minnesota, who also used the term "silo-filler's disease." In addition to these eight cases of nitrogen dioxide pneumonia in silo workers, one other case has been reported by Eckhardt. This was a patient who had been exposed to the fumes of nitrogen dioxide in an enclosed silo chute. Thus, a total of nine cases in humans has been recognized (*Table 1*). (Two more cases, making a total of 11, have been reported since this table was prepared.)

The name "silage gas poisoning" has been used frequently in the past to describe deaths in silos. This term is nonspecific. It has denoted asphyxiation caused by depletion of oxygen in the atmosphere above silage as well as death due to the inhalation of excessive concentrations of carbon dioxide produced by the fermentation of silage. For these reasons, the term "silage gas poisoning" is not acceptable unless qualified further as to the specific etiologic agent.

Another syndrome called "farmer's lung" is known in a chronic stage associated with pulmonary fibrosis. It has been suggested that there might be some relationship between mild episodes of nitrogen dioxide pneumonia and this condition. Farmer's lung is also described as causing sudden death in ill-ventilated barns. Some of the cases that have been known as farmer's

A Note on the Location of Intermittent Claudication

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THAT INTERMITTENT CLAUDICATION occurs in the calf is generally known. This note is to make the following point: Depending upon the level of arterial occlusion, intermittent claudication may occur in muscles around the hip and lower part of the back, in the thigh, and in the foot as well as in the calf (*see accompanying figure*).

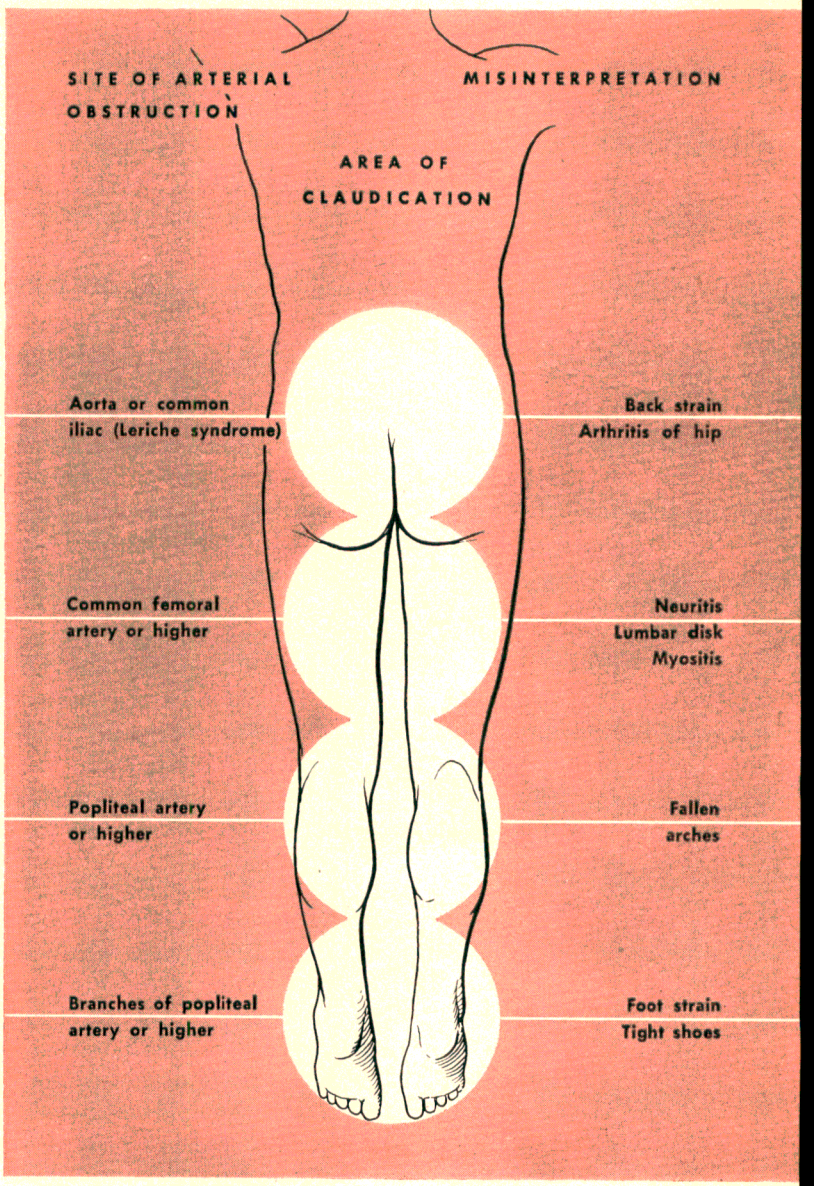
Intermittent claudication is distress originating in ischemic muscles during active contraction. It is a symptom of occlusive arterial disease, usually arteriosclerosis obliterans or thromboangiitis obliterans (Buerger's disease). It most frequently occurs in the lower extremities when muscles are deprived of the increase in blood supply they normally require during periods of activity. A short period of rest restores the balance between blood supply and demand.

The diagnostic feature of intermittent claudication, therefore, is its invariable relation to activity of the involved muscles. It is induced in the calf, for instance, by walking, and is relieved within minutes by rest, if not by slowing the pace. The more violent the exercise, the sooner intermittent claudication occurs. It never occurs at rest. In many ways it is analogous to angina pectoris of effort, for, indeed, intermittent claudication is angina of somatic muscles.

The described character of the distress is of little diagnostic value, however, for patients often deny that it is pain and instead describe it with such varied terms as ache, cramps, numbness, heaviness, tiredness, weakness, knot or fullness. And depending on its location and character, it may be mistaken for disease in the hip or sacroiliac joints, protruded intervertebral disk, sciatic neuritis, myositis, pes planus or chronic foot strain. Except in rare instances of intermittent claudication, pulsations will be diminished in or absent from one or more major arteries proximal to the region of distress.

The treatment of intermittent claudication with drugs or surgical sympathectomy is not routinely successful, although the latter sometimes is helpful in increasing blood flow to the skin of ischemic extremities. Abstinence from tobacco is urgent in cases of thromboangiitis obliterans. In selected cases dramatic relief of intermittent claudication has been achieved by resection of the obstructed segment of diseased artery and replacement of it with an arterial graft.

Patients with intermittent claudication should be encouraged to walk and can be assured that the symptom seldom leads to invalidism. As an indication of muscular ischemia it has no dire prognostic import, for ischemia of the skin is what leads to gangrene and amputation. Accordingly, proper care of the skin of the feet should be of more concern to the patient than whether he can walk one-half block or one-half mile before intermittent claudication occurs.



lung may actually have been due to nitrogen dioxide pneumonia. The syndrome of acute "farmer's lung" is still not fully understood. It may be due to an acute fungous infection of the lungs, or a virus pneumonia. The theory has also been forwarded that the condition is a nonspecific interstitial lung reaction to some material in the fungus-laden dust rather than a true fungous infection of the lungs.

Dickie (University of Wisconsin) has submitted evidence concerning farmer's lung, however, which would indicate that the oxides of nitrogen are not responsible for this particular syndrome. She has reviewed the literature on this condition and has information on 32 cases. She states that a peculiar, noncaseating granulomatous reaction has been found in patients on whom lung biopsies have been done. The exposure is frequently to dry, moldy material in barns and silos. The substance is not irritating at the time it is inhaled. Other individuals working in the same environment are not affected. Usually, minor exposure to the offending dust subsequently reproduces the entire picture.

The usual story is exposure to the moldy grain, hay or silage without noticeable difficulty. Several hours later, chills, fever, malaise, headache and tightness in the chest are evident. Severity of the symptoms varies widely, but some of the patients have been seriously ill because of respiratory failure.

Author	*Exposure*	*Date Hospitalized*	*Steroids*	*Type of Silage*	*Autopsy or Biopsy*	*Clinical Picture and Age*	*Result*
Grayson	8 min. 8/27/54	8/27/54	Yes	Corn	Autopsy	Fulminating pulmonary edema (66)	Died 29 hours after exposure
Grayson	2-3 min. 8/27/54	8/27/54	No	Corn	Neither	Acute bronchopneumonia (31)	Well after 2 weeks
Delaney et al.	10/23-28/55	10/31/55	No	Corn	Autopsy	Pulmonary edema (43)	Died 5 days after exposure
Delaney et al.	4 hours 8/20/55	9/26/55	No	Corn	Neither	Subacute bronchopneumonia with probable bronchiolitis fibrosa obliterans (59)	Spontaneous recovery by 12th hospital day
Lowry & Schuman	Several minutes 9/1/55	9/24/55	No	Corn	Autopsy	Subacute bronchopneumonia with bronchiolitis fibrosa obliterans (28)	Died 1 month after exposure
Lowry & Schuman	9/1/55	9/26/55	No	Corn	Autopsy	Subacute bronchopneumonia with bronchiolitis fibrosa obliterans (31)	Died 28 days after exposure
Lowry & Schuman	Several minutes 9/4/55	9/27/55	Yes	Corn	Neither	Subacute bronchopneumonia with bronchiolitis fibrosa obliterans (48)	Dramatic response to steroids in 12 hours. Recovered.
Lowry & Schuman	Several minutes 9/24/55	10/20/55	Yes	Corn	Neither	Subacute bronchopneumonia with bronchiolitis fibrosa obliterans (45)	Good response to steroids. Recovered.
Eckhardt	Several minutes 8/10/56	9/4/56	No	Alfalfa hay	Biopsy	Subacute bronchopneumonia with bronchiolitis fibrosa obliterans (26)	Spontaneous recovery.

Table 1. *Summary of known cases of Nitrogen Dioxide Pneumonia in Silo-Workers.*

These patients are usually unable to return to contact with the moldy material and some of them are forced to leave the farm because of repeated bouts of fever and dyspnea and, finally, a respiratory handicap.

The term "thresher's lung" also has been used in connection with an acute respiratory illness in people who are threshing hay or wheat. This is apparently the same disease as "farmer's lung."

Inasmuch as there are at least four names associated with this condition (silo-filler's disease, farmer's lung, thresher's lung and silage gas poisoning), I recommend the term, *nitrogen dioxide pneumonia*. This will apply equally well when the disease occurs in nonagricultural workers.

Nitrogen Dioxide Pneumonia of Nonagricultural Origin

One of the most dramatic episodes of nitrogen dioxide pneumonia that has occurred was in the Cleveland Clinic disaster of 1929. In this fire, roentgen-ray films burned and produced a dense, brownish gas that was considered to be noxious and responsible for many deaths. This gas was found to be nitrogen dioxide.

Delaney points out that a similar picture was observed in London during World War II, perhaps due to gases liberated from the explosion of trinitrotoluene. He also voices the suspicion that some of the casualties of the Cocoanut Grove disaster in Boston were due to nitrogen dioxide liberated when the plastic (nitrocellulose) upholstery was burned.

No doubt, fires occur at other places every year where nitrocellulose compounds are burned and nitrogen dioxide gas is produced. Some respiratory illnesses and deaths following accidental fires might be due wholly or in part to nitrogen dioxide inhalation. A serious attempt should be made to find cases of this nature. This will be particularly important if recommendations for prophylaxis of nitrogen dioxide pneumonia during the latent interval prove to be successful.

The disease produced by inhaling the gases from high nitrate ensilage is in every way identical to the disease described in industrial toxicology produced by the fumes of nitric acid and from other sources of nitrate such as gunpowder and other explosives. The disease has been described in people who have been exposed to the fumes of nitric acid which has spilled.

Nitrogen dioxide also has been described as a health hazard in the following occupations: (1) manufacture of nitric acid; (2) nitration of cellulose and other organic materials, as in the manufacture of explosives, dyes, lacquers and certain types of film and celluloid; (3) bleaching of cotton and of raw silk; (4) etching with aqua regia; (5) pickling of metal; (6) cleaning of tanks and towers; (7) decomposition of artificial fertilizer; (8) manufacture of sulfuric acid; (9) welding with an acetylene torch in enclosures, such as tanks and boilers, and (10) electric arc welding.

Smog

One other very important place where we should look for the possibility of nitrogen dioxide pneumonia is in smog. In most of the literature on smog, researchers have incriminated sulfur dioxide. The reason for this is a good one. Sulfur dioxide is one of the more active irritant gases. Irritation begins at about the level of ten parts per million. Above 500 parts per million, even short exposures are dangerous. When it reaches mucous membranes, the moisture present there combines with the sulfur dioxide, suggesting that the ultimate action is that of sulfur acids. At concentrations lower than 500 parts per million, inflammation of all mucous membranes promptly occurs, with violent coughing and sneezing, pharyngitis, laryngitis, bronchitis or pneumonitis, with or without pulmonary edema. Bronchopneumonia may arise. However, in the smogs that have been investigated to date, a concentration of sulfur dioxide in the atmosphere has not been found that has been strong enough to produce any disease. The concentrations that have been discovered at Donora, in London, and in Los Angeles have not been more than enough to be annoying.

Some studies on air pollution, moreover, have shown that there is a significant amount of the oxides of nitrogen present in some urban atmospheres. Connolly and Nobe found that a total of 463 tons per day of nitrogen oxides were emitted to the Los Angeles atmosphere. Recently it was found necessary to fix the maximum allowable concentration of NO_2 in air to 5 P.P.M. If future studies prove the hypothesis that nitrogen dioxide respiratory illness is indeed a factor in the morbidity and mortality accompanying toxic fogs, you can well see that the importance of nitrogen dioxide pneumonia may be far greater than the sum total of 11 cases of silo-filler's disease would signify.

Etiology in Silo-Fillers

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

1. High nitrate soils.
2. Drought, particularly when plants are immature.

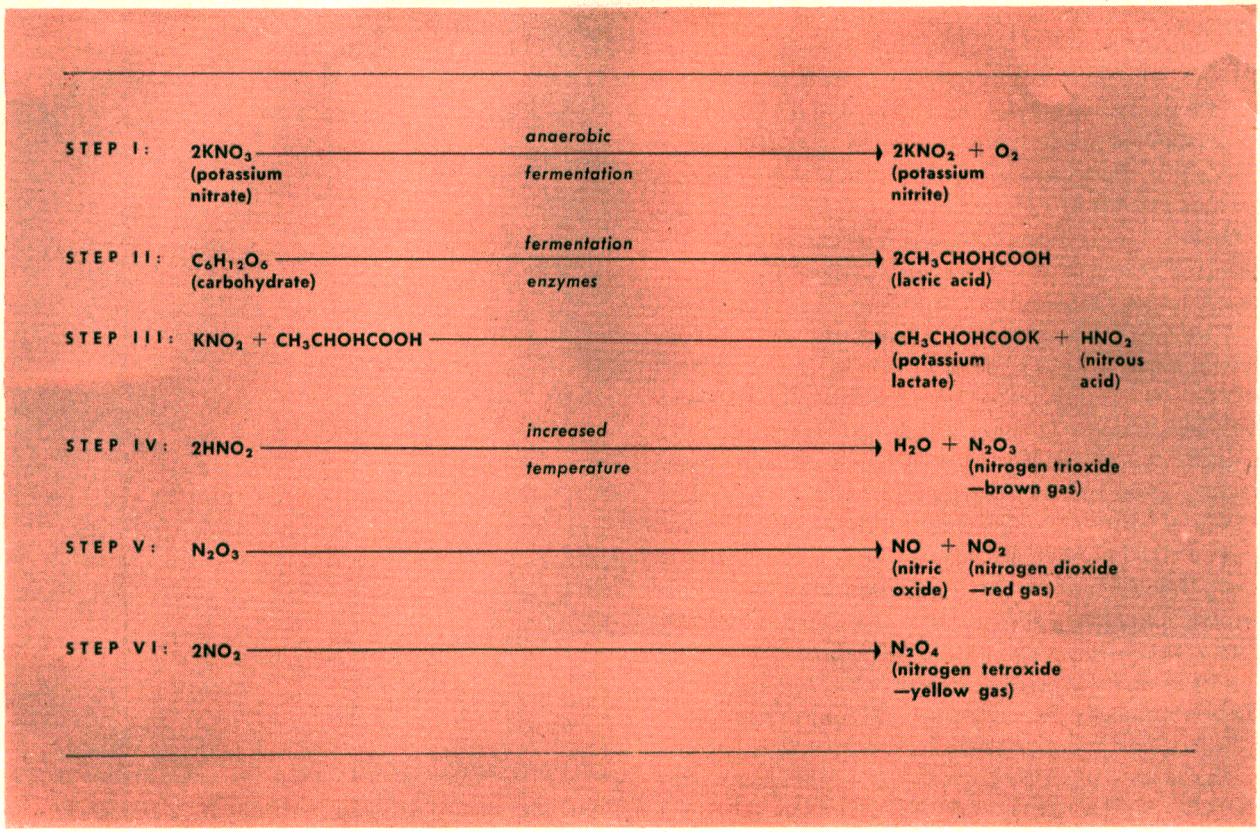


Figure 1. *The formation of nitrogen oxides in silage.*

3. Ultraviolet radiation and increasing light intensities or length of photoperiod.

The cereal grasses, such as oats, wheat, barley, corn, sorghums of all types and many pasture grasses readily concentrate nitrate under drought conditions. Numerous weeds also concentrate nitrates under drought conditions, or naturally carry a high nitrate content. Many important forage crops, besides the small grains, corn and sorghums, may also concentrate high levels of nitrate under adverse growing conditions such as existed in Missouri during 1954 and 1955. These forage crops include corn, alfalfa hay, sorgo silage, sweet potato vines and pigweed.

Drought may not always be necessary for the production of toxic forage, according to Case (Department of Veterinary Medicine, University of Missouri). He reported several "fuming silos" in Missouri in 1957, in areas with adequate rainfall, good corn crops and apparent over-application of nitrogen to the soil.

Nitrates in Water

The same nitrates that get into the corn stalks and cause nitrogen dioxide pneumonia after fermentation also cause another disease in humans that we should remember. Many ponds and some of the shallow wells on farms have had enough nitrite and nitrate contamination to impair the health of both man and animals. This contamination comes from the use of organic or commercial fertilizer in fields near the wells. There have been numerous reports of methemoglobinemia in infants where their formula was prepared with water from wells with a high nitrate content.

Explosion of Silos

Another consequence of high nitrates in silage, which I would like to mention only incidentally, is the explosion of silos. Several silos in Missouri have exploded in recent years, and it is possible that highly nitrated cellulose products were partly responsible.

Nitrate Disease in Cattle

Another consequence of high nitrate concentrations in forage and silage that might be mentioned in passing is forage poisoning in cattle. Overwhelming anoxia occurs that is due to severe methemoglobinemia. This results from conversion of the nitrate to nitrite and its absorption from the digestive tract of the cattle.

Nitrate forage poisoning in farm animals also produces nitrosohemoglobinemia in some cases. Nitro-

sohemoglobin closely resembles the carbon monoxide hemoglobin in its absorption and reflection characteristics. Thus, blood from animals with this type of nitrate poisoning is bright red instead of dark.

Subclinical nitrate intoxication has been recognized in cattle, sheep and swine, produced by sublethal amounts of nitrate ingested over a long period of time. The outstanding lesion seen in this disease is degeneration and reactivity of the vascular tissues in the brain, heart, lungs, liver, kidneys and testes.

Cattle at times may suffer from nitrogen dioxide pneumonia. This is a delayed illness of one to two days in which pulmonary edema occurs. This second type of nitrate forage poisoning is probably caused by fermentation in the cattle's stomachs with subsequent regurgitation and then inhalation of nitrogen dioxide.

There has been confirmation of the existence of nitrogen dioxide pneumonia in cattle. In 1957, Seaton (Iowa Veterinary Diagnostic Laboratory) published his paper, "Pulmonary adenomatosis in cattle produced by nitrogen dioxide poisoning." This disease has been observed in Iowa cattle for four years, and is characterized clinically by tachypnea, dyspnea, expiratory grunting and an excessive discharge of thick mucus from the nostrils. This bovine disease has been reproduced experimentally by the exposure of animals to the oxides of nitrogen. Autopsy studies confirm the identity of the naturally occurring disease and the experimental one.

Since legumes, such as alfalfa, and the forage crops, such as corn and sorghums, readily concentrate high levels of nitrate, it is important to consider the amount of nitrate that may be present in both the hay and the silage. These are the main ration fed to animals. According to Case, any amount of nitrate over 0.5 per cent in the total ration is a potential cause of toxicity in cattle. Even with additional carbohydrate and vitamin A, any amount over 1.5 per cent of nitrate in the total ration is dangerous.

Look for nitrate food poisoning in humans. Inasmuch as cattle can get fatal methemoglobinemia and nitrosohemoglobinemia by eating cereal grasses, it is possible that people may also at times get into the same trouble after eating grain. *I would suggest that we look for nitrite methemoglobinemia in mild forms among our patients.*

Chemistry of Nitrogen Dioxide Pneumonia

Potassium nitrate is changed by anaerobic fermentation into potassium nitrite and oxygen. The nitrite combines with organic acids, such as lactic acid, in the ensilage to form nitrous acid, HNO_2 (*Figure 1*). As the temperature of the ensilage rises with fermentation,

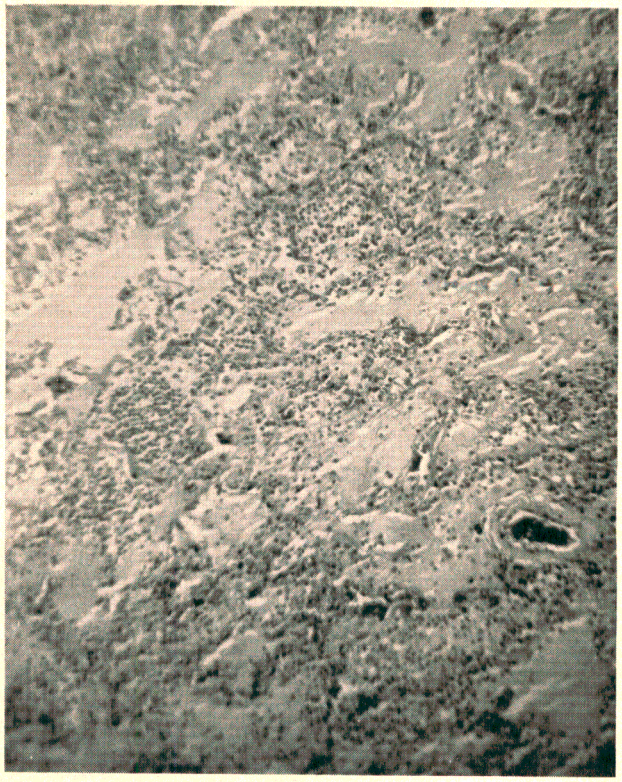


Figure 2. *Section of the lung from Case 1* (TABLE 1) *showing edema and bronchopneumonia.*

the nitrous acid decomposes into water and a mixture of nitrogen oxides which include nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen trioxide (N_2O_3), nitrogen tetroxide (N_2O_4), and nitrogen pentoxide (N_2O_5).

When the yellowish gases rise and then form a layer above this toxic silage, we have what is picturesquely described by the agricultural scientists as "fuming silo." This phrase serves to emphasize the danger when we think of silos.

Nitrous oxide (N_2O) is the sixth oxide of nitrogen and apparently is of no importance in poisoning by silage gas or other fumes. There is no information extant that would indicate that N_2O is present in silage gas, in fumes of nitric acid, in smog or in burning nitrocellulose compounds. Nitrous oxide or nitrogen monoxide is a colorless gas, having a slight characteristic odor. It is not inflammable but it supports the combustion of many substances almost as well as oxygen. It has no irritating action and is used extensively as an anesthetic.

Nitric oxide (NO) is a very stable, colorless, slightly soluble gas, and is a reducing agent. At ordinary temperatures, NO reacts with oxygen or air to form brown nitrogen dioxide (NO_2).

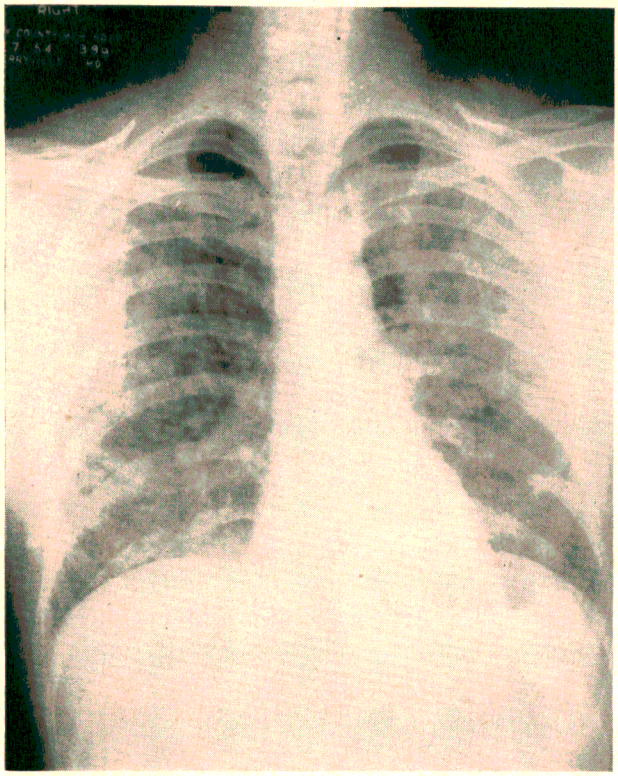


Figure 3. *Roentgenogram of the chest of Case 2* (TABLE 2) *showing bilateral diffuse, patchy and confluent infiltrations throughout the middle two-thirds of the lung fields.*

Nitrogen dioxide (NO_2) is a red gas, readily polymerizes, is water soluble and has an offensive odor.

Nitrogen trioxide (N_2O_3) is a brown gas that dissociates very rapidly into NO and NO_2.

Nitrogen tetroxide (N_2O_4) is a yellow gas that decomposes to nitrogen dioxide (NO_2), is water soluble, and is an oxidizing agent.

Nitrogen pentoxide (N_2O_5), along with nitrogen trioxide, decomposes at ordinary temperatures. On contact with air, it reacts in such a way that the principal product is a mixture of NO_2 and N_2O_4.

The five oxides of nitrogen, in the conditions of moisture, warmth and oxygen supply of the human lung, all first become a mixture of NO_2 and N_2O_4. This is the reason for the term "nitrogen dioxide pneumonia." Nitrogen dioxide (NO_2) and its dimer, nitrogen tetroxide (N_2O_4), are the oxides responsible for the toxicity of the oxides of nitrogen. 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.

The American Industrial Hygiene Association has recently announced the following pertinent facts about nitrogen dioxide: odor—pungent, sweetish; threshold of detection—about 5 p.p.m.; visual threshold—75-150 p.p.m.; relative vapor density—1.59 (air = 1) at 25 degrees C. and 760 mm. Hg.

When nitrogen dioxide is inhaled it is at once changed to the molecular form that corresponds to the body temperature. At 40° C., therefore, approximately 30 per cent of the dioxide is in the form of NO_2 and 70 per cent 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 that have a caustic action. The nitrates have no effect when absorbed, but the nitrites exert a systemic action.

It has been thought that methemoglobinemia might occur from the inhalation of the oxides of nitrogen. It would seem illogical, however, to think that this methemoglobinemia could be severe enough to cause asphyxia by virtue of the lack of oxyhemoglobin. Furthermore, animal studies have demonstrated that all methemoglobin disappears within one to two hours after exposure to NO_2. I think that we should mention methemoglobinemia only to keep in mind that nitrites can produce this condition but not to suggest that nitrite methemoglobinemia is responsible for the disability produced by the inhalation of nitrogen dioxide gas.

Human Pathology

The pathologic pictures that are seen with this disease are as follows:

1. Acute pulmonary edema (fulminating pneumonia).
2. Bronchopneumonia.
3. Bronchiolitis fibrosa obliterans.
4. Bronchitis.
5. Pulmonary fibrosis (not proven).
6. Asthma. There is some evidence that bronchial asthma may be caused in some workers in the chemical industry by the nitrous gases. The clinical picture does not differ from nonindustrial asthma.

In the first case of nitrogen dioxide pneumonia that was described by me the disease was fatal 29 hours following exposure to silage gas. An autopsy was done and the lungs were found to be heavy and full of frothy, white fluid. They were completely consolidated in all lobes. Microscopic examination of the lungs presented a moderate amount of alveolar edema and a very obvious bronchopneumonia (*Figure 2*). This was an example of the fulminating type of the disease, resulting in intractable, severe pulmonary edema.

The second case that I described was the type I

classify as bronchopneumonia. This patient survived and, therefore, we have no concrete evidence as to the actual pathology. But we do have a chest x-ray. This film reveals diffuse, patchy and confluent infiltration throughout the middle two-thirds of both lung fields (*Figure 3*).

In the two cases reported at the Mayo Clinic, the first was also one of pulmonary edema with death, and in the second, the patient suffered from extensive bronchopneumonia. The second patient recovered.

In two cases autopsied by Lowry and Schuman, it was proven that bronchiolitis fibrosa obliterans had occurred as a late complication of acute bronchopneumonia. Bronchiolitis fibrosa obliterans is rare but the pathologic features are distinctive. The lungs contain innumerable uniformly distributed lesions that are grossly visible and palpable as firm, discrete nodules of miliary size. Microscopically, each nodule consists of a small bronchus or bronchiole filled with a rather cellular, fibrinous exudate; organization of this adherent plug of fibrin by ingrowth of fibroblasts from the bronchiole walls tends eventually to occlude the lumen.

Bronchiolitis obliterans can be caused by inhalation of an irritant gas or can occur as a complication of certain infections of the lungs and bronchi. Other gases that are capable of producing this disease include phosgene, chlorine, chlorpicrin, ammonia, hydrogen chloride, cyanogen chloride and probably sulfur dioxide.

Three weeks after the patient described by Eckhardt was exposed to nitrogen dioxide gas in a silo, his chest x-ray showed an immense number of opaque nodules spread over both lung fields. The findings were those of a miliary infiltrate in both lungs. This patient became critically ill but recovered. Two months after the onset of his illness, lung biopsy revealed typical bronchiolitis fibrosa obliterans.

Seven months after exposure, this patient had a second biopsy done, which showed a very marked improvement. At this time, there was a mild degree of focal interstitial fibrosis, nonspecific in type. There was moderate distortion of the bronchioles, but there was no obliteration of the bronchioles. The bronchial epithelium was mildly hyperplastic, with some distortion of the lumen by some mucosal fibrosis. The changes were those of healing, rather than those of active proliferation. This patient did not receive steroid therapy.

Pathology in Animals

It will be instructive to all students of this disease to review the changes found in the lungs of animals which have been deliberately exposed to nitrogen dioxide. Post-mortem examination of mice and guinea pigs (Seaton, 1957) disclosed "tremendously enlarged, firm, cyanotic and edematous lungs as well as general passive hyperemia of the viscera. Histologic examination of the lungs . . . revealed hyperemia, edema and pronounced hyperplasia, as well as hypertrophy of the alveolar and bronchial epithelium." These animals had died 72 hours after exposure to the oxides of nitrogen for two minutes in a bell jar.

In one cow that was exposed to the same gas, death occurred in 94 hours. Both lungs were uniformly involved with the typical gross lesions that occur in pulmonary adenomatosis. Both lungs were greatly enlarged and edematous. The bronchi contained a small amount of pink foam. Extensive alveolar and pulmonary emphysema was to be observed. Large bullae were present in the interlobular septa. The consolidation and the vascular changes associated with pneumonia were not present. Histologic examination of the lungs disclosed the typical lesions of pulmonary adenomatosis. The histologic alterations usually associated with either bacterial or viral pneumonia were absent.

Clinical Picture

The Latent Interval

In all the literature on nitrogen dioxide, a symptom-free interval following exposure is stressed. This latent period is important to remember, inasmuch as seriously affected individuals may be allowed to work or to travel away from medical aid before the acute disease develops. The latent interval has been confirmed experimentally in animals.

All the known cases of nitrogen dioxide pneumonia have occurred after a latent interval that may vary from hours to days. If the inhalation of the oxides of nitrogen produces nitric and nitrous acids, then why does it take so long for disability to develop? The cilia of the bronchial mucosa are not waving in the air. They are waving in a sea of mucus. This mucus, then, must be a barrier which accounts for part of the latent interval in nitrogen dioxide pneumonia. The latent interval might also be caused by the duration of time it requires for the inflammatory response to develop once the acids reach the mucosal cells.

This latent interval is very important. It provides time for therapy to prevent severe illness or death.

Pulmonary Reaction

The longer the exposure to nitrogen dioxide gases, the more intense the fumes, the more severe the pulmonary reaction will be. If the exposure has been very severe, the fulminating type of disease will result. If less severe, acute bronchopneumonia will occur, that, properly treated, will result in survival.

In cases of moderate exposure, the patients develop mild chronic respiratory illnesses that become progressive. These patients complain of a hacking, nonproductive cough, frequent chilly sensations, fever and sore throat. Weeks later, the patient may report to his physician for care and it will be found by chest x-ray that numerous nodules are present in both lung fields. Of particular importance in diagnosis is a roentgen pattern simulating miliary tuberculosis. This condition may continue to progress and may be fatal. *This is bronchiolitis fibrosa obliterans.*

There also occur cases of simple chemical bronchitis from exposure to smaller concentrations of nitrogen dioxide. These patients get well rapidly and apparently have no residual difficulties. It is conceivable that some of the patients in toxic fogs (smog) who develop acute bronchitis may be in this category.

There is no *direct* evidence as yet that any cases of chronic pulmonary fibrosis result from nitrogen dioxide. One might speculate that small repeated exposures may eventually result in a chronic pulmonary disease characterized clinically by the term "chronic pulmonary fibrosis." Studies are under way to determine if this is true.

Differential Diagnosis of Silage Gas Poisoning

In normally wet years, poisoning by oxides of nitrogen is less apt to occur. If any silage gas poisoning cases do occur during wet years, then their cause can be usually ascribed to carbon dioxide poisoning or to asphyxia from oxygen depletion.

Every year casualties are reported and occasionally death results from asphyxiation of workers by carbon dioxide gas arising from fermentation in silos. Numerous studies on ensilage have shown that green fodder, on being placed in the silo, immediately begins to undergo changes opposite to normal plant metabolism. The oxygen of the 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. Carbon dioxide may exist in quantities of up to 75 per cent.

All patients with respiratory disease should be questioned concerning their activities on farms (and in industry) during the previous weeks. If there has been any history of work in or around silos, in drought areas, it may be suspected that nitrogen dioxide inhalation has occurred. *Remember that nitrogen dioxide is heavier than air and is colored brown, red and orange. Remember also that in low concentrations, NO_2 may be invisible but still very toxic.* The patient will give a history of inhaling a very irritating gas. The prodromal symptoms are headache, sensation of fullness in the head, a sense of tightness in the chest and a slight cough. My second patient stated only that he "could not take a deep breath."

Following this, there may be dyspnea, tachypnea, cyanosis, vomiting, vertigo and sometimes unconsciousness. The patients who are most severely affected will arrive in extremus due to acute pulmonary edema. The clinical picture of pulmonary edema in this disease is no different from pulmonary edema in other cardiac or pulmonary conditions.

"Farmer's lung," due to inhalation of moldy hay dust, is probably a separate entity, and is to be distinguished from nitrogen dioxide pneumonia.

Toxicologic Studies

For definite proof of the diagnosis, the silage gas itself, and the silage can be examined chemically. This was done in the first two cases. Gas was collected from the silo in which the two individuals had been poisoned. Chemical analysis (performed at the University of Missouri) indicated that this gas contained the oxides of nitrogen. 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.

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.

Treatment

Therapy that has been used so far in the reported cases is as follows:

1. *Antibiotics* to prevent secondary infection and to treat secondary bacterial bronchitis and pneumonia.
2. *Oxygen.* Pressure oxygen in some cases may be of value.
3. *Bronchodilators.*
4. *Digitalis.* I used digitalization in my patient as a last resort, when he was dying of his pulmonary edema. It seemed to produce temporary relief; but inasmuch as the circulatory failure was secondary to his respiratory illness, the therapy was unsuccessful.
5. *Steroids.* Two of the cases reported by Lowry and Schuman received steroids and a dramatic improve-

ment ensued. These patients recovered. However, three other survivors of this disease were not treated with steroids and at the time of this writing are alive and well (*Table 1*).

The decision to use steroids should always be made on an individual basis until further studies have been completed. It is, of course, possible that cortisone and ACTH may produce a more rapid recovery because of their anti-inflammatory properties. It is also probable, in patients with bronchiolitis fibrosa obliterans, that their recovery will be considerably hastened and in some cases, death may even be prevented.

6. *Detergent aerosols.* The detergent aerosols would probably be of value during episodes of pulmonary edema and dyspnea.

7. *Other Measures.* Expectorants should not be used. Atropine does not diminish edema or improve breathing; furthermore, its acceleratory action on the heart is certainly undesirable. The administration of parenteral fluids, such as saline, plasma or blood is contraindicated. Surgery, except emergency measures to save life, is contraindicated in the active stage of edema. If anesthesia is required, local infiltration or nerve block is the method of choice. Cardiac and respiratory stimulants, such as epinephrine, benzedrine, Coramine and Metrazol do more harm than good. Alcohol is contraindicated in all cases of this character.

8. *Venesection.* Venesection is contraindicated.

9. *Sedation.* Sedation should be used sparingly. Codeine in doses of 32 to 64 mg. is quite effective against cough. If oxygen fails to quiet the patient satisfactorily, morphine may be used subcutaneously in a dose of 10 to 15 mg.

Preventive Measures

Safety programs are being initiated by agricultural departments to educate farmers about the potential danger of fermenting silage. They have recommended that no one be allowed to enter a silo for any purpose, from the time filling begins until one week to ten days after it is finished. Good ventilation should be provided about the base of the silo during this period so that toxic gases, if they develop, will be carried away. Blower fans in silos should be turned on before entering.

Fencing (or other effective means) has been stressed to prevent children and animals from straying into any spaces adjoining a silo during this dangerous period of gas formation.

A simple testing device that will warn workers of the presence of nitrogen dioxide in the atmosphere is being developed.

Chemical Prophylaxis

Before ending this discussion, I would like to present an idea that might be of some value in preventing this disease.

We know that nitrogen dioxide pneumonia is caused by acids entering the respiratory tract. These acids are nitrous and nitric acids. We think that the latent interval is due in part to the mucous barrier between the atmospheric air and the bronchial mucosa. *It would seem logical then that the simple application of a neutralizing agent, such as sodium bicarbonate, to the mucosa of the respiratory tract during the latent interval would be an effective method of preventing tissue destruction.* This could be accomplished best by aerosol. A preparation is available that not only includes a physiologic amount of sodium bicarbonate but also includes a safe detergent that permits the solution to penetrate all parts of the bronchial tree. This aerosol (Alevaire), if administered in time to patients known to have been exposed to the fumes of nitric acid or other nitrate compounds, or to silage gas containing nitrogen dioxide, should prevent or minimize the pathologic effects.

It has been suggested that local injury to the lung surface could result in an inflammatory process having histamine release and thus fluid exudation as one of its consequences. A rational therapy, if this is true, is the administration of antihistamines by aerosol or systemically. Conceivably, in addition, the beneficial action of steroids could be predicted in this instance.

Future Studies

Many ramifications of this disease remain for researchers to probe more fully. Attention should be directed toward the following questions:

1. What causes the latent interval?
2. Of what value will an alkaline aerosol be during the latent interval?
3. Is nitrogen dioxide the poison gas in smog?
4. Should steroid therapy be routine in all phases of this disease?
5. If cereal grasses from drought areas cause methemoglobinemia in cows, does this occur in humans who eat these same cereals?
6. What are the time-dose relationships in the different pathologic categories of this disease?
7. Can chronic pulmonary fibrosis result from repeated occult exposure to nitrogen dioxide in silos and in other occupations?
8. Is nitrogen dioxide gas the true cause of "farmer's lung" and "thresher's lung"?

9. What is the incidence of nitrogen dioxide pneumonia in victims of smoke inhalation at accidental fires?

10. Is nitrate methemoglobinemia a factor in nitrogen dioxide pneumonia?

11. Can high nitrate concentrations in crops be prevented during unpredicted droughts? Would nonnitrated ammonium fertilizers prevent this disease?

12. What is the true incidence of nitrogen dioxide pneumonia in silo-fillers? Is this a new disease or an old one?

13. What is the concentration of NO_2 above "normal" silage in wet years from nitrated fields?

Finally, simple devices for detecting nitrogen dioxide are needed for use by farmers, agricultural extension agents, veterinarians, industrial safety directors, chemical laboratory directors, physicians and public health workers.

Addendum

Since this paper was prepared for publication, information has been received concerning two hitherto unreported cases of nitrogen dioxide pneumonia in silo-fillers. Both of these cases were seen by Dr. Helen A. Dickie and her colleagues at the University of Wisconsin. Both of these cases will be reported by them in the near future. Inasmuch as this brings the total number of cases known to only eleven, it is important to include a brief summary of each in this review:

Case 10: A 64-year-old farmer in Wisconsin entered his silo chute in October, 1955, and was almost overcome by a gas which caused severe coughing and dyspnea. After a latent interval of one week, he developed chills, fever and cough. Chest x-rays revealed a diffuse interstitial and patchy pneumonitis which cleared after nonspecific therapy in three months. There was no biopsy done and steroid therapy was not used.

The description of this case would suggest that the clinical picture here would fit in Category III as detailed in the review. The diagnosis, then, probably was "subacute bronchopneumonia with bronchiolitis fibrosa obliterans." It is also important to call attention to the long latent interval of one week in this particular case.

Case 11: A 45-year-old farmer filled a silo with corn silage September 5, 1955, September 8, 1955, and again on September 15, 1955. On the last occasion, he worked in the silo for two hours. There were no acute symptoms, but after the last episode, he began to feel ill later in the day and several days later reported to his physician with chills, cough, fever and dyspnea. This patient was treated with steroids, in addition to other therapy, and was released from the hospital as clinically well after five weeks. No biopsies were done in this case.

Upon reviewing this case and comparing it with the previous nine cases, I would conjecture that this also could be classified as subacute bronchopneumonia with bronchiolitis fibrosa obliterans due to the inhalation of the oxides of nitrogen.

An extensive bibliography accompanying this article is available upon request from the Editorial Office of GP.

Total Cardiac Arrest

Dr. F. Mason Sones, Jr. of the Cleveland Clinic disclosed to the AHA recently that total cardiac-arrest surgery had been carried out on 50 patients at the clinic since last February.

Patients in the series ranged from three weeks to 54 years of age. Heart stoppage lasted from seven to 58 minutes, with the latter occurring during surgery on a 54-year-old man who suffered mitral valve insufficiency.

For heart stoppage potassium citrate plus a pump oxygenator are used. Two cubic centimeters of a 50 per cent solution of potassium citrate, diluted to 20 cc. with the patient's own blood, is injected into the occluded aorta above the coronary arteries.

Following the operation the surgical team "stands back" and permits the pump oxygenator to take over to perfuse the coronary arteries effectively. No electrical stimulation or outside method is used. The pump oxygenator alone restores a normal beat, and can take from 30 seconds to 10 minutes.

The technique has been used to attempt closure of large interatrial defects, repair of interventricular septal defects, excision of areas of muscle obstructing the right ventricular outflow tract, and correction of aortic stenosis and mitral insufficiency. It has been successful in about two-thirds of the cases attempted. The heart has been stopped, surgery accomplished, and the heart started again in all cases.