MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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ADVERSE PULMONARY REACTIONS TO DRUGS

I. Pulmonary edema

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The tracheobronchial tree may be the major organ of response to hypersensitivity reactions following administration of a variety of drugs causing anaphylaxis. In addition to such responses the lung parenchyma may manifest adverse reactions to orally or systemically administered drugs. These parenchymal reactions present with certain recognizable syndromes including non-cardiogenic pulmonary edema, embolic lung infection, angiothrombosis, diffuse interstitial fibrosis, pulmonary infiltrates with eosinophilia, lower lobe reticular infiltrations, and pathological calcification. It is these syndromes that are the topic of this review.

I. Pulmonary edema.

Although pulmonary edema was described as a complication of opiate intoxication in 1880 by Sir William Osler, it remained a medical curiosity and the subject of individual case reports until the advent of the drug culture of the 1960's. In 1956, '57, and '58 only 4 instances of pulmonary edema due to heroin were seen at Bellevue Hospital (2), whereas in the 17 month period from July 1, 1968, to November 30, 1970, 71 instances of heroin pulmonary edema were seen at the Morrisania City Hospital in New York (19). Four such patients have been admitted to the Medical Intensive Care Unit at Parkland in the last 6 months.

Although pulmonary edema is most commonly associated with heroin poisoning, this is a reflection of the overwhelming predilection for heroin among narcotic addicts. Data from the Federal Bureau of Narcotics indicates that among known narcotic addicts in the United States, in excess of 92% are addicted to heroin (9). Pulmonary edema has also been described, however, due to intoxication with morphine, methadone, and propoxyphene (Darvon).

Most opium is grown in Middle Eastern or Asian countries and is exported as morphine. In illegal laboratories, usually in France or Italy, it is acetylated to diacetylmorphine (heroin) and smuggled into the United States in a relatively pure form. As it passes through the hands of wholesale distributors it is progressively diluted from 20 to 100 fold with a variety of substances including quinine, lactose, mannitol, and baking soda. Quinine is the favorite dilutant, since its bitter taste disguises the similarly bitter taste of heroin and prevents the addict from estimating the amount of heroin in the material he has been sold. In a study of 132 street samples, it was found that 12 packages had no heroin at all, and the concentration of the drug in the remainder ranged from less than 1% to 77% (5). Heroin adulterated to 5% provides a

morphine equivalent of approximately 15 mg; 1% to 3% heroin provides the addict with virtually no "kick" and is known as "junk", whereas more than 20% heroin may result in lethal overdose. The powdered drug is sold to addicts in small envelopes termed a "bag". It is dissolved in a small amount of water and heated to boiling by a match flame or a cigarette lighter in a crude receptacle such as a teaspoon or bottle cap. The injection apparatus is usually improvised from an easily obtainable medicine dropper with its tip fitted tightly into the hub of hypodermic needle by means of a paper flange. Such droppers are preferred to the easily available disposable plastic syringes, because the rubber bulb is easier to manipulate than the rigid plunger of a syringe during self injection into a vein. The apparatus used by addicts is called "the works" and the intravenous addict a "mainline shooter".

Overdose tends to occur in one of several settings. In the first place, the illicit drug user has no way of predicting the strength of the material, and this lack of awareness of potency of the heroin packet is the most frequent cause of overdose. Second, the addict who has been incarcerated, hospitalized, or otherwise kept drug free may return to his drug abuse with the maximum amount of heroin he used previously, disregarding his abstinence-related loss of tolerance for the drug. Third, the neophyte may immitate his drug abusing, drug tolerant colleagues and inject what for him is an inordinately large dose of heroin. Fourth, when a narcotic pusher realizes that police are preparing to arrest him, he may dump virtually pure heroin on the market causing a marked increase of concentration of injected drug. Fifth, a pusher may wish to get rid of an addict and does so by supplying him with unusually potent heroin in a deliberate attempt to induce lethal overdose.

Once overdose has occurred, the user experiences the usual torpor, but this rapidly progresses to stupor which is usually accompanied by irregular, slow respiration. Coma and respiratory arrest may occur, and in some cases death occurs so rapidly that the needle is still found in the vein at the time the body is discovered. Two antidotes are frequently used by the addict community. The first of these is to apply ice to the narcotized subjects, most commonly to the genitalia. Second, the stuporous addict may be given milk intramuscularly, intravenously, or by mouth. Evidence of such therapy in a comatose patient presenting to the emergency room may suggest the correct diagnosis.

Although the method of reporting patients is extremely variable from one series to another, it is possible to gain a relatively clear impression of the clinical spectrum with

which the patients present to an emergency room (2, 7, 19, 22). Patients with heroin induced pulmonary edema are young, ranging in age from 15 to 37 with a mean age of 22 years. Ninety-four percent of reported patients are men, and the majority are Black or Latin. Approximately 27% of the patients have a mixed overdose with the most common additional drug being alcohol. Sedatives are also frequently used with heroin, the most popular of which is Glutethemide known to the trade as "Cibas". Data is not available to indicate the percentage of patients with overdose that develop pulmonary edema. However, of those overdose patients presenting to an emergency room that are considered sick enough for hospital admission, 52% have or subsequently develop pulmonary edema.

At the time of presentation almost all patients are comatose or semicomatose. Those patients that are not comatose usually give a history of having been so before arrival. Seventy-two percent of the patients are apneic or have a markedly depressed respiratory rate. Paradoxically, approximately 22% of the patients demonstrate tachypnea with respiratory rates as great as 50. Based on information obtained from the unreliable histories available, the patients with tachypnea have passed through an episode of slow respiratory rate before presenting with tachypnea and dyspnea as pulmonary edema develops. Ninety percent of the patients have a tachycardia greater than 100 beats per minute, but only 8% are hypotensive at the time of admission. Eighty nine percent of the patients have constricted pupils, but in approximately 5% the pupils are normal and in an additional 5% the pupils are dilated. The latter is thought to be due to cerebral anoxia in some patients and a mixed drug overdose in others. Fever is present in 16% of patients at time of admission, and it cannot be explained by obvious infection. In approximately 47% of the patients the examiner is able to find evidence of repeated intravenous injections, most commonly in the antecubital fossae. It has been pointed out by Helpern and Rho (3) that narcotic addicts are very adept at intravenous injections and leave no external manifestations of injection even though the procedure is performed in an unsterile manner. Further pertinent physical findings include cyanosis at time of admission, and of those who ultimately develop pulmonary edema, 75% demonstrate rales in the lung bases on presentation to the hospital.

Of those patients ultimately developing pulmonary edema, 90% will demonstrate such by x-ray at time of admission. The roentgen changes of acute heroin intoxication consist of an

alveolar pattern of opacification with ill defined, fluffy, coalesent densities involving both lungs, generally in a symmetrically fashion. One may encounter the classic "bat wing" distribution of bilateral alveolar edema, or the edema may involve only one lung or part of one lung. On occasions it may be localized to only one lobe, and it may shift rapidly from lobe to lobe and from one lung to the other. When pulmonary edema is unilobar, it may be indistinguishable from pneumonia. In the less severe forms of pulmonary edema, there may be coarse reticular changes of the lung parenchyma suggesting an interstitial pattern. The pulmonary edema in acute heroin intoxication is roentgenographically similar to pulmonary edema from other causes except for a normal sized cardiac silhouette.

At time of admission the electrocardiogram is likely to show a variety of non-specific changes of the ST-T waves. A small number of patients have evidence suggesting pulmonary hypertension including peaked P waves or a right bundle branch block pattern. Approximately 10% of the patients will demonstrate atrial fibrillation, and a smaller proportion will have other types of conduction disturbance.

Approximately 60% of the patients will show a leukocytosis of greater than 11,000 cells/mm^3 with no evidence of infection. Nineteen percent of the patients have a white count in excess of 20,000 cells/mm^3 with an additional 20% having less than 5,000 cells/mm^3. Those patients with a high white count tend to have a shift to the left with a large number of immature polymorphonuclear leukocytes. However, Duperstein and Kaufam (19) report that 25% of their patients had greater than 50% lymphocytes. On urinalysis, 41% of the patients have been reported to have glycosuria, and 46% have been reported to have proteinuria.

Blood sugars are not measured in most series, but in one group of 149 patients 10 were reported to have a glucose of less than 60 mg % and 3 of these had less than 40 mg %. In none of the patients was the clinical picture improved by administration of 50% glucose intravenously. The same series reports that a large number of patients had hyperglycemia, and the average blood glucose level for patients with pulmonary edema was 190 mg %. However, these authors could not be sure that the patients had not received glucose before the determination was performed.

Because of the variability of reporting, arterial blood gas values cannot be precisely stated. On average, however, arterial oxygenation is markedly depressed at the time the patient presents with pulmonary edema with the pO_2 characteristically being less than 50 mm Hg while the patient breathes

room air, and less than 200 mm Hg breathing 100% oxygen (22). The pCO_2 is extremely variable with most patients demonstrating hypoventilation but with some demonstrating hyperventilation (pCO_2 <40 mm Hg). On average, the pCO_2 on admission is in the low 50's. The pH is reduced out of proportion to the increase in pCO_2 indicating a combined respiratory and metabolic acidosis with an average pH of less than 7.20.

Immediate treatment of patients with heroin pulmonary edema is directed at adequate ventilation and oxygenation, although the administration of 50% glucose would also seem reasonable because of the report of hypoglycemia in a few patients. In most patients ventilation and oxygenation can be successfully carried out by a simple oxygen delivery device such as a nasal cannula and the use of specific narcotic antagonists. In more severely ill patients, in addition to the use of narcotic antagonists intubation will be necessary so that ventilation may be maintained by intermittent positive pressure breathing. In very severely ill patients, continuous positive pressure breathing may become necessary in order to maintain adequate arterial oxygenation.

Until recently the narcotic antagonist available to the clinician has been N-allylnormorphine (Nalline). This drug is specific for morphine and its congeners; it does not antagonize the effects of barbiturates, other sedatives, or analgesics with the exception of propoxyphene (Darvon). On a specific dose basis it does not equally antagonize all of the narcotics, but this is not important in the clinical setting of acute drug overdose. The effects of Nalline are divergent and depend on the preceding dose of narcotic. In a dose of 10 mg in the absence of preceding narcotics, Nalline depresses respiration and body temperature in a manner comparable to that of 10 to 30 mg of morphine. It provokes dysphoria in many subjects, and it moderately constricts the pupils. When a single dose of 10 to 20 mg of morphine is followed one hour later by 10 mg of Nalline, the latter will counteract to a considerable degree morphine induced miotic effects and morphine euphoria, but under these conditions will not counteract morphine induced respiratory depression. If, however, the dose of morphine is sufficient to induce severe respiratory depression, then administration of 10 mg of Nalline tends to restore normal respiration. The manner by which Nalline counteracts respiratory depression produced by narcotics is not clear. The most popular theory is that the antagonist has a stronger affinity for respiratory center receptors than does morphine. If morphine occupies the receptors, the antagonist displaces it, thus substituting a milder respiratory depression that may simulate a return to normalcy. If the receptors are unoccupied, as in the normal subject, the antagonist produces respiratory depression. This theory does not satisfy all circumstances,

especially the fact that a mild respiratory depression may be uneffected or even intensified by the antagonist. Whatever the pharmacological mode of action, clinically it should be noted that Nalline may depress respiration in the comatose patient if the cause of coma is not narcotic. In the comatose patient 5 or 10 mgs may be given intravenously and the 5 mg dose repeated if necessary after an interval of 15 minutes for two additional doses. If three doses of Nalline do not cause an improvement in respiratory rate or volume, one should be very suspicious that the coma and depression are due to some other cause. If the initial dose of Nalline appears to aggravate respiratory depression, it should not be repeated. Even though respiratory rate and minute volume are improved by Nalline, drowsiness and a semiconscious state may persist; Nalline should not be administered again, however, unless respiratory depression recurs. The duration of action is approximately 90 minutes, and additional Nalline may be required as long as 3 hours after the initial dose because of recrudescence of symptoms. In some patients Nalline may produce marked agitation; these tend to be patients who have tachypnea rather than depressed respiration. Agitation after Nalline may indicate pulmonary edema with severe hypoxemia, hypoglycemia, or a mixed overdose. In the absence of a depressed respiratory rate, the use of Nalline may be contraindicated as it may precipitate a withdrawal crises.

In June, 1972, a new antagonist, N-allyl-nor-oxymorphone (Narcan), originally described in 1961 (30), became available commerically. Unlike Nalline, it does not possess morphine like properties when used alone. Specifically, it does not produce respiratory depression, psychotomimetic effects, or pupillary constriction. When administered intravenously the onset of action of Narcan is apparent in approximately 2 minutes. The initial adult dose is 0.4 mgms (1 ml) and if improvement in respiratory function is not obtained rapidly, it may be repeated at 2 to 3 minute intervals. Like Nalline, failure to obtain significant improvement after 2 or 3 doses suggests that the cause of coma and respiratory depression is not narcotic.

When treated with a narcotic antagonist and oxygenation, and ventilatory support when necessary, clinical, radiological, and arterial blood gas improvement is usually dramatic. The patients frequently become alert within two hours. The physical findings of pulmonary edema characteristically clear over the course of 24 hours. Radiological clearing is usually marked within 2 days, but complete clearing radiologically takes on average 4 days and may take as long as 2 weeks. Two cautions are necessary, however; first, Steinberg and Karliner (7) report that in some patients severe pulmonary edema developed several hours after recovery from coma. Although these authors do not document this carefully, they indicate that edema may occur as long as 24 hours after drug injection. Second, although the exact incidence cannot be determined from published

reports, bacterial pneumonia following pulmonary edema is relatively common. Patients whose x-rays show a progressive worsening, especially in a localized area, rather than a progressive clearing should be assumed to have this complication.

Assessment of lung function indicates that abnormalities persist longer than indicated by clinical or radiologic response (10, 22). The physiological dead space to tidal volume ratio (V_D/V_T) is larger than normal for at least 5 days. The vital capacity and total lung capacity are dramatically reduced acutely and tend to remain abnormal for at least 10 days. Two patients studied 10 and 12 weeks after initial insult were still abnormal (10). Lung compliance evidently parallels the changes in VC and TLC. Conversely, measurements of air flow and airway resistance are normal. The diffusing capacity tends to be markedly decreased and does not tend to improve over a 10 day period following the pulmonary edema. These findings of persisting functional abnormalities are in contradistinction to the limited observations available on patients with pulmonary edema due to left ventricular failure; in this latter group of patients pulmonary functional analysis tends to be normal shortly after an episode of pulmonary edema. These findings suggest that the edema fluid has a different consistency in patients with heroin pulmonary edema causing it to be more slowly reabsorbed.

The cause of heroin pulmonary edema is not known, but it is clearly not cardiogenic in origin. Although reported effects of morphine on the cardiovascular system vary in detail, heroin does not cause sufficient hemodynamic change to initiate pulmonary edema (15, 44). Measurements in 8 narcotic addicts with clinical and radiographical signs of acute pulmonary edema following overdose of heroin indicated a normal pulmonary capillary pressure, mild elevation of the pulmonary artery pressure (32/12 mm Hg, mean 20 mm Hg), and an elevated cardiac index and stroke volume (4.5 L/min/M^2 and 54 ml/beat/M^2). Moreover the concentration of proteins have been measured in pulmonary edema fluid obtained from patients with heroin pulmonary edema and from patients with acute left ventricular failure (47). The concentrations of proteins in blood serum were similar in the two groups of patients. In the cardiac patients the mean concentration of protein in the pulmonary edema fluid was only 40% that of serum, whereas in the patients with heroin pulmonary edema the mean concentration of protein in the edema fluid was virtually the same as that in the serum. This observation suggests that patients with heroin pulmonary edema have increased pulmonary capillary permeability.

The cause of increased vascular permeability in narcotic overdose is unknown. Several mechanisms have been proposed, but none of these completely explains the findings. An allergic reaction seems unlikely, since pulmonary edema has resulted following the first exposure to narcotic (23) and since pulmonary edema has not been reported following prolonged use of narcotics therapeutically in patients with serious disease. Reactions to the foreign material used as a dilutant likewise seem unreasonable, since reactions have occurred to oral ingestion and to nasal sniffing of narcotic. The most frequently suggested explanation for pulmonary edema has been an abnormal capillary permeability caused by the hypoxemia associated with narcotic induced respiratory depression. This syndrome has been likened to the pulmonary edema sometimes seen at altitude. Hypoxemia seems to me unlikely to be the cause of pulmonary edema for the following reasons. Hypoxemia of a similar order of magnitude is observed in many clinical settings, including non-narcotic sedative drug overdose, where pulmonary edema does not ensue. The syndrome is peculiar to narcotics abuse. Second, the hypoventilation observed in these patients at time of admission to the emergency room is mild as indicated by an average pCO_2 of 50 mm Hg. This degree of hypoventilation is insufficient to produce severe hypoxemia. Third, pulmonary edema associated with altitude hypoxemia is not characteristically fulminate, but the pulmonary edema associated with heroin occurs so rapidly that the patient may die while the injecting needle is still in the vein (3). Finally, the proposed mechanism of altitude pulmonary edema is pre-capillary arteriolar constriction with edema exuding through larger pulmonary arteries; the measured pulmonary hypertension in patients with heroin pulmonary edema is of a low order of magnitude (15). The most attractive explanation for heroin induced pulmonary edema is a direct toxic effect of the narcotic in high concentration on the pulmonary vasculature. Detracting from this possibility is the fact that pulmonary edema has not been observed following extremely high doses of morphine used for anesthesia (45), and the fact that intravenous administration of heroin to primates in doses sufficient to cause profound hypoventilation did not cause pulmonary edema (22). Thus, one must conclude that the pathogenesis of narcotic pulmonary edema remains to be explained.

II. Embolic lung infections

Although not due to drugs per se, embolic lung infection is a distinct clinical syndrome occurring with the intravenous use of illicit drugs. It is commonly associated with tricuspid endocarditis, but the site of origin of the embolic infected material may be suppurative thrombophlebitis. Since cardiac murmurs are frequently absent in tricuspid endocarditis, and

since it may be impossible to detect infected veins on physical examination, the differentiation of the two syndromes in the living patient may be impossible.

By May, 1970, there were 93 reported cases of endocarditis in drug addicts (82). Thirty of these patients had tricuspid endocarditis, while in 63 the endocarditis was associated with the aortic or mitral valve. Whereas a variety of exotic organisms were isolated from patients with left sided endocarditis, 27 of 28 patients with tricuspid endocarditis in which the causative organism was isolated were infected with staphylococcus. Two of these were Staphylococcus albus and the remainder were Staphylococcus aureus. Only one case was associated with pseudomonas. Left-sided endocarditis was sometimes associated with previously existing valvular disease, but in none of the patients with tricuspid endocarditis was the valve thought to be abnormal before the infection. In none of the patients with left-sided endocarditis was there embolic lung infection, but this syndrome occurred in 23 of the 24 cases of tricuspid endocarditis where information is available.

Whether the original site of infection is a peripheral vein or the tricuspid valve, the clinical findings are largely caused by septic pulmonary embolism. Most patients present with fever and cough, commonly unproductive, which may have been present for several days. The patients are usually extremely toxic, and pleuritic chest pain and dyspnea are common. Physical examination of the chest characteristically reveals few changes relative to the amount of disease seen on the chest x-ray. The heart exam is usually normal. The initial radiological appearances are very variable; chest x-ray may initially show only very small linear opacities. With time, however the radiographic pulmonary lesions are striking. These lesions are usually multiple, and may appear first in one portion of the lung, and then another. Serial films reveal central cavitation of lesions which finally regress to thin wall cavities with eventual closure. While some lesions are regressing, new lesions appear. The incidence of empyema is high, and tension pneumothorax is not uncommon. Systemic arterial emboli with abcess formation is not rare, especially to the kidneys, spleen, and brain. These usually occur after the pulmonary abcesses have been present for a protracted interval, and are thought to arise from septic pulmonary vein thrombophlebitis. Even with reasonable antimicrobial therapy, 10 of 30 reported cases of tricuspid endocarditis died.

III. Angiothrombosis

The syndrome of angiothrombosis also occurs in drug addicts. It is related to the intravenous injection of tripelennamine

(Pyribenzamine) in patients with "blue velvet" addiction or to intravenous injection of secobarbital (Seconal) in patients with "red devil" addiction. Addiction to tripelennamine was originally described in 1957, but pulmonary lesions due to this habit were described first in 1964; lesions due to secobarbital were described first in 1966.

Blue velvet is the name applied by narcotic addicts to tripelennamine. It is usually taken by the addict with an additional drug, most commonly paregoric. The mixture is prepared by boiling 30-60 ml of paregoric until approximately 5 ml of a turbid fluid remains. It is then allowed to cool. Camphor floats to the top of the mixture and is removed with cotton. A 50 mg tablet of tripelennamine is then crushed and added to the mixture. The fluid is aspirated through cotton into a medicine dropper and then injected intravenously. The resulting euphoria may last for several hours. However, the ingredients of paregoric are irritating and rapidly lead to occlusive sclerosis of veins into which they are instilled. Vessels larger than the antecubital veins are ultimately sought, and the blue velvet addict may be recognized by scarred femoral, popliteal, axillary, and jugular veins. Red devil addiction consists of injecting the dissolved contents of secobarbital capsules intravenously. The clinical syndrome of angiothrombosis is similar to that of multiple pulmonary emboli or primary pulmonary hypertension. The patient develops an insidiously progressive pulmonary hypertension with progressive dyspnea out of proportion to the physical and radiological findings. A dry non productive cough may be prominent. If the patient is seen before the onset of right ventricular failure, physical findings are those of pulmonary hypertension: an increase in the pulmonic component of the second sound, a right ventricular heave, and perhaps a pulmonic murmur. Characteristically the lungs are free from abnormal findings, although patients have been described with minimal expiratory wheezing and with minimal basilar inspiratory rales. Chest x-rays may reveal accentuated pulmonary arteries centrally and cardiomegaly with right ventricular predominance. There may be minimal increased stranding in the lung fields, an indication of the mild fibrosis that accompanies vascular thrombosis. The electrocardiogram may have changes suggesting pulmonary hypertension and right ventricular predominance. Pulmonary functional analysis indicates a restrictive ventilatory defect with decreased total lung capacity, decreased vital capacity, and a mildly impaired carbon monoxide diffusing capacity. Arterial oxygenation may be normal or moderately low, and chronic hyperventilation is likely. As in other forms of pulmonary vascular occlusive disease, the course may be rapidly down hill once symptoms have developed.

The cause of pulmonary vascular thrombosis in patients with the "blue velvet" syndrome is the talc used as a filler in tripelennamine tablets, and in the "red devil" lesions the cause is starch spherules contained in secobarbital capsules. Similar syndromes have been reported in heroin addicts from the material used to dilute the heroin. Work in animals by Puro and his colleagues (57) has demonstrated extreme pulmonary toxicity of talc injected intravenously. The tissue response is granuloma formation about a talc crystal nidus and endothelial proliferation of the vessel wall with resultant pulmonary arteriolar thrombosis. These lesions may be overlooked in a lung biopsy specimen obtained in a patient with pulmonary hypertension, since examination with a light microscope is not adequate; polarizing lenses must be used to disclose the talc crystals. In a case so identified, the only known therapy is to convince the patient to desist in self administration of pulmonary emboli.

IV. Diffuse interstitial fibrosis

In addition to pulmonary disease caused by illicit drugs there are four syndromes of pulmonary disease caused by therapeutic drugs. One of these is diffuse pulmonary fibrosis. This lesion was first reported in association with hexamethonium therapy for systemic hypertension (63-66, 68, 72, 78) and its occurrence with that drug and with busulfan (Myleran) treatment of chronic granulocytic leukemia (70, 71, 73-76, 80) is best documented. Pulmonary fibrosis as part of a more generalized fibrosing process has also been described with methysergide therapy for headaches (77), and its occurrence with diphenylhydanton therapy for seizure disorder has been debated (67, 69).

In the series reporting pulmonary fibrosis in association with hexamethonium approximately 6% of all patients treated developed the pulmonary lesion. All of the patients had malignant hypertension; most of the patients were men, and the hypertension responded variably to the drug. After 3 to 15 months of hexamethonium, respiratory symptoms usually started abruptly, although in a few patients onset was more insidious. The first symptom was usually dyspnea, and this characteristically progressed rapidly to dyspnea at rest. In contradistinction to heart failure, which was common in these patients, the dyspnea was relieved by lying supine. Cough was not usually a prominent feature, and if cough was present it was not productive of sputum. At some time during the course fever was likely to develop. Physical examination revealed tachypnea, cyanosis, and basilar inspiratory rales, but clubbing was not observed in any case. The roentgenographic findings consisted

of bilateral reticular infiltrates or linear densities. Most of the patients had a leukocytosis, at least during the terminal phase of illness. Eighty-six percent of the reported patients died in respiratory failure during their first episode of symptoms despite discontinuation of hexamethonium. In one surviving patient reinstitution of hexamethonium after recovery did not result in a recrudescence of symptoms. Since hexamethonium has largely been abandoned in the treatment of hypertension, the most recently reported case was 1962.

Pulmonary fibrosis in the course busulfan therapy for leukemia is very similar to that described for pulmonary fibrosis due to hexamethonium. Patients have usually been taking busulfan for several months, usually in excess of a year. The leukemia is usually in remission and the patient relatively asymptomatic until an abrupt onset of dyspnea, weakness, and fever. Cough may be troublesome, but it is typically not productive. Chest x-rays demonstrate diffuse, bilateral, reticular infiltrates. Pulmonary functional analysis has been carried out on a few of these patients, and findings are those of a restrictive lung defect: reduced total lung capacity, reduced vital capacity, normal measurements of flow, decreased compliance and a decreased diffusion capacity.

At least 4 patients with busulfan lung have had dramatic improvement of their respiratory symptoms with the discontinuance of busulfan and treatment with adrenal cortical steroids. An additional patient has had marked improvement of symptoms with the discontinuation of busulfan without the use of steroids. In one patient reinstitution of busulfan did not cause an exacerbation of pulmonary fibrosis. It would appear that such therapy prevents progression of pulmonary disease rather than a reversal of fibrosis already present, since chest x-rays and pulmonary function tests remain abnormal, and the patients ultimately show extensive pulmonary fibrosis at autopsy.

The histological lesion of both hexamethonium and busulfan lung has been the subject of some controversy among pathologists. Many report a predominantly interstitial fibrosis with alveoli lined bylarge cuboidal cells and relatively little intra-alveolar exudate or fibrosis. This lesion is indistinguishable from idiopathic pulmonary fibrosis (Hamman-Rich Syndrome). Other pathologists report relatively little interstitial fibrosis. Instead, the fibrosis is described as predominantly intra-alveolar organization of fibrous tissue, a process frequently observed in organizing pneumonias. This histological picture suggests chronic leaking of high protein exudate into alveoli from altered capillary permeability. This is further suggested in some cases by the finding of hyaline membranes.

Heard and Cooke (80) suggest that subclinical busulfan lung is more common than realized from the limited number of case reports. In an autopsy study they found that 6 of 14 cases of chronic granulocytic leukemia treated with busulfan had changes of fibrinous edema and atypical cells. In the lungs from a fatal case of busulfan pulmonary fibrosis, the histological changes were similar but more severe. Only one of seven patients with leukemia untreated by busulfan showed minimal fibrinous edema, and atypical cells were absent. These findings suggest that the pulmonary lesion is a direct action of the drug and not a hypersensitivity reaction. Similar dose related pulmonary fibrosis has been reported with an anticancer chemotherapeutic agent, bleomycin, and experimental pulmonary fibrosis can consistently be produced with paraquat.

V. Pulmonary infiltrates with eosinophilia

In 1932 and 1936 Loeffler described a syndrome which has been subsequently identified by his name. It is characterized by variable, migrating infiltrations in chest roentgenograms and peripheral blood eosinophilia associated with a benign clinical course of brief duration. The x-ray infiltrates may be bilateral or unilateral, large or small, single or multiple, homogenous or spotty, and may occupy any part of the pulmonary field. During approximately a two-week course, migration, decrease in size and gradual disappearance of the x-ray changes are expected. Over 25% of Loeffler's original cases were detected during routine chest x-ray examination, and symptoms were absent. Conversely, cough may be severe, either dry or productive of small quantities of white, mucoid sputum. Malaise, anorexia, fever and generalized aching may be present. Expiratory wheezing and dyspnea suggesting asthma may initiate the attack. Physical findings are frequently absent, but occasionally fine moist rales are heard. Pleural, pericardial and peritoneal effusions containing eosinophils have occurred. Peripheral blood eosinophilia without immature forms may reach 80%. No correlation exists between degree of eosinophilia and amount, duration or intensity of the pulmonary infiltration.

Subsequently, in 1943, tropical eosinophilia was described as a separate entity, although the findings were similar to those of Loeffler's syndrome. Tropical eosinophilia was ultimately associated with infestation by mites or microfilaria. Loeffler's syndrome was shown to be associated frequently with parasites, especially ascariasis. Because of the varying terminology, the ultimate association of eosinophilic pneumonia with a variety of etiological agents, and because many patients

are much more symptomatic than originally described by Loeffler, Reeder and Goodrich (82) suggested that a better name for this syndrome is pulmonary infiltration with eosinophilia.

Drugs associated with pulmonary infiltrates and eosinophilia have included prontosil, penicillin, para-aminosalicylic acid (PAS) mephenesin carbamate (tolseram), sulfonamides, aurothioglucose (Solganal), chlorporpamide, and methotrexate. The syndrome produced by drugs is similar to the one described for Loeffler's syndrome, excepting that many of the patients are extremely ill and the duration of illness may be quite prolonged. The syndrome has been observed as early as 6 days and as late as 100 days after the onset of the offending drug. Peripheral eosinophilia varies from as low as 4% of a normal white blood cell count to as high as 80% with a total WBC count of 42,900/mm^3. Eosinophilia characteristically reaches its peak as the pulmonary infiltrates regress. These infiltrates may be small and migratory as in the classic Loeffler's syndrome, or they may involve virtually the entire lung at one interval and be protracted in course. The infiltrates are of an alveolar density. Most patients have recovered promptly on discontinuing the offending drug, but some patients have required adrenal cortical steroid therapy because of the life threatening nature of the illness. Such treatment is usually dramatic with an amelioration of symptoms promptly. Because of recovery in virtually all patients, morphological material is almost non-existent. One description indicates that the consolidation noted grossly is due to leukocytic exudation into interstitial tissues and small air spaces, primarly by mature eosinophils. However, macrophages, histiocytes, a small to moderate number of lymphocytes, and occasional plasma cells were also present in the interstitu, small air spaces, and small bronchioles. Some alveoli had granular pneumocytes such as those seen in desquamative interstitial pneumonia. The air spaces contain multinucleated, histiocytic giant cells.

The recently described syndrome of pulmonary infiltration with eosinophilia due to methotrexate therapy in children with acute lymphocytic leukemia deserves special emphasis (95, 96). Clarysse, et al, (96) have reported this syndrome in 7 consecutive patients and Acute Leukemia Group B (96) has described it in 38 of 93 patients in whom a remission of acute lymphoblastic leukemia was induced with Prednisone therapy and maintained by intermittent methotrexate. The pulmonary disorder appeared 12 to 100 days after the initiation of methotrexate therapy, at which time the leukemia in all patients was in complete hematologic remission. Pulmonary disease began insidiously with a non productive irritating cough. This was followed by malaise, temperature of 102° to 104°, and increasing dyspnea. Many of the patients became critically ill with severe dyspnea, tachypnea, and cyanosis (arterial oxygen saturation 62% to 68%). The chest

roentgenograms showed progressive, bilateral diffuse, interstitial pulmonary infiltrates more marked at the bases, with patchy areas of consolidation in severe cases. No pleural effusions occurred, but progressive cardiomegaly developed in 3 patients. Administration of methotrexate was continued throughout the pulmonary illness in most patients, and the acute phase of illness lasted 10 to 40 days regardless of whether methotrexate therapy was continued. Once improvement had begun, the lung fields cleared rapidly without residual change in most instances. Total blood eosinophil counts ranged from 86 to 1620/mm^3, but it is not indicated at what point these observations were made nor the concomitant total white cell count. Lung biopsy in one patient showed aggragates of mixed inflammatory cells filling alveolar spaces and to a lesser extent within the interstitial tissue. Large mononulcear cells predominated and often formed poorly defined, non-caseating granulomas containing multinucleated giant cells. Foci of eosinophils and clusters of lymphocytes were also seen. In one of three patients who died with the presumptive diagnosis of this syndrome, Pneumocystis carinii was found at the time of autopsy. It is not clear whether the methotrexate pulmonary lesion is similar to that associated with other drugs.

VI. Nitrofurantoin pulmonary reaction

Although an anaphylactoid reaction to nitrofurantoin (Furadantin) was reported in 1957, the first parenchymal reaction was reported in 1962 (98). Since that time, 28 cases have been reported, and the reactions are distinctive enough to be classified separately from pulmonary infiltrates with eosinophilia. Twenty two cases of acute and six cases of chronic reaction have been reported.

Typically, in the acute syndrome symptoms begin from two hours to 10 days after the initial dose of the drug, but the acute lesion has been described as late as one year after the onset of nitrofurantoin treatment. There is an abrupt onset of fever, chills, cough, and dyspnea. Physical findings are somewhat minimal in relation to the degree of illness. Tachypnea is usually present, and basilar rales may be heard. Several patients have had a non specific, macular skin rash. In 21 of 22 reported chest x-rays, the changes were limited to the lower lobes, most commonly bilaterally. In contradistinction to pulmonary infiltrates with eosinophilia the radiographic appearance is that of a reticular infiltrate, and 50% of the patients have been reported to have pleural effusions. Thirty percent of the patients with the acute syndrome do not have eosinophilia, and in those with eosinophilia it tends to be of a low order of magnitude. Although

the patients may be extremely ill, cessation of the drug results in a very dramatic improvement of all symptoms and radiographic findings, usually within one day. Because of the severity of illness, some patients have been given adrenal cortical steroids, but it is not clear whether these patients cleared faster than patients not so treated.

Six patients have been reported who received nitrofurantoin for periods from 6 months to 6 years before pulmonary symptoms developed. In these patients the onset of pulmonary symptoms was gradual, and the duration of symptoms varied from 7 weeks to 6 years before the nitrofurantoin therapy was stopped. Only one patient had fever. In all cases the chest x-ray demonstrated a non specific, diffuse, bilateral interstitial infiltrate that frequently was most severe at the bases and was not associated with pleural effusions. Pulmonary functions were typical of restrictive disease with an impaired carbon monoxide diffusing capacity. Lung biopsy in all patients revealed chronic interstitial edema and fibrosis. The histological appearance was not diagnostic, and was similar to that seen in idiopathic, chronic diffuse interstitial fibrosis. Five of the six patients had moderate to definite improvement after the use of nitrofurantoin was discontinued and steroids administered. Only one case did not improve significantly. This patient had pulmonary symptoms for 6 years in contrast to the other patients in whom symptoms had been present for 7 weeks to 1 1/4 years. Thus, there appears to be a correlation between the duration of pulmonary symptoms and the amount of improvement. There does not appear to be any correlation between the length of time on nitrofurantoin therapy and the severity of illness, or its reversibility.

VII. Pathological calcification

"Metastatic" calcification of the lungs is known to occur in a wide variety of diseases, most commonly destructive lesions of bone. It has also been reported in association with chronic renal disease, hyperparathyroidism due to adenomas, vitamin D intoxication, and excessive intake of milk and alkali. In all of these circumstances the patients had pulmonary calcification in association with involvement of other organs.

Cooke and Hyland (113) have reported a single patient with extensive pulmonary calcification which occurred in an 8 month interval following the administration of large amounts of calcium gluconate, vitamin D and dihydrotachysterol in an effort to control severe manifestations of tetany. The extensive calcification of the lungs did not cause apparent symptoms, and pulmonary function tests were said to be normal, although these were not reported in detail. At the time of death from his primary disease process the patient was found to have calcification in numerous pulmonary foci as large as the diameter of an alveolus. Most of the deposits lay within the walls of

alveoli; the alveolar septa were moderately fibrotic. There were no other foci of metastatic calcification. The cause of the lungs as a single focus for this lesion could not be determined.

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